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Total synthesis of kealiiquinone: the regio-controlled strategy for accessing its 1-methyl-4-arylbenzimidazolone core†

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A practical, concise and straightforward total synthesis of kealiiquinone **1**, a naphtho[2,3-*d*]imidazole alkaloid obtained from the Micronesian marine sponge *Leucetta* sp. was accomplished. The squaric acid chemistry to construct the 1,4-quinoid ring and the regioselective *N*-methylation through a benzo[*c*][1,2,5]selenadiazolium heterocycle are the key features in this report. The full details of the representative approaches involving the different attempted synthetic strategies are also presented. Finally a successful total synthesis of this complex secondary metabolite is described.

Introduction

Natural secondary metabolites obtained from marine sponges have been an extensive source of pharmacologically active new drugs.[1] Representative examples obtained from the sponge *Leucetta chagosensis* include clathridine, naamidines A, G, H,[2] and (−)-spiroleucettadine.[3] In 1990 Scheuer and Clardy isolated two new imidazole alkaloids from the *Leucetta* sp. sponge, the pyronaamidine and kealiiquinone **1** (Fig. 1).[4]

Kealiiquinone **1**, is a complex natural compound, which contains a 1,4-quinoid ring (A ring), fused to a regio-differentiated *N*-methyl-4-arylbenzimidazolone with the aryl and the methyl groups at opposite hemispheres of the alkaloid. Due to its attractive molecular architecture and to its modest biological activity, two total syntheses have been developed to date (Scheme 1).

The first total synthesis of kealiiquinone was described by Ohta.[5] This strategy was mainly based upon the central ring (B ring, Scheme 1) formation in acid media *via* a Friedel–Crafts-type condensation. The procedure is overall efficient, however a functionalized imidazole as building block as well as the use of several protecting groups (four of them) could be pointed as limitants to scale up the process. The second total synthesis of kealiiquinone was described by Lovely.[6] In this approach, the same two main features about the use of a functionalized imidazole, as well as the Friedel–Crafts-type condensation also in acidic media for equally constructing the central B ring of the alkaloid are found. Notwithstanding great similarities can be identified, the synthesis was completed but several (four of them) organic redox fluctuations (oxidation–reduction–oxidation) are found. Additionally the biological assays of activity were carried out in a successful way.[7]

A particular and well-identified synthetic challenge in the total synthesis of keliiquinone is the regioselective *N*-methylation at the first position nitrogen of the imidazolone ring (see

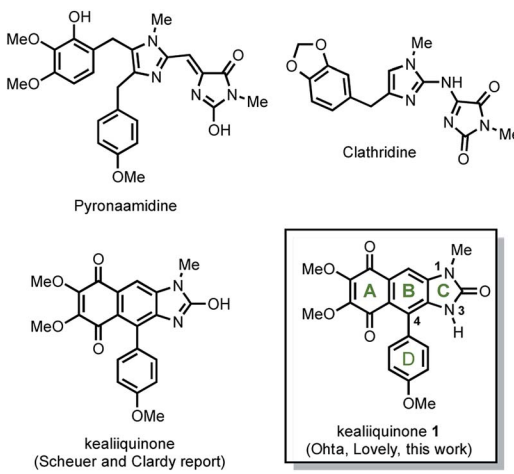

Fig. 1 Representative imidazole alkaloids isolated from the *Leucetta* sp. sponge.

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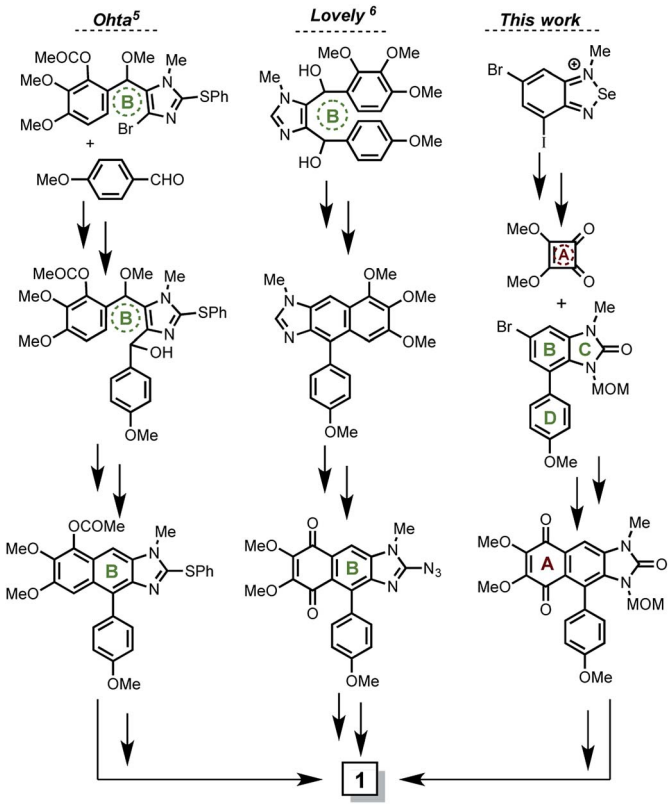


Scheme 1 Described total synthesis of kealiiquinone to date.

Fig. 1), this is the key objective of our work to complete the total synthesis of **1**. To highlight the importance of the aforementioned molecular regio-differentiation, is worth to mention the efforts to address this problem, mainly by Lovely group.[8] In the same context, our group recently described the total synthesis of the 3-methylkealiiquinone,[9] in route to the total synthesis of the natural alkaloid **1**.

In regards to previous reports, our procedure overcomes the necessity for using imidazole as building block as described by Ohta and Lovely. This is an advantage in our strategy since it allowed us to scale up in a straightforward fashion the starting materials. Also a metallation–sulphinilation–oxidation sequence at the first imidazole carbon was necessary for the final imidazolone construction in the Ohta route, which did not occur in ours. On the other hand, at least four sequences implying REDOX fluctuations were presented in the Lovely kealiiquinone synthesis, while in our route only two of them were used and correspond to the protecting groups used. Additionally as we described[9] our strategy is modular and is possible to introduce different functional groups in the 1,4-quinone as well as in the aryl pendant rings. Finally is important to mention that the regiodifferentiation to get selective methylation in final natural alkaloid include several steps. In our synthesis the use of protecting groups is necessary. However we use only two protecting groups instead of four as in the Ohta protocol.

Considering all of these reports, herein we describe the full details about representative strategies attempted to prepare **1**. Also we present our developed route, which was totally focused in the regioselective *N*-methylation of the imidazole ring and finally allowed us to accomplish the total synthesis of kealiiquinone **1** by late stage construction of the 1,4-quinoid ring (A ring).

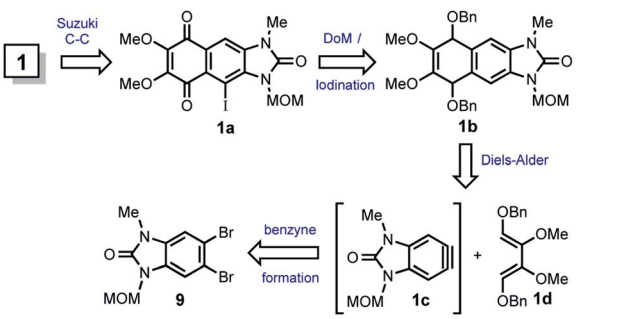
Results

The first attempted strategy to prepare **1** is following outlined (Scheme 2).

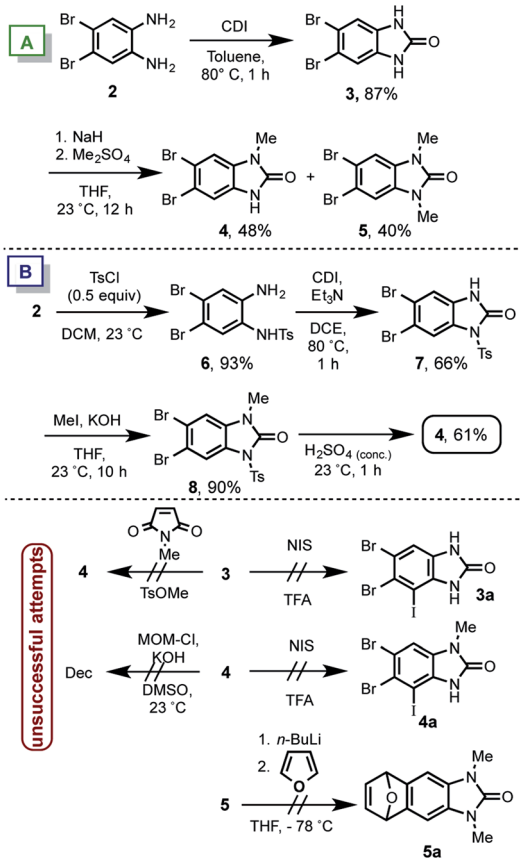
In this route, kealiiquinone **1** can be obtained from the iodoquinone **1a** by MOM removal and cross-coupling reaction with the *p*-anisyl boronic acid. The 1,4-quinone **1a** could be obtained by oxidation of the Diels–Alder adduct **1b**, where the MOM group may act as protecting-directing group for the directed *ortho*-metalation (DoM)/iodination.[10] The compound **1b** is the result of the Diels–Alder reaction between diene **1d** and benzyne **1c**, which comes from **9**. Thus, different routes intended to prepare **9** are following summarized (Scheme 3).

We prepared the known symmetric aniline **2**,[11] that reacted with CDI in toluene at 80 °C affording the benzimidazolone **3**. Then, by using dimethylsulfate, the single methylation for accessing to the non-symmetric benzimidazolone **4** was not observed. Instead a mixture of **4** and **5** in almost (1 : 1) ratio was obtained (Scheme 3A). Accordingly to the required nitrogens differentiation in **4**, a different route was attempted (Scheme 3B). Therein the mono-tosylation of **2**, was achieved giving rise to **6** in 93% of yield. The subsequent benzimidazolone formation by using CDI in DCE yielded **7** in 66%, which was methylated in presence of methyliodide to furnish **8** in 90% of yield. Finally the treatment with sulphuric acid lead to **4** in 61%. This derivative shows the desired non-symmetric mono-methylated benzimidazolone.

Several other trials (Scheme 3C) to obtain **4** such as the use of *N*-methylsuccinimide or methyltosylate as methylating reagent on **3** resulted in no reaction. On the other hand accordingly with the **1b** structure (see Scheme 2), a MOM group is necessary as protecting-directing group for the DoM/iodination sequence. Thereby the incorporation of MOM was tried in **4**, unfortunately the decomposition of starting material was found after different attempts. Upon the failure to attach a single MOM group in **4**, it was decided to install the iodine atom of the iodoquinone **1a**. Different trials by using NIS/TFA in **3** or **4** to get **3a**/**4a**



Scheme 2 First strategy towards the total synthesis of kealiiquinone **1**.

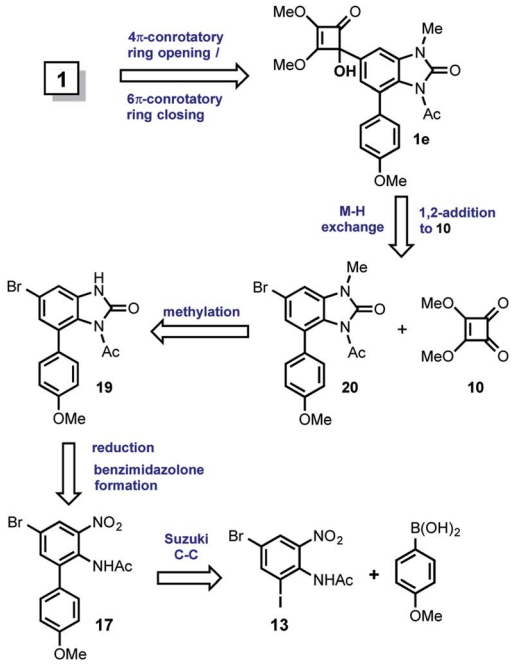


Scheme 3 Synthesis of benzimidazolones **4** and **5** for preparing **9**.

respectively only showed the low reactivity of the starting material and as consequence no reaction was observed. Even tough we did not succeed in the compound **9** synthesis, it was tested the benzyne formation since is the key step in the proposed route. Thus, compound **5** was mixed with *n*-BuLi at −78 °C in presence of furane. Several conditions changing base equivalents, time and temperatures were assayed, however we were unable to get any Diels–Alder adduct **5a** (see ESI†). Presumably due to an electron-rich dienophile formation in a direct electron demand Diels–Alder reaction.

In this point, we decided to change substantially the general strategy towards the total synthesis of **1**. A very important aspect was not to complete the total synthesis by using a Friedel–Crafts strategy as key step, since Ohta and Lovely previously described it. Based upon our expertise,[9] we focused in the construction of the quinone ring as the last step of the route, we planned the use of the squaric acid chemistry[12] for building up it. Accordingly, the new synthetic strategy is described (Scheme 4).

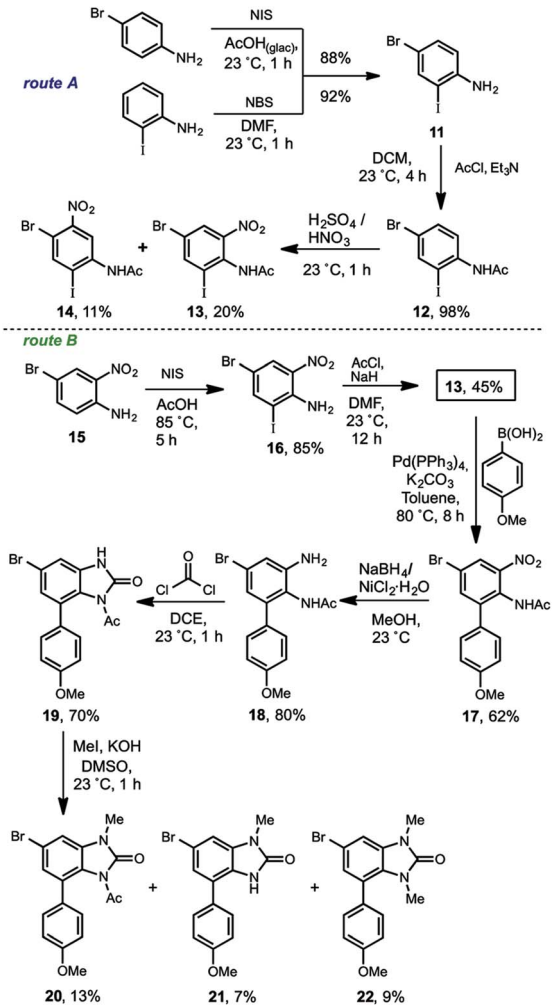
In this approach, kealiiquinone **1** comes from the tertiary alcohol **1e** *via* the thermally-promoted electrocyclic sequence 4π-conrotatory ring opening/6π-conrotatory ring closure. The alcohol **1e** can be the result of the 1,2-addition between the dimethylsquarate **10** and the organolithium generated form **20** by metal–halogen (M–H) exchange. Compound **20** is obtained by the methylation of the bromobenzimidazolone **19** which can be prepared by the nitro group reduction concomitant phosgene treatment of **17**. Finally this *ortho*-nitroarylaniline can be



Scheme 4 Second strategy towards the total synthesis of kealiiquinone **1**.

synthesized by a Suzuki cross-coupling reaction within *p*-anisylboronic acid and the regio-differentiated bromoiodoacetylnitroaniline **13**. The most relevant aspect in this alternative is the regioselective proposal for introducing the desired methyl group at first position nitrogen of the natural compound. This regiochemistry is based upon the different oxidation states at the adjacent nitrogens (Scheme 5).

The synthesis of the arylbenzimidazolone **20** was developed by two convergent routes (route A and B), which merged in **13**. In the route A, two commercially available compounds were used for starting. In one side *para*-bromoaniline was iodinated and on the other side the *ortho*-iodoaniline was brominated in 88% and 92% of yield respectively, to get **11**. After an extensive experimental analysis, we determined this as a good point for the acetyl group introduction, which produced **12** almost quantitatively. Next, the sulfonitric mixture gave rise to a low-yielding and non-selective nitration that produced the regioisomers **13** (20%) and **14** (11%). Other attempts such as nitration of **11** to get **16**[13] for the regioselective introduction of the nitro group *ortho* to the amino, resulted in no reaction. Regarding the non-selective nitration, although the regioisomeric mixture of **13** and **14** is chromatographically separable, the strong acid medium promoted the deacetylation of **12** giving poor yields for each compound, thus resulting in a no viable alternative. In consequence, another route (route B) with the initially adjacent installed nitrogens but in different oxidation states was envisioned. Thereby the known compound **15**,[14] was synthesized from *o*-nitroaniline. The iodination of **15** gave rise to **16** in 85% of yield, which was acetylated in a modest 45% to furnish the convergence compound **13**. This moderate yield is more evident if the acetylation reactions of **16** to **13** with **11** to **12** are compared.



Scheme 5 Synthesis of the regio-differentiated arylbenzimidazolone **20**.

The bulkiness of the iodine atom in **16** as well as of the nitro group, severely restricted the functionalization of the amino group due to a bis-*ortho*-substitution effect.[15] This steric effect was observed during all of our work development including the fails for some basic-resistant groups (TIPS, MOM, Piv) we tried to introduce. Nevertheless a moderate overall yield at this stage was obtained, we decided to continue with the route to validate it. The following Suzuki cross-coupling reaction between **13** and the *p*-anisyl boronic acid afforded the arylnitroaniline **17** in 62% of yield. The non-acidic Hassanloie[16] conditions for chemoselective nickel-catalyzed nitro group reduction, gave rise to **18** in 80% without acetyl removal. This compound was subjected to benzimidazolone formation by phosgene treatment to furnish **19** in 70% of yield. Finally, the methylation of **19** in basic medium was carried out, unfortunately a very complex reaction mixture was observed. Several optimization assays were done, however in the best of our results a very low-yielding mixture consisting of the desired compound **20** (13%), methyl-deacetylated benzimidazolone **21** (7%) and the bismethylated derivative **22** (9%) were isolated. This result evidenced the extremely poor resistance of the acetyl group to basic conditions[17] and strongly limits the scalability. Therefore the M–H exchange over **20** (see Scheme 4) was not carried out.

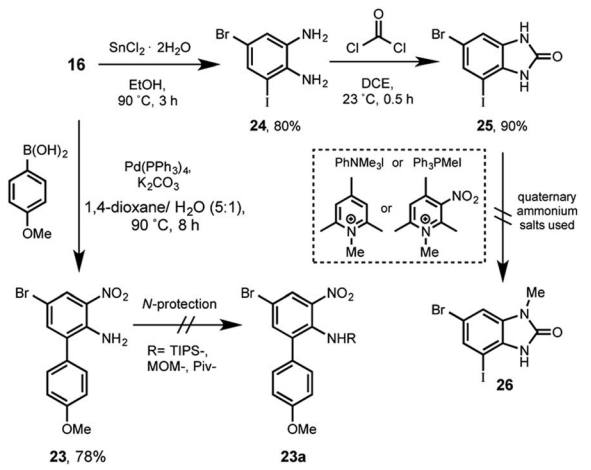
After this set of reactions we preliminarily concluded two relevant points: (1) the haloaniline **16** was identified as a very important building block due to the properly functionalization for further orthogonal reactions. In **16**, there is a nitro group, which was reduced and regioselective methylated, an iodine atom for the chemoselective Suzuki cross-coupling and a bromine for organolithium generation *via* M–H exchange. (2) Even tough this second strategy failed, it could be useful with a more basic-resistant group instead of an acetyl. However was not possible by this route.

Thus, an alternative procedure based on **16** to introduce regioselectively a basic-resistant group was started (Scheme 6).

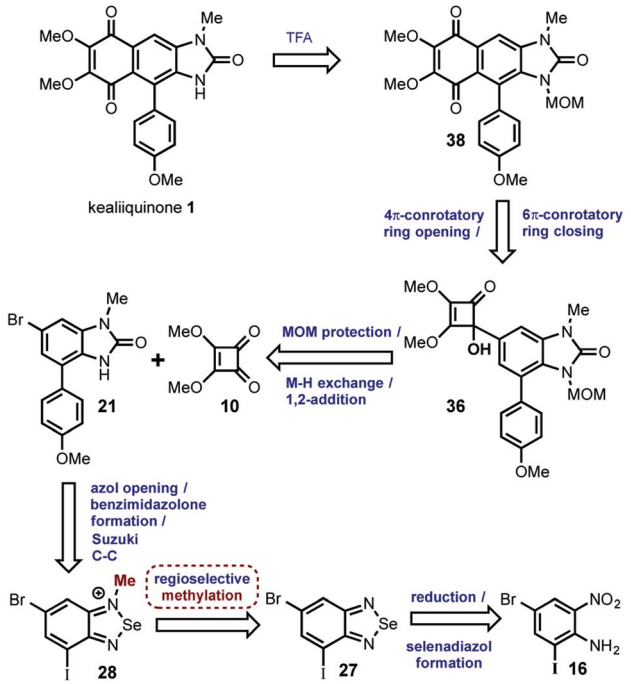
In this strategy the aniline **16** participated in a Suzuki cross-coupling reaction with *p*-anisylboronic acid, giving rise to the arylnitroaniline **23** in 78% of yield. Next, after too many attempts to functionalized the amino group with basic-resistant groups such as TIPS, MOM or Piv (see ESI†), we systematically failed. Presumably due to the aforementioned bis-*ortho*-substitution steric effect.

Previous to rule out this sequence, an additional alternative was considered. For instance, **16** was reduced in presence of tin(II) chloride affording **24** in 80%. The following reaction with phosgene allowed the formation of **25** in excellent 90%. In this stage the regioselective methylation was rationalized by using a bulky methylating reagent, in order to direct the reaction at first position nitrogen. Different quaternary ammonium salts such as triphenylanilinium, methyltriphenylphosphonium, *N*-methylcollidine or the *N*-methylnitrocollidine were tested. All of them did not show any reaction to yield the regioselective-methylated derivative **26**.

Frustratingly we can preliminarily summarize that after three different strategies and more than three hundred experiments, we were unable to establish a successful route for the total synthesis of kealiiquinone **1**. Therefore a deep analysis of the developed work revealed potential compounds such as **25**



Scheme 6 Attempts to synthesize the aniline **23a** and benzimidazolone **26**.



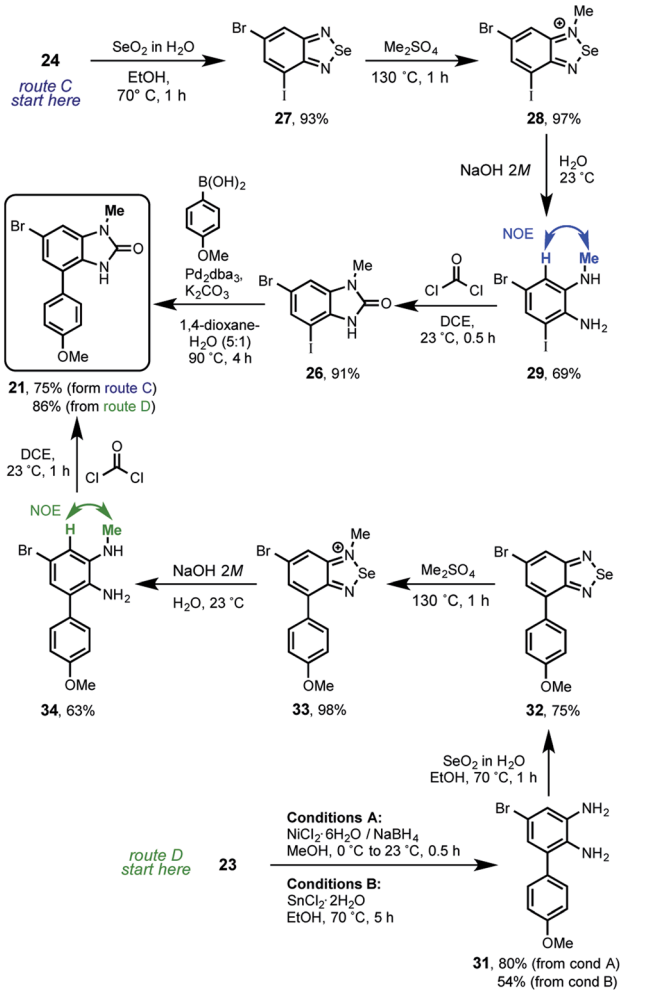
Scheme 7 Successful retrosynthetic analysis of the kealiiquinone **1**.

(Scheme 6), which is an excellent chemo-differentiated building block for orthogonal Suzuki cross-coupling and M–H exchange reactions. Also we identified the compound **21** (Scheme 5). This resulted a very attractive derivative, since it contains the desired methyl group regioselectively installed, the *p*-anisyl group in the correct position, the third-position nitrogen available for a protecting group introduction and finally a bromine atom for the organolithium generation by M–H exchange.

On the other side after an extensive bibliographic search[18] it was found an excellent opportunity in the selenium chemistry described by Milata[19] for the regioselective methylation of 2-aminoanilines that can give the desired regiodifferentiated methylbenzimidazolone after the reaction with phosgene. The compounds **16**, **25** and **21** were considered in this approach that finally allowed us the total synthesis of kealiiquinone **1**. The overall strategy is illustrated in the following retrosynthetic analysis (Scheme 7).

In this strategy the naturally occurring kealiiquinone **1**, was obtained from **38** after MOM-deprotection in acidic medium. This protected 1,4-quinone is the result of the electrocyclic 6π-ring closure carried out in the thermal ring expansion of **36**. This tertiary alcohol comes from the 1,2-addition of the organolithium generated from **21** to the dimethylsquarate **10**. The mentioned arylbenzimidazolone was obtained from the slenadiazolium **28** after the regioselective methylation of the corresponding selenadiazol **27** that is obtained form the halonitroaniline **16**.

From this analysis it was determined that compound **21** is key to complete the total synthesis of kealiiquinone **1**. Thereby two routes (C and D) were developed allowing for accessing in good yield as well as in a regio-controlled fashion to the 1-methyl-4-arylbenzimidazolone core of kealiiquinone (Scheme 8).



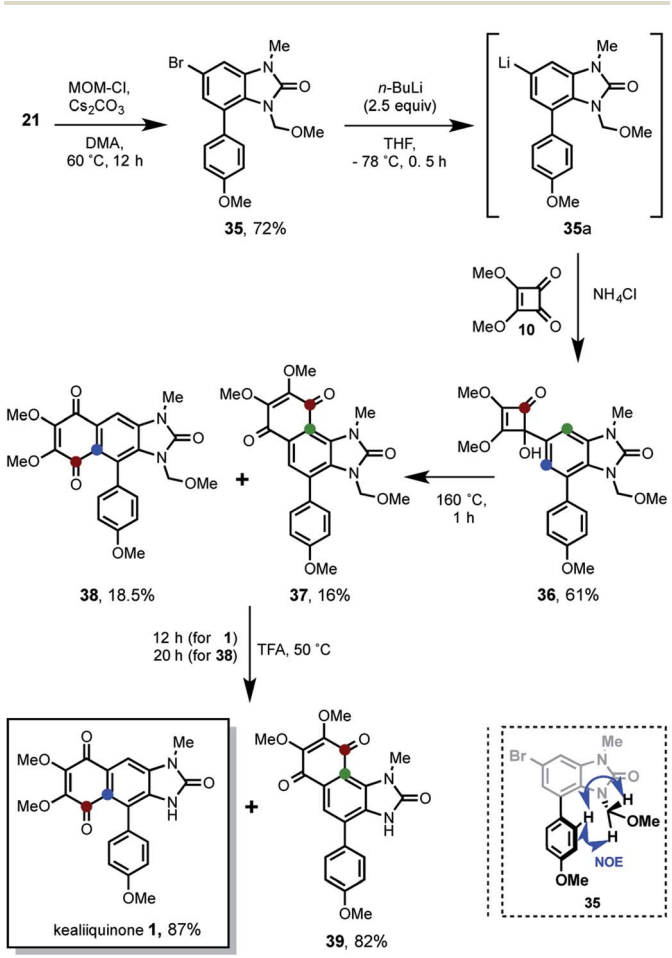
Scheme 8 Synthetic route for accessing to the 1-methyl-4-arylbenzimidazolone **21** of the kealiiquinone.

The route C started with the reaction between the 2-aminoaniline **24** and selenium dioxide, to produce the benzo[*c*][1,2,5]selenadiazol **27** in excellent 93% of yield. In agreement with the Milata[19] reports, these derivatives are methylated by heating in dimethyl sulfate as solvent. Based upon our previous strategies results (see Scheme 5), it was rationalized that the steric hindrance provided by the iodine atom, would direct the methylation to the nitrogen at the first position. To our delight we found the regioselective methylation in such expected nitrogen, giving rise to the 1-methylbenzo[*c*]selenadiazol-1-ium **28** nearly to quantitative yield. Is worth to mention that these two last steps proceeded without any purification. Next, the ring opening of **28** in basic-medium yielded the aniline **29** in 69%. The NOESY experimentation for this compound unequivocally confirmed the required regioselective methylation (see ESI†). The route continued with the benzimidazolone formation by phosgene treatment of **29** furnishing the 1-methyl-6-bromo-4-iodobenzimidazol-2-one **26** in 91% of yield. This compound was used for the MOM-group introduction trials, however it was found only complex reaction mixtures after exhaustive attempts (see

ESI†). Therefore it was introduced in a different synthetic stage. The route C concludes with the Suzuki cross-coupling within **26** and *p*-anisylboronic acid leading to **21** in 75%. On the other hand, the route D started with the reduction of nitroaniline **26** by using two reaction conditions. The first are the Hassanloie-reducing[16] conditions using sodium borohydride in presence of nickel chloride to get **31** in 80%. As alternative, the usage of tin(II) chloride in ethanol yielded the nitro group reduction in 54%. Similarly the reaction with selenium dioxide of this 2-aminoarylaniline furnished the structurally related 4-arylbenzo-[*c*][1,2,5]selenadiazol **32** in 75% of yield. Under the same rationale, the regioselective methylation took place by heating **32** at 130 °C in dimethyl sulfate, giving rise to the 4-anisylbenzo[*c*][1,2,5]selenadiazolium **33** in excellent 98% of yield. The following ring opening in basic medium provided **34** in 63%. The regioselective methylation of this route was unequivocally confirmed by NOESY experimentation in this compound (see ESI†). Afterwards the treatment of **34** with phosgene convergently produced **21** in 75%.

After carry out this group of experiments, gratifyingly we were able to establish a regio-controlled strategy for accessing to the 1-methyl-4-arylbenzimidazolone core of kealiiquinone.

Finally, the total synthesis of the natural alkaloid was accomplished (Scheme 9).



Scheme 9 Completion of the total synthesis of kealiiquinone **1**.

After the successful preparation of the regio-differentiated 1-methyl-4-*p*-anisylbromobenzimidazolone **21**, the challenge to address is the introduction of a basic-resistant protecting group, which tolerates the M–H exchange reaction conditions. We focused our attention to the MOM group, since is a strong basic-resistant group even used for DoM reactions,[9] can be deprotected in relative milder acid medium and has moderate steric hindrance. This former aspect is very important because our previous experimentation (see Schemes 6 and 8) showed great difficulties to introduce big groups in the third position of benzimidazolone. We assumed was due to the bis-*ortho*-substitution effect. Thus, after the fail to introduce de MOM group in **26** (see Scheme 8) such functionalization was attempted in **21**. In this way, **35** was obtained in 72% of yield with the desired MOM-protection at nitrogen. In view that benzimidazolone is bidentated at nitrogen and oxygen, the regioselectivity in the nitrogen MOM-functionalization was confirmed by NOESY experiments (see ESI† and down of Scheme 9). Then the M–H exchange generated *in situ* the organolithium **35a**, which reacted with the dimethylsquarate **10** yielding 61% of the tertiary alcohol **36**. The following heating of **36** at 160 °C along 1 h, promoted the thermal 4π-conrotatory ring opening/6π-conrotatory ring closure for the π-homologation system. This transformation take place through the accepted ketene intermediates,[20] which have been described for this chemistry.[12] The reaction furnished a (1 : 1) regioisomeric mixture of the 1,4-quinones **37** and **38** in 16% and 18.5% of yield respectively. For simplicity we refer to them as angular and linear compounds. This expected result showed the desired linear 3-MOM-kealiiquinone **38** as well as an angular 3-MOM-kealiiquinone **37** which posses a novel naphtho[1,2-*d*]imidazole nucleus. Is important to highlight that even though the yields are moderately-low, they are the result of a two consecutives reactions (hydroquinone formation/oxidation to 1,4-quinone). Therefore this two-step one-pot reaction represents a *ca.* 40% and 43% of yield respectively for each transformation calculated in linear manner. Finally the MOM group-removal by heating at 50 °C in trifluoroacetic acid lead to the completion of the total synthesis of kealiiquinone **1** in 87% of yield after 12 h.

Table 1 Comparison of ^{1}H MNR data of kealiiquinone[a]

Kealiiquinone (**1**)			
^{1}H NMR acquired in DMSO-d_6			
Natural[a]	Ohta[b]	Lovely[c]	This work
3.58 (s, 3H)	3.39 (s, 3H)	3.40 (s, 3H)	3.39 (s, 3H)
3.78 (s, 3H)	3.82 (s, 3H)	3.83 (s, 3H)	3.82 (s, 3H)
3.83 (s, 3H)	3.85 (s, 3H)	3.85 (s, 3H)	3.85 (s, 3H)
3.92 (s, 3H)	3.94 (s, 3H)	3.94 (s, 3H)	3.94 (s, 3H)
6.88 (d, 2H)	6.98 (d, 2H)	6.98 (d, 2H)	6.98 (d, 2H)
7.12 (d, 2H)	7.13 (d, 2H)	7.13 (d, 2H)	7.13 (d, 2H)
7.69 (s, 1H)	7.68 (s, 1H)	7.68 (s, 1H)	7.68 (s, 1H)
—	11.03 (bs, 1H)	11.02 (bs, 1H)	11.03 (bs, 1H)

[a] The spectroscopic data were obtained from ref. 4. [b] The spectroscopic data were obtained from ref. 5. [c] The spectroscopic data were obtained from ref. 6.

Table 2 Comparison of ^{13}C MNR data of Kealiiquinone

Kealiiquinone (**1**)			
^{13}C NMR obtained in DMSO-d_6			
Natural[a]	Ohta[b]	Lovely[c]	This work
182.4	181.3	181.3	181.3
181.8	181.1	181.1	181.1
159.0	158.5	158.5	158.5
158.3	154.8	154.8	154.8
148.2	147.8	147.8	147.8
147.8	134.0	145.2	145.2
146.0	132.6	134.0	134.0
137.9	129.9	132.7	132.7
131.1	127.7	129.9	129.9
130.6	126.5	127.7	127.7
129.4	126.5	126.4	126.4
124.1	123.5	123.5	123.5
122.9	122.6	122.6	122.6
113.3	113.9	113.9	113.9
105.1	104.6	104.5	104.5
61.0	60.8	60.8	60.8
61.0	60.8	60.8	60.8
55.4	55.0	55.0	55.0
29.2	26.8	26.8	26.8

[a] The spectroscopic data were obtained from ref. 4. [b] The spectroscopic data were obtained from ref. 5. [c] The spectroscopic data were obtained from ref. 6.

From the angular derivative was also obtained in 82% of yield along of 20 h of reaction.

The spectroscopic data were compared and they match with those reported by Ohta and Lovely (Tables 1 and 2).

The Table 1 shows a very good correlation among the spectroscopic data for the ^{1}H NMR of kealiiquinone reported by Ohta and Lovely and our synthetic alkaloid. Certainly the naturally occurring compound we obtained is in the carbonyl tautomer form at the benzimidazolone ring more than an enol-form such as was isolated by Scheuer and Clardy.[4] Previously, this observation has been pointed out.[5,6]

On the other hand the spectroscopic data obtained for the ^{13}C NMR of our synthetic kealiiquinone also matched with the reports of Ohta and Lovely (Table 2).

We found an excellent correlation in the comparison of the ^{13}C NMR spectroscopic data. Also we found a better correlation with Ohta and Lovely reports than form original isolation report. Surely due to the thermodynamically more stable ketonic-form of kealiiquinone instead to its enolic-form as mentioned by Lovely.[6]

Therefore kealiiquinone **1**, was successfully synthesized.

Conclusions

In summary, we have developed a new, convergent and modular total synthesis of the naturally occurring marine alkaloid kealiiquinone **1**. Our procedure was completely focused in the regioselective methylation at the first nitrogen position of its arylbenzimidazolone core. Accordingly, several experimentations we described, progressively guided us to the final successful strategy through which we were able to synthesized in a regio-controlled manner the 1-methyl-4-(*p*-anisyl)benzimidazolone fragment as key building block of **1**. This was a big challenge addressed *via* a selenadiazolium intermediate formation. On the other hand unless of the thermal ring expansion, which is the only step showing moderately-low yield, the rest of this route proceeds in good to excellent yields. Our strategy required only two protecting groups whose procedures for introduction and removal took place under mild and efficient conditions. The use of MOM as basic-resistant protecting group resulted in an excellent choice since we demonstrated that bulkier analogues such as TIPS or Piv were not possible to introduce owing to a bis-*ortho*-substitution effect. Finally as expected, in the thermal ring expansion result, it was found a non-described angular analogue of kealiiquinone that contains an attractive naphtho[1,2-*d*]imidazole moiety. The complete characterization for the final naturally occurring alkaloid kealiiquinone **1**, concisely matched with the previous reports confirming the ketonic-form in its imidazolone ring.

Experimental section

General information

All moisture and oxygen sensitive reactions were carried out in flame-dried round bottom flasks under an inert atmosphere of nitrogen. Unless otherwise specified, all commercial materials were used as received without further purification. Anhydrous solvents were purchased from Sigma Aldrich in SureSeal® bottles. Column chromatography was performed using silica gel of size 100–200 and 230–400 mesh (Sigma Aldrich). Thin layer chromatography was performed with TLC Silica gel 60 F256 plates, and visualization was effected with short wavelength UV light (254 nm). Compounds were characterized using ^{1}H NMR, ^{13}C NMR. (Copies of ^{1}H NMR and ^{13}C NMR spectra are provided for all the compounds.) Data of known compounds were compared with existing literature characterization data and the references are given. ^{1}H and ^{13}C NMR spectra were recorded with 500 MHz and Bruker advance 400 MHz instruments using deuterated solvents purchased from Sigma Aldrich like $CDCl_3$. ^{1}H spectra were referenced with tetramethyl silane (TMS, 0.0 ppm) or chloroform ($CDCl_3$, 7.26 ppm) and are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (δ = 77.16 ppm). All the starting materials were synthesized according to reported procedures in the literature. High resolution mass (HRMS) analysis was obtained using MAXIS IMPACT BRUKER. Chemical nomenclature was generated using Chemdraw. Infrared (IR) spectra were recorded using Perkin-Elmer system 2000 FT-IR spectrometer. Melting points of solids were measured using Fisher-Johns melting point apparatus.

Scheme 1 to prepare 4,5-dibromobenzene-1,2-diamine (2)

***N*,*N*′-(1,2-Phenylene)bis(4-methylbenzenesulfonamide) (a).** A 1000 mL round bottom flask charged with *o*-phenylenediamine

(5.0 g, 46.296 mmol), was dissolved in pyridine (30 mL). To the reaction mixture was added *p*-toluenesulfonyl chloride (17.6 g, 92.592 mmol), and it was stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure. The reaction mixture was washed with 200 mL of HCl (1 N), followed by extracted with EtOAc (200 mL). The organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (25% EtOAc/hexane) to provide the compound **a** (16.6 g, 86%) as pale white solid. $R_f = 0.6$ (50% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, $J = 8.2$ Hz, 4H), 7.21 (d, $J = 8.2$ Hz, 4H), 7.04–7.01 (m, 2H), 6.97–6.95 (m, 2H), 6.93 (bs, 2H), 2.39 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.3, 135.6, 130.9, 129.8, 127.70, 127.5, 126.3, 21.7. HRMS (ESI+): (*m*/*z*) calcd for $C_{20}H_{20}N_2O_4S_2$ $[M]^+ = 416.0864$ found 416.0860.

***N,N′*-(4,5-Dibromo-1,2-phenylene)bis(4-methylbenzenesulfonamide) (b).** Bis-tosylated phenylenediamine (15.0 g, 36.057 mmol) was charged to a 500 mL two neck dried round flask and was dissolved in dry dichloromethane (150 mL). To the reaction mixture was added Br_2 (7.4 mL, 144.230 mmol, 4 equiv.) at 0 °C, and then refluxed it for 12 h. The reaction mixture was poured into ice-cold water (200 mL) and solid was formed. The resulting solid was filtered-off and dried in vacuum to get *N*,*N*′-(4,5-dibromo-1,2-phenylene)bis(4methylbenzenesulfonamide) **b** (17.2 g, 86%) as pale solid. Mp 196–198 °C. IR (neat, ν/cm^{-1}): 3249, 3215, 1596, 1464, 1304, 1158, 706. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, $J = 8.1$ Hz, 4H), 7.28 (d, $J = 7.9$ Hz, 4H), 7.20 (s, 2H), 6.84 (s, 2H), 2.42 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.0, 135.0, 130.9, 130.2, 130.1, 127.7, 122.7, 21.8. HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{19}Br_2N_2O_4S_2$, $[M + H]^+ = 572.9153$, found 572.9112.

4,5-Dibromobenzene-1,2-diamine[21] (2). A 250 mL two necked round bottom flask was charged with 4,5-dibromo-bistosylated compound **c** (10.0 g, 17.42 mmol) and concentrated sulphuric acid (20 mL, 34.832 mmol) was added at room temperature. The reaction mixture was stirred at 23 °C for 1 h and then it was poured into ice–cold water (100 mL). The reaction mixture was neutralized with 50% NaOH solution until the colour of the solution is off-white and the solid was formed. The resulting solid was filtered-off and dried *in vacuo* to afford 4,5-dibromobenzene-1,2-diamine 2 (4.5 g, 97%) as an orange solid. Mp > 250 °C. $R_f = 0.3$ (100% EtOAc). IR (neat, ν/cm^{-1}): 3385, 3313, 1628, 1569, 1485, 1272, 860, 689. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (2H, s), 3.40 (4H, s). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 135.5, 120.6, 113.7. HRMS (ESI+): *m*/*z* calcd for $C_6H_7Br_2N_2$ $[M + H]^+ = 264.8976$, found 264.8971.

Sequence followed in Scheme 3

5,6-Dibromo-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (3). 4,5-dibromo phenylenediamine **2** (1.0 g, 3.80 mmol) was charged into a 100 mL two-necked round bottom flask and dissolved in 30 mL of toluene. To the reaction mixture was added carbonyldiimidazole (0.928 g, 5.7033 mmol, 1.5 equiv.) and stirred at 80 °C for 2 h. The reaction mixture was poured into ice-cooled water (50 mL) and immediately a white solid was formed. The solid was filtered-off and dried under vacuum to afford 5,6-dibromo-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **3** (0.8 g, 87%) as white solid. Mp >300 °C. $R_f = 0.3$ (100% EtOAc). IR (neat, ν/cm^{-1}): 3155, 3055, 2990, 2837, 2734, 1690, 1478, 1362, 1020, 775. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.8 (s, 2H), 7.22 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.0, 130.7, 113.9, 112.7. HRMS (ESI+): *m*/*z* calcd for $C_7H_5Br_2N_2O$, $[M + H]^+ = 290.8769$, found 290.8742.

Methylation of 3. A dried 50 mL two-neck flask was charged with 5,6-dibromo-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazole-2-one **3** (0.2 g, 0.34 mmol, 1 equiv.) was dissolved in 15 mL of dry THF. To the reaction mixture was added NaH (0.1 g, 2.07 mmol, 7 equiv.) and was stirred for 10 minutes at room temperature. Dimethyl sulphate (0.18 mL, 2.76 mmol, 10 equiv.) was added dropwise to the reaction mixture over a period of 5 minutes. The mixture was stirred at room temperature for 1 hour and quenched by the addition of H_2O (10 mL). The resulted reaction mixture was extracted with EtOAc (4 × 25 mL) and water (50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and finally concentrated under reduced pressure to obtain crude. The resulted crude was purified by column chromatography (30% EtOAc/hexane) to afford mono methylated compound **4** (0.021 g, 48%) as off white solid and bis-methylated compound **5** (0.043 g, 40%) as an orange solid.

Data for 5,6-dibromo-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4). Mp 292–294 °C. $R_f = 0.3$ (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3069, 2991, 1690, 1625, 1596, 1496, 1390, 1083, 827, 746, 709. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (1H, s), 7.25 (1H, s), 3.25 (3H, s). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.4, 131.8, 129.4, 113.9, 113.8, 112.6, 111.9, 26.5. HRMS (ESI+): *m*/*z* calcd for $C_8H_7Br_2N_2O$ $[M + H] = 304.8925$, found 304.8915.

Data for 5,6-dibromo-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (5). Mp: 218–220 °C. $R_f = 0.5$ (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3386, 3195, 3062, 2922, 1702, 1508, 1140, 772. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22 (2H, s), 3.39 (6H, s). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 154.2, 130.4, 115.8, 111.8, 27.3.

***N*-(2-Amino-4,5-dibromophenyl)-4-methylbenzenesulfonamide (6).** A flame dried 100 mL round bottom flask was charged with 4,5-dibromobenzene-1,2-diamine **2** (0.8 g, 4.90 mmol) and was dissolved in 15 mL of dry DCM. To the reaction mixture was added *p*-toluenesulphonyl chloride (0.59 g, 2.94 mmol, 0.6 equiv.). The reaction mixture was stirred at room temperature for 12 h and then the solvent was evaporated under the reduced pressure. The resulted crude was purified by column chromatography (30% EtOAC/hexane) to get the *N*-tosylated-4,5-dibromo-phenylenediamine **6** (0.6 g, 93% yield) as white solid. The yield was calculated based on starting material recovered. Mp 142–145 °C. $R_f = 0.5$ (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3440, 3356, 3255, 1614, 1597, 1478, 1317, 1154, 812, 664. ^{1}H NMR (500 MHz, $CDCl_3$): 7.64 (d, $J = 7.63$ Hz, 2H), 7.31 (d, $J = 7.78$ Hz, 2H), 7.02 (s, 1H), 6.66 (s, 1H), 5.93 (bs, 1H), 4.16 (bs, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 144.8, 144.6, 135.1, 132.7, 129.8, 127.5, 124.7, 121.1, 121.0, 111.1, 21.6. HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{13}Br_2N_2O_2S_2$ $[M + H]^+ = 418.9064$, found 418.9055.

5,6-Dibromo-1-tosyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (7). To a 50 mL round bottom flask was charged with *N*-tosylated

4,5-dibromophenylenediamine **6** (0.1 g, 0.237 mmol) and was dissolved in 5 mL of dry dichloroethane. To the reaction mixture Et_3N (0.05 mL, 0.3577 mmol, 1.5 equiv.) was added. Then carbonyldiimidazole (0.046 g, 0.2877 mmol, 1.2 equiv.) was added at room temperature. The reaction mixture was stirred at 60 °C for 3 h. The resulted solid was filtered-off and washed with EtOAC (10 mL), dried in high vacuum, to afford 5,6-dibromo-1-tosyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **7** (0.097 g, 66%) as light yellowish solid. Mp 237–239 °C. $R_f = 0.3$ (100% EtOAc). IR (neat, ν/cm^{-1}): 2923, 1749, 1613, 1485, 1177, 664. ^1H NMR (500 MHz, $CDCl_3$): 11.8 (s, 1H) 7.98 (s, 1H), 7.93 (d, $J = 8.9$ Hz, 2H), 7.47 (d, $J = 8.09$ Hz, 2H), 7.36 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 149.7, 146.0, 133.5, 129.8, 129.2, 127.3, 126.5, 118.3, 116.1, 115.3, 114.0, 20.8. HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{11}Br_2N_2O_3S$, $[M + H]^+ = 444.8857$, found 443.8833.

5,6-Dibromo-1-methyl-3-tosyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (8). To a solution of 5,6-dibromo-1-tosyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **7** (0.90 g, 0.3611 mmol, 1 equiv.) in 20 mL of dry THF, was added powdered KOH (0.041 g, 0.7223 mmol, 2 equiv.) at room temperature. To the reaction mixture was added MeI (0.15 mL, 0.7223 mmol, 2 equiv.) and stirred at 23 °C for 10 h. The reaction mixture was quenched by water and extracted with EtOAc (30 mL) and washed with brine (10 mL). The organic layers were dried over Na_2SO_4, concentrated in vacuum and the resulted crude was purified by column chromatography (30% EtOAc/hexane) to afford compound **8** (0.090 g, 90%) as white solid. Mp 200–202 °C. $R_f = 0.4$ (50% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3213, 3115, 3092, 2916, 2851, 1746, 1612, 1484, 1368, 1175, 663. ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.01 (d, $J = 8.24$ Hz, 2H), 7.35 (d, $J = 8.09$ Hz, 2H), 7.18 (s, 1H), 3.26 (s, 3H), 2.44 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 146.3, 134.3, 130.4, 129.9, 128.3, 125.9, 119.5, 117.6, 117.5, 112.5, 27.3, 21.7. HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{13}Br_2N_2O_3S$ $[M + H]^+ = 458.9014$ found 458.9003.

5,6-Dibromo-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (4). A 20 mL two-necked round bottom flask was charged with 5,6-dibromo-1-methyl-3-tosyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **8** (0.090 g, 0.3478 mmol) and 1 mL of concentrated sulfuric acid was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution (10 mL) and resulted solid was filtrated-off to furnish 5,6-dibromo-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **4** (0.037 g, 61%) as off-white solid.

3,4-Dimethoxycyclobut-3-ene-1,2-dione (10). In a 500 mL two-neck round bottom flask connected to a Dean–Stark reflux condenser, was added squaric acid (2.5 g, 21.93 moles, 1 equiv.) and dissolved in MeOH (50 mL) at 70 °C. To the reaction mixture was added trimethyl orthoformate (5.4 mL, 46.05 moles, 2.1 equiv.) and refluxed for 48 h. The reaction mixture was evaporated under reduced pressure. The crude of reaction was washed with EtOAc (2 × 50 mL) and extracted with H_2O (2 × 100 mL). The collected organic fractions were dried with Na_2SO_4, filtered, and concentred under reduced pressure. The resulting crude was purified by column chromatography (30% EtOAc/hexane) to provide the compound **3** (1.35 g, 43%) as white solid. The spectroscopic data match with those previously described. Mp = 38–40 °C. $R_f = 0.35$ (40% EtOAC/hexane). IR (neat, ν/cm^{-1}): 2988, 1806, 1736, 1724, 1582, 1417, 1339, 1072, 1011, 900, 782. ^1H NMR (500 MHz, $CDCl_3$): δ 4.37 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.2, 184.6, 61.1.[22]

Sequence followed in Scheme 5

Route A

*4-Bromo-2-iodoaniline (**11**)*

Procedure A. 4-Bromoaniline (0.5 g, 2.941 mmol) was charged in 100 mL two necked round bottom flask and dissolved in 10 mL of glacial acetic acid. To the reaction mixture was added *N*-iodosuccinimide (0.650 g, 2.941 mmol, 1 equiv.) portion-wise and stirred at 23 °C for 1 h. The reaction mixture was neutralized by addition saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (50 mL). The resulted crude was purified by column chromatography (8% EtOAc/hexane) to furnish **11** (0.5 g, 88%) as light yellowish solid.

Procedure B. A 100 mL round bottom flask was charged with 2-iodoaniline (4.5 g, 20.6422 mmol) and was dissolved in 25 mL of dry dimethylformamide. To this reaction mixture was added *N*-bromosuccinimide (3.6 g, 20.6422 mmol, 1 equiv.) portion-wise and stirred at 23 °C for 1 h. The resulted reaction mixture was evaporated and extracted with EtOAC (100 mL) and water (200 mL). The organic layers were evaporated under reduced pressure and the resulted crude was purified by column chromatography (10% EtOAc/hexane) to give 4-bromo-2-iodoaniline **11** (5.6 g, 92%) as light yellowish solid. Mp 69–71 °C. $R_f = 0.6$ (24% EtOAC/hexane). IR (neat, cm^{-1}): 3383, 3288, 3176, 2923, 2853, 1866, 1738, 1621, 1557, 1471, 1384, 1283, 1251, 1081, 1020, 870, 830, 807. ^1H NMR ($CDCl_3$, 500 MHz): 7.73 (d, $J = 2.2$ Hz, 1H), 7.22 (dd, $J = 8.5$, 2.2 Hz, 1H), 6.62 (d, $J = 8.5$ Hz, 1H), 4.05 (s, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz); δ 146.1, 140.5, 132.2, 115.7, 110.0, 84.2, 77.2. HRMS (ESI+): *m*/*z* calcd for C_6H_6BrIN $[M + H]^+ = 297.8728$, found 297.8726.

*N-(4-Bromo-2-iodophenyl)acetamide (**12**).* A flame dried 100 mL round bottom flask was charged with 4-bromo-2-iodoaniline **11** (5.5 g, 18.5810 mmol) and dissolved in 25 mL of dry dichloromethane. To the reaction mixture was added triethylamine (2.6 mL, 18.581 mmol, 1 equiv.) at room temperature followed by the dropwise addition of acetyl chloride (1.3 mL 18.581 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 5 h and then the solvent evaporated under the reduced pressure. The resulted crude was purified by column chromatography (15% EtOAC/hexane) to get the *N*-(4-bromo-2-iodophenyl)acetamide **12** (6.2 g, 98% yield) as pale white solid. Mp 210–212 °C. $R_f = 0.5$ (40% EtOAC/hexane). IR (neat, ν/cm^{-1}): 3275, 3068, 2928, 1892, 1737, 1656, 1562, 1514, 1459, 1368, 1282, 1245, 1086, 1031, 1006, 870, 816, 724. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.12 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 1.9$ Hz, 1H), 7.45 (dd, $J = 8.8$, 2.1 Hz, 1H), 7.38 (s, 1H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.3, 140.6, 137.6, 132.4, 122.9, 117.5, 77.12, 24.9. HRMS (ESI+): *m*/*z* calcd for C_8H_8BrINO $[M + H]^+ = 339.8834$, found 339.8817.

*Nitration on N-(4-bromo-2-iodophenyl)acetamide (**12**).* To a solution of *N*-(4-bromo-2-iodophenyl)acetamide **12** (4.0 g,

11.8343 mmol, 1 equiv.) in 20 mL of concentrated sulfuric acid, was added sulfonitric mixture (4 mL) at 0 °C. The reaction mixture was stirred at 23 °C for 3 h. The reaction mixture was quenched by saturated $NaHCO_3$ solution (100 mL) and extracted with EtOAc (200 mL) and washed with brine (100 mL). The organic layers were dried over Na_2SO_4, concentrated in vacuum and the resulted crude was purified by column chromatography to afford the two regioisomeric compounds **13** (0.6 g, 20%) as light yellow solid and the compound **14** (0.5 g, 11%) as pale white solid.

Spectra data for N-(4-bromo-2-iodo-6-nitrophenyl)acetamide (13). Mp 182–184 °C. R_f = 0.4 (40% EtOAC/hexane). IR (neat, ν/cm^{-1}): 3264, 2923, 2853, 1666, 1560, 1522, 1506, 1446, 1366, 1325, 1281, 1123, 1062, 1014, 968, 887, 882. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.87 (s, 1H), 8.15 (s, 1H), 7.52 (s, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.4, 150.3, 143.5, 138.6, 116.9, 108.6, 93.3, 25.0. HRMS (ESI+): *m*/*z* calcd for $C_8H_7BrIN_2O_3$ $[M + H]^+$ = 384.8685, found 384.8679.

Spectra data for N-(4-bromo-2-iodo-6-nitrophenyl)acetamide (14). Mp 179–181 °C. R_f = 0.3 (40% EtOAC/hexane) IR (neat, ν/cm^{-1}): 3257, 3083, 3083, 2992, 1730, 1706, 1663, 1552, 1503, 1439, 1367, 1334, 1276, 1247, 1110, 1034, 1009, 870, 738. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.61 (s, 1H), 7.99 (s, 1H), 7.35 (s, 1H), 2.25 (s, 3H).^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.4, 150.3, 143.5, 138.8, 117.00, 108.5, 93.4, 25.0. HRMS (ESI+): *m*/*z* calcd for $C_8H_7BrIN_2O_3$ $[M + H]^+$ = 384.8685, found 384.8662.

Route B

4-Bromo-2-iodo-6-nitroaniline (16). A 500 mL two-necked round-bottom flask, was charged with a solution of 4-bromo-2-nitroaniline **15** (2.0 g, 9.216 mmol, 1 equiv.) in glacial AcOH (25 mL) and heated to 80 °C. *N*-iodosuccinimide (4.0 g, 18.416 mol, 2 equiv.) was added portion-wise and stirred for 2 h. The reaction mixture was poured into ice-cooled water (50 mL) and immediately an orange colour solid was formed. The resulted solid was filtered-off, washed with DCM (50 mL) and dried under vacuo. The aqueous portion was neutralized with saturated $NaHCO_3$ (50 mL) solution, followed by extraction with EtOAc (100 mL). The combined organic fractions were washed with brine (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure to afford additional amount of such solid. The orange solid obtained from filtration and extraction process were collected to furnish **16** (2.2 g, 85%) that was used without further purification for next step. Mp 135–137 °C. R_f = 0.5 (20% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3572, 3453, 3101, 1541, 1435, 1346, 1241, 1070, 872, 671. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, J = 2.3 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H), 6.67 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 143.3, 131.9, 129.4, 108.1, 88.0. HRMS (ESI): *m*/*z* calcd for $C_6H_4BrIN_2O_2$ $[M + H]^+$ = 342.8501, found 342.8504.

N-(4-Bromo-2-iodo-6-nitrophenyl)acetamide (13). A dried 100 mL round bottom flask was charged with 4-bromo-6-iodo-2-nitroaniline **16** (1.0 g, 2.9321 mmol) and dissolved in 25 mL of dry dimethylformamide. To the reaction mixture was added sodium hydride (0.281 g, 11.7.30 mmol, 4 equiv.) at 0 °C followed by the dropwise addition of acetyl chloride (4.1 mL, 58.642 mmol, 20 equiv.). The reaction mixture was stirred at room temperature for 12 h and then the solvent evaporated under the reduced pressure. The resulted crude was purified by column chromatography (20% EtOAC/hexane) to get the *N*-(4-bromo-2-iodo-6-nitrophenyl)acetamide **13** (0.380 g, 45% yield) as pale white solid.

N-(5-Bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-yl)acetamide (17). To a solution of *N*-(4-bromo-2-iodo-6-nitrophenyl) acetamide **13** (0.5 g, 1.305 mmol) in toluene (30 mL) and water (3 mL) was added 4-methoxyphenyl boronic acid (0.44 g, 2.872 mmol, 2.2 equiv.), sodium carbonate (0.34 g, 3.262 mmol, 2.5 equiv.) and $Pd(PPh_3)_4$ (0.12 g, 0.1044 mmol, 8 mol%). The reaction mixture was purged with N_2 and stirred at 80 °C for 8 h. The reaction was quenched by addition of water and extracted with EtOAc. The organic layers were washed with brine (100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The resulted crude was purified by column chromatography (25% EtOAc/hexane) to yield *N*-(5-bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-yl)acetamide **17** (0.297 g, 62%) as yellowish solid. Mp 172–174 °C. R_f = 0.4 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3319, 3236, 3083, 2997, 2951, 2926, 2854, 2832, 1739, 1673, 1608, 1511, 1455, 1362, 1334, 1243, 1181, 1030, 966, 883, 836, 814, 717. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.45 (s, 2H), 7.25 (d, J = 10.2 Hz, 3H), 7.09 (s, 1H), 7.02 (d, J = 11.3 Hz, 2H), 3.87 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 160.1, 135.1, 134.4, 132.2, 130.3, 127.9, 125.7, 124.0, 119.1, 114.9, 55.6, 24.9. HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{14}BrN_2O_4$ $[M + H]^+$ = 365.0317, found 365.0119.

N-(3-Amino-5-bromo-4′-methoxy-[1,1′-biphenyl]-2yl)acetamide (18). *N*-(5-Bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-yl)acetamide **17** (0.2 g, 0.5494 mmol, 1 equiv.) was charged in a 250 mL two-necked round-bottom flask and dissolved in MeOH (30 mL). To the resulting solution was added $NaBH_4$ (0.208 g, 5.4945 mmol, 10 equiv.) portion wise within 5 minutes at 0 °C and followed by $NiCl_2 \cdot 6H_20$ (0.021 g, 0.1648 mmol, 0.3 equiv.). The reaction mixture was stirred at 23 °C for 0.5 h and was poured into ice-cold water. The resulting mixture was extracted with EtOAc (200 mL) and water (200 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (60% EtOAc/hexane) to furnish *N*-(3-amino-5-bromo-4′-methoxy-[1,1′-biphenyl]-2-yl)acetamide **18** (0.144 g, 80%) as yellowish solid. Mp 185–187 °C. R_f = 0.3 (100% EtOAc). IR (neat, ν/cm^{-1}): 3481, 3360, 3320, 3233, 2950, 2928, 2832, 1674, 1645, 1608, 1511, 1425, 1364, 1291, 1242, 1178, 1033, 928, 828, 815, 805, 735, 718. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 2.1 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.63 (s, 1H), 4.13 (s, 2H), 3.85 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.6, 159.6, 144.5, 140.1, 130.2, 123.2, 121.1, 120.5, 119.4, 114.2, 55.5, 23.3. HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{16}BrN_2O_2$ $[M + H]^+$ = 335.0395, found 335.0374.

1-Acetyl-5-bromo-7-(4-methoxyphenyl)-1,3-dihydro-2H-benzo[d] imidazol-2-one (19). To a 100 mL two-neck round-bottom flask, was added *N*-(3-amino-5-bromo-4′-methoxy-[1,1′-biphenyl]-2-yl) acetamide **18** (0.140 g, 0.4191 mmol) and dissolved in 15 mL of DCE at room temperature. Then, a solution of phosgene 15 wt% in toluene (0.8 mL, 3.3528 mmol, 8 equiv.) was added drop wise to the reaction mixture and stirred for 1 h. The reaction mixture was poured into ice-cooled water (30 mL) and immediately a white solid was formed. The resulting solid was filtered-off and dried under vacuum to give **19** (0.105 g, 70%) as

an off-white solid. The compound was used without purification for next step. Mp 194–196 °C. R_f = 0.3 (40% EtOAc/hexane). IR (neat) ν/cm^{-1} = 2938, 2837, 2274, 1714, 1667, 1611, 1515, 1466, 1442, 1367, 1383, 1388,1309, 1287, 1246, 1143, 1045, 1020, 995, 840, 762. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.57 (s, 1H), 7.24 (d, J = 7.5 Hz, 2H), 7.13 (s, 1H), 7.12 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 2.50 (s, 3H).^{13}C NMR (126 MHz, DMSO-d_6): δ 168.6, 158.5, 152.9, 132.3, 131.2, 130.3, 128.1, 125.5, 123.22, 116.4, 113.6, 110.1, 55.0, 39.5, 25.5. HRMS (ESI+): m/z calcd for $C_{16}H_{14}BrN_2O_3$ $[M + H]^+$ = 361.0188, found 361.0176.

*Methylation of N-(3-amino-5-bromo-4′-methoxy-[1,1′-biphenyl]-2-yl)acetamide (**19**).* A dried 50 mL two-neck flask was charged with dry DMSO (10 mL), powdered KOH (0.14 g, 2.55 mol, 4 equiv.) and was stirred for 10 minutes at room temperature. Then 6-bromo-4-iodo-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **19** (0.230 g, 0.638 mol, 1 equiv.) was added in portions to the reaction mixture followed by the drop wise addition of MeI (0.25 mL, 3.833 mmol, 6 equiv.) over a period of 5 minutes. The mixture was stirred at room temperature for 1 h and quenched by the addition of H_2O (20 mL). The crude was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and finally concentrated under reduced pressure. The resulted crude was purified by column chromatography (20% EtOAc/hexane) to furnish **20** (32 mg, 13%) as pale solid, **21** (16 mg, 7%) as white solid and **22** (20 mg, 9%) as white solid.

*Spectral data for 3-acetyl-6-bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**20**).* The following compound was obtained by column chromatography purification with a 20% EtOAc/hexane gradient. Mp 229–231 °C. R_f = 0.6 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3035, 2976, 2939, 2832, 1738, 1722, 1605, 1595, 1517, 1450, 1364, 1272, 1251, 1185, 1174, 1024, 994, 827. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 1.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.35 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 158.5, 152.4, 133.8, 131.2, 130.2, 128.2, 125.9, 121.9, 116.8, 113.7, 109.7, 55.1, 27.3, 25.5. HRMS (ESI+): m/z calcd for $C_{17}H_{16}BrN_2O_3$ $[M + H]^+$ = 375.0344, found 375.0341.

*Spectral data for 6-bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**21**).* The following compound was obtained by column chromatography purification with a 30% EtOAc/hexane gradient as white solid. Mp 225–227 °C. R_f = 0.4 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3137, 3048, 2953, 2927, 2833, 1703, 1608, 1578, 1517, 1450, 1380, 1339, 1291, 1247, 1178, 962, 823, 767. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 1.4 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.9, 155.0, 132.7, 129.2, 128.5, 125.1, 124.3, 124.2, 114.9, 114.7, 109.5, 55.5, 27.2. HRMS (ESI+): m/z calcd for $C_{15}H_{14}BrN_2O_2$ $[M + H]^+$ = 333.0239, found 333.0218.

*Spectral data for 6-bromo-4-(4-methoxyphenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**22**).* The following compound was obtained by column chromatography purification with a 25% EtOAc/hexane gradient as white solid. Mp 154–156 °C. R_f = 0.55 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}) = 3071, 2945, 1696,1607, 1481, 1450, 1388, 1241, 1176, 1122, 1025, 832, 741, 692. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 1.9 Hz, 1H), 7.08 (d, J = 1.9 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H), 3.42 (s, 3H), 2.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6, 155.1, 131.8, 130.9, 129.2, 126.6, 126.5, 126.1, 113.5, 113.2, 109.4, 55.4, 30.4, 27.4. HRMS (ESI+): m/z calcd for $C_{16}H_{16}BrN_2O_2$ $[M + H]^+$ = 347.0395, found 347.0396.

Sequence followed in Scheme 6

5-Bromo-3-iodobenzene-1,2-diamine (24). 4-Bromo-2-iodo-6-nitroaniline **16** (6.4 g, 18.768 mmol, 1 equiv.) was charged in a 500 mL two-necked round-bottom flask, dissolved in EtOH (300 mL) and heated to 70 °C. To the resulting solution was added $SnCl_2 \cdot 2H_2O$ (21.2 g, 93.841 mmol, 5 equiv.) portion wise within 5 minutes and continued to be stirred at 70 °C for 3 h. The reaction mixture was poured into ice-cold water. The resulting solid was filtered-off and dried *in vacuo* to give 5-bromo-3-iodobenzene-1,2-diamine **24** (4.65 g, 80%) as an off-white solid which was used without further purification. Mp 136–138 °C. R_f = 0.4 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3493, 3396, 3064, 1640, 1567, 1458, 1080, 765, 705. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 3.63 (bs, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.3, 135.1, 131.1, 119.1, 111.9, 86.2. HRMS (ESI+): m/z calcd for $C_6H_7BrIN_2$ $[M + H]^+$ = 312.8837, found 312.8863.

6-Bromo-4-iodo-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (25). To a 500 mL two-neck round-bottom flask, was added 5-bromo-3-iodobenzene-1,2-diamine **24** (4.5 g, 14.469 mmol, 1.0 equiv.) and was dissolved in 100 mL of DCE at room temperature. Then, a solution of phosgene 15 wt% in toluene (11.0 mL, 101.286 mmol, 7 equiv.) was added drop-wise to the reaction mixture and stirred for 1 h. The reaction mixture was poured into ice-cooled water (100 mL) and immediately a white solid was formed. The resulting solid was filtered-off and dried under vacuum to give **25** (4.55 g, 90%) as an off-white solid. The compound was used without purification for next step. Mp 212–214 °C. R_f = 0.4 (60% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3064, 2944, 1703, 1605, 1572, 1481, 1444, 1247, 1023, 954, 825. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.06 (s, 1H), 10.99 (s, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.05 (d, J = 1.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 155.0, 132.9, 131.0, 130.7, 113.3, 111.3, 73.9. HRMS (ESI+): m/z calcd for $C_7H_5BrIN_2O$ $[M + H]^+$ = 338.8630, found 338.8661.

5-Bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-amine (23). To a solution of 4-bromo-2-iodo-6-nitroaniline **16** (2.5 g, 7.3099 mmol, 1.0 equiv.) in 1,4-dioxane (30 mL) and water (2 mL) were added *p*-anisyl boronic acid (1.76 g, 12.6315 mmol, 1.6 equiv.), potassium carbonate (2.0 g, 14.6198 mmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (0.675 g, 0.6315 mmol, 8 mol%). The reaction mixture was purged with N_2 and stirred at 90 °C for 6 h. The reaction was quenched by addition of water and extracted with EtOAc. The organic layers were washed with brine (100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The resulted crude was purified by column chromatography (20% EtOAc/hexane) to afford 5-bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-amine **23** (1.84 g, 78%) as yellow solid. Mp 117–119 °C. R_f = 0.5 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3469, 3356, 3097, 3010, 2954, 2928, 2904, 2834, 2532, 1607, 1578,

1496, 1461, 1388, 1358, 1321, 1287, 1241, 1174, 1028, 876, 819, 696. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6.27 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.2, 142.2, 138.9, 132.9, 132.8, 130.4, 127.6, 127.4, 115.1, 107.4, 55.5. HRMS (ESI+): m/z calcd for $C_{13}H_{12}BrN_2O_3$ $[M + H]^+$ = 323.0031, found 323.0009.

Sequence followed in Scheme 8

Route C

*6-Bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2H-benzo-6-bromo-4-iodo-benzo[c][1,2,5]selenadiazole (**27**).* To a solution of 5-bromo-3-iodobenzene-1,2-diamine **24** (3.8 g, 12.218 mmol) in 60 mL of dry ethanol, was added SeO_2 (1.9 g, 18.3279 mmol, 1.5 equiv.) in water. The reaction mixture was stirred at 70 °C for 1 h, then the resulted solid was filtered-off and dried under vacuum. The yellowish solid was obtained from filtration process was collected to furnish 6-bromo-4-iodobenzo[*c*][1,2,5] selenadiazole **27** (4.4 g, 93%) that was used without further purification for next step. Mp 168–170 °C. R_f = 0.8 (40% EtOAc/hexane). IR (neat) ν/cm^{-1}: 3295, 3229, 2955, 2915, 2850, 1738, 1729, 1571, 1469, 1392, 1245, 1195, 1178, 1048, 991, 940, 850, 740, 719. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 1.7 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.8, 157.6, 141.9, 125.7, 125.5, 91.1. HRMS (ESI+): m/z calcd for $C_6H_3BrIN_2Se$ $[M + H]^+$ = 388.7690, found 388.7676.

*6-Bromo-4-iodo-1-methylbenzo[c][1,2,5]selenadiazol-1-ium (**28**).* A 100 mL two-necked round bottom flask was charged 6-bromo-4-iodobenzo[*c*][1,2,5]selenadiazole **27** (4.3 g, 0.011 mmol, 1 equiv.) and dimethyl sulphate (22.0 mL, 0.2216 mmol, 20 equiv.). The reaction mixture was heated at 130 °C for 1 h. To the resulted reaction mixture was added diethyl ether at room temperature to get an orange solid. This solid was filtered-off and dried well. The orange solid obtained from filtration process was collected to furnish 6-bromo-4-iodo-1-methylbenzo [*c*][1,2,5]selenadiazol-1-ium **28** (4.5 g, 97%) as orange solid. Mp: 224–226 °C. R_f = 0.8 (40% EtOAc/hexane). IR (neat) ν/cm^{-1}: 3071, 3002, 2863, 2573, 2230, 1572, 1510, 1478, 1441, 1478, 1392, 1311, 1284, 1202, 1157, 1013, 845, 749. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (d, J = 1.6 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 4.46 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 154.6, 150.2, 141.3, 132.5, 119.1, 97.8, 52.7, HRMS (ESI+): m/z calcd for $C_7H_5BrIN_2Se^+$ $[M + H]^+$ = 402.7841, found 402.7837.

*5-Bromo-3-iodo-N^1-methylbenzene-1,2-diamine (**29**).* A 50 mL two-necked round bottom flask was charged with 25 mL of 2 M NaOH solution. To this solution was added 6-bromo-4-iodo-1-methylbenzo[*c*][1,2,5]selenadiazol-1-ium **28** (4.5 g, 11.1940 mmol) portion wise at room temperature. The reaction mixture was stirred at 23 °C vigorously for 1 h. The reaction mixture was extracted with EtOAc (100 mL) and the organic layers were collected, dried over Na_2SO_4, concentrated under reduced pressure. The resulted crude was purified by column chromatography (15% EtOAc/hexane) to afford 5-bromo-3-iodo-*N*^{1}-methylbenzene-1,2-diamine **29** (3.2 g, 69%) as red solid. Mp 61–63 °C. R_f = 0.6 (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3363, 3346, 3079, 2975, 2931, 2883, 2847, 2794, 2553, 2457, 1578, 1505, 1470, 1445, 1430, 1399, 1274, 1224, 1058, 833, 822, 774, 674. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 2.1 Hz, 1H), 6.69 (d, J = 2.1 Hz, 1H), 3.57 (bs, 3H), 2.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.7, 134.3, 129.0, 113.7, 113.3, 86.4, 31.1. HRMS (ESI+): m/z calcd for $C_7H_9BrN_2$ $[M + H]^+$ = 326.8994, found 326.8998. The regioselectivity of this methylation reaction was confirmed by NOESY experiments (see spectra file).

*6-Bromo-4-iodo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**26**).* In a 250 mL two-neck round-bottom flask, was added 5-bromo-3-iodo-*N*^{1}-methylbenzene-1,2-diamine **29** (3.2 g, 9.815 mmol) and dissolved in 50 mL of DCE at room temperature. Then, a solution of phosgene 15 wt% in toluene (8.5 mL, 78.527 mmol, 8 equiv.) was added drop-wise to the reaction mixture and stirred for 1 h. The reaction mixture was poured into ice-cooled water (200 mL) and immediately a white solid was formed. The resulting solid was filtered-off and dried under vacuum to give **26** (2.7 g, 91%) as an off-white solid. The compound was used without purification for next step. Mp 136–138 °C. R_f = 0.5 (60% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3376, 3113, 3032, 2919, 2850, 2258, 1687, 1616, 1586, 1485, 1440, 1376, 1307, 1240, 1178, 1105, 1074, 959, 879, 826, 736, 718, 670. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.07 (d, J = 1.0 Hz, 1H), 3.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.9, 131.7, 131.6, 130.2, 114.8, 110.9, 73.0, 27.5. HRMS (ESI+): m/z calcd for $C_8H_7BrIN_2O$ $[M + H]^+$ = 352.8786, found 352.8784.

*6-Bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2H-benzo [d]imidazol-2-one (**21**).* To a solution of 6-bromo-4-iodo-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **26** (2.5 g, 7.207 mmol) in 1,4-dioxane (60 mL) and water (5 mL) were added *p*-anisyl boronic acid (1.35 g, 8.649 mmol, 1.2 equiv.), potassium carbonate (2.48 g, 18.019 mmol, 2.5 equiv.) and $Pd_2(dba)_3$ (0.68 g, 0.7207 mmol, 1 mol%). The reaction mixture was purged with N_2 and stirred at 90 °C for 6 h. The reaction was quenched by addition of water and extracted with EtOAc (200 mL). The organic layers were washed with brine (100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The resulted crude was purified by column chromatography (30% EtOAc/hexane) to afford 6-bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **21** (1.8 g, 75%) as white solid. Mp 225–227 °C. R_f = 0.55 (60% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3137, 3048, 2953, 2927, 2833, 1703, 1608, 1578, 1517, 1450, 1380, 1339, 1291, 1247, 1178, 962, 823, 767. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 1.4 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.9, 155.0, 132.7, 129.2, 128.5, 125.1, 124.2, 114.9, 114.7, 109.5, 55.5, 27.2. HRMS (ESI+): m/z calcd for $C_{15}H_{14}BrN_2O_2$ $[M + H]^+$ = 333.0239, found 333.0218.

Sequence followed in Scheme 8

Route D

*Synthesis of 5-bromo-4′-methoxy-[1,1′-biphenyl]-2,3-diamine (**31**)*

Conditions A. To a 100 mL two-necked round bottom flask was added 5-bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-amine **23** (0.300 g, 0.9345 mmol, 1 equiv.) and dissolved in 15 mL of dry

ethanol at 70 °C. To the reaction mixture $SnCl_2 \cdot 2H_2O$ (1.05 g, 4.6728 mmol, 5 equiv.) was added portion wise and the reaction mixture was stirred at 70 °C for 5 h. Then the reaction mixture was poured into 50 mL of ice-cold water and extracted with EtOAc (100 mL) followed by washing with brine (20 mL). The resulted organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulted crude was purified by column chromatography (30% EtOAc/hexane) to afford 5-bromo-4′-methoxy-[1,1′-biphenyl]-2,3-diamine **31** (0.160 g, 50%) as orange solid.

Conditions B. 5-Bromo-4′-methoxy-3-nitro-[1,1′-biphenyl]-2-amine **23** (3.2 g, 9.9688 mmol, 1 equiv.) was charged in a 500 mL two-necked round-bottom flask and was dissolved in MeOH (100 mL). To the reaction mixture was added $NaBH_4$ (3.8 g, 99.688 mmol, 10 equiv.) portion-wise within 5 minutes at 0 °C followed by $NiCl_2 \cdot 6H_20$ (0.720 g, 2.9906 mmol, 0.3 equiv.). The reaction mixture was stirred at 23 °C for 1 h. The reaction mixture was poured into ice-cold water and the resulting mixture was extracted with EtOAc (200 mL) and water (200 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude such obtained was purified by column chromatography (30% EtOAc/hexane) to furnish 5-bromo-4′-methoxy-[1,1′-biphenyl]-2,3-diamine **31** (1.78 g, 54%) as yellowish solid. Mp 137–139 °C. $R_f = 0.3$ (40% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3407, 3394, 3310, 3224, 3054, 3009, 2961, 2922, 2840, 1607, 1557, 1510, 1463, 1241, 1174, 1024, 830, 778, 699. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, $J = 8.7$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 6.83 (d, $J = 2.1$ Hz, 1H), 6.82 (d, $J = 2.1$ Hz, 1H), 3.85 (s, 3H), 3.45 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.3, 136.3, 131.7, 130.7, 130.6, 130.3, 124.1, 118.1, 114.5, 111.4, 55.5. HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{14}BrN_2O$ $[M + H]^+$ = 293.0290 found 293.0286.

*6-Bromo-4-(4-methoxyphenyl)benzo[c][1,2,5]selenadiazole (**32**).* To a solution of 5-bromo-4′-methoxy-[1,1′-biphenyl]-2,3-diamine **31** (1.75 g, 5.9931 mmol) in 10 mL of dry ethanol, was added SeO_2 (0.98 g, 8.9897 mmol, 1.5 equiv.) in water. The reaction mixture was stirred at 70 °C for 1 h, and the resulted solid was filtered-off and dried under vacuum. The yellowish solid was obtained from filtration process and collected to furnish 6-bromo-4-(4-methoxyphenyl)benzo[*c*][1,2,5]selenadiazole **32** (1.7 g, 75%) which was used without further purification for next step. Mp 188–190 °C. $R_f = 0.8$ (40% EtOAc/hexane). IR (neat) ν/cm^{-1}: 3072, 2986, 2955, 2930, 2907, 2832, 1877, 1718, 1665, 1606, 1585, 1501, 1463, 1316, 1289, 1235, 1185, 1060, 1035, 952, 884, 829, 797, 763, 745. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, $J = 1.8$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 1.8$ Hz, 1H), 7.05 (d, $J = 8.8$ Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2, 160.2, 158.0, 136.1, 130.81, 130.6, 128.9, 125.9, 123.7, 114.0, 55.4. HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{10}BrN_2OSe$ $[M + H]^+$ = 368.9142, found 368.9147.

*6-Bromo-4-(4-methoxyphenyl)-1-methylbenzo[c][1,2,5]selenadiazol-1-ium (**33**).* A 100 mL two-necked round bottom flask was charged with 6-bromo-4-(4-methoxyphenyl)benzo[*c*][1,2,5]selenadiazole **32** (1.62 g, 4.4277 mmol) and dimethyl sulphate (5.0 mL, 44.2779 mmol, 10 equiv.). The reaction mixture was heated at 130 °C for 1 h. To the resulted reaction mixture was added diethyl ether to get a yellowish solid. This solid was filtrated-off and dried in vacuum to furnish 6-bromo-4-(4-methoxyphenyl)-1-methylbenzo [*c*][1,2,5]selenadiazol-1-ium **33** (1.8 g, 98%) that was used without further purification for next step. Mp 208–210 °C. $R_f = 0.8$ (40% EtOAc/hexane). IR (neat) ν/cm^{-1}: 3059, 2941, 2841, 2540, 1605, 1585, 1492, 1443, 1375, 1287, 1246, 1143, 1045, 1020, 995, 840, 827, 762. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.31 (d, $J = 1.4$ Hz, 1H), 7.95 (d, $J = 1.4$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 7.15 (d, $J = 8.7$ Hz, 1H), 4.52 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.5, 153.5, 151.8, 136.9, 133.3, 131.7, 130.1, 126.4, 117.1, 114.2, 55.4, 38.6. HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{10}BrN_2OSe$ $[M]^+$ = 382.9298, found 382.9296.

*5-Bromo-4′-methoxy-N^3-methyl-[1,1′-biphenyl]-2,3-diamine (**34**).* A 250 mL two-necked round bottom flask was charged with 50 mL of 2 M NaOH solution. To this solution was added 6-bromo-4-(4-methoxyphenyl)-1-methylbenzo[*c*][1,2,5] selenadiazol-1-ium **33** (1.7 g, 4.691 mmol) portion wise. The reaction mixture was stirred at 23 °C vigorously for 1 h. The reaction mixture was extracted with EtOAc (100 mL) and the organic layers were collected, dried over Na_2SO_4 and concentrated under reduced pressure. The resulted crude was purified by column chromatography (15% EtOAc/hexane) to afford 5-bromo-4′-methoxy-N^3-methyl-[1,1′-biphenyl]-2,3-diamine **34** (0.9 g, 63%) as red solid. Mp 120–122 °C. $R_f = 0.4$ (20% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3384, 3310, 3039, 2098, 2934, 2854, 2834, 1608, 1596, 1565, 1513, 1501, 1460, 1472, 1288, 1241, 1176, 1025, 821, 776, 709. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.28 (m, 1H), 7.00–6.96 (m, 1H), 6.80 (d, $J = 1.5$ Hz, 1H), 6.74 (d, $J = 2.1$ Hz, 1H), 3.86 (d, $J = 7.4$ Hz, 2H), 3.41 (bs, 3H), 2.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2, 140.4, 130.9, 130.7, 130.4, 130.1, 122.4, 114.5, 112.7, 112.7, 55.5, 31.2. HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{16}BrN_2O$ $[M]^+$ = 307.0446, found 307.0455. The regioselectivity of this methylation reaction was confirmed by NOESY experiments (see spectra file).

*6-Bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**21**).* In a 250 mL two-neck round-bottom flask, was added 5-bromo-4′-methoxy-N^3-methyl-[1,1′-biphenyl]-2,3-diamine **34** (0.9 g, 2.931 mmol, 1.0 equiv.) and dissolved in 20 mL of DCE at room temperature. Then, a solution of phosgene 15 wt% in toluene (3.2 mL, 29.31 mmol, 10 equiv.) was added drop wise to the reaction mixture and stirred for 1 h. The reaction mixture was poured into ice-cooled water (300 mL) and extracted with EtOAc (100 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (30% EtOAc/hexane) to afford 6-bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **21** (0.82 g, 86%) as a pale white solid. Mp 225–227 °C. $R_f = 0.55$ (60% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3137, 3048, 2953, 2927, 2833, 1703, 1608, 1578, 1517, 1450, 1380, 1339, 1291, 1247, 1178, 962, 823, 767. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.24 (d, $J = 1.8$ Hz, 1H), 7.06 (d, $J = 1.4$ Hz, 1H), 7.02 (d, $J = 8.7$ Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.9, 155.0, 132.7, 129.2, 128.5, 125.1, 124.2, 114.9, 114.7, 109.5, 55.5, 27.2. HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{14}BrN_2O_2$ $[M + H]^+$ = 333.0239, found 333.0218.

Sequence followed in Scheme 9

6-Bromo-3-(methoxymethyl)-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (35). A dried 100 mL two-necked round bottom was charged with 6-bromo-4-(4-methoxyphenyl)-1-methyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **21** (1.76 g, 5.3162 mmol) and 50 mL dry dimethylacetamide. To the reaction mixture was added Cs_2CO_3 (8.6 g, 26.581 mmol, 5.0 equiv.), followed by addition of MOM-Cl (2.0 mL, 26.581 mmol, 5.0 equiv.) dropwise at room temperature and stirred at 50 °C for 12 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (200 mL). The organic layers were collected and dried over Na_2SO_4, concentrated under reduced pressure. The resulted crude was purified by column chromatography (27% EtOAc/hexane) to afford the MOM-protected compound **35** (1.44 g, 72%) as pale white solid. Mp 144–146 °C. R_f = 0.5 (50% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3056, 2996, 2938, 2855, 1700, 1604, 1515, 1449, 1372, 1289, 1246, 1172, 1087, 1066, 1021, 955, 910, 826, 753, 696. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 4.80 (s, 1H), 3.85 (s, 2H), 3.42 (s, 2H), 3.03 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7, 155.2, 132.2, 130.7, 129.2, 127.3, 127.1, 125.1, 114.3, 113.6, 109.7, 72.2, 55.9, 55.5, 27.5. HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{18}BrN_2O_3$ $[M + H]^+$ = 377.0501, found 377.0496.

Metal–halogen exchange and 1,2 addition of compound (36). A flame-dried 250 mL two-neck round-bottom flask was charged with MOM-protected benzimidazolone **35** (0.33 g, 0.8776 mmol) dissolved in dry THF (30 mL) and stirred at −78 °C (acetone/dry ice bath). Afterwards it was added 1.6 M solution of *n*-BuLi in hexane (1.4 mL, 2.1941 mmol, 2.5 equiv.) drop wise. The clear solution was stirred at −78 °C temperature for additional 15 minutes, then a solution of dimethylsquarate (0.1 g, 0.7021 mmol, 0.6 equiv.) in dry THF (3 mL) was added drop-wise to the reaction mixture, and the stirring was continued at −78 °C for 30 minutes. The reaction was quenched by addition of saturated NH_4Cl solution (10 mL) and stirred for 10 minutes allowing to reach room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude material. The resulted crude was purified by column chromatography (75% EtOAc/hexane) to furnish the intermediate **36** (0.15 g, 61%) as white sponge like solid. Mp 60–62 °C. R_f = 0.3 (75% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3308, 2932, 2838, 1771, 1687, 1611, 1514, 1459, 1338, 1242, 1175, 1087, 1053, 1056, 982, 833, 758, 690. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 1.7 Hz, 1H), 7.01 (d, J = 1.7 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 4.82 (s, 2H), 4.10 (s, 3H), 4.02 (s, 3H), 3.86 (s, 3H), 3.46 (s, 3H), 3.39 (s, 1H), 3.03 (s, 3H). HRMS (ESI+): *m*/*z* calcd for $C_{23}H_{25}N_2O_7$ $[M + H]^+$ = 441.1662, found 441.1658.

*Thermolysis of **36**.* A flame dried 20 mL glass vial was charged with the intermediate **36** (0.14 g). Without the addition of solvent, the vial was placed in a preheated oil bath for 1 hour in which temperature was previously adjusted and fixed at 160 °C. After this period, the vial was removed from the hot bath allowed to reach room temperature and dissolved in DCM (20 mL). The DCM was evaporated under reduced pressure and the crude of reaction such obtained was purified by column chromatography (28% EtOAc/hexane) to afford the angular compound **37** (22 mg, 18.5%) as a yellow solid and the linear isomer **38** (19 mg, 16%) as a yellow solid.

7,8-Dimethoxy-3-(methoxymethyl)-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[1,2-*d*]imidazole-2,6,9(3*H*)-trione (37). Mp 145–147 °C. R_f = 0.5 (28% EtOAc/hexane). IR (neat, ν/cm^{-1}): 2922, 2852, 1720, 1664, 1623, 1611, 1514, 1455, 1379, 1342, 1284, 1242, 1242, 1081, 1047, 1028, 964, 811, 756, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.30 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 4.84 (s, 2H), 4.12 (s, 3H), 4.09 (s, 3H), 3.87 (s, 3H), 3.72 (s, 3H), 3.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 181.4, 181.0, 160.1, 156.9, 148.3, 146.3, 132.3, 131.3, 130.5, 129.3, 128.8, 125.5, 125.1, 114.5, 113.8, 72.5, 61.5, 61.4, 56.2, 55.5, 34.3. HRMS (ESI+): *m*/*z* calcd for $C_{23}H_{23}N_2O_7$ $[M + H]^+$ = 439.1505, found 439.1487.

6,7-Dimethoxy-3-(methoxymethyl)-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[2,3-*d*]imidazole-2,5,8(3*H*)-trione (38). Mp 191–193 °C. R_f = 0.5 (60% EtOAc/hexane). IR (neat, ν/cm^{-1}): 2939, 2836, 1707, 1664, 1654, 1611, 1600, 1514, 1469, 1454, 1382, 1340, 1282, 1241, 1178, 1123, 1080, 1045, 1027, 958, 908, 828, 812, 755. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 4.46 (s, 2H), 4.05 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.53 (s, 3H), 3.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.0, 181.6, 159.5, 155.4, 148.3, 145.4, 134.2, 131.4, 130.0, 128.2, 127.4, 126.0, 124.1, 113.8, 105.4, 72.0, 61.4, 61.4, 55.9, 55.4, 27.8. HRMS (ESI+): *m*/*z* calcd for $C_{23}H_{23}N_2O_7$ $[M + H]^+$ = 439.1505, found 439.1501.

Removal of MOM-group from kealiiquinone analogous

7,8-Dimethoxy-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[1,2-*d*]imidazole-2,6,9(3*H*)-trione (39). To a 25 mL of two-necked round bottom flask was charged with 7,8-dimethoxy-3-(methoxymethyl)-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[1,2-*d*]imidazole-2,6,9(3*H*)-trione **37** (9 mg, 0.0205 mmol) and was dissolved in trifluoroacetic acid (3 mL). The reaction mixture was stirred at 60 °C for 20 h and it was neutralized with 20 mL of sat. $NaHCO_3$ solution followed by extracted with EtOAc (30 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The crude was purified by crystallization method (EtOAc/hexane 1 : 2) to afford angular isomer of kealiiquinone **39** (6 mg, 82%) as light red solid. Mp > 300 °C. R_f = 0.4 (50% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3159, 2953, 2921, 2851, 1708, 1665, 1646, 1623, 1515, 1460, 1377, 1330, 1249, 1195, 1104, 1059, 1031, 962, 908, 829, 735. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.93 (s, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 4.13 (s, 3H), 4.10 (s, 3H), 3.89 (s, 3H), 3.75 (s, 3H). HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}N_2O_6$ $[M + H]^+$ = 395.1243, found 395.1238.

Kealiiquinone

6,7-Dimethoxy-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho[2,3-*d*]imidazole-2,5,8(3*H*)-trione (1). To a 25 mL two-necked round bottom flask was charged with 7,8-dimethoxy-3-(methoxymethyl)-4-(4-methoxyphenyl)-1-methyl-1*H*-naphtho

[1,2-*d*]imidazole-2,6,9-(3*H*)-trione **37** (9 mg, 0.0205 mmol) and was dissolved in trifluoroacetic acid (3 mL). The reaction mixture was stirred at 60 °C for 12 h and it was neutralized with 20 mL of sat. $NaHCO_3$ solution followed by extracted with EtOAc (30 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The crude was purified by crystallization method (EtOAc/hexane 1 : 2) to afford kealiiquinone **1** (6.5 mg, 87%) as red solid. Mp 291–293 °C. $R_f = 0.4$ (50% EtOAc/hexane). IR (neat, ν/cm^{-1}): 3183, 2954, 2921, 2852, 1712, 1665, 1648, 1625, 1611, 1516, 1460, 1333, 1288, 1253, 1198, 1186, 1107, 1060, 1031, 961, 830, 747, 724, 670. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.68 (s, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 7.9$ Hz, 2H), 3.93 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.3, 181.2, 158.6, 154.8, 147.8, 145.2, 134.0, 132.6, 129.9, 127.7, 126.5, 123.5, 122.8, 113.9, 104.6, 60.8, 60.8, 55.1, 26.8. HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{19}N_2O_6$ $[M + H]^+$ = 395.1243, found 395.1242. The spectroscopic data match for those reported by Ohta[5] and Lovely.[6]

Conflicts of interest

There are no conflicts to declare.

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