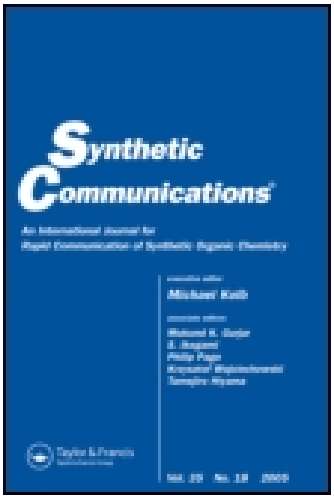


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

New Efficient Synthesis of Ubiquinones

Paolo Bovicelli [a] , Giorgio Borioni [a] , Danilo Fabbrini [a] & Maurizio Barontini [a]
[a] CNR Institute of Biomolecular Chemistry-Rome Section, Sapienza University of Rome, Department of Chemistry , Rome, Italy
Published online: 28 Jan 2008.

To cite this article: Paolo Bovicelli , Giorgio Borioni , Danilo Fabbrini & Maurizio Barontini (2008) New Efficient Synthesis of Ubiquinones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:3, 391-400, DOI: 10.1080/00397910701771066

To link to this article: http://dx.doi.org/10.1080/00397910701771066

Synthetic Communications®, 38: 391–400, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701771066

New Efficient Synthesis of Ubiquinones

Paolo Bovicelli, Giorgio Borioni, Danilo Fabbrini, and Maurizio Barontini

CNR Institute of Biomolecular Chemistry–Rome Section, Department of Chemistry, Sapienza University of Rome, Rome, Italy

Abstract: A strategy for the ecofriendly and high-yielding synthesis of ubiquinones starting from simple materials and using mild conditions is reported. CoQ_1, CoQ_2, CoQ_3, and CoQ_9 were prepared.

Keywords: coenzyme Q, halogenations, iridol, ubiquinones

The development of new antioxidant drugs is of primary importance to improve the pharmacological treatment of diseases in which oxidative stress plays a pathological role, such as asthma, rheumatoid arthritis, Alzheimer's disease, cataracts, and atherosclerosis.

A cofactor for all these diseases seems to be the lack of equilibrium between oxidative processes and systems of defense in our organism. In this case, the intake of hexogen antioxidants with the diet is essential to prevent the development of pathologies.[1]

One of the most important classes of antioxidants is ubiquinones.[2] These compounds, commercially known as coenzymes Q_n (CoQ_n), are constituted by a dimethoxy-benzoquinone structure carrying an all-*trans* polyprenyl chain.[3] They are present in almost all kinds of life[4] in which mechanisms of electron transfer are involved.[5] Ubiquinones are powerful antioxidants and as such are commonly used in diet integrators.[6] One of

Received in the U.K. May 3, 2007
Address correspondence to Paolo Bovicelli, CNR Institute of Biomolecular Chemistry–Rome Section, Department of Chemistry, Sapienza University of Rome, P.le A. Moro 5, Box 34, I-00185 Rome (Italy). E-mail: paolo.bovicelli@uniroma1.it

the most important ubiquinones is CoQ_{10}, which is an endogen for the human species[7] and is also as employed as anti-aging compound and nutrient in creams to preserve the epithelium from damage due to aggressive environmental oxidants.[8]

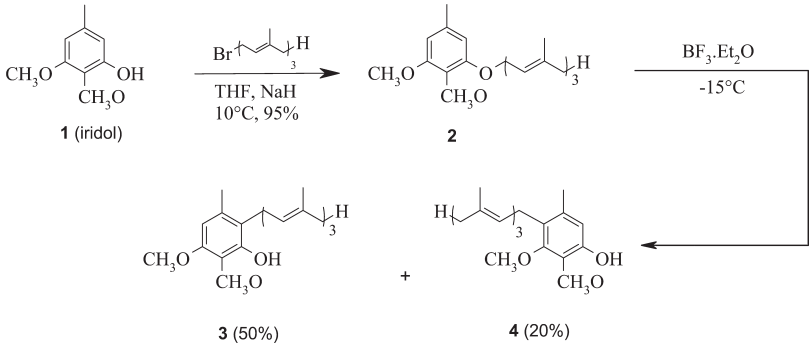
Because of these properties, the demand for ubiquinones, especially for the natural CoQ_{10}, is increasing daily, though all other ubiquinones have powerful antioxidant properties as well and could be used as hexogen species. The development of new, simple, and sustainable syntheses of such compounds is highly attractive.

Recently, we described a new approach for the synthesis of ubiquinones, exploiting a method for the oxyfunctionalization of aromatic compounds developed in recent years.[9] In this synthesis, iridol is the compound we use as a key intermediate, and a Lewis acid–promoted allyl rearrangement on a suitable ether derived from iridol is the key step.[10]

In that procedure, BF_3 etherate was used at $-20^{\circ}C$, and the allyl shift occurred either onto the *ortho* or the *para* positions with respect to the initial position of the ethereal moiety. The main problem with this procedure is that the regioselectivity of the isoprenyl chain rearrangement is low (Scheme 1).

To avoid the competitive *para*-rearrangement, we planned to block the C-6 position of iridol, making use of the bromination–methanolysis procedure, but under all the conditions we tried, the bromination reaction was not selective, and thus a mixture of mono- and dibromo derivatives of iridol was obtained.

Subsequently, we submitted 3,4,5-trimethoxytoluene to a formylation reaction followed by an easy oxidation with hydrogen peroxide, which led to a phenol derivative. This oxidation step, known as the Dakin reaction,[11] is much more efficient and is easier to carry out than the corresponding Baeyer–Villiger one; furthermore, it can be performed in a one-pot procedure.

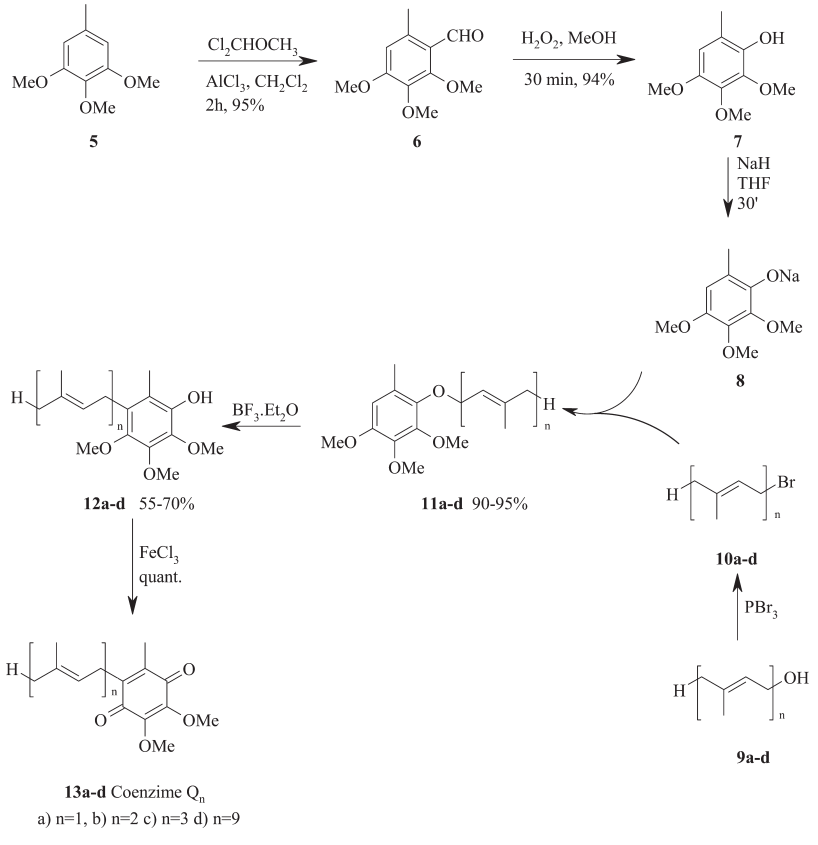


Scheme 1.

The sodium salt of the obtained phenol was reacted with a suitable allyl bromide to give the corresponding ether, and further treatment with BF_3 etherate led to the expected product upon rearrangement of the allyl side chain onto the vacant *meta* position (Scheme 2). This kind of rearrangement is possible because the *meta* position is the only free one, and its mechanism is not concerted.

By this method, good results were obtained for every allyl side chain we used. In the case of the solanesyl group, yields were lower than those obtained for shorter chains but still good. Worthy of note is that in no case was isomerization of the allyl chain evidenced by our analytical methods.

Compounds **11a–d** were prepared by etherification of sodium phenoxide, **8**, with the suitable allyl bromide. Isopropyl and geranyl bromide are commercially available. Farnesyl bromide was previously prepared by treating farnesol with PBr_3; solanesyl bromide was prepared by treating solanesol with PBr_3. Solanesol was extracted from a waste powder sample



Scheme 2.

obtained from a tobacco manufacturer.[12] The extraction was carried out by shaking the powder with hexane for 2 h and filtering the mixture. A rapid chromatography on silica gel, eluting with hexane, gave a sufficiently pure product.

The corresponding ethers **11a–d** were obtained in all cases in yields higher than 90%. Rearrangement of aryl-allyl ethers were performed in good yields (55–70%) in the presence of $BF_3 \cdot Et_2O$ as the Lewis acid, and the final oxidation step was carried out by treating **12a–d** with $FeCl_3$ (an almost quantitative process). $FeCl_3$ is the simplest oxidant we used, but a number of other oxidants gave the same result.

Our research of convenient methods to prepare ubiquinones prompted us to develop a synthetic scheme in which an allyl shift promoted by Lewis acids is the key step. At first iridol was used as substrate, but the rearrangement of the corresponding allyl ethers occurred satisfactorily only in the case of short isoprenyl chains. The finding that the allyl shift can also occur onto a vacant *meta* position led us to use 2-hydroxy-3,4,5-trimethoxytoluene as the phenol to be etherified and rearranged. This strategy worked well for every allyl chain we used, and CoQ_1, CoQ_2, CoQ_3, and CoQ_9 were prepared in good to excellent yields. The only limitation of this method, which in principle allows the preparation of every ubiquinone, is the availability of the suitable allyl alcohol; however, methods are known to extend isoprenyl chains. Thus the method can be considered of general value for the synthesis of every ubiquinone, CoQ_{10} included.

EXPERIMENTAL

2,3,4-Trimethoxy-6-methylbenzaldehyde (6)

In a round-bottomed flask equipped with a dropping funnel, 256 mg (1.4 mmol) of 3,4,5-trimethoxytoluene and 386 mg (2.9 mmol) of $AlCl_3$ were vigorously stirred in 20 mL of anhydrous CH_2Cl_2 in an ice bath under an inert atmosphere. Then 0.11 mL (138 mg, 1.2 mmol) of α,α-dichloromethyl methyl ether previously dissolved in 5 mL of anhydrous CH_2Cl_2 was added dropwise. The temperature was then allowed to raise to 25°C, and after an additional 2 h, the reaction as monitored by thin-layer chromatography (TLC) (9:1 hexane/EtOAc) was complete, leading to a unique product. The reaction was then quenched with ice until its color turned light yellow. The obtained mixture was concentrated, and the residue was extracted with EtOAc. The organic solution was washed with brine until neutrality and dried over Na_2CO_3, and the solvent was removed under a vacuum. The product (280 mg, 95%), obtained as a colorless oil, was pure enough for the next step. Physicochemical data were consistent with those reported in the literature.[13]

2,3,4-Trimethoxy-6-methylphenol (7)

Compound **7** (329 mg, 1.5 mmol) and 25 mg (0.2 mmol) of $NaHSO_4$ were mixed with 15 mL of MeOH. To the mixture, 0.22 mL (3.8 mmol) of a 50% solution of hydrogen peroxide was added. After 30 min, the substrate was completely converted into a single product. MeOH was removed under a vacuum at room temperature, and the crude was extracted with EtOAc. The organic solution was washed with brine until neutrality, then dried over Na_2SO_4 and evaporated under reduced pressure to give phenol **7** (280 mg, 94%) as a practically pure compund. Physicochemical data agreed with those of the literature.[14]

2,3,4-Trimethoxy-6-methylphenyl Prenyl Ether (11a)

To a solution of **7** (289 mg, 1.47 mmol) dissolved in THF (10 mL), NaH (53 mg, 2.21 mmol) was added, and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and a white power was obtained. A solution of prenyl bromide (0.20 mL, 1.76 mmol) in THF (5 mL) was added dropwise to a solution of the sodium phenate **8** in 5 mL of anhydrous THF cooled in an ice bath. Then the temperature was allowed to raise to 25°C, and the mixture was stirred for 12 h. The mixture was quenched with a 5% solution of NH_4Cl and diluted with EtOAc (20 mL), and the two phases separated. The aqueous layer was extracted twice with EtOAc (20-mL portions), and the combined organic solutions were washed with brine until neutrality (10-mL portions). The resulting solution was dried over anhydrous Na_2SO_4, and the solvent was removed under a vacuum. The crude product was purified by flash chromatography (9:1 hexane/EtOAc). Compound **11a** (370 mg, 95%) was obtained as a light yellow oil. IR (CCl_4, cm^{-1}): 1200, 1660. ^1H NMR ($CDCl_3$) δ (ppm): 1.71 (3H, d, $J = 1$ Hz), 1.78 (3H, d, $J = 0.9$ Hz), 2.22 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 3.92 (3H, s), 4.41 (2H, d, $J = 7.3$ Hz), 5.55 (1H, t-sett, $J = 0.9$, 7.3 Hz), 6.44 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.3, 25.6, 26.3, 39.6, 56.0, 61.0, 61.1, 69.5, 108.3, 120.2, 124.0, 131.8, 140.8, 141.2, 147.2. HR-MS (ES Q-TOF) calcd. for $C_{15}H_{22}O_4$ $(M + Na)^+$: 289.1416. Found: 289.1710.

Geranyl 2,3,4-Trimethoxy-6-methylphenyl Ether (11b)

NaH (59 mg, 2.47 mmol) was added to a solution of **7** (325 mg, 1.65 mmol) dissolved in THF (10 mL). The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure until a white power was obtained. Anhydrous THF (5 mL) was added, the mixture was cooled in an ice bath, and then a solution of geranyl bromide (0.54 mL, 2.48 mmol) in THF (5 mL) was added dropwise. The mixture was warmed

to room temperature and stirred for 12 h. The reaction was worked up as described for **11a**. Compound **11b** (512 mg, 93%) was obtained as a light yellow oil. IR (CCl_4, cm^{-1}): 1220, 1460, 1660. ^1H NMR ($CDCl_3$) δ (ppm): 1.59 (3H, s), 1.68 (3H, s), 2.07 (3H, s), 2.08 (4H, broad), 2.22 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.44 (2H, d, $J = 6.6$ Hz), 5.09 (1H, m), 5.54 (1H, br t, $J = 6.6$ Hz), 6.43 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.5, 16.2, 17.6, 25.6, 26.3, 39.6, 56.1, 61.0, 61.1, 69.5, 108.3, 120.3, 123.9, 126.3, 131.6, 140.8, 141.2, 144.3, 147.2, 149.0. HR-MS (ES Q-TOF) calcd. for $C_{20}H_{30}O_4$ $(M + Na)^+$: 357.2042. Found: 357.2226.

Farnesyl 2,3,4-Trimethoxy-6-methylphenyl Ether (11c)

NaH (47 mg, 1.95 mmol) was added to a solution of **7** (257 mg, 1.30 mmol) dissolved in THF (10 mL). The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure until a white power was obtained. Anhydrous THF (5 mL) was added, the mixture was cooled in an ice bath, and then a solution of farnesyl bromide (0.49 mL, 1.70 mmol) in THF (5 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 12 h. The reaction was worked up as described for **11a**. Compound **11c** (495 mg, 95%) was obtained as a light yellow oil. IR (CCl_4, cm^{-1}): 1215, 1470, 1660, 2910. ^1H NMR ($CDCl_3$) δ (ppm): 1.60 (3H, s), 1.68 (3H, s), 1.70 (3H, s), 2.10 (8H, m), 2.22 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 3.92 (3H, s), 4.45 (2H, d, $J = 6.6$ Hz), 5.09 (2H, m), 5.56 (1H, t, $J = 6.6$ Hz), 6.43 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 16.0, 16.2, 16.3, 17.6, 25.6, 26.3, 26.7, 39.6, 39.7, 56.1, 61.0, 61.1, 69.6, 108.4, 120.4, 123.9, 124.3, 126.3, 131.2, 135.3, 141.0, 141.2, 144.4, 147.3, 149.0. HR-MS (ES Q-TOF) calcd. for $C_{25}H_{38}O_4$ $(M + Na)^+$: 425.2668. Found: 425.2724.

2,3,4-Trimethoxy-6-methylphenyl Solanesyl Ether (11d)

Solanesol (0.83 mL, 1.18 mmol) in THF (1 mL) at $-5^\circ C$ was treated with a solution of PBr_3 (0.38 mmol) in THF (1 mL). After 1 h, the mixture was diluted with a 1:1 solution of hexane and diethyl ether (5 mL). The organic layer was washed twice with a 5% solution of $NaHCO_3$ (3 mL) and brine (3 mL). The organic phase was then dried over Na_2SO_4, and the solvent was removed under a vacuum. The residue was taken up in anhydrous THF (5 mL) and added dropwise at $0^\circ C$ to a solution of **8** (278 mg, 0.79 mmol) in THF (10 mL) prepared as for **11a**–**c**. The mixture was stirred at room temperature for 12 h and then treated with a 5% solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc (10 mL portions); the organic solutions were combined and washed with brine until neutrality (3–4 × 5-mL portions). The final solution was dried over Na_2CO_3, and the

solvent was removed under a vacuum. By flash chromatography (95:5 hexane/EtOAc), a pure product (575 mg, 90%) was obtained as a yellow-brown oil. IR (neat, cm^{-1}): 1200, 1650. ^1H NMR ($CDCl_3$) δ (ppm): 1.60 (24H, br s), 1.67 (3H, br s), 1.69 (3H, br s), 1.95–2.05 (32H, m), 2.22 (3H, s), 3.81 (3H, s), 3.86 (3H, s) 3.93 (3H, s), 4.44 (2H, d, $J = 6.6$ Hz), 5.05–5.10 (8H, m), 5.56 (1H, t, $J = 6.6$ Hz), 6.44 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 16.0 (br), 16.26, 16.33, 17.6, 25.6, 26.3, 26.7 (br), 39.7 (br), 56.1, 61.05, 61.2, 69.6, 108.3, 120.3, 123.8, 124.2, 124.3 (br), 124.4, 126.3, 131.2, 134.9, 135 (br), 135.3, 140.9, 141.3, 144.3, 149.05. HR-MS (ES Q-TOF) calcd. for $C_{55}H_{86}O_4$ $(M + Na)^+$: 833.6424. Found: 833.6518.

2,3,4-Trimethoxy-6-methyl-5-prenylphenol (12a)

The prenyl ether **11a** (361 mg, 1.36 mmol) dissolved in 5 mL of Et_2O was treated with $BF_3 \cdot Et_2O$ (1.72 mL, 13.6 mmol) at room temperature. After 30 min, a saturated solution of NaCl (10 mL) was added, and the mixture was extracted three times with EtOAc (10 mL). The organic extracts were washed with brine until neutrality, dried over anhydrous Na_2SO_4, and brought to dryness under a vacuum. By flash chromatography (9:1 hexane/EtOAc), the desired product (253 mg, 70%) was obtained as a light yellow oil. IR (CCl_4, cm^{-1}): 1200, 1650, 3470. ^1H NMR ($CDCl_3$) δ (ppm): 1.69 (3H, d, $J = 1.5$ Hz), 1.78 (3H, d, $J = 1.3$ Hz), 2.14 (3H, s), 3.32 (2H, d, $J = 6.6$ Hz), 3.76 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 5.05 (1H, m), 5.64 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 11.3, 17.9, 25.6 (2C), 60.7, 61.1, 61.2, 117.4, 123.0, 129.5, 131.3, 137.7, 143.3, 143.5, 144.3. HR-MS (ES Q-TOF) calcd. for $C_{15}H_{22}O_4$ $(M + Na)^+$: 289.1416. Found: 289.1606.

5-Geranyl-2,3,4-trimethoxy-6-methylphenol (12b)

The geranyl ether **11b** (424 mg, 1.27 mmol) dissolved in 5 mL of Et_2O was treated with $BF_3 \cdot Et_2O$ (1.61 mL, 12.7 mmol) at room temperature. After 30 min, a saturated solution of NaCl (10 mL) was added, and the mixture was extracted three times with EtOAc (10 mL). The organic extracts were washed with brine until neutrality and dried over anhydrous Na_2SO_4, and the solvent was stripped off under a vacuum. By flash chromatography (9:1 hexane/EtOAc), the desired product (318 mg, 75%) was obtained as a light brown oil. IR (CCl_4, cm^{-1}): 1205, 1650, 3465. ^1H NMR ($CDCl_3$) δ (ppm): 1.58 (3H, s), 1.65 (3H, s), 1.76 (3H, s), 2.01 (4H, m), 2.13 (3H, s), 3.33 (2H, d, $J = 6.6$ Hz), 3.76 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 5.00–5.10 (2H, br), 5.63 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 11.3, 16.1, 17.6, 25.5, 25.6, 26.6, 39.7, 60.7, 61.1, 61.2, 117.5, 123.0, 124.3, 129.7, 131.3, 134.9, 137.7, 143.3, 143.5, 144.3. HR-MS (ES Q-TOF) calcd. for $C_{20}H_{30}O_4$ $(M + Na)^+$: 357.2042. Found: 357.2226.

5-Farnesyl-2,3,4-trimethoxy-6-methylphenol (12c)

Farnesyl ether **11c** (180 mg, 0.45 mmol) dissolved in 3 mL of Et_2O was treated with $BF_3 \cdot Et_2O$ (0.56 mL, 4.50 mmol) at room temperature. After 30 min, a saturated solution of NaCl (6 mL) was added, and the mixture was extracted three times with EtOAc (6 mL). The combined extracts were washed with brine until neutrality, dried over anhydrous Na_2SO_4, and brought to dryness under a vacuum. Upon flash chromatography (9:1 hexane/EtOAc), the desired product (126 mg, 70%) was obtained as a brown oil. IR (CCl_4, cm^{-1}): 1200, 1650. ^1H NMR ($CDCl_3$) δ (ppm): 1.58 (6H, br s), 1.67 (3H, s), 1.77 (3H, s), 1.90–2.10 (8H, m), 2.14 (3H, s), 3.33 (2H, d, $J = 6.6$ Hz), 3.76 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 5.05–5.12 (3H, m), 5.64 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 11.3, 16.0, 16.2, 17.6, 25.5, 25.6, 26.6, 26.7, 39.7 (2C), 60.7, 61.1, 61.2, 117.5, 123.0, 124.1, 124.4, 129.2, 129.6, 131.2, 135.0, 137.7, 143.3, 143.5, 144.4. HR-MS (ES Q-TOF) calcd. for $C_{25}H_{38}O_4$ $(M + Na)^+$: 425.2668. Found: 425.2724.

2,3,4-Trimethoxy-6-methyl-5-solanesylphenol (12d)

The solanesyl ether **11d** (272 mg, 0.30 mmol) dissolved in 5 mL of Et_2O was treated with $BF_3 \cdot Et_2O$ (0.4 mL, 3 mmol) at room temperature. After 30 min, a saturated solution of NaCl (10 mL) was added, and the mixture was extracted three times with EtOAc (10 mL). The combined extracts were washed with brine until neutrality, dried over anhydrous Na_2SO_4, and freed from the solvent under a vacuum. Flash chromatography (9:1 hexane/EtOAc), allowed us to obtain the desired product (149 mg, 55%) as a dark brown oil. IR (CCl_4, cm^{-1}): 1210, 1600. ^1H NMR ($CDCl_3$) δ (ppm): 1.60 (24H, s), 1.68 (3H, s), 1.77 (3H, s), 1.90–2.10 (32H, m), 2.13 (3H, s), 3.33 (2H, d, $J = 6.6$ Hz), 3.75 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 5.05–5.20 (9H, m), 5.60 (1H, s). ^{13}C NMR ($CDCl_3$) δ (ppm): 11.3, 16.0 (br), 16.2, 17.6, 25.5, 25.6, 26.7 (br), 39.7 (br), 60.7, 61.1, 61.2, 117.5, 123.0, 124.1, 124.3 (br), 124.4, 129.6, 131.2, 134.9 (br), 135.0, 137.7, 143.3, 143.4, 144.4. HR-MS (ES Q-TOF) calcd. for $C_{55}H_{86}O_4$ $(M + Na)^+$: 833.6424. Found: 833.6520.

Ubiquinone Q_1 (13a)

A solution of **12a** (225 mg, 0.85 mmol) in EtOH (2 mL) was diluted with water (10 mL), and an excess of $FeCl_3$ (8.5 mmol) was added. The mixture was stirred at room temperature for 2 h and then extracted with three portions of EtOAc (10 mL). The organic extracts were pooled and washed with three portions of brine (5 mL) to give CoQ_1 as a pure product (220 mg, $>97\%$). Physicochemical data are in agreement with the literature.[13]

Ubiquinone Q_2 (13b)

A solution of **12b** (336 mg, 1 mmol) in EtOH (2 mL) was diluted with water (10 mL), and an excess of $FeCl_3$ (10 mmol) was added. The mixture was stirred at room temperature for 2 h and then extracted with three portions of EtOAc (10 mL). The organic extracts were combined and washed with three portions of brine (5 mL) to give CoQ_2 as a pure product (320 mg, >95%). Physicochemical data are in agreement with the literature. (The obtained compound was compared with an authentic sample purchased from Sigma-Aldrich Co.).

Ubiquinone Q_3 (13c)

A solution of **12c** (272 mg, 0.68 mmol) in EtOH (1.5 mL) was diluted with water (7 mL), and an excess of $FeCl_3$ (6.8 mmol) was added. The mixture was stirred at room temperature for 2 h and then extracted with three portions of EtOAc (10 mL). The organic extracts were combined and washed with three portions of brine (5 mL) to give CoQ_3 as a pure product (253 mg, 93%). Physicochemical data are in agreement with the literature.[15]

Ubiquinone Q_9 (13d)

A solution of **12d** (360 mg, 0.48 mmol) in a 1:1 mixture of EtOH and *i*-PrOH (1 mL) was diluted with water (10 mL), and an excess of $FeCl_3$ (4.8 mmol) was added. The mixture was stirred at room temperature for 2 h, then extracted with three portions of EtOAc (10 mL). The combined organic extracts were washed with three portions of brine (5 mL) to give CoQ_9 as a pure product (325 mg, 90%). Physicochemical data are in agreement with the literature.[16]

REFERENCES

1. Cross, C. E.; Halliwell, E.; Borish, E. T.; Pryor, W. A.; Ames, B. N.; Saul, R. L.; McCord, J. M.; Harman, D. Oxygen radicals and human disease. *Ann. Intern. Med.* **1987**, *107*, 526–545.
2. Kagan, V. E.; Serbinova, E. A.; Stoyanovsky, D. A.; Khwaja, S.; Packe. Assay of ubiquinones and ublquinols as antioxidants. *Methods Enzymol.* **1994** *234*, 343–354.
3. Lipshutz, B. H.; Mollard, P.; Pfeiffer, S. S.; Chrisman, W. A short, higly efficient synthesis of coenzyme. *J. Am. Chem. Soc.* **2002**, *124*, 14282–14283, and references therein.
4. Georgellis, D.; Kwon, O.; Lin, E. C. Quinones as the recloy signal for the Arc two–components system of backteria. *Science* **2001**, *292*, 2314–2316.

5. Landi, L.; Cabrini, L.; Fiorentini, D.; Sartor, G.; Pasquali, P.; Masotti, L. The role of the side chain in the antioxidan activity of ubiquinones. *Free Radic. Res. Commun.* **1991**, *14* (1), 1–8.
6. See, for example, Prasad, K. N.; Cole, W. C.; Haase, G. M. Formulations comprising multiple dietary and endogenously made antioxidants and Vitamin B. U.S. Pat. Appl. Publ. 2006263446, 2006.
7. (a) Kishi, T. *Fragrance Journal* **2005**, *33* (8), 21–27; (b) Takahashi, T.; Okamoto, M.; Kishi, T. Biochemical functions of endogenous and exogenous coenzyme. *New Food Industry* **2003**, *45* (7), 1–10.
8. Alleva, R.; Tomasetti, M.; Battino, M.; Curatola, G.; Littarru, G. P.; Folkers, K. The roles of coenzyme Q10 and vitamin E on the peroxidation of human low density lipoprotein subfractions. *Proc. Natl. Acad. Sci. USA* **1995**, *92* (20), 9388–9391.
9. Bovicelli, P.; Mincione, E.; Antonioletti, R.; Bernini, R. Colombari, M. Selective halogenation of aromatics by dimeth. *Synth. Commun.* **2001**, *31*, 67.
10. Bovicelli, P.; Antonioletti, R.; Barontini, M.; Borioni, G.; Bernini, R.; Mincione, E. New convenient synthesis of iridol. An approach to synthesis of ubiquinones. *Tetrahedron Lett.* **2005**, *46* (8), 1255–1257.
11. Matsumoto, H.; Kobayashi, H.; Hotta, Y. Acid–catalyzed oxidation of benzaldehydes to phenols by hydorogen peroxide. *J. Org. Chem.* **1989**, *49*, 4740–4741.
12. Carruthers, W.; Johnstone, R. A. W. Alcohols of tobacco. Solanesol and n-docosanol. *Chem. Ind.* **1960**, 867–868.
13. Liang, L.; Fener, C. A novel and convenient synthesis of coenzyme Q1. *Synth. Commun.* **2004**, *34* (22), 4049–4053.
14. Adam, W.; Shimizu, M. The acid–catalyzed oxidation of methoxybenzenes to p-benzoquinones by dimethyldioxirane. *Synthesis* **1994**, *6*, 560–562.
15. Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.-K.; Lowe, R.; Mollard, P.; Stevens, K. L. A convergent approach to coenzyme. *J. Am. Chem. Soc.* **1999**, *121*, 11664–11673.
16. Kuznetsova, T. A.; Dmitrenok, A. S.; Sobolevskaya, M. P.; Shevchenko, L. S.; Mikhailov, V. V. Ubiquinone Q9 from a marine isolate of an actinobacterium no cardia sp. *Russ. Chem. Bl., Inter. Ed.* **2002**, *51* (10), 1951–1953.