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Protecting-Group-Free Total Synthesis and Biological Evaluation of 3-Methylkealiiquinone and Structural Analogues

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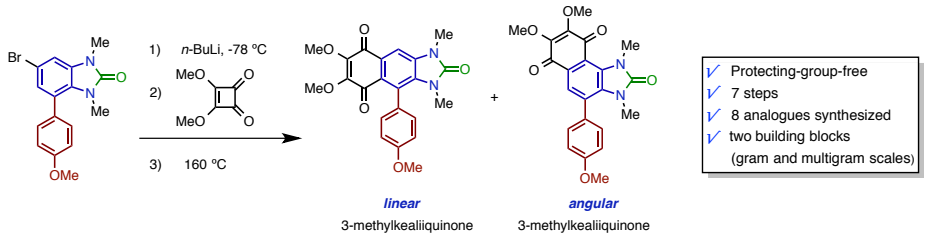
Supporting Information Placeholder



ABSTRACT: The modular protecting-group-free total synthesis of 3-methylkealiiquinone, an analogue of the marine alkaloid kealiiquinone, was accomplished in seven steps. A regioselectively-constructed functionalized arylbenzimidazolone moiety and dimethyl squarate were used as the only two building blocks. A thermal ring expansion via 6π-conrotatory ring closure to build the quinone fragment gave rise to the desired linear analogue of the natural compound along with a non-described structurally attractive angular naphtho[1,2-*d*]imidazole regioisomer. The IC_{50} values for the compounds were determined on three cancer cell lines.

Naturally occurring compounds[1] represent an excellent platform in the initial search for efficient and active anticarcinogens. These secondary metabolites isolated from marine sources have been a major contributor to the development of new drugs.[2] Recently, some imidazole alkaloids have been isolated from the Micronesian marine sponges of the genera *Leucetta* and *Clathrina*.[3] Kealiiquinone **1** (Figure 1) is the most complex naphtho[2,3-*d*]imidazole derivative obtained therefrom, and showed modest cytotoxicity against MCF7 cancer cells.[4]

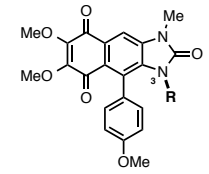


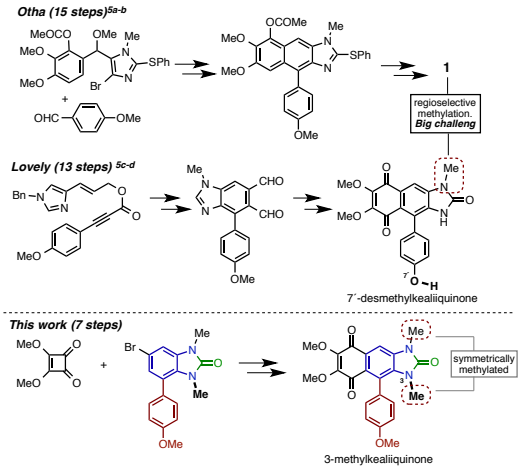
Figure 1. Structures of kealiiquinone and 3-methylkealiiquinone.

To date only two approaches[5] toward the fully functionalized kealiiquinone core, which eventually concluded in its total synthesis, have been reported (Scheme 1).

Ohta[5a-b] described the total synthesis of kealiiquinone by using an intramolecular Friedel-Carfts alkylation/oxidation sequence as key step, to form the naphtho[2,3-*d*]imidazole core. Even tough this route showed in general good yields, the synthesis is based upon the imidazole chemistry; this strongly limits the orthogonality in different stages of the process. In consequence the use of at least two protecting groups was necessary. This implied several organic redox fluctuations, which were reflected in the fifteen total synthetic steps.

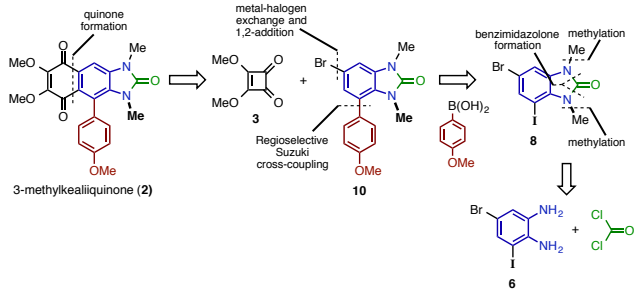
On the other hand the total synthesis of the 7′-desmethylkealiiquinone was recently reported by Lovely.[5c-d] In the route a [4+2] cycloaddition/ oxidation sequence was used to build the central rings of the natural product. For this synthetic protocol, moderate to good yields are observed in general. However the procedure also uses the imidazole core as base, to construct the natural product. Additionally, it was necessary the use of at least one protecting group which finally impact on the thirteen steps to complete the route.

Scheme 1. Approaches for the synthesis of the kealiiquinone core.



Inspired by the molecular architecture and preliminary biological activity of **1**,[4] it was decided to apply our protecting-group-free synthetic approach for the symmetrized 3-methylkealiiquinone analogue,[6] which is outlined in Scheme 2.

Scheme 2. Retrosynthesis of 3-methylkealiiquinone (2).

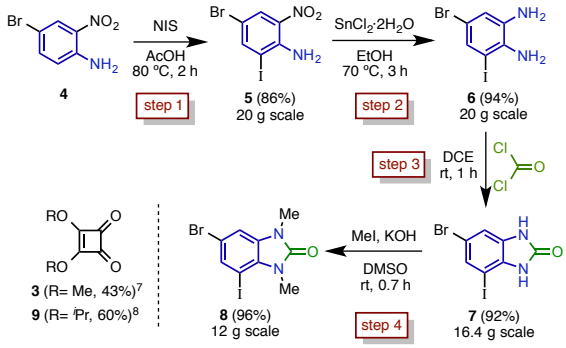


This convergent protecting-group-free strategy involves the synthesis of two main building blocks, the dimethyl squarate **3** and the arylbenzimidazolone **10**. From **3** the 1,4-quinoid ring was constructed trough a thermal ring expansion via 6π-conrotatory ring closure. Prior to this transformation, **3** participates as electrophile in the 1,2-addition of the anion formed from **10** by metal-halogen exchange. The 3-methylkealiiquinone arylbenzimidazolone fragment **10** was envisioned as the remaining building block. This compound was synthesized by two-step sequence, the first step consisting of a regioselective Suzuki cross-coupling between 4-anisylboronic acid and the benzimidazolone **8**, the second step was the *N*-bismethylation. Finally, compound **8** is formed by the reaction of phosgene with the corresponding 3,5-dihalogenated *o*-phenylenediamine **6**.

This convergent, modular and straightforward strategy uses the central ring of the natural compound as key building block, allowing an excellent scalability of the arylbenzimidazolone moiety, since this does not depend on the imidazole chemistry used in the last two reports.[5] Thus, this approach inserts the appropriate functional groups at initial stages of the synthesis, avoiding redox-fluctuations such as add-remove-add groups as employed in the routes of Ohta[5a-b] and Lovely.[5c-d]

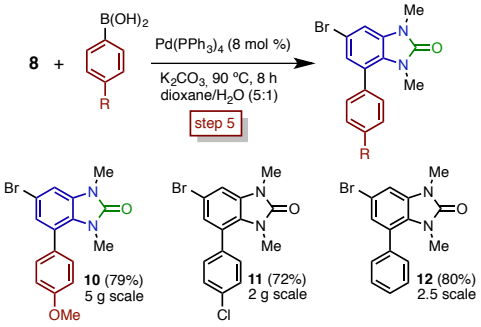
Our synthesis started with preparation of the two main building blocks **10** and **3**. In such a way, the synthesis of the dimethylbenzimidazolone **8** was necessary to prepare **10** (Scheme 3).

Scheme 3. Multigram scale synthesis of the benzimidazolone 8 and the building blocks 3 and 9.



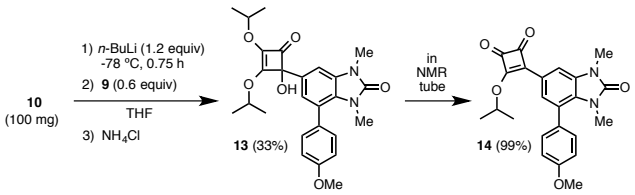
The dimethylbenzimidazolone **8**, bearing bromo and iodo groups at appropriate positions for further orthogonal Suzuki cross-coupling, was constructed regioselectively. Thus, its preparation started with the iodination of **4**[9] in acidic media to obtain **5**[10] in a good yield (86%). Then, the reduction of the nitro group gave rise to **6** in an excellent 94% yield. The reaction with phosgene subsequently afforded the benzimidazolone core, providing **7** in 92% yield. The final methylation furnished the chemo differentiated benzimidazolone **8**. This four-step and high yielding sequence was performed on a multigram scale without the use of any chromatography for purification. On the other side of the convergent synthetic process, the isopropyl and methyl squarates **9**[8] and **3**,[7] were synthesized according literature procedures, also on gram scales. The starting material **8** was used for the synthesis of the fully functionalized arylbenzimidazolone core **10** via orthogonal Suzuki cross-coupling. We also took the opportunity to prepare two further analogues, **11** and **12**, in a modular fashion and on gram scales by using different arylboronic acids. In this reaction we also observed few amounts of the bis-coupled product (scheme 4).[11]

Scheme 4. Synthesis of arybenzimidazolones 10-12.



Once the building blocks **10** and **3** were obtained, the fifth step of the synthetic proposal was completed. Thus, everything was ready to complete the synthesis of **2** by metal-halogen exchange and 1,2-addition to the squarate esters. However, it has been described that dimethyl squarate **3** is sensitive and prone to hydrolysis.[12] Thus, prior to attempting the proposed route it was decided to test a model system by using the more stable diisopropyl squarate **9** (Scheme 5).

Scheme 5. Model system for the 1,2-addition of the arylbenzimidazolone 10 to squarate 9.

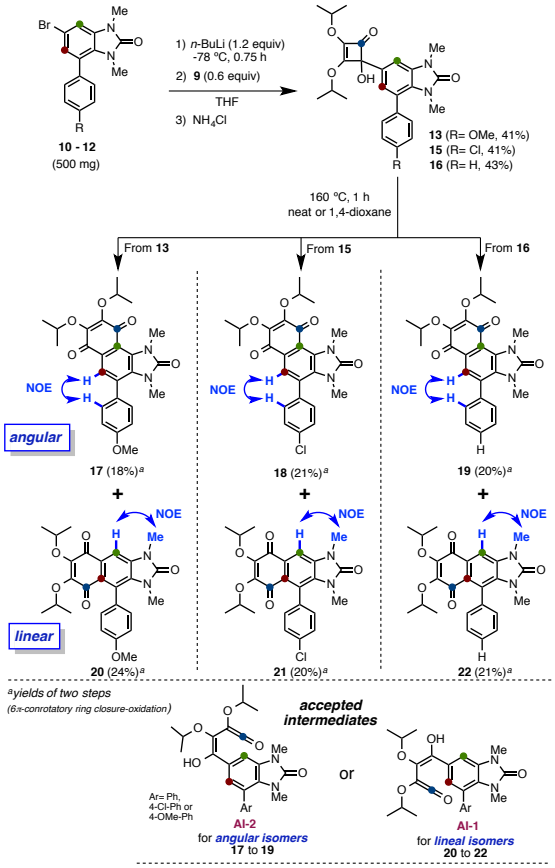


Metal-halogen (M-H) exchange on a hundred-milligram scale of **10** by using 1.2 equiv of *n*-butyllithium, followed by the addition of 0.6 equiv of diisopropyl squarate **9**, gave **13** in 33% yield. After a number of assays, the optimal reaction stoichiometry was determined to be that mentioned above. The fast isolation and characterization allowed us to identify this tertiary alcohol. However, within a short period of time (less than 2 hours) the sample in the NMR tube exhibited carbonyl regeneration via acidic solvolysis promoted by the deuterated solvent ($CDCl_3$). Thereby, **14** was obtained in almost quantitative yield. The same transformation was observed for the rest of the synthesized sample of **13** once in slightly acidic solution.

This short study provided several important pieces of information about our synthetic route: 1) the M-H exchange and 1,2-addition over squarate **9** was possible, but an acid-sensitive tertiary alcohol was obtained, 2) we found no 1,2-addition with the benzimidazolone carbonyl, 3) as compared with literature,[7] here, much milder acidic conditions gave rise to the solvolysis of the tertiary alcohol and concomitant carbonyl regeneration, and 4) as soon as prepared, the 1,2-addition products should be immediately subjected to thermolysis in order to obtain the 1,4-quinoid ring.[8, 13]

Considering all the aforementioned learned aspects, it was decided to complete our route to obtain model systems of the fully functionalized kealiiquinone core (Scheme 6).

Scheme 6. Synthesis of the fully functionalized kealiiquinone core model systems 17-22.



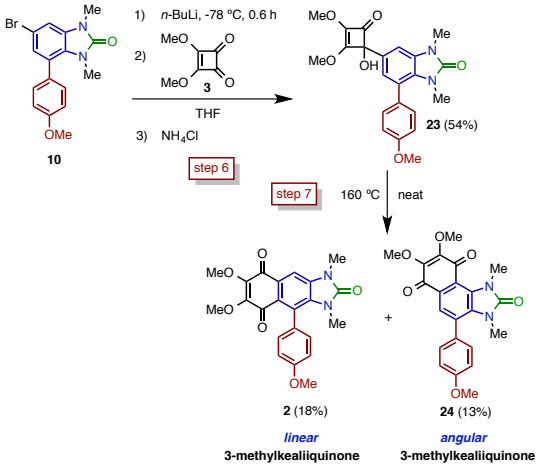
The previously optimized conditions for the M-H exchange/1,2-addition sequence were used for generating the lithiated arylbenzimidazolones form **10-12** which were subsequently reacted with the diisopropyl squarate **9**. In this way, on 500-milligram scales of each arylbenzimidazolone, the corresponding tertiary alcohols **13**, **15** and **16** were obtained in modest yields (41% to 43%). As previously mentioned, their rapid isolation prevented decomposition and allowed full characterization of these compounds, followed immediately by heating to 160 ºC. Depending on whether or not the compound melted at this temperature, this heating step was carried out either neat or in dioxane. After one hour of reaction, a perfectly separable mixture of two compounds essentially in a 1:1 ratio was observed. These products were detected for each of the three thermolysis reactions. To our delight, both of the observed compounds are the products of a thermal ring expansion, which proceed via 6π-conrotatory ring closure. From this transformation it was possible to directly access to the 1,4-quinoid ring without the need for an additional oxidation reaction. One set of products corresponds to the desired kealiiquinone model system with all of the fused rings organized in linear fashion (**20-22**). The second group of products showed a novel naphtho[1,2-*d*]imidazole architecture (**17-19**), which for simplicity we refer to them as angular isomers. This modular route allowed the synthesis of electron-donating (**17** and **20**), electron-withdrawing (**18** and **21**) as well as electron-neutral (**19** and **22**) model systems at the pendant phenyl ring of the molecule, also isopropoxy groups at the 1,4-quinoid ring. The known chemistry of squaric acid can be inferred to explain the formation of these two regioisomers. In agreement with the

previously described mechanism for this chemistry,[8,13] the accepted formation of a ketene intermediate[14] such as **AI-1** explains the formation of the linear regioisomers (**20-22**), while the accepted formation of a ketene intermediate[14] such as **AI-2** explains the formation of the angular regioisomers (**17-19**). Both regioisomers were unequivocally assigned by NOESY experimentation (see SI).

It is important to mention here that after the thermolysis of **13**, **15** and **16** a hydroquinone was formed[8,13] that spontaneously oxidized to the corresponding quinoid form. This is a two-step one-pot reaction, in consequence the final yields for **17-22** are the result of these two steps and are higher overall. Thereby, the yields are ca. 45% to 49% for each single step calculated in a linear manner. Moreover, the synthesis was carried out in a protecting-group-free manner.

Based on the understanding gained from our model systems, the protecting group-free total synthesis of 3-methylkealiiquinone (**2**) was then attempted (Scheme 7).

Scheme 7. Protecting-group-free total synthesis of the 3-methylkeliiquinone (2) and its angular analogue (24).



The arylbenzimidazolone **10** was subjected to M-H exchange using 1.2 equiv of *n*-butyllithium. The generated anion was reacted with 0.6 equiv of dimethyl squarate **3** yielding the alcohol **23** in 54% yield. This represents the sixth step in the overall route. Thereafter, neat thermolysis at 160 ºC for one hour, gratifyingly afforded the desired 3-methylkealiiquinone **2** (18%) in a separable mixture with its angular isomer **24** (13%).[15] We were unable to achieve significant improvement of the yield even after several attempts at optimization.[16] This final reaction marks the seventh and final step of our synthesis, none of which involved the use of protecting groups.

This was a consisting result that gave the expected linear and angular compounds according to the model systems observations in Scheme 6. Additionally, although the final yield appears to be low, it should be reiterated that this is the result of two steps, both of which are protecting-group-free. This means that it was possible to obtain good amounts of the methylated natural compound kealiiquinone **2**, as well as its novel angular isomer **24**, after just a single column purification.

Finally to complete this work, the biological assays of activity by testing the synthesized compounds in three cancer cell lines and one non-carcinogenic line were carried out. Thereby cell lines of cervix (HeLa), lung (A549) and colon (SW620) as well as non-carcinogenic human keratinocytes cell line (Ha-CaT) were examined and compared versus *cis*-platin (CDDP) as control of activity (Table 1).

Table 1. Determination of IC_{50} values for the synthesized compounds in different cancer cell lines.

Comp.	Hela[a]	A549[a]	SW620[a]	Ha-Cat[a]
2	> 100	> 100	> 100	> 100
24	> 100	> 100	> 100	> 100
20	76.9 ± 8.2	57.2± 5.6	57.3 ± 6.9	> 100
17	> 100	> 100	> 100	> 100
21	> 100	> 100	> 100	> 100
18	> 100	> 100	> 100	> 100
22	76.5 ± 7.6	64.3 ±4.3	61.3 ± 3.7	> 100
19	> 100	> 100	> 100	> 100
10	57.4 ± 3.8	63.7 ±5.2	68 ± 7.1	> 100
11	76.3 ± 4.9	76.1 ±6.2	> 100	> 100
12	> 100	> 100	> 100	> 100
CDDP	1.6 ± 0.1	2.4 ± 0.1	2.7 ± 0.2	2.6 ± 0.3

[a] The IC_{50} values are in μM units.

The electron-rich analogue of naturally occurring kealiiquinone **20** as well as its electronic-neutral congener **22** showed modest cytotoxicity in the three cancer cell lines but low cytotoxicity in the non-carcinogenic HaCaT. Surprisingly, very similar biological activity was observed for the benzimidazolones **10** and **11**, which no contain the 1,4-quinone moiety. Several others computational studies surrounding these results are currently been carrying out in our group to describe a functional group pattern of activity.

In summary, a modular, original and straightforward route to the total synthesis of the 3-methylkealiiquinone **2** was developed, which is a closely related analogue of the natural compound **1**. The synthetic strategy was carried out in a protecting-group-free manner and in seven steps, allowing the preparation of the fully functionalized kealiiquinone core. The synthesis of eight structurally-analogous derivatives was also achieved. Additionally, the described procedure allowed the discovery of a novel naphtho[1,2-*d*]imidazole architecture. Finally, it is worth mentioning the short synthetic route (seven steps), the use of only two building blocks (**10** and **3**) for the full synthesis, their multigram scalability, the avoidance of protecting groups and redox fluctuation, and the non-dependent imidazole chemistry of the process. These features represent significant improvements over the last two described syntheses. While the compounds displayed only modest cytotoxic activity, the modular developed route described herein opens the possibility to synthesize a range of derivatives that could potentially increase the observed biological activity.

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 masses (HRMS) analysis were obtained under the following procedure: samples were introduced by direct infusion at 3 μl min^{-1} to the electrospray ionization source of a quadrupole time-of-flight mass spectrometer (Bruker Daltonics ESI-QTOF-MS maXis impact), equipped with Data Analysis 4.1. ESI was operated in positive mode with ion spray voltage 4 500 V, nitrogen dry gas 4 L min^{-1}, drying temperature 180 ºC and gas pressure 0.4 Bar. Mass calibration was accomplished based based on sodium formate clusters. 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.

Sequence followed in Scheme 3. *4-bromo-2-nitroaniline* (**4**):[9] The synthesis of compound **4** was reported in literature. However, we synthesized the compound based on our developed procedure. To a 500 mL round-bottom flask charged with 2-nitroaniline (20 g, 144.9 mmol) in 1,4-dioxane (100 mL) was added NBS (25.6 g, 144.9 mmol, 1.0 equiv) portion wise over 5 minutes. The solution was stirred at room temperature for 1 hour. The reaction mixture was poured into H_2O (200 mL) and extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with saturated solution of Na_2CO_3 (500 mL) followed by brine (100 mL) and dried over Na_2SO_4, concentrated under reduced pressure to afford the regioselective mono brominated compound **4** (28 g, 90%) as light brownish solid. m.p.=100-102 °C. R_f = 0.35 (20% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3470, 3345, 2916, 2850, 1730, 1622, 1557, 1496, 1336, 1242, 1097, 813. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 2.3 Hz, 1H), 7.42 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 6.10 (bs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.7, 138.6, 132.5, 127.9, 120.4, 107.9. HRMS (ESI): m/z calculated for $C_6H_6BrN_2O_2$ $[M+H]^+$ = 216.9613, found 216.9632.

*4-bromo-2-iodo-6-nitroaniline (**5**):* Synthesis of compound **5**[10] was reported in literature. However, we synthesized the compound **5** based on our developed procedure. To a 500 mL two-necked round-bottom flask, was charged with a solution of 4-bromo-2-nitroaniline **4** (20 g, 92.16 mmol, 1 equiv) in glacial AcOH (120 mL) and heated to 80 °C. *N*-iodosuccinimide (40 g, 184.16 mmol, 2 equiv) was added portion wise and stirred for 2 hours. The reaction mixture was poured into ice-cooled water (300 mL) and immediately an orange color solid was formed. The resulted solid was filtered-off, washed with DCM (200 mL) and dried under vacuo. The aqueous portion was neutralized with saturated $NaHCO_3$ (200 mL) solution, followed by extraction with EtOAc (3 x 50 mL). The combined organic fractions were washed with brine (100 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 was collected to furnish **5** (22 g, 86%) that was used without further purification for next step. m.p. = 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 (EI): m/z calculated for $C_6H_4BrIN_2O_2$ $[M]^+$= 341.8501, found 341.8504.

*5-bromo-3-iodobenzene-1,2-diamine (**6**):*[17] 4-bromo-2-iodo-6-nitroaniline **5** (20 g, 58.65 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 $SnCl_2 \cdot 2H_2O$ (66 g, 307.91 mmol, 5 equiv) portion wise within 5 minutes and continued to be stirred at 70 °C for 3 hours. 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 **6** (18.1 g, 94%) as an off-white solid which was used without further purification. m.p. = 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 calculated for $C_6H_7BrIN_2$ $[M+H]^+$= 312.8863, found 312.8837.

*6-bromo-4-iodo-1,3-dihydro-2H-benzo[d]imidazol-2-one (**7**):* In a 500 mL two-neck round-bottom flask, was added 5-bromo-3-iodobenzene-1,2-diamine **6** (16.4 g, 52.73 mmol, 1.0 equiv) and dissolved in 200 mL of DCE at room temperature. Then, a solution of phosgene 15 wt. % in toluene (40 mL, 319.13 mmol, 7 equiv) was added drop wise to the reaction mixture and stirred for 1 hour. The reaction mixture was poured into ice-cooled water (300 mL) and immediately a white solid was formed. The resulting solid was filtered-off and dried under vacuum to give **7** (92%, 16.3 g) as an off-white solid. The compound was used without purification for next step. m.p. = 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 calculated for $C_7H_5BrIN_2O$ $[M+H]^+$= 338.8661, found 338.8630.

*6-bromo-4-iodo-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**8**):*A dried 500 mL two-neck flask was charged with dry DMSO (180 mL), powdered KOH (14 g, 249.25 mmol, 7 equiv) and was stirred for 30 minutes at room temperature. 6-bromo-4-iodo-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **7** (12 g, 35.60 mmol, 1 equiv) was added in portions to the reaction mixture followed by the drop wise addition of MeI (22 mL, 356.08 mmol, 10 equiv) over a period of 5 minutes. The mixture was stirred at room temperature for 1 hour and quenched by the addition of H_2O (200 mL). A white solid was formed. This resulted solid was filtered-off, washed

with water (100 mL) and dried under vacuo. The aqueous portion was extracted with EtOAc (4 x 25 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and finally concentrated under reduced pressure to obtain additional amount of such solid. The withe solid obtained from extraction and filtration stages were collected to furnish **8** (12.5 g, 96%), which was used for next step without purification. m.p.=163-165 °C. R_f = 0.6 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3066, 2940, 1699, 1572, 1481, 1444, 1384, 1247, 1097, 1023, 825, 735, 692. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 1.5 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 3.71 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.8, 134.4, 132.3, 129.9, 114.6, 110.5, 70.6, 30.0, 27.4. HRMS (ESI): m/z calculated for $C_9H_9BrIN_2O$ $[M+H]^+$= 366.8943, found 366.8933.

*3,4-dimethoxycyclobut-3-ene-1,2-dione (**3**)*:[6] 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 mmol, 1 equiv) and dissolved in MeOH (50 mL) at 70 °C. To the reaction mixture was added trimethyl orthoformate (5.4 mL, 46.05 mmol, 2.1 equiv) and refluxed for 48 h. The reaction mixture was evaporated under reduced pressure. The crude of reaction was washed with EtOAc (2x50 mL) and extracted with H_2O (2 x 100 mL). The collected organic fractions were dried with Na_2SO_4, filtered, and concentered 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. m.p. = 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. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.37 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.2, 184.6, 61.1.

*3,4-diisopropoxycyclobut-3-ene-1,2-dione (**9**)*:[7a] To a solution of squaric acid (5.0 g, 43.86 mmol, 1 equiv) in isopropanol (100 mL) was added H_2SO_4 (3 mL) and stirred at 80 °C for 48 hours. The reaction mixture was cooled and evaporated under reduced pressure. The crude was washed with EtOAc (100 mL) and extracted with 200 mL water. The combined organic fractions were evaporated, and the crude was purified by column chromatography (20% EtOAc/Hexane) to afford the 3,4-diisopropoxycyclobut-3-ene-1,2-dione **9** (5.2 g, 60%) as white solid. m.p. = 39-41 °C. R_f = 0.6 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2965, 2393, 1870, 1811, 1720, 1582, 1479, 1413, 1352, 1034, 922, 829. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (hept, *J* = 6.2 Hz, 2H), 1.45 (d, *J* = 6.2 Hz, 12 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.3, 184.1, 78.9, 22.8.

Reactions in Scheme 4. General Procedure for Suzuki-Miyaura cross-coupling reaction. To a solution of 6-bromo-4-iodo-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one **8** (1.0 equiv) in 1,4-dioxane (50 mL) and water (3 mL) were added boronic acid (2.0 equiv), potassium carbonate (2.5 equiv) and $Pd(PPh_3)_4$ (8 mol%). The reaction mixture was purged with N_2 and stirred at 90 °C for 8 hours. 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. After column chromatography purification it was obtained the corresponding arylbenzimidazolones **10-12**.

*6-bromo-4-(4-methoxyphenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**10**):* The following reaction (5 g scale of **8**) was carried out based upon the general procedure for Suzuki-Miyaura cross coupling reaction using 4-methoxy phenyl boronic acid. The crude material was purified by flash column chromatography over silica gel with the system (25% EtOAc/Hexane) to afford the cross-coupled product **10** (3.7 g, 79%) as white solid and the bis-coupled product **10a** (600 mg, 12%) as an off-white solid. m.p.=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)(OMe), 3.42 (s, 3H) (NMe1), 2.97 (s, 3H) (NMe3). ^{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 (OMe), 30.4 (NMe1), 27.4 (NMe3). HRMS (ESI): m/z calculated for $C_{16}H_{16}BrN_2O_2$ $[M+H]^+$= 347.0395, found 347.0396.

Data for bis-coupled product. *4,6-bis(4-methoxyphenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**10a**):* m.p.=134-136 °C. R_f = 0.5 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3030, 2894, 1728, 1604,1465, 1246, 1144, 937, 804, 636. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 1.7 Hz, 1H), 7.12 (d, *J* = 1.7 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H), 3.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.4, 159.1, 155.6, 134.2, 133.8, 131.3, 131.1, 130.6, 128.2, 126.5, 124.9, 123.1, 114.4, 113.5, 104.7, 55.53, 55.50, 30.5, 27.5. HRMS (ESI): m/z calculated for $C_{23}H_{23}N_2O_3$ $[M+H]^+$ = 375.1709, found 375.1716.

*6-bromo-4-(4-chlorophenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**11**):* The following reaction (2.0 g scale of **8**) was carried out according to above mentioned general procedure for Suzuki-Miyaura cross-coupling reaction using 4-chlorophenyl boronic acid. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford cross-coupled product **11** (1.83 g, 72%) as yellowish solid and bis-coupled product **11a** (220 mg, 10%) as white solid. m.p.=170-172 °C. R_f = 0.5 (30% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2999, 2912, 1797, 1617, 1433, 1256, 1073, 735. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.11 (s, 1H), 7.05 (s, 1H), 3.42 (s, 3H), 2.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.1, 135.5, 134.6, 132.0, 131.1, 128.5, 126.4, 126.3, 124.9, 113.4, 109.9, 30.6, 27.5. HRMS (ESI): m/z calculated for $C_{15}H_{13}BrClN_2O$ $[M+H]^+$ = 350.9900, found 350.9917.

*Data for bis-coupled product. 4,6-bis(4-chlorophenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**11a**):* m.p. = 132-134 °C. R_f = 0.45 (30% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2954, 1714, 1682, 1611, 1591, 1453, 1338, 1248, 1084, 1013, 790, 753, 727. HRMS (ESI): m/z calculated for $C_{21}H_{17}Cl_2N_2O$ $[M+H]^+$= 383.0718, found 383.0736.

*6-bromo-1,3-dimethyl-4-phenyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**12**):* The following reaction (2.5 g scale of **8**) was carried out according to above mentioned general procedure for Suzuki-Miyaura cross-coupling reaction using phenyl boronic acid. The crude material was purified by flash column chromatography over silica gel with the system (15% EtOAc/Hexane) to afford cross-coupled product **12** (1.68 g, 81%) as an off-white solid and the bis-coupled product **12a** (280 mg, 13%) as white solid. m.p.= 124-126 °C. R_f = 0.5 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3055, 2917, 1737, 1599, 1469, 1107, 1061, 827, 569. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 3H), 7.35 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.10 (d, *J* = 3.2 Hz, 2H), 3.43 (s, 3H), 2.94 (s, 3H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 155.2, 137.1, 131.9, 129.9, 129.6, 128.3, 128.2, 126.5, 126.4, 113.3, 109.6, 30.5, 27.5. HRMS (ESI): m/z calculated for $C_{15}H_{14}BrN_2O$ $[M+H]^+$= 317.0290, found 317.0301.

*Data for bis-coupled product. 1,3-dimethyl-4,6-diphenyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**12a**):* m.p.=134-136 °C. R_f = 0.5 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2956, 1697, 1622, 1472, 1439, 1389, 1252, 1125, 768, 701, 667. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.8 Hz, 2H), 7.48 – 7.40 (m, 7H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.21 (dd, *J* = 8.3 Hz, 2H), 3.51 (s, 3H), 3.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.6, 141.1, 138.4, 134.6, 131.4, 130.0, 128.9, 128.1, 128.0, 127.25, 127.20, 126.8, 125.2, 123.3, 105.3, 30.5, 27.5. HRMS (ESI): m/z calculated for $C_{21}H_{19}N_2O$ $[M+H]^+$= 315.1497, found 315.1511.

Sequence in Scheme 5. *6-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-en-1-yl)-4-(4-methoxyphenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**13**):* A flame-dried 100 mL two-neck round-bottom flask was charged with compound **10** (100 mg, 1 equiv) dissolved in dry THF (10 mL) and stirred at -78 °C (acetone/dry ice bath). Afterwards it was added 1.6 *M* solution of *n*-BuLi in hexane (0.2 mL, 0.0691 mmol, 1.2 equiv) drop wise. The clear solution was stirred at that temperature for additional 15 minutes, then a solution of isopropyl squarate **9** (35 mg, 0.1734 mmol, 0.6 equiv) in dry THF (2 mL) was added dropwise 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), stirred for 10 minutes and allowed to reach room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude material, which was purified by basic column chromatography (60% EtOAc/Hexane- 1% Et_3N) to yield **13** (45 mg, 33%) as colorless sponge like solid. m.p.= 208-210 °C. R_f = 0.2 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3288, 2980, 2800, 1619, 1609, 1420, 1328, 1286, 985, 838, 763, 690. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 5.62 (hept, *J* = 6.2 Hz, 1H), 4.01 (hept, *J* = 6.2 Hz, 1H), 3.88 (s, 3H), 3.50 (s, 3H), 3.00 (s, 3H), 1.54 (d, *J* = 6.2 Hz, 6H), 1.20 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.3, 193.2, 191.6, 173.9, 159.8, 155.3, 131.1, 131.05, 131.02, 129.2, 125.2, 124.7, 120.8, 113.7, 105.0, 80.1, 64.5, 55.5, 30.6, 27.7, 25.5, 23.1. HRMS (ESI): m/z calculated for $C_{26}H_{31}N_2O_6$ $[M+H]^+$= 467.2182, found 467.2169.

*3-isopropoxy-4-(7-(4-methoxyphenyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole -5-yl) cyclobut-3-ene-1,2-dione (**14**):* This compound was formed inside the NMR tube, after c.a. 2 hours of carried out the NMR experiment acquisition for compound **13**. It was obtained (40 mg, 99%) of a light yellowish solid corresponding to pure **14** formed due to acidic conditions of deuterated chloroform. m.p.= 280-230 ºC. R_f= 0.5 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3300, 3159, 1865, 1708, 1423, 1344, 1244, 1071, 745. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 1.5 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 5.63 (hept, d, *J* = 6.2 Hz, 1H), 3.89 (s, 3H), 3.51 (s, 3H), 3.01 (s, 3H), 1.55 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.3, 193.2, 191.6, 173.9, 159.8, 155.3, 131.2, 131.08, 131.05, 129.2, 125.2, 124.7, 120.8, 113.7, 105.1, 80.2, 55.5, 30.6, 27.7, 23.2. HRMS (ESI): m/z calculated for $C_{23}H_{23}N_2O_5$ $[M+H]^+$= 407.1607, found 407.1605.

Sequence in Scheme 6: 1) Metal-Halogen exchange/1,2-addition. General procedure for metal-halogen exchange reaction and 1,2-addition: A flame-dried 250 mL two-neck round-bottom flask was charged with benzimidazolones **10-12** (500 mg, 1 equiv) 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 (1.2 equiv) drop wise. The clear solution was stirred at that temperature for additional 15 minutes, then a solution of isopropyl squarate **9** (0.6 equiv) in dry THF (1 mL) was added dropwise 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 and allowed to reach room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude material.

*6-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-en-1-yl)-4-(4-methoxyphenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**13**):* After basic column chromatography (60% EtOAc/Hexane- 1% Et_3N), compound **13** (280 mg, 41%) was obtained as colorless sponge like solid.

*4-(4-chlorophenyl)-6-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-en-1-yl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**15**):* After basic column chromatography (60% EtOAc/Hexane- 1% Et_3N), compound **15** (280 mg, 41%) was obtained as colorless sponge like solid. m.p.= 100-102 °C. R_f = 0.2 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3287, 2978, 2900, 1768, 1682, 1620,1464, 1383, 1313, 1156, 1047, 1014, 942, 828, 743. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 1.7 Hz, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 4.93 (hept, *J* = 6.1 Hz, 2H), 3.45 (s, 3H), 2.98 (s, 3H), 2.63 (s, 1H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.6, 178.4, 165.4, 155.5, 136.6, 134.2, 133.7, 131.2, 130.6, 128.3, 127.3, 123.5, 121.4, 104.8, 87.3, 77.7, 74.1, 30.6, 27.6, 22.93, 22.90, 22.7, 22.5. HRMS (ESI): m/z calculated for $C_{25}H_{28}ClN_2O_5$ $[M+H]^+$= 471.1687, found 471.1661.

*6-(1-hydroxy-2,3-diisopropoxy-4-oxocyclobut-2-en-1-yl)-1,3-dimethyl-4-phenyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**16**):* The crude **16** (500 mg scale) was purified by basic column chromatography (60% EtOAc/Hexane–1% Et_3N) to yield pure **16** (300 mg, 43%) of white sponge like solid. m.p.= 180-182 °C. R_f = 0.2 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3287, 2981, 1766, 1683, 1622, 1469, 1384, 1371, 1311, 1251, 1093, 1044, 945, 864, 704. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.41 (m, 3H), 7.37 – 7.34 (m, 2H), 7.23 (d, *J* = 1.7 Hz, 1H), 7.07 (d, *J* = 1.7 Hz, 1H), 4.93 (hept, *J* = 6.2 Hz, 2H), 3.45 (s, 3H), 2.96 (s, 3H), 2.74 (s, 1H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.7, 165.5, 155.5, 138.1, 133.7, 131.0, 130.4, 130.0, 128.1, 128.0, 127.3, 124.9, 121.5, 104.5, 87.4, 77.6, 74.0, 30.5, 27.5, 22.9, 22.9, 22.7, 22.5. HRMS (ESI): m/z calculated for $C_{25}H_{29}N_2O_5$ $[M+H]^+$= 437.2076, found 437.2056.

Sequence in Scheme 6: 2) Thermolysis reactions. General procedure for thermolysis: A 20 mL glass vial was charged with the tertiary alcohol **(13** or **15** or **16)**. The vial was placed during 1 hour in a preheated oil bath which temperature was

previously adjusted and fixed at 160 °C. Depending on whether or not the compound melted at this temperature, this heating step was carried out either neat or in dioxane (1 mL). After this period of time the reaction mixture was removed form the oil bath allowing to reaching room temperature and dissolve in DCM (20 mL). The DCM was evaporated under reduced pressure and the crude of reaction such obtained was purified by column chromatography (20% EtOAc/Hexane) to afford the two regioisomer as linear (**20**-**22**) and angular (**17**-**19**) compounds.

*Thermolysis of **13***. The tertiary alcohol **13** (280 mg) was subjected to the general procedure for thermolysis. The column chromatography purification (18% EtOAc /Hexane system) affords the angular compound **17** (49 mg, 18%) as yellow solid and the linear compound **20** (68 mg, 24%) as yellowish solid (20% EtOAc/Hexane system).

*7,8-diisopropoxy-4-(4-methoxyphenyl)-1,3-dimethyl-1H-naphtho[1,2-d]imidazole-2,6,9(3H)-trione (**17**):* m.p.= 192-194 °C. R_f= 0.55 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2955, 2924, 2851, 1711, 1655, 1608, 1466, 1379, 1245, 1200, 1129, 1059, 939, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.96 (hept, *J* = 6.3 Hz, 1H), 4.89 (hept, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 2.99 (s, 3H), 1.36 (d, *J* = 6.3 Hz, 6H), 1.34 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.0, 181.9, 160.0, 156.9, 148.8, 146.8, 133.7, 130.7, 128.9, 128.0, 125.1, 124.5, 114.7, 113.9, 113.8, 76.1 76.0, 55.5, 34.2, 31.3, 22.9, 22.8. HRMS (ESI): m/z calculated for $C_{26}H_{29}N_2O_6$ $[M+H]^+$= 465.2026, found 465.2048.

*6,7-diisopropoxy-4-(4-methoxyphenyl)-1,3-dimethyl-1H-naphtho[2,3-d]imidazole-2,5,8(3H)-trione (**20**):* m.p.= 186-188 °C. R_f = 0.5 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2960, 2924, 2853, 1720, 1611, 1514, 1344, 1245, 1185, 1031, 949, 747. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.89 (hept, *J* = 6.2 Hz, 1H), 4.82 (hept, *J* = 6.2 Hz, 1H), 3.88 (s, 3H), 3.52 (s, 3H), 2.74 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 6H), 1.25 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.7, 182.4, 159.4, 155.3, 148.7, 145.6, 133.4, 132.5, 130.5, 128.1, 127.5, 124.9, 124.1, 113.6, 105.2, 76.0, 75.7, 55.3, 30.0, 27.7, 22.8, 22.7. HRMS (ESI): m/z calculated for $C_{26}H_{29}N_2O_6$ $[M+H]^+$= 465.2026, found 465.2042.

*Thermolysis of **15**.* The tertiary alcohol **15** (280 mg) was subjected to the general procedure for thermolysis. The column chromatography purification (17% EtOAc /Hexane system) affords the angular compound **18** (58 mg, 21%) as yellow solid and the linear compound **21** (55 mg, 20%) as yellowish solid (19% EtOAc/Hex system).

*4-(4-chlorophenyl)-7,8-diisopropoxy-1,3-dimethyl-1H-naphtho[1,2-d]imidazole-2,6,9(3H)-trione (**18**):* m.p.= 185-187 °C. R_f = 0.6 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2957, 2925, 1714, 1646, 1588, 1470, 1378, 1197, 1127, 1056, 945, 748. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 4.96 (hept, *J* = 6.2 Hz, 1H), 4.90 (hept, *J* = 6.2 Hz, 1H), 3.74 (s, 3H), 2.99 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 6H), 1.35 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 181.82, 181.81, 156.8, 148.8, 146.8, 135.3, 135.1, 133.5, 130.9, 130.8, 128.7, 126.6, 125.2, 124.0, 115.0, 76.2, 76.1, 34.3, 31.4, 22.9, 22.8. HRMS (ESI): m/z calculated for $C_{25}H_{26}ClN_2O_5$ $[M+H]^+$= 469.1530, found 469.1567.

*4-(4-chlorophenyl)-6,7-diisopropoxy-1,3-dimethyl-1H-naphtho[2,3-d]imidazole-2,5,8(3H)-trione(**21**):* m.p.= 146-148 °C. R_f= 0.55 (40% EtOAc/Hex). IR (neat) ν/cm^{-1} = 2971, 2926, 2870, 1720, 1650, 1613, 1484, 1348, 1259, 1179, 1088, 1034, 950, 735. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.86 (hept, *J* = 6.2 Hz, 1H), 4.82 (hept, *J* = 6.2 Hz, 1H), 3.51(s, 3H), 2.73 (s, 3H), 1.33 (d, *J* = 6.2 Hz, 6H), 1.24 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.4, 182.3, 155.2, 148.6, 145.7, 134.8, 134.1, 133.6, 132.1, 130.8, 128.5, 127.5, 123.8, 123.5, 105.4, 76.1, 75.9, 30.0, 27.8, 22.8, 22.7. HRMS (ESI): m/z calculated for $C_{25}H_{26}ClN_2O_5$ $[M+H]^+$= 469.1530, found 469.1561.

*Thermolysis of **16***. The tertiary alcohol **16** (300 mg) was subjected to the general procedure for thermolysis. The column chromatography purification (18% EtOAc /Hexane system) affords the angular compound **19** (55 mg, 20%) as yellow solid and the linear compound **22** (56 mg, 21%) as yellowish solid (19% EtOAc/Hex system).

*7,8-diisopropoxy-1,3-dimethyl-4-phenyl-1H-naphtho[1,2-d]-imidazole-2,6,9(3H)-trione(**19**):* m.p.= 141-143 °C. R_f = 0.6 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2953, 2919, 2838, 1725, 1651, 1593, 1473, 1376, 1288, 1196, 1129, 1101, 1059, 944, 708. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.45 (bs, 3H), 7.34 (bs, 2H), 4.96 (hept, *J* = 6.2 Hz, 1H), 4.90 (hept, *J* = 6.2 Hz, 1H), 3.73 (s, 3H), 2.96 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 6H), 1.35 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): 181.93, 181.90, 156.9, 148.7, 146.8, 136.9, 133.5, 130.7, 129.6, 128.8, 128.4, 128.1, 125.1, 124.2, 114.8, 76.1, 76.0, 34.2, 31.2, 22.9, 22.8. HRMS (ESI): m/z calculated for $C_{25}H_{27}N_2O_5$ $[M+H]^+$= 435.1920, found 435.1947.

*6,7-diisopropoxy-1,3-dimethyl-4-phenyl-1H-naphtho[2,3-d]-imidazole-2,5,8(3H)-trione(**22**):* m.p.= 154-156 °C. R_f = 0.55 (40% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2977, 2934, 2247, 1713, 1652, 1595, 1479, 1444, 1346, 1267, 1178, 1095, 1036, 949, 743. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.47-7.40 (m, 3H), 7.28-7.22 (m, 2H), 4.88 (hept, *J* = 6.2 Hz, 1H), 4.82 (hept, *J* = 6.2 Hz, 1H), 3.53 (s, 3H), 2.69 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 6H), 1.24 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.6, 182.3, 155.3, 148.6, 145.7, 136.3, 133.5, 132.1, 129.4, 128.1, 128.0, 127.4, 125.0, 123.9, 105.3, 76.0, 75.7, 29.8, 27.8, 22.8, 22.7. HRMS (ESI): m/z calculated for $C_{25}H_{27}N_2O_5$ $[M+H]^+$= 435.1920, found 435.1948.

Sequence in Scheme 7. *6-(1-hydroxy-2,3-dimethoxy-4-oxocyclobut-2-en-1-yl)-4-(4-methoxyphenyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (**23**):* A flame-dried 250 mL two-neck round-bottom flask was charged with benzimidazolone **10** (500 mg, 1 equiv) dissolved in dry THF (30 mL) and stirred at -78 °C (acetone/dry ice bath). Afterwards it was added drop wise a solution of *n*-BuLi 1.6 *M* in hexane (1.0 mL, 1.734 mmol, 1.2 equiv). The clear solution was stirred at that temperature for additional 15 minutes. Then a solution of methyl squarate **3** (123 mg, 0.867 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 (20 mL) and stirred for 10 minutes allowing reaching room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude material. The crude material was purified by column chromatography (60% EtOAc/Hexane-1% Et_3N) to yield **23** (200 mg, 54%) as colorless floppy solid.

m.p.= 220-222 °C. R_f = 0.3 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 3304, 2950, 1755, 1703,1673,1622, 1514, 1462, 1329, 1243, 1178, 1124, 1027, 838, 735, 693. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 1.5 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.10 (s, 3H), 4.01 (s, 3H), 3.87 (s, 3H), 3.45 (s, 3H), 2.98 (s, 3H), 2.04 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 184.0, 166.1, 159.5, 155.5, 135.6, 131.1, 131.0, 130.2, 130.0, 127.6, 124.7, 121.7, 113.5, 104.3, 87.7, 60.5, 58.9, 55.5, 30.5, 27.6. HRMS (ESI): m/z calculated for $C_{22}H_{23}N_2O_6$ $[M+H]^+$= 411.1556, found 411.1528.

Thermolysis reaction. *Procedure for thermolysis of (**23**):* A 20 mL glass vial was charged with the tertiary alcohol **23** (200 mg). Without the addition of solvent, the vial was placed during 1 hour in a preheated oil bath which temperature was previously adjusted and fixed at 160 °C. After this period, the reaction mixture was removed from the hot bath allowing reaching 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 (34% EtOAc/Hexane) affording the angular compound **24** (13%, 25 mg) as a yellow solid and the linear 3-methylkealiiquinone **2** (18%, 33 mg) as a yellow solid. In this reaction we also identified the compound **25** (35 mg, 18%) as a yellowish solid, which is the product of the carbonyl regeneration via solvolysis.

Linear 3-methylkealiiquinone: *6,7-dimethoxy-4-(4-methoxyphenyl)-1,3-dimethyl-1H-naphtho[2,3-d]imidazole-2,5,8(3H)-trione (**2**).* m.p.= 201-203 °C. R_f= 0.5 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2919, 2849, 1714, 1655, 1621, 1514, 1454, 1347, 1281, 1176, 1028, 909, 832, 776. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 4.05 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.53 (s, 3H), 2.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 182.0, 181.7, 159.5, 155.3, 148.0, 145.5, 133.5, 132.6, 130.4, 127.9, 127.1, 125.0, 123.7, 113.7, 105.2, 61.37, 61.36, 55.4, 29.9, 27.6. HRMS (ESI): m/z calculated for $C_{22}H_{21}N_2O_6$ $[M+H]^+$= 409.1403, found 409.1433.

*Angular 3-methylkealiiquinone: 7,8-dimethoxy-4-(4-methoxyphenyl)-1,3-dimethyl-1H-naphtho[1,2-d]imidazole-2,6,9(3H)-trione (**24**):* m.p.= 165-167 °C. R_f = 0.55 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2926, 1714, 1662, 1621, 1514, 1454, 1382, 1347, 1230, 1176, 1028, 909, 832, 747. ^{1}H NMR (500 MHz,): δ 7.78 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 4.12 (s, 3H), 4.09 (s, 3H), 3.88 (s, 3H), 3.73 (s, 3H), 3.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 181.5, 181.1, 160.1, 156.9, 148.1, 146.3, 133.8, 130.9, 130.7, 128.8, 128.2, 124.7, 124.6, 114.3, 113.8, 61.5, 61.4, 55.5, 34.2, 31.3. HRMS (ESI): m/z calculated for $C_{22}H_{21}N_2O_6$ $[M+H]^+$= 409.1403, found 409.1431.

*3-methoxy-4-(7-(4-methoxyphenyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl) cyclobut-3-ene-1,2-dione (**25**):* m.p.= 225-227 °C. R_f = 0.4 (60% EtOAc/Hexane). IR (neat) ν/cm^{-1} = 2965, 2251, 1781, 1737, 1703, 1591, 1515, 1439, 1248, 1180, 1098, 1026, 915, 838, 727. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 4.58 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H), 3.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.7, 193.2, 191.5, 173.7, 159.8, 155.2, 131.2, 131.0, 130.8, 129.1, 125.2, 124.9, 120.5, 113.7, 105.1, 61.8, 55.5, 30.6, 27.7. HRMS (ESI): m/z calculated for $C_{21}H_{19}N_2O_5$ $[M+H]^+$= 379.1294, found 379.1278.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Biological essays of activity for compounds **2**, **24**, **20**, **17**, **21**, **18**, **22**, **19**, **10**, **11**, **12** and **CDDP** as well as Copies of ^{1}H and ^{13}C for all of compounds

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Notes

The authors declare no competing financial interest.

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