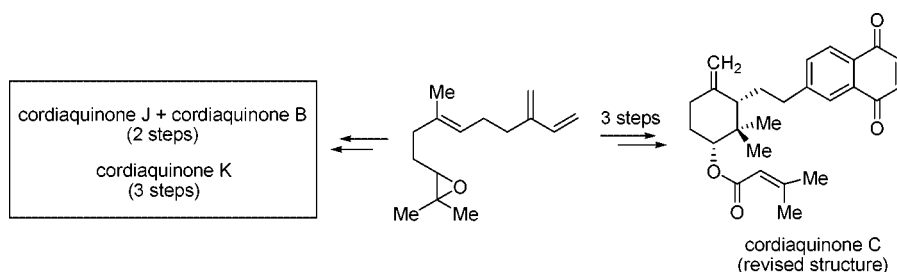# Synthesis of Cordiaquinones B, C, J, and K on the Basis of a Bioinspired Approach and the Revision of the Relative Stereochemistry of Cordiaquinone C[†]

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Four members of the cordiaquinone family (cordiaquinones B, C, J, and K) were synthesized on the basis of a bioinspired scenario in five to six steps from *trans,trans*-farnesol. As key reactions we used the acid-catalyzed cyclization of a suitable epoxy terpenoid and a Diels−Alder reaction between a diene and benzoquinone. The relative stereochemistry of cordiaquinone C is opposite to that reported in the isolation paper and is in agreement with a plausible scenario for the biosynthesis of cordiaquinones from a common (*E*)-configured naphthoquinone epoxide precursor. A fast and clean methodology for the synthesis of the naturally occurring (*Z*)-*β*-farnesene from *cis*-nerolidol is also reported.

Introduction

Cordiaquinones A−K constitute a family of 10 naturally occurring merosesquiterpenoids that possess a naphthoquinone moiety (Scheme 1). Cordiaquinones A−D[1,2] were isolated from the roots of *Cordia corymbosa*, E-H[3] from the roots of *Cordia limnaei*, while J and K[4] from the roots of *Cordia curassavica*. They exhibit antifungal properties against *Cladosporium cucumerinum* and the yeast *Candida albicans* as well as larvicidal properties against the yellow fever-transmitting mosquito *Aedes aegypti*.

There is no direct experimental evidence for the biosynthetic origin of cordiaquinones. In our opinion, it is likely[5] (Scheme 2) that they arise from the acid-catalyzed cyclization of epoxide **A**, which in turn could derive from a Diels−Alder reaction[6] of the naturally occurring epoxy *β*-farnesene[7] (**B**) or *β*-farnesene with benzoquinone, followed by an oxidation of the cyclo adduct.

In light of our recent findings that slightly acidic zeolite NaY promotes the selective monocyclization of epoxy polyene terpenes,[8] we envisioned the NaY-catalyzed cyclization of the (*E*)-configured epoxide **A** as a promising route to the synthesis of cordiaquinones C, J, and K (Scheme 3). Thus, alcohol **C** and cordiaquinone J could directly derive from (*E*)-**A**. Furthermore, alcohol **C** is the precursor of cordiaquinone K. We would like to point out that the initially proposed structure of cordiaquinone J is a diastereomer of the revised one, as proved through their syntheses by Yabuta and co-workers.[9] Based on a common biosynthetic scenario, epoxide **A** having an (*E*)

† Dedicated to Professor M. Orfanopoulos on the occasion of his 60th birthday.

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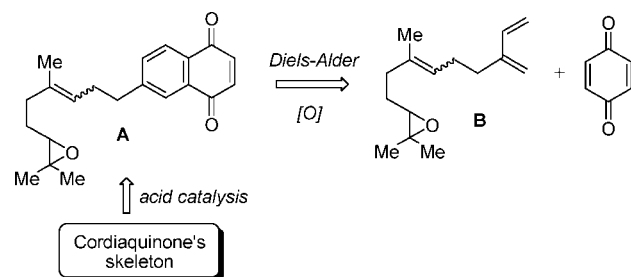
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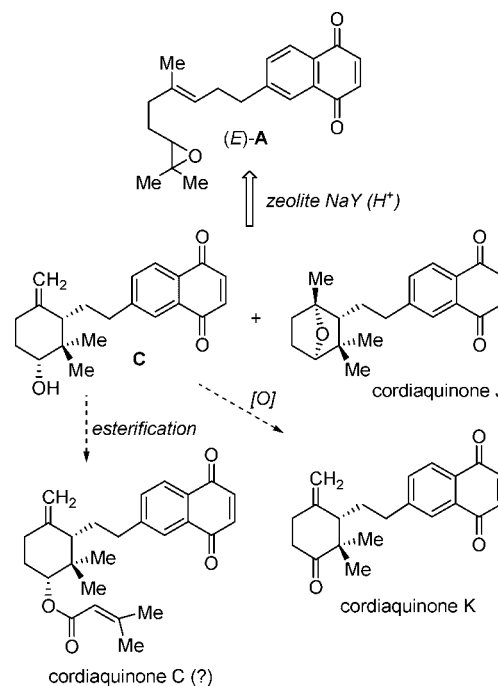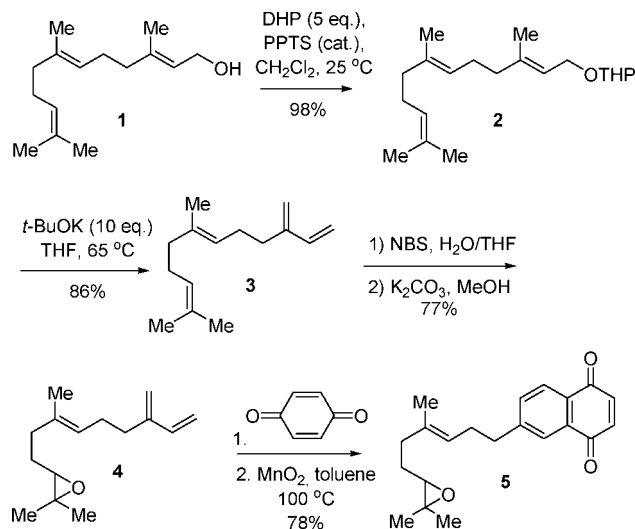
SCHEME 1. Cordiaquinones A–K
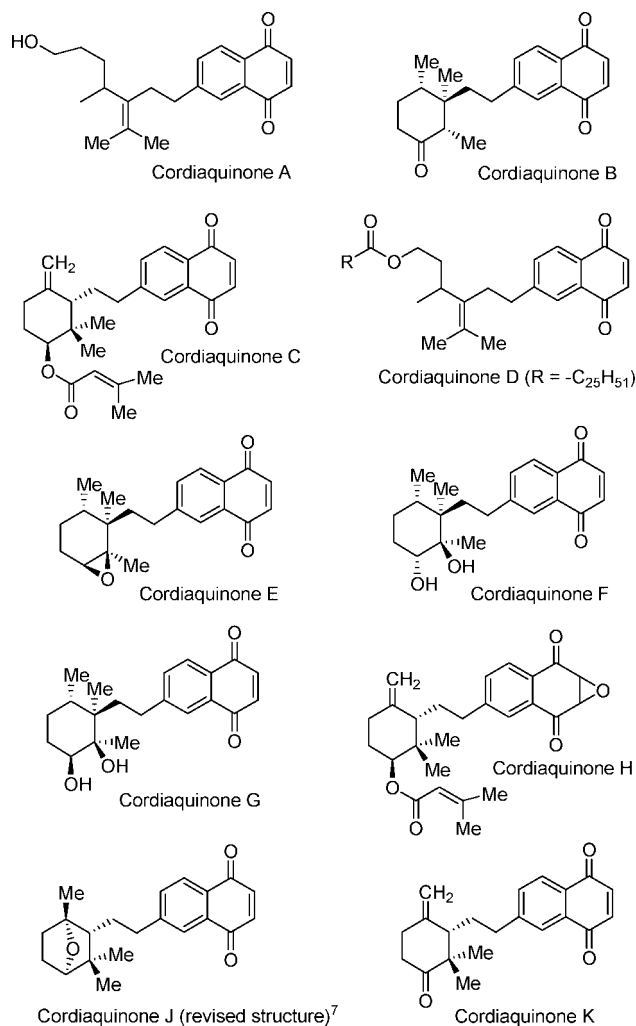
SCHEME 2. Postulated Biosynthetic Scenario for Cordiaquinones

SCHEME 3. Proposed Synthesis of Cordiaquinones C, J, and K Based on the Zeolite NaY-Promoted Cyclization of the (*E*)-Configured Epoxide A

SCHEME 4. Synthesis of Naphthoquinone Epoxide 5 from Farnesol

configuration on the C6–C7 double bond, (*E*)-**A**, will lead upon acid catalysis to cordiaquinone J (revised structure) and to alcohol **C** with *cis*-stereochemistry, which contradicts, however, the trans stereochemistry appearing in the proposed structure[2,3] of cordiaquinones C and H. To shed light on this discrepancy, we started our synthetic journey by studying the cyclization of the (*E*)-configured epoxide **A**.

Results and Discusssion

For the synthesis of a suitable precursor, the (*E*)-configured epoxide **A** (compound **5**, Scheme 4), *trans,trans*-farnesol (**1**) was the starting material. *trans,trans*-Farnesol was protected as a THP ether (**2**) in 98% yield by reaction with 5 equiv of 3,4-

dihydro-2*H*-pyran in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The THP-protected farnesol **2** was treated with *t*-BuOK in THF,[10] in the presence of a catalytic amount of 18-crown-6, and furnished exclusively (*E*)-*β*-farnesene (**3**) in 86% yield. The epoxidation of **3** by reaction with *N*-chlorosuccinimide in THF/H$_2$O followed by treatment of the resulting chlorohydrin with K$_2$CO$_3$ in methanol yielded the naturally occurring epoxy (*E*)-*β*-farnesene (**4**) in 77% overall yield as the only regioisomer. Finally, Diels–Alder reaction of diene **4** with 1.4 equiv of benzoquinone (14 h in refluxing toluene), followed by addition of a 6-fold excess of

(9) Yajima, A.; Saitou, F.; Sekimoto, M.; Maetoko, S.; Nukada, T.; Yabuta, G. *Tetrahedron* **2005**, *61*, 9164–9172.

(10) Otera, J.; Niibo, Y.; Okuda, K. *Chem. Lett.* **1986**, *11*, 1829–1832.

activated MnO$_2$ (one pot) and heating to reflux for 30 min, yielded the desired epoxy naphthoquinone **5** in 78% yield (51% overall yield from **1**). A similar reaction sequence is known in the literature,[11] in which the naphthoquinone skeleton is constructed in two separate steps, with the first step (Diels−Alder reaction) being carried out in the presence of BF$_3$ as a catalyst at ambient temperature. In our case, the Lewis acid promoted version was avoided due to the presence of the acid-sensitive epoxide functionality on **4**, yet we were happy to realize that naphthoquinones can derive from dienes and benzoquinone under thermal conditions in just one pot.

To our disappointment, all attempts to perform the direct biomimetic synthesis of cordiaquinones skeleton using the NaY-promoted cyclization of epoxide **5** failed. Upon adsorption of **5** within NaY, an intense brown-red color appeared immediately with formation of an unidentified polymeric material. We assume that the quinone moiety undergoes a strong complexation to the acidic site of the zeolite, with subsequent unwanted side reactions, thus leading to the failure of our proposed cyclization scenario. To overcome this failure, a modified strategy was followed, based on which, the intrazeolite cyclization occurred prior to the formation of the naphthoquinone moiety. Thus, on treatment of the epoxy β-farnesene (**4**) with NaY for 5 min, the monocyclized alcohols **6** (exo double bond) and **7** (endo double bond) were primarily formed, along with bicyclic ether **8** and the allylic alcohol **9**[7] in 80% combined yield and in a relative ratio (**6**+**7**)/**8**/**9** = 70/25/5 (Scheme 5). The ratio of the exo/endo double regioisomers **6/7** was ~6/1. This product distribution resembles substantially the results obtained from our previous studies[8] on the cyclization of epoxy polyene terpenoids promoted by NaY and once more exemplifies the unique ability of NaY as a selective monocyclization catalyst on its reaction with epoxy polyene terpenoids. It is noteworthy that treatment of epoxide **4** with a catalytic amount of SnCl$_4$ in dry dichloromethane afforded in low yield a complex mixture of products. For the zeolite-promoted reaction of epoxide **4**, we used low loading levels of **4** relative to the zeolite supercages (~0.2 mmol of **4** per 1 g of dry NaY). We also observed (NMR, GC−MS) that on prolonged zeolite treatment (10−20 min) new products appear, with a simultaneous decrease in the relative yield of **6/7**. The alcohols **6/7** (inseparable mixture) and the bicyclic ether **8** were isolated from the crude reaction mixture by column chromatography. The regioisomers **6** and **7** reacted with benzoquinone/MnO$_2$ in refluxing toluene to form naphthoquinones **10**(exo) and **11**(endo) in 77% isolated yield and in a relative ratio **10/11** = 6/1. Similarly, bicyclic ether **8** furnished after an identical reaction sequence (Scheme 5) cordiaquinone J (**12**) in 75% yield (13% overall yield from epoxide **4**).

The separation between the exo and endo regioisomers **10** and **11** was impossible by column chromatography. The purification of the major one (**10**) was crucial, as it could be the precursor of cordiaquinones K and C (or its epimer). Thus, the mixture of **10** and **11** reacted with 0.25 equiv of the powerful enophile *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD[12]). The trisubstituted double bond of the thermodynamically more stable **11** reacted instantaneously with PTAD to form a mixture of ene products,[13] as seen in the crude ^{1}H NMR spectrum, while

SCHEME 5. Intrazeolite Cyclization of Epoxy β-Farnesene (4) and the Synthesis of Cordiaquinones J and K
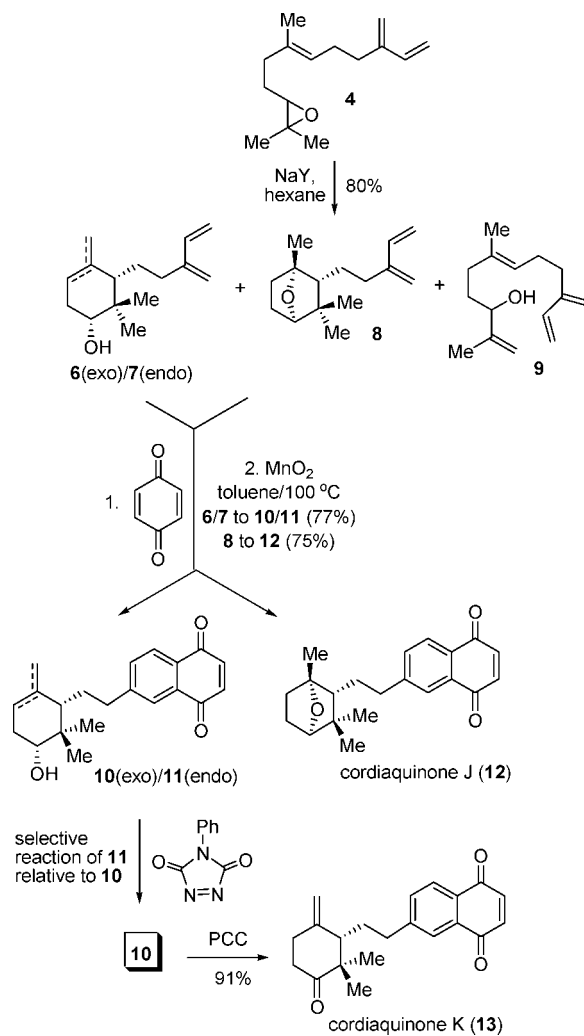
10 bearing a less nucleophilic disubstituted double bond remained intact.[14] After column chromatography, the exo isomer **10** was isolated free of the undesired regioisomer **11** and oxidized with PCC to produce cordiaquinone K (**13**, Scheme 5) in 91% yield (21% overall yield from epoxide **4**).

For the completion of the synthesis of cordiaquinone C (or its epimer), a simple esterification of **10** with 3,3-dimethylacryloyl chloride (DMAP/Et$_3$N) was realized as a next step. Despite the consumption of the reactant **10**, a complex mixture of products was formed without the expected product being among them. To overcome this problem, we decided to esterify the mixture of alcohols **6** and **7** and then attach the naphthoquinone moiety. Thus, treatment of **6/7** with LiHMDS[15] followed by addition of 3,3-dimethylacryloyl chloride afforded the regioisomeric dimethylacryloyl esters **14** (exo) and **15** (endo) in 85% yield (**14/15** ~6/1). Surprisingly, treatment of **6/7** with 3,3-dimethylacryloyl chloride in the presence of DMAP/Et$_3$N afforded apart of **14/15**, their non conjugated terminal double isomers on the ester functionality (3′-methylbut-3′-enoate) in

(11) Castro, M. A.; del Corral, J. M. M.; Gordaliza, M.; Garcia, P. A.; Gamito, A. M.; Gualberto, S. A.; Batista, R.; San Feliciano, A. *Synthesis* **2005**, 3202–3208.

(12) Vougioukalakis, G. C.; Orfanopoulos, M. *Synlett* **2005**, 713–731.

(13) For the reaction of α-cyclogeranyl derivatives, such as **10**, with PTAD, see: Tsangarakis, C.; Zaravinos, I.-P.; Stratakis, M. *Synlett* **2005**, 1857–1860.

(14) For a similar isolation of one among other regioisomeric alkenes using their reaction with *m*-CPBA, see: Basabe, P.; Bodero, O.; Marcos, I. S.; Diez, D.; de Roman, M.; Blanco, A.; Urones, J. G. *Tetrahedron* **2007**, *63*, 11838–11843.

(15) Nemoto, T.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2003**, *59*, 6889–6897.

SCHEME 6. Final Steps toward the Synthesis of Cordiaquinone C (Revised Structure 16)

SCHEME 7. Synthesis of the Proposed Structure of Cordiaquinone C (28)
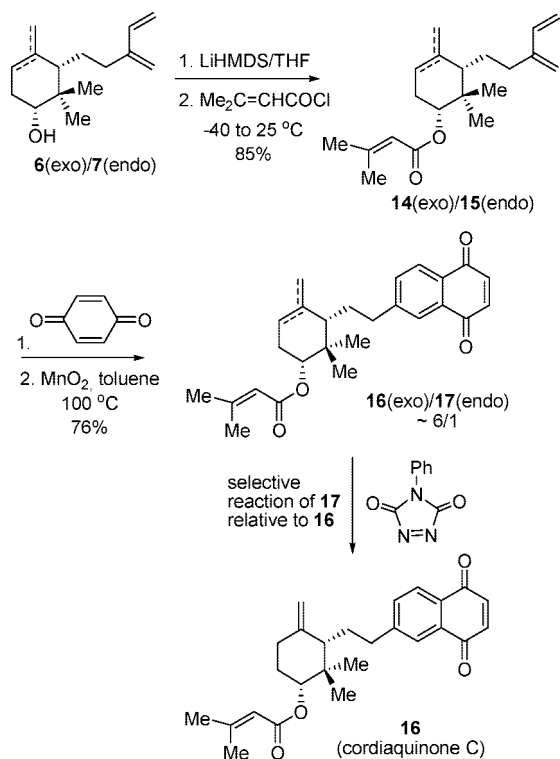
appreciable relative yield (~35%). The regioisomeric mixture **14/15** reacted with benzoquinone/MnO$_2$ to form in 76% isolated yield the non-chromatographically separable naphthoquinones **16** (exo) and **17** (endo), and in a relative ratio 6/1 (Scheme 6). Treatment of **16/17** with PTAD, as described in the purification of **10**, resulted to the isolation of pure **16** whose ^{1}H and ^{13}C NMR spectra were in agreement with those of cordiaquinone C (19.5% overall yield from epoxide **4**). This result strongly corroborates the proposed biosynthetic scenario presented in Scheme 3.

Following the spectroscopic proof that compound **16** is cordiaquinone C, we attempted the synthesis of the proposed structure of cordiaquinone C, which is essentially the trans diastereomer of **16**. The synthetic route (Scheme 7) toward accomplishing this goal was identical to the synthesis of **16**, with the only difference that the configuration of β-farnesene was (*Z*). As starting material, we used the commercially available natural product *cis*-nerolidol (**18**). Reaction of **18** with 5 equiv of SOCl$_2$ at −78 °C afforded mainly farnesyl chloride with *Z* geometry on the C6−C7 double bond (**19**), yet possessing a mixture of *E/Z* isomers on the C2−C3 double bond in a ratio ~3/1. The presence of the two geometrical isomers on the C2−C3 double bond of **19** is not a problem, as both isomers converge to the same desired product in the accompanying step. Thus, the crude mixture **19** underwent dehydrochlorination in the presence of *t*-BuOK to afford exclusively (*Z*)-β-farnesene (**20**) in 64% isolated yield over the two steps. Although (*Z*)-β-farnesene is a natural pheromone and a constituent of several essential oils, a clean method for its preparation, free from other regio- or geometrical isomers, is not available. The (*Z*)-β-farnesene was epoxidized selectively on the terminal trisubstituted double bond under identical conditions applied to its (*E*)-isomer **3**, to form **21** in 72% isolated yield. Epoxide **21** was treated with NaY for 5 min to afford in 79% yield primarily
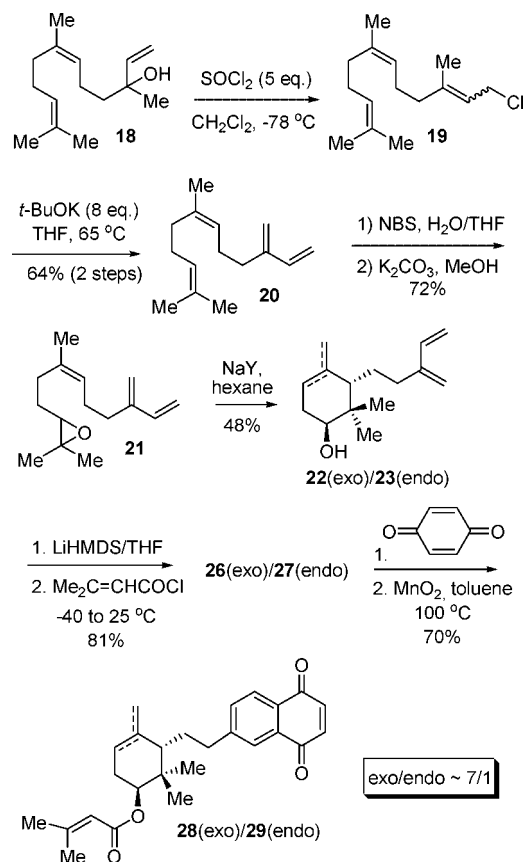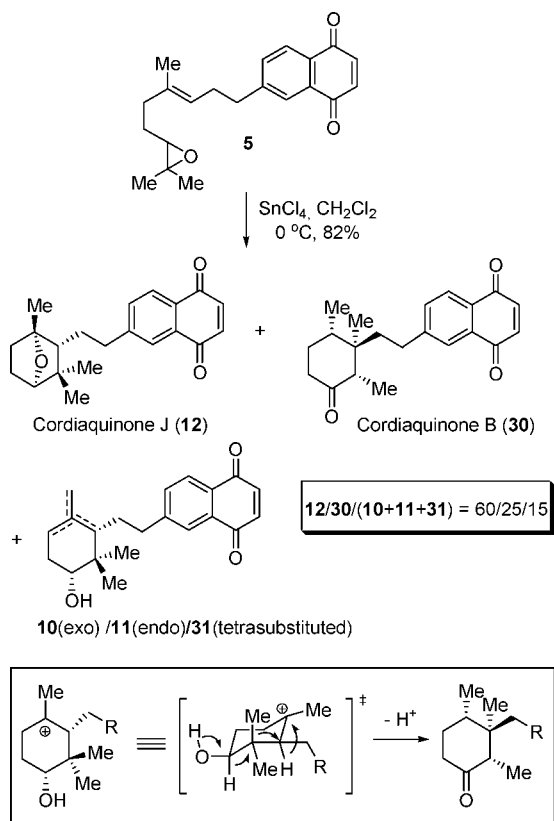
the desired *trans*-alcohols **22** (exo) and **23** (endo), as well as the bicyclic ether **24** and the allylic alcohol **25**, analogous to **8** and **9**. The relative product ratio was **22/23/24/25** = 66/12/7/15. The inseparable mixture of **22** and **23** underwent esterification upon treatment with LiHMDS/3,3-dimethylacryloyl chloride to form **26** (exo) and **27** (endo) in 81% yield and in ~6/1 relative ratio. Finally, reaction of **26/27** with benzoquinone/MnO$_2$ afforded naphthoquinone **28** (the proposed structure of cordiaquinone C), as well as its endo regioisomer **29** (70% isolated yield; 12.5% overall yield from *cis*-nerolidol; relative ratio **28/29** ~ 7/1). Surprisingly, upon treatment of the mixture of **28/29** with PTAD, as applied to the mixtures **10/11** or **16/17**, the undesired minor **29** was completely unreactive. We attribute this lack of reactivity to the axial orientation of the −OCOCH=C(CH$_3$)$_2$ substituent, which hinders triazolinedione approach on the cycloalkene double bond. Nevertheless, neither the ^{1}H nor the ^{13}C NMR spectroscopic data of compound **28** are in agreement with those of cordiaquinone C, which again indicates that, the relative stereochemistry of the substituents on the two stereogenic centers of cordiaquinone C is *cis* instead of the proposed trans. We also propose that the relative stereochemistry of cordiaquinone H[3] is cis instead of trans, as reasonably, cordiaquinone H arises via an epoxidation of the quinone ring of cordiaquinone C.

Regardless the failure to provide a direct access to cordiaquinones skeleton through the zeolite-promoted cyclization of naphthoquinone epoxide **5**, we examined the cyclization of **5** under Lewis acid catalysis. From the already abundant studies on the acid-catalyzed epoxy polyene terpene cyclization, it well

SCHEME 8. Cyclization of Epoxide 5 Catalyzed by SnCl₄ and the Reasonable Pathway for the Formation of Cordiaquinone B

Yabuta's group accomplished the enantioselective synthesis of cordiaquinones K[20] and J,[9] while revised the structure of cordiaquinone J, as through its synthesis it was found that the initially proposed structure was a diastereomer of the reported on in the isolation paper. Those synthetic routes, however, require multiple steps compared to our approach, while they lack of a biomimetic inspiration.

Conclusions

In conclusion, we have presented a short and efficient synthesis of cordiaquinones B, C, J, and K on the basis of a bioinspired approach. In addition, the relative stereochemistry of cordiaquinone C was revised from trans to cis. As a key step, we used the acid-catalyzed cyclization of a suitable terpenoid epoxide. The naphthoquinone moiety of cordiaquinones was introduced via a Diels−Alder reaction either at an early or at a later stage, depending on the specific synthetic route. The cyclization was carried out using as catalysts either a Lewis acid (homogeneous conditions) or zeolite NaY (heterogeneous conditions), depending on the nature of the reacting epoxide. The current results exemplify once more the valuable role of zeolite NaY as a unique, efficient, and highly useful acidic catalyst in epoxy terpene cyclization.[10]

Experimental Section

(E)-β-Farnesene (3). In one-necked flask containing dry CH₂Cl₂ (40 mL) were dissolved trans,trans-farnesol, **1** (1.5 g, 6.75 mmol), pyridinium p-toluenesulfonate (0.15 g, 0.6 mmol), and 3,4-dihydro-2H-pyran (3.1 mL, 34 mmol). After 1 h, dichloromethane was added, and the organic layer was washed with water. Removal of the solvent under vacuum afforded the THP-protected farnesol (**2**) in 98% yield. ^{1}H NMR of **2**: 5.36 (t, $J = 6.5$ Hz, 1H), 5.10 (m, 2H), 4.62 (t, $J = 3.5$ Hz, 1H), 4.23 (dd, $J_1 = 13.0$ Hz, $J_2 = 6.5$ Hz, 1H), 4.02 (dd, $J_1 = 13.0$ Hz, $J_2 = 6.5$ Hz, 1H), 3.89 (m, 1H), 3.51 (m, 1H), 1.94−2.15 (m, 8H), 1.67 (s, 6H), 1.59 (s, 6H), 1.45−1.90 (m, 6H). The THP−farnesol **2** was dissolved in dry THF (40 mL). Subsequently, 6.75 g (54 mmol, 10 equiv) of t-BuOK was added in one portion, and the mixture was heated to 60 °C for 16 h. By adding 10% of 18-crown-6 relative to the t-BuOK the reaction was completed within 3 h. After extraction with hexane and removal of the solvent under vacuum, the residue was chromatographed using hexane/ethyl acetate = 80/1 to afford 0.96 g of pure (E)-β-farnesene, **2** (86% yield). ^{1}H NMR: 6.38 (dd, $J_1 = 17.5$ Hz, $J_2 = 11.0$ Hz, 1H), 5.25 (d, $J = 17.5$ Hz, 1H), 5.17 (t, $J = 7.0$ Hz, 1H), 5.10 (t, $J = 7.0$ Hz, 1H), 5.06 (d, $J = 11.0$ Hz, 1H), 5.02 (s, 1H), 5.00 (s, 1H), 2.17−2.25 (m, 4H), 2.08 (m, 2H), 1.98 (m, 2H), 1.68 (s, 3 H), 1.61 (s, 6H). ^{13}C NMR: 146.1, 139.0, 135.4, 131.3, 124.4, 124.0, 115.7, 113.0, 39.7, 31.4, 26.7, 26.6, 25.7, 17.7, 16.0.[7]

(E)-2,2-Dimethyl-3-(3-methyl-7-methylenenona-3,8-dienyl)ox-irane (4). In one-necked flask containing 35 mL of THF and 10 mL of H₂O was added at 0 °C (E)-β-farnesene, **3** (0.78 g, 3.82 mmol). Immediately after, recrystallized NBS (0.80 g, 4.54 mmol) was added in portions over a period of 10 min. After the disappearance of **3**, ether was added and the reaction mixture was extracted to afford the crude bromohydrin. The bromohydrin was added to a slurry containing methanol (40 mL) and K₂CO₃ (1.0 g, 7.2 mmol). The dehydrochlorination was complete within 30 min. After aqueous workup and solvent removal, the residue was chromatographed with hexane/ethyl acetate = 40/1 to afford 0.65 g of epoxide **4** as a single regioisomer (77% yield). ^{1}H NMR: 6.36

documented that Lewis acids are the superior catalysts.[16] The reaction of **5** with 0.5 equiv of SnCl₄ in dichloromethane at 0 °C afforded after 40 min and in 82% yield a mixture of **12** (cordiaquinone J, 60% relative yield), **30** (cordiaquinone B, 25% relative yield), as well as a minor content (15% relative yield) of all three regioisomeric monocyclized products **10**, **11**, and **31** (Scheme 8). Similar results were obtained by using BF₃ as a catalyst, with the only difference that the relative ratio of **12** (cordiaquinone J)/**30** (cordiaquinone B) was ~4/1. Cordiaquinone B exhibits pronounced activity[17] against Gram-positive bacteria and mycobacteria. The formation of 2,3,4-trimethyl-cyclohexanones upon treatment of epoxypolyene terpenes with Lewis acids is well documented[18] and proposed to proceed through the 1,2-rearrangement reaction of two hydrides and one methyl, shown in the transition state of Scheme 8. To the best of our knowledge, this is the first example of taking advantage of this highly stereoselective pathway for the direct synthesis of a natural product.

The cyclization results of epoxide **5** in a homogeneous medium (SnCl₄) compliment those by using zeolite NaY in a heterogeneous environment (epoxide **4**), thus allowing the synthesis of four members of the cordiaquinone family, employing the same concept; the acid-catalyzed rearrangement of an epoxide. The enantioselective synthesis of (−)-cordiaquinone B has been reported by Asaoka and co-workers.[19] Later on,

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(dd, $J_1 = 17.5$ Hz, $J_2 = 10.5$ Hz, 1H), 5.23 (d, $J = 17.5$ Hz, 1H), 5.20 (t, $J = 6.0$ Hz, 1H), 5.05 (d, $J = 10.5$ Hz, 1H), 5.00 (s, 1H), 4.98 (s, 1H), 2.70 (t, $J = 6.0$ Hz, 1H), 2.06−2.25 (m, 6H), 1.56−1.69 (m, 2H), 1.62 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H). ^{13}C NMR: 146.0, 138.9, 134.5, 124.6, 115.8, 113.1, 64.1, 58.3, 36.3, 31.3, 27.4, 26.6, 24.9, 18.7, 16.0.

(E)-6-(6-(3,3-Dimethyloxiran-2-yl)-4-methylhex-3-enyl)naphthalene-1,4-dione (5). In one-necked flask containing toluene (5 mL) were dissolved the epoxide **4** (0.33 g, 1.5 mmol) and benzoquinone (0.22 g, 2.0 mmol). The mixture was heated to 100 °C for 16 h until the epoxide was consumed. Within the same flask was subsequently added 0.78 g (9.0 mmol) of activated MnO$_2$, and the slurry was heated to 100 °C for 30 min. The reaction mixture was cooled and filtered through a short pad of Celite. After evaporation of the solvent, the residue was chromatographed with hexane/ethyl acetate = 10/1 to afford 0.38 g of epoxide **5** (78% yield). ^{1}H NMR: 7.98 (d, $J = 7.5$ Hz, 1H), 7.89 (d, $J = 3.0$ Hz, 1H), 7.55 (dd, $J_1 = 7.5$ Hz, $J_2 = 3.0$ Hz, 1H), 6.94 (s, 2H), 5.18 (t, $J = 7.0$ Hz, 1H), 2.78 (t, $J = 7.5$ Hz, 2H), 2.66 (t, $J = 6.5$ Hz, 1H), 2.36 (m, 2H), 2.09 (m, 2H), 1.57 (m, 2H), 1.53 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H). ^{13}C NMR: 185.4, 184.9, 149.3, 138.7, 138.5, 136.0, 134.1, 131.8, 129.9, 126.6, 126.2, 123.1, 64.3, 58.3, 36.3, 36.1, 29.2, 27.4, 24.9, 18.7, 16.0. HRMS (EI): calcd for C$_{21}$H$_{24}$O$_3$ 324.17255, found 324.17250.

Zeolite NaY-Promoted Cyclization of Epoxide 4. To a slurry of dry NaY (2.0 g) in hexane (15 mL) was added epoxide **4** (80 mg). After 5 min, the heterogeneous mixture was filtered, and the solid residue was washed with methanol (3 × 10 mL) for 30 min each time. The combined solvents were evaporated under vacuum to afford 0.64 g a mixture containing the regiosiomeric alcohols **6** and **7**, bicyclic ether **8**, and the noncyclized allylic alcohol **9** in a relative ratio (**6** + **7**)/**8**/**9** = 70/25/5. The nonseparable mixture of **6** and **7** (36 mg) as well as ether **8** (14 mg) was isolated from the reaction mixture by column chromatography using hexane/ethyl acetate = 10/1. ^{1}H NMR of **6** (exo): 6.36 (dd, $J_1 = 17.5$ Hz, $J_2 = 11.0$ Hz, 1H), 5.21 (d, $J = 17.5$ Hz, 1H), 5.04 (d, $J = 11.0$ Hz, 1H), 5.00 (s, 1H), 4.98 (s, 1H), 4.90 (br s, 1H), 4.63 (br s, 1H), 3.41 (dd, $J_1 = 9.5$ Hz, $J_2 = 4.0$ Hz, 1H), 2.32−2.37 (m, 2H), 1.98−2.04 (m, 2H), 1.82−1.86 (m, 1H), 1.64−1.78 (m, 2H), 1.47−1.54 (m, 2H), 1.02 (s, 3H), 0.72 (s, 3H). ^{13}C NMR of **6**: 147.3, 146.8, 139.0, 115.6, 113.2, 108.5, 77.2, 51.5, 40.5, 32.9, 32.2, 30.4, 25.9, 24.1, 15.7. MS (EI): 220 (M$^+$, 2), 202 (M$^+$ − H$_2$O, 7), 187 (31), 159 (32), 119 (51), 79 (100). HRMS (EI): calcd for C$_{15}$H$_{24}$O 220.18272, found 220.18212. ^{1}H NMR of **7** (endo), characteristic absorptions: 3.46 (dd, $J_1 = 13.5$ Hz, $J_2 = 6.0$ Hz, 1H), 0.97 (s, 3H), 0.83 (s, 3H). ^{1}H NMR of **8**: 6.37 (dd, $J_1 = 17.5$ Hz, $J_2 = 10.5$ Hz, 1H), 5.22 (d, $J = 17.5$ Hz, 1H), 5.06 (d, $J = 10.5$ Hz, 1H), 5.02 (s, 1H), 5.00 (s, 1H), 3.73 (d, $J = 5.0$ Hz, 1H), 2.14−2.23 (m, 2H), 1.90−1.95 (m, 1H), 1.66−1.72 (m, 1H), 1.45−1.56 (m, 4H), 1.34 (s, 3H), 1.24−1.27 (m, 1H) 1.08 (s, 3H), 1.03 (s, 3H). ^{13}C NMR of **8**: 146.6, 139.0, 115.6, 113.2, 86.7, 86.1, 55.8, 45.3, 39.0, 31.5, 26.3, 26.1, 25.8, 23.4, 18.9. MS (EI): 220 (M$^+$, 7), 205 (9), 187 (16), 153 (68), 135 (84), 93 (100), 79 (93), 67 (90), 55 (92).

cis-6-(2-(3-Hydroxy-2,2-dimethyl-6-methylenecyclohexyl)ethyl)naphthalene-1,4-dione (10). An analogous transformation for the final step of the synthesis of cordiaquinone J applied to the mixture of alcohols **6** and **7** afforded a mixture of **10** and **11** in 77% yield. ^{1}H NMR of **10** (exo): 8.00 (d, $J = 7.5$ Hz, 1H), 7.88 (s, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 6.95 (s, 2H), 4.97 (s, 1H), 4.70 (s, 1H), 3.41 (dd, $J_1 = 9.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.88 (m, 1H), 2.54 (m, 1H), 2.40 (m, 1H), 2.03 (m, 1H), 1.89 (m, 2H), 1.72 (m, 1H), 1.52−1.58 (m, 1H), 1.24−1.30 (m, 1H), 1.00 (s, 3H), 0.76 (s, 3H). ^{13}C NMR of **10** (exo): 185.5, 185.0, 150.2, 147.0, 138.8, 138.5, 134.1, 131.9, 129.9, 126.7, 126.1, 109.1, 76.8, 51.5, 40.4, 35.2, 32.0, 27.4, 26.1, 22.7, 16.5, 14.1. HRMS (EI): calcd for C$_{21}$H$_{24}$O$_3$ 324.17255, found 324.17288. ^{1}H NMR of **11** (endo) characteristic absorptions: 5.29 (s, 1H), 3.47 (dd, $J_1 = 8.0$ Hz, $J_2 = 6.0$ Hz, 1H), 0.93 (s, 3H), 0.87 (s, 3H).

Cordiaquinone J (12). The bicyclic ether **8** (9 mg, 0.04 mmol) reacted with 1.5 equiv of benzoquinone/6 equiv of activated MnO$_2$ in refluxing toluene for 17 h under identical conditions applied to the synthesis of **5** to afford after column chromatography (hexane/ethyl acetate = 8/1) 10 mg (75% yield) of racemic cordiaquinone J (**12**) whose NMR spectroscopic data are in full agreement with those reported in the isolation paper[4] and in the synthesis of the revised structure by Yabuta and co-workers.[9] ^{1}H NMR: 8.01 (d, $J = 8.0$ Hz, 1H), 7.89 (s, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 6.95 (s, 2H), 3.76 (d, $J = 5.5$ Hz, 1H), 2.67−2.88 (m, 2H), 1.91 (m, 1H), 1.65 (m, 2H), 1.50 (m, 2H), 1.36 (s, 3H), 1.29(m, 1H), 1.11 (s, 3H), 1.09 (s, 3H). ^{13}C NMR: 185.4, 184.9, 149.7, 138.76, 138.5, 133.8, 132.0, 130.0, 126.8, 125.98, 88.6, 86.1, 55.6, 45.3, 38.9, 36.4, 29.5, 26.1, 25.7, 23.4, 18.9.

Cordiaquinone K (13). The pure exomethylenic alcohol **10** (7 mg, 0.022 mmol), obtained after treatment of the mixture **10/11** with PTAD, reacted with PCC (10 mg, 0.04 mmol) in dichloromethane (0.3 mL). The reaction was complete within 2 h. After removal of solvent under vacuum, the residue was passed through a short pad of silica using CH$_2$Cl$_2$/Et$_2$O = 1/1 to isolate 6.2 mg of racemic cordiaquinone K (91% yield). ^{1}H NMR: 7.99 (d, $J = 8.0$ Hz, 1H), 7.84 (s, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 6.95 (s, 2H), 5.12 (s, 1H), 4.90 (s, 1H), 2.69 (m, 2H), 2.52 (m, 3H), 2.34 (m, 1H), 2.21 (m, 1H), 1.90 (m, 1H), 1.46 (m, 1H), 1.20 (s, 3H), 1.03 (s, 3H). ^{13}C NMR: 214.7, 185.3, 184.9, 149.1, 144.5, 138.8, 138.5, 134.0, 131.9, 130.1, 126.8, 126.1, 114.1, 56.0, 49.0, 37.6, 34.0, 30.7, 29.0, 27.2, 21.3.

cis-2,2-Dimethyl-4-methylene-3-(3-methylenepent-4-enyl)cyclohexyl 3-Methylbut-2-enoate (14). To a solution of alcohols **6/7** (58 mg, 0.26 mmol) in dry THF (2 mL) were added at −40 °C and under an inert atmosphere DMAP (80 mg, 0.66 mmol, 2.5 equiv) and a 1 M solution of LiHMDS in THF (330 μL, 0.33 mmol, 1.25 equiv). After 15 min, 3,3-dimethylacryloyl chloride (0.15 mL, 1.33 mmol, 5 equiv) was syringed, and the mixture was allowed to react for an additional 2 h at room temperature. Then, it was quenched with saturated solution of NaHCO$_3$. After extraction, the solvent was removed under vacuum, and the residue was chromatographed (hexane/ethyl acetate = 80/1) to afford 66 mg of a mixture of **14/15** (85% yield). ^{1}H NMR of the major **14**: 6.36 (dd, $J_1 = 17.5$ Hz, $J_2 = 10.5$ Hz, 1H), 5.66 (br s, 1H), 4.99−5.24 (m, 4H), 4.90 (s, 1H), 4.72 (dd, $J_1 = 8.5$ Hz, $J_2 = 3.5$ Hz, 1H), 4.66 (s, 1H), 2.31 (m, 2H), 2.17 (s, 3H), 2.01 (m, 2H), 1.89 (s, 3H), 1.55−1.90 (m, 5H), 0.96 (s, 3H), 0.81 (s, 3H). ^{13}C NMR of the major **14**: 166.3, 156.4, 147.0, 146.8, 139.0, 116.5, 115.6, 113.2, 109.2, 77.3, 52.0, 39.2, 31.5, 30.3, 28.8, 27.5, 27.4, 26.2, 24.4, 20.2. MS (EI): 302 (M$^+$, <1), 202 (7), 187 (8), 159 (6), 131 (14), 83 (100).

cis-3-(2-(5,8-Dioxo-5,8-dihydronaphthalen-2-yl)ethyl)-2,2-dimethyl-4-methylenecyclohexyl 3-methylbut-2-enoate (16, Cordiaquinone C). The mixture of **14/15** underwent reaction with quinone/MnO$_2$ as described in the synthesis of **5** to form a mixture of **16** (exo) and **17** (endo) in 76% yield and in a relative ratio **16/17** ~6/1. The exomethylenic **16** was purified from its mixture with **17** by reacting **16/17** with 0.25 equiv of PTAD in CDCl$_3$, just as the regioisomeric mixture **10/11** did. ^{1}H NMR of **16** (cordiaquinone C): 8.01 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 3.0$ Hz, 1H), 7.57 (dd, $J_1 = 8.0$ Hz, $J_2 = 3.0$ Hz, 1H), 6.95 (s, 2H), 5.64 (br s, 1H), 4.97 (s, 1H), 4.71 (s, 1H), 4.69 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.87 (m, 1H), 2.55 (m, 1H), 2.36 (m, 1H), 2.16 (s, 3H), 2.07 (m, 1H), 1.73−1.97 (m, 4H), 1.88 (s, 3H), 1.63 (m, 1H), 0.93 (s, 3H), 0.81 (s, 3H). ^{13}C NMR of **16** (cordiaquinone C): 185.4, 185.0, 166.2, 156.8, 150.1, 146.7, 138.8, 138.5, 134.1, 131.9, 130.0, 126.7, 126.1, 116.3, 109.8, 76.9, 51.8, 39.2, 35.0, 30.9, 28.7, 27.4, 26.4, 20.2, 18.6. HRMS (EI): calcd for C$_{26}$H$_{30}$O$_4$ 406.21441, found 406.21476.

(Z)-β-Farnesene (20).[21] A flame-dried two-necked flask was charged with dry dichloromethane (50 mL), and *cis*-nerolidol, **18** (1.73 g, 7.8 mmol), and pyridine (5 mL, 8 equiv) were added. The

(21) (a) Anet, E. F. L. *J. Aust. J. Chem.* **1970**, *23*, 2101–2108. (b) Hegedus, L. S.; Varaprath, S. *Organometallics* **1982**, *1*, 259–263.

flask was cooled to −78 °C, and then SOCl$_2$ (2.85 mL, 39.0 mmol) was added dropwise. After 30 min, the reaction mixture was quenched with water, and the organic layer was washed with a saturated solution of NaHCO$_3$. The crude reaction mixture was seen by ^{1}H NMR to be (2*E*,6*Z*)-farnesyl chloride, (2*Z*,6*Z*)-farnesyl chloride, and *cis*-nerolidyl chloride in a relative ratio of 4/1/1, respectively. The crude mixture of the chlorides was treated with 8 equiv of *t*-BuOK in THF for 2 h at 60 °C. After workup and chromatographic purification, using hexane as eluant, 1.02 g of (*Z*)-β-farnesene (**20**) was isolated (64% overall yield from *cis*-nerolidol). ^{1}H NMR: 6.38 (dd, J_1 = 17.5 Hz, J_2 = 11.0 Hz, 1H), 5.24 (d, J = 17.5 Hz, 1H), 5.14 (t, J = 7.0 Hz, 1H) 5.12 (t, J = 7.0 Hz, 1H), 5.06 (d, J = 11.0 Hz, 1H), 5.02 (s, 1H), 5.00 (s, 1H), 2.19 (m, 4H), 2.04 (m, 2H), 1.70 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.61 (s, 6H). ^{13}C NMR: 146.3, 139.1, 135.7, 131.7, 125.0, 124.5, 115.8, 113.2, 32.2, 31.9, 26.8, 26.7, 25.9, 23.6, 17.8. MS (EI): 204 (M$^+$, 5), 189 (3), 161 (31), 133 (51), 93 (92), 69 (100).

Reaction of Epoxide 4 with SnCl$_4$. To a solution of epoxide **5** (162 mg, 0.50 mmol) in dry dichloromethane (2 mL) were added at 0 °C and 0.25 mL of SnCl$_4$ (1 M in CH$_2$Cl$_2$). After 40 min, the reaction was quenched with saturated solution of NaHCO$_3$, and the organic layer was washed with brine. The organic residue (132 mg) was chromatographed using hexane/ethyl acetate = 10/1 as

eluant to afford 63 mg of cordiaquinone J (**12**), 28 mg of cordiaquinone B (**30**), and 20 mg of an inseparable mixture containing the regioisomers **10**, **11**, and **31** in a relative ratio of ~0.8/1.0/0.4, respectively. ^{1}H NMR of cordiaquinone B (**30**): 8.00 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.56 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 6.95 (s, 2H), 2.78 (dt, J_1 = 13.0 Hz, J_2 = 5.5 Hz, 1H), 2.62 (m, 2H), 2.40 (m, 2H), 2.13 (m, 1H), 1.91 (m, 1H), 1.58−1.73 (m, 3H), 1.01 (d, J = 7.5 Hz, 3H), 0.99 (d, J = 7.5 Hz, 3H), 0.61 (s, 3H). ^{13}C NMR: 213.1, 185.3, 184.8, 149.5, 138.8, 138.5, 133.9, 132.1, 130.1, 126.9, 125.9, 50.4, 43.7, 41.5, 38.8, 36.3, 30.8, 29.5, 22.6, 15.2, 7.8.

Supporting Information Available: Experimental details for the synthesis of compounds **21**−**28**. Copies of ^{1}H and ^{13}C NMR spectra of all compounds; copies of the HRMS spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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