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Synthetic Route Discovery and Introductory Optimization of a Novel Process to Idebenone

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Supporting Information

ABSTRACT: An environmentally benign, convenient, high yielding, and cost-effective synthesis leading to idebenone is disclosed. The synthesis includes a bromination process for the preparation of 2-bromo-3,4,5-trimethoxy-1-methylbenzene, a protocol for the Heck cross-coupling reaction using either thermal or microwave heating, olefin reduction by palladium catalyzed hydrogenation, and a green oxidation protocol with hydrogen peroxide as oxidant to achieve the benzoquinone framework. The total synthesis is composed of six steps that provide an overall yield of 20% that corresponds to a step yield of 76%.

INTRODUCTION

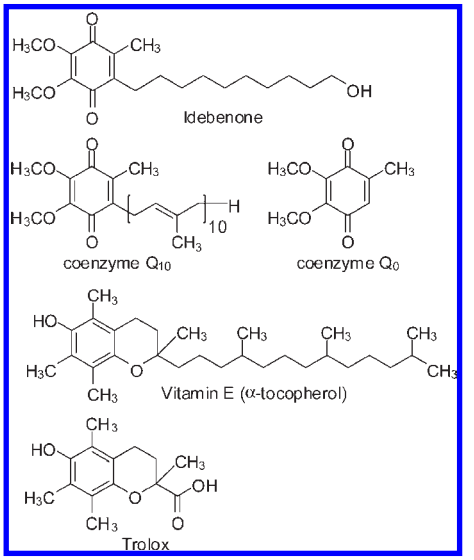
Idebenone was originally designed and synthesized as an experimental drug intended for the treatment of various cognitive defects such as Alzheimer's[1] and Parkinson's diseases.[2] Idebenone has also been investigated as an agent for the treatment of ischemic stroke,[3] inhibition of lipid peroxidation in the brain[4] and cardiac mitochondria,[5] improvement of mitochondrial oxygen utilization,[6] short-term memory and learning disabilities,[7] reduction of hepatocyte injury,[8] and treatment of oxidative eye diseases.[9] In recent years, various clinical studies involving idebenone for the treatment of neuromuscular diseases such as Friedreich's ataxia[10] and Duchenne muscular dystrophy[11] have also been concluded or are currently under way. A clinical trial dedicated to investigation of idebenone's effect on Leber's hereditary optic neuropathy was also recently concluded.[12] Lately several other clinical trials using idebenon as a therapeutic agent were initiated and include treatment of mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes,[13] and primary progressive multiple sclerosis.[14]

Idebenone was also proved[10e,15] to be a free radical scavenger for a variety of reactive species such as the oxidant peroxynitrite. The antioxidant efficiency of idebenone compared with vitamin E and Trolox (Chart 1) revealed that the efficacy of idebenone varies in the range 50−100% of that of the latter two. The much shorter and much more carbon poor side chain of idebenone (C_{10}) compared to that of coenzyme Q_{10} (C_{40}), see Chart 1, provide idebenon with a minor hydrophobicity that facilitates it to intercept free radicals both in hydrophobic and hydrophilic environments.

The antioxidant properties of idebenone have also attracted interest from the "beauty industry" and provided antiaging remedies for topical applications for treatment of wrinkles.[16]

The recent renewed interest and the apparently large range of application areas for idebenone **10** combined with our own long-standing research activity related to oxidation processes in organic synthesis and transition metal-catalyzed synthesis spurred our curiosity to investigate previous syntheses of idebenone **10** and analogue compounds. Surprisingly few and in general environmentally unfriendly synthetic processes[17−24] to

Chart 1. Idebenone, Coenzyme Q_0, Coenzyme Q_{10}, Vitamin E, and Trolox



idebenone **10** have been disclosed. The major divergence of these processes and syntheses was found in the nature of the substrate, in the type of oxidation processes that provided the benzoquinone framework, and how the alkyl chain was connected to the ring, whereof the most disclosures utilize some sort of Friedel−Crafts reaction.

METHODS AND RESULTS

Our effort to design and realize a novel total synthesis leading to idebenone was constrained by several requirements, namely (1) it should be cost-effective and (2) preferably based on readily

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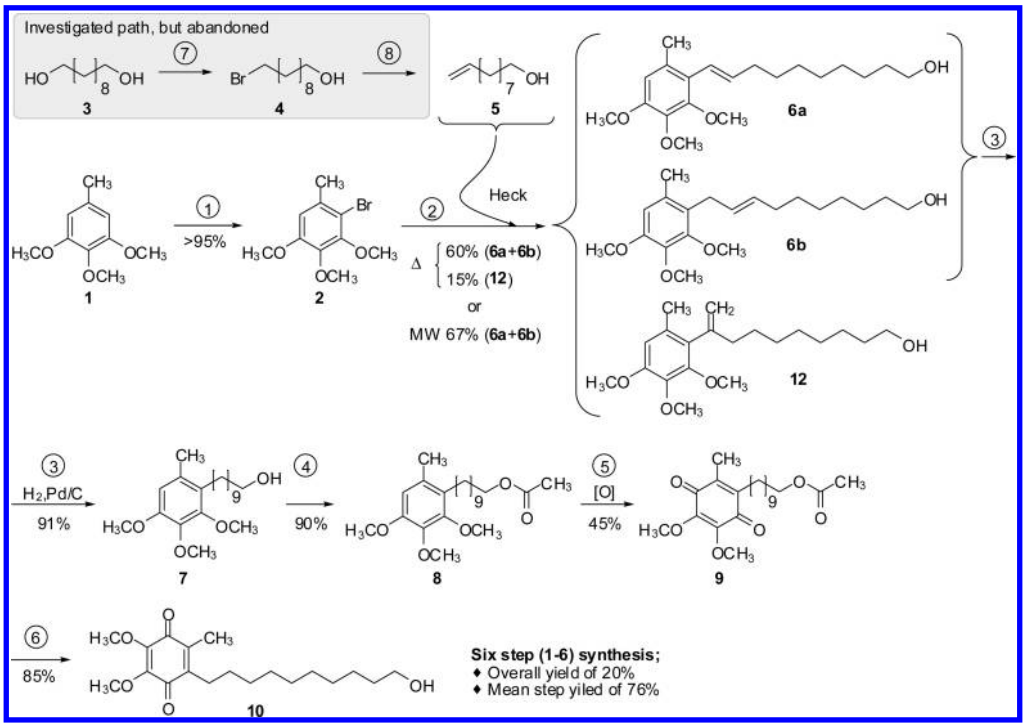
Scheme 1. A New Expedient High-Yielding Total Synthesis of Target Molecule Idebenone 10

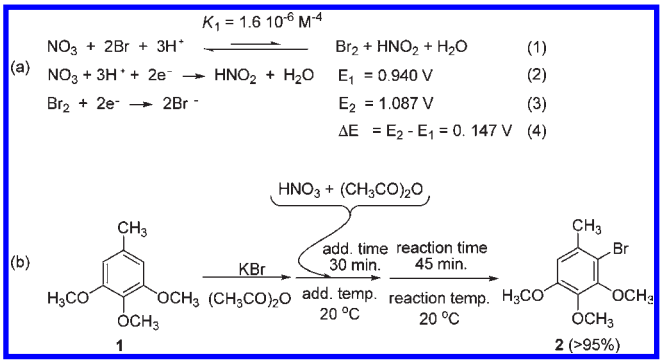


available reagents, (3) it should be scalable, (4) it should preferably be usable for the operation in continuous flow fashion, and (5) it should include as many environmentally friendly steps and operations as possible.

One of the crucial steps of our outlined synthesis, see Scheme 1, emerged to be a coupling of an aromatic moiety and an alkyl chain that together constitute the entire Carbone skeleton of our target molecule idebenone. In this context, we assessed various transition metal catalysis coupling reactions, whereof the Heck coupling[25] appeared to be the most attractive for the preparation of the target carbon skeleton.

For this purpose, we needed access to 2-bromo-3,4,5-trimethoxy-1-methylbenzene (**2**) and dec-9-en-1-ol (**5**), whereof the bromobenzene **2** could be prepared from the readily available 1,2,3-trimethoxy-5-methylbenzene (**1**). A large number of brominating protocols have previously been disclosed, unfortunately most of them will not fulfill some of our important objectives, namely low environmental impact and easy scalability. In this context, we designed and realized recently[26] a novel bromination protocol where we utilized the two low-cost compounds 1,2,3-trimethoxy-5-methylbenzene (**1**) as substrate and potassium bromide as the only bromine source. KBr as bromine source is very attractive since this compound has low toxicity and is easy to handle even at large scale. The bromination proceeds in a one-pot process where two distinct, but concurrent reactions proceed: (1) Molecular bromine is produced from potassium bromide reacting with nitric acid [see path a of Scheme 2], but at any time during the bromination process, the quantity of bromine is very small. (2) The minute quantities of molecular bromine that are produced are concurrently consumed in an electrophilic substitution by means of Br^+.[27] The low molecular bromine concentration during the whole course of the bromination give rise to high selectivity and excellent yield (>95%). The bromination process operates excellently with activated arenes and it appears that this process operates according

Scheme 2. Bromination of 1,2,3-Trimethoxy-5-methylbenzene 1 with KBr As the Only Bromine Source[a]



[a] Reaction a: Production of molecular bromine. Reaction b: Overall bromination process.

to an electrophilic substitution by means of the Br^+ ion. Since Br is a deactivating group (when monobromination has taken place), the monobrominated arenes turn out to be substantially less reactive compared to the starting arene. This fact contributed also to the high selectivity (>95% yield and quantitative conversion) of the brominating protocol developed for the production of the brombenzene **2**. Several more examples are given in our previous disclosure.[26]

With the low cost and environmentally friendly process for the production of the aromatic bromide **2** available, the next step ought to be a coupling reaction. The Heck coupling involving the bromobenzene **2** and the commercially available dec-9-en-1-ol (**5**), Scheme 3, appeared to be a potential path to produce the complete Carbone skeleton needed for the Idebenone.

For the outlined coupling reaction, three various palladium catalysts were investigated: (1) palladium acetate [$Pd(OAc)_2$],

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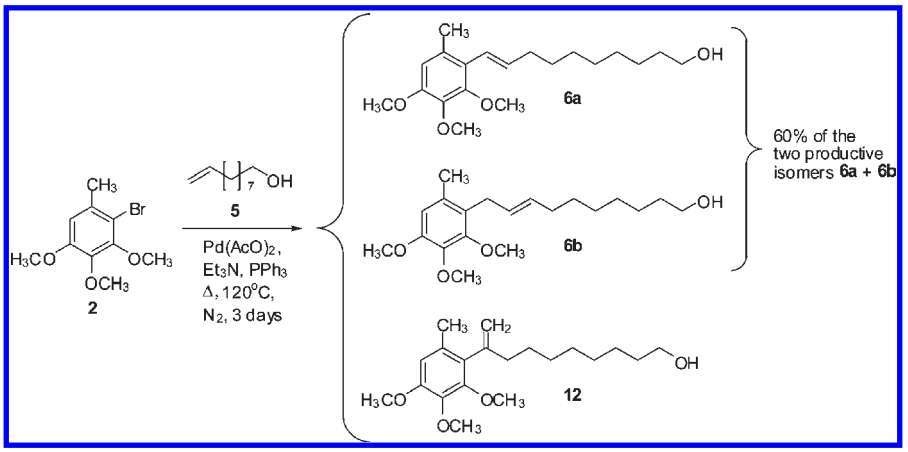
Scheme 3. Heck Coupling Reaction Conducted with Conventional Heating, Using an Oil Bath



(2) tetrakis(triphenylposphine)palladium(0) [$Pd(PPh_3)_4$], and (3) [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (known as PEPPSI -IPr).[28] The three catalysts were selected due to their ligand variation, namely an inorganic salt, a Pd catalyst with only phosphine ligands, and finally a catalyst with NHC ligand. The $Pd(OAc)_2$ catalyst provided the highest substrate conversion (≈80%), using a reaction temperature of 120 °C for a reaction period of 72 h with triethylamine as base and triphenylphosphine as ligand for the palladium catalyst.

Three isomers **6a**, **6b**, and **12** were produced, whereof the two most abundant and productive isomers **6a** and **6b** were isolated in a yield of >60%. An undesired byproduct, the olefin **12**, was produced (≈15%) as a result of the coupling of the bromobenzene **2** at C2 of the olefine **5**, a reaction that takes place with the presence of either carbonyl or hydroxyl groups in the olefin.[29]

Even though the outcome of the Heck coupling was satisfactory, this protocol had a serious drawback from an industrial scale point of view, namely the requirement of a very long reaction time (3 days). To optimize the Heck coupling with respect to two concurrent goals, namely (1) minimizing the reaction time and (2) increasing the reaction yield (and thus maximizing the potential throughput), we investigated the Heck cross-coupling reaction using microwave irradiation as the energy source as an alternative to thermal heating. A selection of the experiments involving microwave irradiation is given in Table 1.

Initially we utilized identical reaction conditions for the procedure that used classical heating with an oil bath (that is summarized in Scheme 3). The microwave irradiation driven protocol is shown in Scheme 4. The five experimental variables reaction time, solvent, reaction temperature, base, and catalyst were investigated. This screening revealed that $Pd(PPh_3)_4$ as the catalyst in combination with diisopropylethylamine as base and *N*,*N*-dimethylfomamide (DMF) as solvent conducted at a reaction temperature of 120 °C provided a higher outcome (giving an isolated yield of 67%) compared with the experiment with thermal heating (Scheme 3). Moreover, the microwave protocol required a considerably shorter reaction time, namely only 30 min in the microwave reactor in contrast to 3 days (72 h) when using conventional thermal heating. The selectivity with microwave heating was also significantly improved, as only the desired olefin isomers **6a** and **6b** were produced. Furthermore, when $Pd(OAc)_2$ was used as catalyst under similar microwave reactor condition, a poor yield of 21% was achieved. The PEPPSI-IPr catalyst also gave a low yield of 14%.

However, with an augmented quantity of the $Pd(OAc)_2$ catalyst (from 2.6 mol % to 5.2 mol %), and increased reaction temperature (from 120 to 160 °C, see Table 1, entry 16), a similar yield as with $Pd(PPh_3)_4$ as catalyst was achieved (≈60%), and the undesired isomer **12** was not produced. If the amine base was substituted with K_2CO_3 (Table 1, entry 8), no improvement was observed (affording a yield of ≈32%), but also under these conditions only the desired isomers **6a** and **6b** were produced.

A two-step synthetic pathway leading to dec-9-en-1-ol (**5**) was also investigated. This investigation was undertaken in order to provide an extended process that hopefully resulted in an overall reduced cost. The process leading to dec-9-en-1-ol (**5**) involves decan-1,10-diol (**3**) as the basic substrate (pathways 7 and 8 of Scheme 1) and includes a monobromination of the diol **3** to 10-bromo-decan-1-ol (**4**) that in the subsequent step is subjected to a dehydrohalogenation to produce dec-9-en-1-ol (**5**).

The bromoalkanol **4** was initially synthesized according to an environmentally mild solvent free process disclosed by Goverdhan and collaborators[36] for the synthesis of bromoalkanols using diols under microwave irradiation. The product was purified and isolated from the disubstituted derivative in a medium yield of 45%, though the literature suggested a yield of 80%. By means of statistical experimental design[30] and multivariate regression[31] techniques, we were able to improve both the yield and the chemoselectivity to 64% and 90%, respectively. Moreover an optimized procedure for industrial scale application was also developed.[32] A dehydrohalogenation method developed by Baughman and collaborators[37] was adopted for the preparation of the alkenol **5**, as the last step of the additional pathway utilizing potassium *tert*-butoxide as the reagent for the dehydrohalogenation reaction. Nevertheless, the alkenol **5** was isolated only in a poor yield (≈20%), which weakened the importance of this additional pathway even with the efficiency of the first step 7 and the use of the inexpensive decan-1,10-diol (**3**) as substrate. However, attempts to optimize this step by means of multivariate design and modeling[30,31] similar to step 7[32] of Scheme 1 has not yet been carried out.

A palladium on charcoal catalyzed hydrogenation was utilized for the synthesis of 10-(2,3,4-trimethoxy-6-methylphenyl)decan-1-ol (**7**). All fractions of the isomers from the Heck coupling (**6a**, **6b**, **12**) were subjected to hydrogenation conditions, and the olefin **12** was not reactive probably due to stereic reasons. The two reactive isomers **6a** and **6b** were successfully hydrogenated to provide 10-(2,3,4-trimethoxy-6-methylphenyl)decan-1-ol (**7**) in excellent yield (91%).

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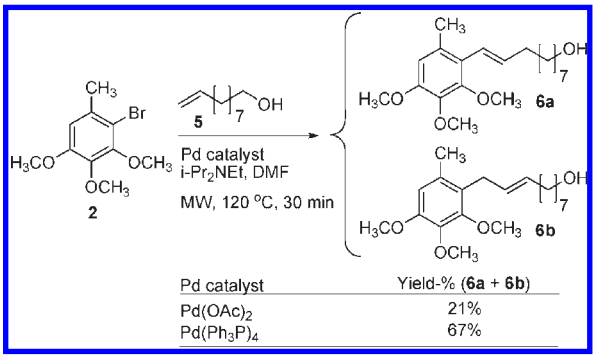
Table 1. Heck Coupling Reaction Conducted under Microwave Irradiation Conditions

	reaction conditions[a]					measured responses	
entry	catalyst	solvent	base	t [min]	T [°C]	y [%][g]	y_{total} [%][h]
1	$Pd(PPh_3)_4$[b]	DMF	i-Pr_2NEt	30	120	67	67
2	PEPSSI[b]	DMF	i-Pr_2NEt	30	120	14	14
3	$Pd(OAc)_2$[c]	DMF	i-Pr_2NEt	30	120	21	23
4	$Pd(OAc)_2$	DMF	i-Pr_2NEt	30	100	48	48
5	$Pd(OAc)_2$	DMSO	i-Pr_2NEt	15	135	26	29
6	$Pd(OAc)_2$	DMSO	i-Pr_2NEt	30	120	43	47
7	$Pd(PPh_3)_4$[b]	DMSO[d]	K_2CO_3[f]	10	100	55	55
8	$Pd(OAc)_2$	H_2O/EtOH[e]	K_2CO_3[f]	10	90	32	32
9	$Pd(OAc)_2$	H_2O/TBAI[d]	K_2CO_3[f]	10	90		
10	$Pd(OAc)_2$[b]	DMF	Et_3N	10	80		
11	$Pd(OAc)_2$	DMF	i-Pr_2NEt	30	120	33	38
12	$Pd(OAc)_2$[c]	DMF	i-Pr_2NEt	30	120	15	15
13	$Pd(OAc)_2$	DMF	i-Pr_2NEt	60	120	30	34
14	$Pd(OAc)_2$	DMF	i-Pr_2NEt	30	150	32	40
15	$Pd(OAc)_2$	DMF	i-Pr_2NEt	30	160	40	47
16	$Pd(OAc)_2$	DMF	i-Pr_2NEt	45	160	70	78

[a] General procedure: Substrate **2** (0.76 mmol, 0.2 g), 9-decen-1-ol **5** (1.25 mmol, 0.22 mL), catalyst (0.040 mmol, 9 mg), PPh_3 (0.080 mmol, 21 mg), base (1.25 mmol, 0.22 mL), and solvent (1 mL) were transferred to a thick walled Pyrex microwave vial that was closed with a silicon septum and subjected to microwave irradiation. [b] 0.020 mmol. [c] 0.060 mmol. [d] 2 mL/0.5 mmol. [e] 1 mL/1 mL. [f] 2 mmol. [g] Measured yield of the productive fraction of isomers. [h] Measured yield of all isomers (total sum of isomers).

Scheme 4. The Heck Coupling Reaction by Means of Microwave Irradiation

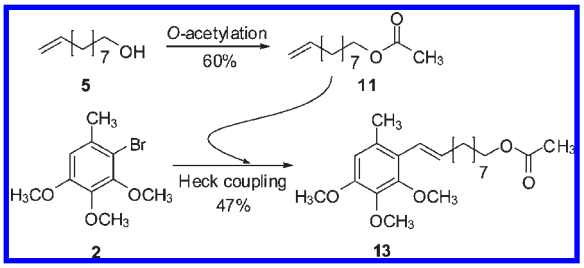


The next step of the synthetic path involves the oxidation of the aromatic ring of compound **7** to the corresponding benzoquinone framework **9**. The existence of the free hydroxyl group in the alkyl chain called for the introduction of a protecting group in order to prevent oxidation of the hydroxyl group. A solvent-free protocol previously disclosed by Phukan[38] involving the conversion of the free hydroxyl group to an *O*-acetyl group was utilized. The hydroxyl protection proceeded smoothly to provide 10-(2,3,4-trimethoxy-6-methylphenyl)decyl acetate (**8**) in a yield of 90%.

It is worth mentioning that an alternative path was also attempted, a synthetic pathway that was based on the use of Phukan protocol[38] for *O*-acetylation of dec-9-en-1-ol (**5**) followed by Heck coupling of dec-9-enyl acetate **11** with the aryl bromide **2** in order to prepare compound **13** (Scheme 5).

Dec-9-enyl acetate **11** was produced in good yield (60%), which, however, is slightly lower than in the step that compound **8** is produced, while product **13** was produced only in a moderate yield of 47%. Thus this pathway was abandoned.

Scheme 5. Alternative Pathway Leading to the Heck Product 13



Oxidation of compound **8** with the goal to produce the benzoquinone framework **9** was another critical step of our idebenone synthesis. Previously, our group[33] have disclosed a green high-yielding two-step telescoped oxidation process for the synthesis of coenzyme Q_0 (CoQ_0) using the aromatic compound **1** as substrate and hydrogen peroxide and nitric acid as the oxidizing agents in a two-step telescoped fashion. With this process, we adapted a protocol that oxidized the sterically crowded aromatic compound **8** to 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl acetate (**9**) by using hydrogen peroxide as the only oxidant (Scheme 6). The increased reactivity of the aromatic compound **8** compared to that of trimethoxytoluene **1** (as is used in the CoQ_0 process)[33] can be explained by the presence of the C_{10} alkyl side chain, which increases the electron density of the aromatic ring by acting as an extra electron donor. As a result, the phenol **8′** exhibits an increased reactivity towards oxidation that requires milder conditions than those used for trimethoxytoluene **1**.

The oxidation of the aromatic compound **8** proceeded with high conversion (>70%). However, the workup and purification of the target intermediate [10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl acetate, **9**] was challenging, but a nonoptimized protocol resulted in a modest yield of 45%.

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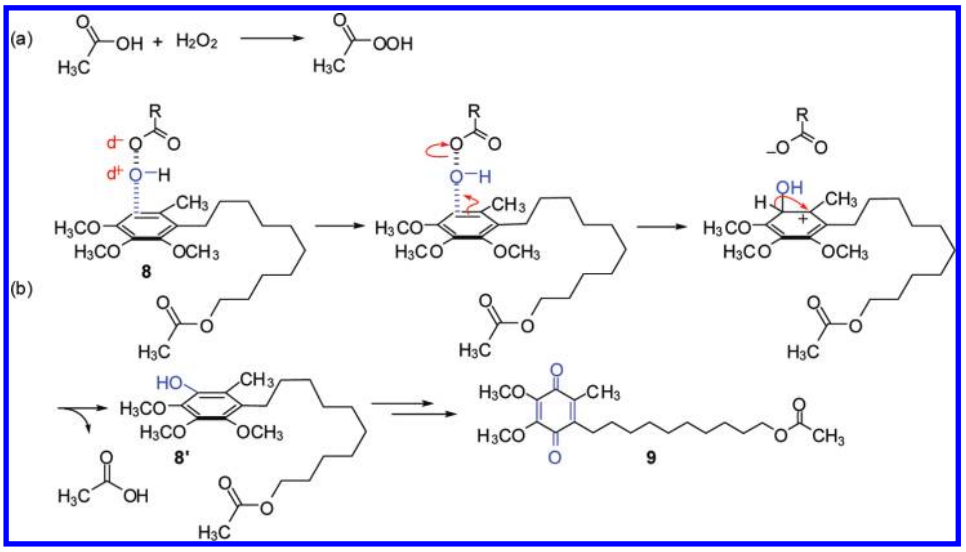
Scheme 6. Oxidation Process[a]



[a] Reaction a: Peracetic acid is produced in situ. Reaction b: The aromatic ring of 10-(2,3,4-trimethoxy-6-methylphenyl)decyl acetate (**8**) is oxidized to provide 10-(3-hydroxy-4,5,6-trimethoxy-2-methylphenyl)decyl acetate (**8′**) that subsequently is oxidized to 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl acetate (**9**).

The final step of the synthetic path (step 6 of Scheme 1) involves the deprotection of **9** by treatment with sodium carbonate in a methanol−water mixture at room temperature, which gave target molecule idebenone (**10**) in high yield (85%).

Additional studies related to the work described herein are either completed or in progress, and include (1) organic solvent nanofiltration for removal of trace quantities of palladium after the Heck coupling reactions (completed), (2) investigation of continuous flow processes for the bromation of the aromatic compound **1** (step 1, Schme 1), and finally (3) optimization of lowest yielding step 5 (oxidation) using a pre-experimental design with the future goal of optimization by means of statistical experimental design and multivariate regression, similar to the optimization study previously reported by us for the bromination of diol **3** (step 7 of Scheme 1).[32]

CONCLUSIONS

A six-step total synthesis leading to idebenone (**10**) was designed, developed, and partly optimized. Overall isolated yield involving the reaction steps 1−6, Scheme 1, was 20%, which corresponds to an average step yield of 76%. An additional two steps pathway that lead to one of the starting reagents, were also investigated but not included in the final process. Key steps including a green brominating process (>95% yield), a palladium-catalyzed Heck coupling reaction mediated by microwave irradiation (67% yield), and an environmentally benign oxidation process transferring an aromatic intermediate to the corresponding benzoquinone framework (≈70% yield in reaction mixture) have been designed and developed.

EXPERIMENTAL SECTION

General Methods. Mass spectra were acquired on a GC-MS instrument using a gas chromatograph equipped with fused silica column (L 30 m, 0.25 mm i.d., 0.25 μm film thickness) and He as carrier gas. ^{1}H NMR spectra were recorded on an NMR spectrometer operating at 400 MHz for ^{1}H and 101 MHz for ^{13}C. Chemical shifts were referred to the solvent peak of $CDCl_3$/$CHCl_3$ (δH = 7.26 ppm, δC = 77.2 ppm). Starting materials and reagents were purchased commercially and used without further purification. The reaction products were analyzed by GC-MS. Silica gel 60 (0.040−0.0063 mm) and alumina oxide (basic, grade I) was used for the flash chromatography. F-254 TLC plates were used in order to follow the progress of the reactions, to determine the purity of substance, and to identify the various fractions from the flash chromatography separation. The spots of substances on the thin layer were visualized under UV light at λ = 254 nm. The elemental analysis was performed by an VarioEL CHNS (by Elementar Analysensystem GmbH, serial no. 11053037). The experiments that were performed using microwaves as the energy source were conducted by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0−400 W at 2.45 GHz, in the temperature range of 40-250 °C, a pressure range of 0−20 bar (2 MPa, 290 psi) with reactor vial volumes of 0.2−20 mL.

2-Bromo-3,4,5-trimethoxy-1-methylbenzene, 2 [72326-72-8].[34]. Nitric acid (65%, 1.6 mmol, 0.11 mL) was added to acetic anhydride (5.0 mL). This mixture was, by means of a syringe-pump, added dropwise over a period of 30 min to a mixture of 3,4,5-trimetoxytoluene (**1**, 1.5 mmol) and KBr (2.0 mmol) in acetic anhydride (2.5 mL). After complete addition of the oxidant, the reaction mixture was stirred for another 45 min at 20 °C. Water (10 mL) was added to the reaction mixture and mixed for 30−40 min at room temperature. The quenched reaction mixture was then extracted with ethyl ether (3 × 10 mL). The organics were combined and washed with saturated brine solution, dried over sodium sulphate, and filtered, and the solvent was then removed under reduced pressure to achieve 2-bromo-3,4,5-trimethoxy-1-methylbenzene (**2**) in a yield of >95% (colorless-yellowish oil). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.36 [s, 3H], 3.83 [s, 3H], 3.85 [s, 3H], 3.88 [s, 3H], 6.60 [s, 1H]. ^{13}C NMR (200 MHz): δ 22.43, 56.67, 61.52, 106.62, 134.22, 136.48, 153.68. MS m/z (%):

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262 (100), 260 (99), 217 (25), 202 (40), 166 (20), 151 (25), 138 (47), 123 (38), 108 (12), 77(20), 63 (15), 51 (27). TLC system: hexane:ethyl acetate = 11:1, R_f 0.45.

10-Bromodecan-1-ol, 4 [53463-68-6].[35]. The same procedure as used by Goverdhan et al.[36] was followed. A mixture of 1,10-decanediol (**3**, 4.23 mmol, 0.736 g), 48% aq hydrobromic acid (9.13 mmol, 0.74 g, 0.5 mL), and tetrabutylammonium bromide (0.84 mmol, 0.27 g) was added in a heavy walled Pyrex microwave vial (2−5 mL) covered with a silicon septum and exposed to microwave irradiation for 5 min at 100 °C by means of a MicroWell10 single-mode microwave cavity (Biotage). Then the reaction mixture was cooled and extracted with dichloromethane (3 × 10 mL). The product **4** was purified from the dibrominated derivative by using flash chromatography and isolated in a yield of 45%. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.26 [br s, 10H], 1.38 [qn, 2H], 1.52 [qn, 2H], 1.81 [qn, 2H], 1.89 [s, 1H, interchangeable with D_2O], 3.36 [t, 2H], 3.58 [t, 2H]. ^{13}C NMR (200 MHz): δ 26.13, 28.56, 29.14, 29.76, 29.83, 33.20, 33.23, 34.44, 63.48. MS m/z (%): 192 (6), 190 (7), 164 (14), 162 (16), 150 (46), 148 (48), 137 (22), 135 (23), 97 (80), 83 (86), 69 (100), 55 (94). IR (FT): ν 3327, 2923, 2852, 1463, 1371, 1256, 1054, 721, 644, 561. TLC system: hexane:ethyl acetate = 8:2, R_f 0.40.

Dec-9-en-1-ol, 5 [13019-22-2]. The same procedure as used by Baughman et al.[37] was followed. A solution of 10-bromodecan-1-ol (**4**, 4 mmol, 0.95 g) in 1:1 THF/toluene was prepared in a round-bottomed flask. The flask was cooled to 0 °C and then *t*-BuOK (6.51 mmol, 0.73 g) was added over a period of 30 min. After the addition the reaction mixture was quenched with 1 M HCl (50 mL). The organic phase was extracted with diethyl ether (3 × 50 mL), washed with sodium hydrogen carbonate (2 × 80 mL) then with saturated brine solution, dried over sodium sulphate, and filtered and the solvent was then removed under reduced pressure. The product **4** was purified by means of flash chromatography and isolated in the scarce yield of 20%. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.29 [br, s, 11H], 1.55 [qn, 2H], 2.02 [q, 2H], 3.63 [t, 2H], 4.91 [dqn, 1H], 4.98 [dq, 1H], 5.80 [m, 1H]. MS m/z (%): 156 (7), 138 (32), 109 (76), 95 (86), 81 (98), 67 (100). TLC system: hexane:ethyl acetate = 7:4, R_f 0.47.

10-(2,3,4-Trimethoxy-6-methylphenyl)dec-9-en-1-ol, 6a [new] + 10-(2,3,4-Trimethoxy-6-methylphenyl)dec-8-en-1-ol, 6b [new]. A mixture of 2-bromo-3,4,5-trimethoxytoluene (**2**, 7.66 mmol), dec-9-en-1-ol (**5**, 12.5 mmol, 2.3 mL), triethylamine (14.3 mmol, 2 mL), palladium acetate (0.20 mmol), and triphenylphosphine (0.80 mmol) was added to a Shield Tube. The mixture was flashed with nitrogen for 3 min, shield, and then heated in an oil bath at 120 °C for 3 days.[29a] After the end of the reaction course the cold reaction mixture was filtered through Celite, in order to remove the catalyst, and the filter was washed with diethyl ether (3 × 10 mL). The organic phase was washed with water and dried with anhydrous sodium sulphate. Subsequently the solvent was removed under vacuum and the product **6** was purified, by means of flash chromatography, and isolated as a mixture of position isomers regarding the double bond, in a yield of 60% (measured yield by means of ^{1}H NMR and 3,4-dimethoxyacetophenone as internal standard). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.28 [br, s, 9H], 1.54 [qn, 2H], 1.95 [q, 2H], 2.23 [s, 3H], 3.27 [d, 2H], 3.62 [t, 2H], 3.80 [t, 9H], 5.39 [m, 2H], 6.50 [s, 1H]. MS m/z (%): 336 (75), 221 (56), 195 (100), 190 (80), 182 (95), 167 (25), 91 (22), 79 (12), 55 (34). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 70.88; H, 9.66. TLC system: hexane:ethyl acetate = 8:2, R_f 0.32.

10-(2,3,4-Trimethoxy-6-methylphenyl)decan-1-ol, 7 [new]. A mixture of 10-(2,3,4-trimethoxy-6-methylphenyl)dec-9-en-1-ol (**6**, 0.44 mmol, 0.148 g), ethanol (5 mL), and 10% palladium on charcoal (15 mg) was added to a round-bottomed flask equipped with a three-way valve. The reaction mixture was stirred at 25 °C for 3 h under hydrogen atmosphere with the use of a balloon. After the end of the reaction course the mixture was filtered through Celite in order to remove the catalyst and the filter was washed with diethyl ether (20 mL). The solvent form the organic phase was removed under reduced pressure to give product **7** as a colorless oil in a yield of 91% (measured yield by means of ^{1}H NMR and 3,4-dimethoxyacetophenone as internal standard). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.29 [br s, 15H], 1.56 [qn, 2H], 2.25 [s, 3H], 2.52 [t, 2H], 3.64 [t, 2H], 3.84 [t, 9H], 6.48 [s, 1H]. ^{13}C NMR (200 MHz): δ 20.15, 26.37, 27.37, 30.07, 30.12, 30.18, 30.24, 30.70, 31.02, 33.46, 56.58, 61.36, 61.68, 63.75, 109.97, 128.08, 132.07, 140.88, 151.52, 152.52. MS m/z (%): 338 (48), 195 (100), 180 (82), 165 (14), 150 (19), 137 (14), 91(13), 79 (10), 55 (20). IR (FT): ν 3403, 2923, 2852, 1737, 1676, 1597, 1493, 1463, 1403, 1331, 1269, 1236, 1196, 1121, 1071, 1027, 987, 922, 877, 829, 767, 723, 616, 568. Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 69.82; H, 9.61. TLC system: hexane: ethyl acetate = 7:3, R_f = 0.40.

10-(2,3,4-Trimethoxy-6-methylphenyl)decyl Acetate, 8 [new]. The same procedure as used by Phukan[38] was followed. A mixture of 10-(2,3,4-trimethoxy-6-methylphenyl)decan-1-ol (**7**, 1 mmol, 0.338 g), acetic anhydride (5 mmol, 0.47 mL), and iodine (0.1 mmol, 10.6 mg) was added to a round-bottomed flask equipped with a reflux condenser. The reaction mixture was stirred at 25 °C for 1 h. Water (10 mL) was then added and the quenched reaction mixture was extracted with diethyl ether (3 × 10 mL). The organic phases were combined and washed first with sodium thiosulphate (10 mL, 0.1 M), then with sodium hydrogen carbonate (3 × 10 mL), and finally with saturated brine solution, dried over sodium sulphate, and filtered and the solvent was then removed under reduced pressure to achieve **8** as a colorless oil in a yield of 90% (measured yield by means of ^{1}H NMR and 3,4-dimethoxyacetophenone as internal standard). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.29 [br, s, 14H], 1.61 [qn, 2H], 2.04 [s, 3H], 2.25 [s, 3H], 2.52 [t, 3H], 3.84 [t, 9H], 4.05 [t, 2H], 6.48 [s, 1H]. ^{13}C NMR (200 MHz): δ 19.91, 21.43, 26.32, 27.13, 29.01, 29.67, 29.88, 29.93, 30.47, 30.79, 56.34, 61.13, 61.43, 65.08, 109.73, 127.82, 131.83, 140.64, 151.28, 152.34, 171.72. MS m/z (%): 380 (84), 320 (25), 306 (40), 195 (100), 180 (98), 165 (51), 150 (76), 137 (42), 105 (39), 91 (36), 79 (32), 55 (41). IR (FT): ν 2924, 2853, 1738, 1600, 1494, 1464, 1404, 1364, 1332, 1235, 1196, 1123, 1033, 988, 923, 829, 722, 606, 561, 542. Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 68.64; H, 9.34. TLC system: hexane:ethyl acetate = 8:2, R_f 0.56. Bp 115−120 °C.

10-(4,5-Dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl Acetate, 9 [58186-28-0].[39]. A mixture of 10-(2,3,4-trimethoxy-6-methylphenyl)decyl acetate (**8**, 3 mmol, 1.14 g), acetic acid (3 mL), hydrogen peroxide (35%, 9 mmol, 0.90 mL), and *p*-toluenesulfonic acid (0.11 mmol, 57 mg) was added to a round-bottomed flask equipped with a reflux condenser and stirred at 75 °C for 25 min. Then the warm reaction mixture was poured in ice-cold water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phases were combined, washed with water (4 × 100 mL), dried over sodium sulphate, and filtered and the solvent was then removed under reduced pressure to give crude product **9** as a light red oil in a

yield of 70%. Product was further purified by means of flash chromatography (Hex:EtOAc = 8:2) and isolated in a yield of 45%. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.27 [br, s, 14H], 1.61 [qn, 2H], 2.01 [s, 3H], 2.04 [s, 3H], 2.44 [t, 2H], 3.98 [s, 6H], 4.06 [t, 2H]. ^{13}C NMR (200 MHz): δ 12.31, 21.42, 26.30, 26.80, 29.01, 29.13, 29.62, 29.74, 29.80, 29.86, 30.21, 61.54, 65.04, 139.07, 143.49, 144.72, 171.64, 184.56, 185.12. MS m/z (%): 380 (20), 338 (30), 306 (12), 197 (100), 183 (76), 167 (17), 153 (24), 81 (17), 67 (23), 55 (37). TLC system: hexane: ethyl acetate = 8:2, R_f 0.32.

2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione (Idebenone), 10 [58186-27-9].[39]. Sodium carbonate (0.095 mmol, 11 mg) was added to a solution of 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dienyl)decyl acetate (**9**, 0.2 mmol, 76.2 mg) in methanol (1.3 mL) and water (0.32 mL) at 25 °C. The mixture was stirred at 25 °C for 20 h. Water (10 mL) was then added and the quenched reaction mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, washed with a saturated solution of sodium chloride (2 × 10 mL), dried over sodium sulphate, and filtered and the solvent was then removed under reduced pressure to achieve product **10** as a yellow-red oil in a yield of 80% (85% measured yield by means of ^{1}H NMR and 3, 4-dimethoxyacetophenone as internal standard). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.28 [br, s, 14H], 1.53 [br, s, 2H], 2.01 [s, 3H], 2.44 [t, 2H], 3.64 [t, 2H], 3.98 [d, 6H]. ^{13}C NMR (200 MHz): δ 12.57, 26.35, 27.04, 29.35, 29.92, 30.02, 30.16, 30.44, 33.44, 61.80, 63.73, 139.33, 143.74, 144.94, 184.81, 185.38. MS m/z (%): 338 (14), 209 (20), 195 (100), 180 (30). IR (FT): ν =3399, 2925, 2853, 1738, 1646, 1609, 1494, 1455, 1376, 1332, 1264, 1235, 1203, 1157, 1119, 1058, 947, 745. TLC system: hexane:ethyl acetate = 8:4, R_f 0.30.

Dec-9-enyl Acetate, 11 [50816-18-7].[40] The same procedure as used by Phukan[38] was followed. A mixture of dec-9-en-1-ol (**5**, 1 mmol, 0.178 mL), acetic anhydride (5 mmol, 0.47 mL), and iodine (0.1 mmol, 10.6 mg) was added to a round-bottomed flask equipped with a reflux condenser. The reaction mixture was stirred at 25 °C for 1 h. Water (10 mL) was then added and the quenched reaction mixture was extracted with dichloromethane (3 × 10 mL). The organic phases were combined and washed first with sodium thiosulphate (10 mL, 0.1 M), then with sodium hydrogen carbonate (3 × 10 mL), and finally with saturated brine solution, dried over sodium sulphate, and filtered and the solvent was then removed under reduced pressure to achieve **11** in a yield of 67%. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.31 [br, s, 10H], 1.62 [qn, 2H], 2.04 [q, 2H], 2.05 [s, 3H], 4.05 [t, 2H], 4.94 [dqn, 1H], 5.00 [dq, 1H], 5.81 [m, 1H]. ^{13}C NMR (200 MHz): δ 21.6, 26.5, 29.2, 29.5, 29.6, 29.8, 29.9, 34.4, 65.3, 114.8, 139.8, 171.9. MS m/z (%): 198 (4), 155 (4), 138 (84), 123 (42), 108 (98), 94 (100), 79 (98), 66 (94). IR (FT): ν 3075, 2930, 2854, 1740, 1642, 1469, 1433, 1391, 1363, 1229, 1036, 992, 908, 721, 637, 609. TLC system: hexane:ethyl acetate = 7:3, R_f 0.87.

■ ASSOCIATED CONTENT

Supporting Information. General procedures, ^{1}H NMR spectra (**2**, **4**−**11**), ^{13}C NMR spectra (**2**, **4**, **7**−**11**), IR spectra (**4**, **7**, **8**, **10**, **11**), and DEPT-135 spectra (**7**, **8**, **9**, **10**). This material is available free of charge via the Internet at http://pubs.acs.org.

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