PERKIN 1

Synthesis, iron(II)-induced cleavage and *in vivo* antimalarial efficacy of 10-(2-hydroxy-1-naphthyl)-deoxoqinghaosu (-deoxoartemisinin)

Dong-Ye Wang,[a] Yikang Wu,*[a] Yu-Lin Wu,*[a] Ying Li*[b] and Feng Shan[b]

[a] *State Key Laboratory of Bio-organic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China. E-mail: yikangwu@pub.sioc.ac.cn; E-mail: ylwu@pub.sioc.ac.cn*
[b] *Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, China*

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A convenient methodology for attaching an acid-stable UV chromophore onto the qinghaosu (artemisinin) framework with readily available dihydroqinghaosu acetate as the starting material is presented. The resulting derivatives of deoxoqinghaosu may be used as a sensitive probe in the mechanistic and biological/pharmacological investigations. As the first application of the present methodology, naphth-2-ol is attached to qinghaosu nucleus through a carbon–carbon single bond by a boron trifluoride-catalyzed Friedel–Crafts alkylation. A previously undetected racemization at C-9 mediated by an enol ether under the reaction conditions ($BF_3 \cdot OEt_2$, CH_2Cl_2) that have been widely used for preparing C-10 derivatives of dihydroqinghaosu is observed. The knowledge gained from the present work may assist the rational design of new trioxane-type antimalarial agents.

Introduction

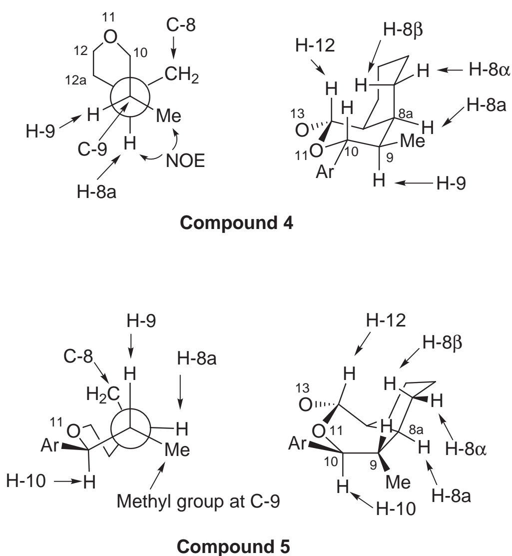
Qinghaosu (artemisinin, **1**, abbreviated as QHS below), a sesquiterpene 1,2,4-trioxane, was isolated[1] in 1971 from the Chinese medicinal herb qinghao (*Artemisia annua* L.), which has been used as a herbal remedy for fever and malaria for millennia in China. In preliminary pharmacological tests this compound already showed rather high antimalarial activity and surprisingly low toxicity, giving the first sign of its great potential as a novel weapon against malaria (a disease that affects some 200–300 million people worldwide every year), especially the multidrug-resistant[2] variants. Following the impressive success of large-scale clinical trials in several southern provinces of China, QHS (together with its derivatives artemether and artesunate) and dihydro-QHS were approved by the Chinese authorities as new antimalarial drugs in 1986, 1987 and 1992, respectively. By that time the outstanding antimalarial efficacies of QHS-derived compounds were also undoubtedly confirmed in clinical trials under the supervision of the World Health Organization (WHO) in many other countries. From then on QHS-derived antimalarial drugs have found extensive clinical applications around the world.

Since the discovery of qinghaosu many fundamental aspects of the biological action and the molecular pharmacology of this type of endoperoxide have been elucidated. The unique 1,2,4-trioxane framework of QHS-type compounds, which is totally different from that of all previously existing antimalarial agents, strongly suggests an entirely different mode of action. A considerable number of efforts have therefore been dedicated to the elucidation of their antimalarial mechanism. Although so far no definite conclusion can be drawn yet, the cleavage of the peroxide bond caused by Fe^{II} ion, one of the abundant ions in parasitized erythrocytes, has been paid almost exclusive attention. It is generally agreed now that the carbon-centred free radicals generated in the course of degradation–rearrangement of QHS and the like may play a major role in the killing of malaria parasites.

While working[3] over the years on the synthesis and structure–activity relationship of QHS derivatives and analogues, we also paid substantial attention to mechanistic studies. Recently we reported on the Fe^{II}-induced cleavage[4] of the peroxide bond in QHS and its derivatives and the DNA damage associated with this process. We introduced a unified mechanistic framework[5] to rationalize the divergent results from different Fe^{II}-induced cleavage experiments and to facilitate the evaluation of their relevance to the *in vivo* parasiticidal activity. In order to afford a sounder basis for probing the chemical and biological processes that QHS-derived compounds may participate in, we designed and synthesized a few novel QHS derivatives that carry a UV chromophore through a C–C σ bond. This type of compound is expected to greatly improve the feasibility of tracing the backbone of the QHS-derived compounds in the course of chemical and/or biological degradation because of the ease of detection with UV light of instrumentally practical wavelengths and the much better stability of the C–C bond (connecting the QHS nucleus and the UV chromophore) to the acids than the 'traditional' hemiacetal O–C bond as in the dihydroqinghaosu derivatives. Below, we report the synthesis and Fe^{II}-induced degradation–rearrangement of one (two) such compound(s), along with their *in vivo* antimalarial efficacy.

Results and discussion

The synthesis of 10-(2-hydroxy-1-naphthyl)-deoxoQHS was achieved as shown in Scheme 1. Starting from the known **2**[6] prepared by a simple reduction of **1** with $NaBH_4$ in MeOH, acetylation with acetic anhydride–pyridine in CH_2Cl_2 in the presence of a catalytic amount of DMAP [4-(dimethylamino)-pyridine] led to the acetate **3**[7] in 87% yield. The following Friedel–Crafts alkylation at C-1 of the 2-naphthol using **3** (an activated[8] acetal) as alkylating agent proceeded smoothly under the catalysis of $BF_3 \cdot OEt_2$, giving **4** and **5** in 68% yield as a nearly 1:1 mixture. Although pure analytical samples of both compounds could be obtained by very careful column chromatography followed by recrystallization, which made it possible for us to characterize **4** and **5** separately, it is not practical to



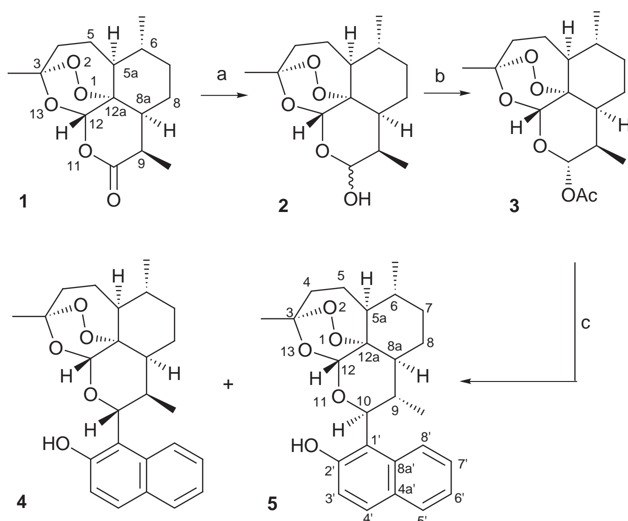


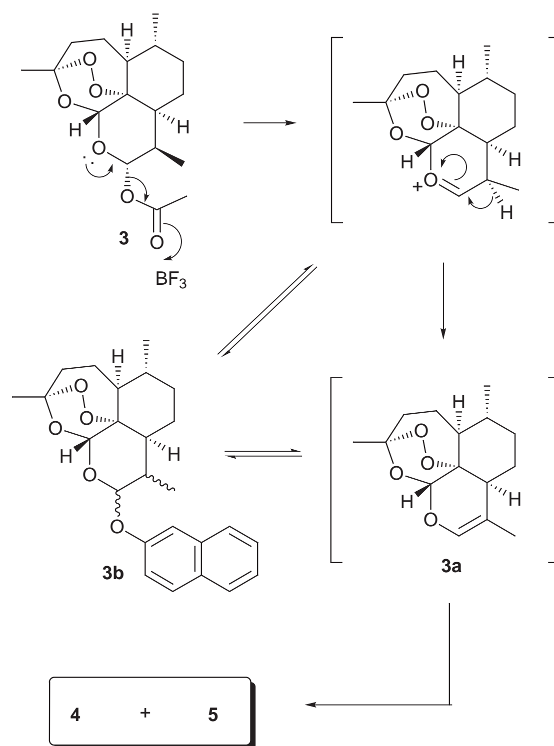
Fig. 1 Newman representations viewing from C-9 along the C-9–C-8a bond and partial structures of compounds **4** and **5**.

Scheme 1 *Reagents, conditions and yields*: (a) $NaBH_4$, MeOH, 90%; (b) Ac_2O, py, DMAP, 87%; (c) $BF_3{\cdot}OEt_2$, 2-naphthol, CH_2Cl_2, 68%.

conduct preparative separation due to the extremely similar chromatographic behavior of the two compounds. For this reason, the mixture of **4** and **5** as recovered from column chromatography was used in the following Fe^{II} cleavage experiments.

The structural assignments of **4** and **5** were made on the basis of the spectroscopic data. These two compounds gave almost the same ^1H NMR spectra. The H-10 in both compounds appears as a doublet with a *J*-value of about 11 Hz, indicating a nearly 180° dihedral angle (*anti*) with respect to H-9. The chemical shifts of the doublets are, however, different (δ 5.58 in **4** and 6.36 in **5**). The doublets for the methyl groups at C-9 show a similar difference in their chemical shifts (δ 0.60 *vs.* 0.93). Obviously, **4** and **5** are a pair of diastereomers that have opposite configurations at C-9 and C-10. To assign the absolute configurations at these positions, DQF-COSY, NOESY, and HMQC (2D NMR) experiments were performed. Compound **4** shows several diagnostic cross-peaks (*e.g.*, one correlating H^{β}-8/H-10 and another two correlating the Me at C-9 with H^{α}-8 and H-8a, respectively) in the NOESY spectrum. If judging only from the planar drawing of **4**, one might think that there should not be any NOE between the Me at C-9 and H-8a, since they are *trans* to each other. However, the actual dihedral angle between them is about 60° as shown in a Newman representation (Fig. 1). Therefore, the observed NOE poses no contradiction. Other NOEs expected for this configuration are all observed.

The other isomer (**5**) has different configurations at C-9 and C-10, which lead to a conformational change from the chair (as in **4**) to a skewed-boat to avoid the severe repulsions between, *e.g.*, the aryl group and H^{β}-8 as well as H-12. However, the methyl group at C-9 and the aryl group at C-10 are still in a *trans* arrangement, with the protons at these two carbons almost *anti* to each other as suggested by the splitting ($J = 11$ Hz) of H-10 in the ^1H NMR spectrum and further confirmed by the NOEs in the NOESY spectrum. Unlike in enomer **4**, this time there is absolutely no NOE at all between H^{α}-8 and the Me at C-9. Nevertheless, a strong cross-peak correlating H-9/H^{α}-8 and another correlating H-12/H^{β}-8 are still recorded. The occurrence of the unexpected racemization at C-9 is believed to occur *via* enol ether **3a** (see Scheme 2), which has been obtained



Scheme 2

previously[7] under comparable conditions. A small-scale diagnostic run using **3a** instead of **3** as the starting material under the same reaction conditions did show spots on TLC at the positions where **4** and **5** were supposed to appear. Close monitoring of the reaction of **3** also disclosed that a product of low polarity (presumably **3b**) formed quickly in substantial amounts before any **4** and **5** could be spotted on TLC, but disappeared gradually with the formation of **4** and **5**. It deserves to be noted here that such conversion of configuration at C-9 during modification at C-10 has not been recorded before, although similar reaction conditions have been broadly used for preparing numerous dihydroQHS derivatives including artemether, arteether, and artesunate (marketed antimalarial drugs) in the last two decades.

The cleavage experiment of **4** and **5** with $FeSO_4$ (Scheme 3) was carried out in aq. acetonitrile at 37 °C for 3 days (the starting material was still not fully consumed). The reaction is remarkably slower than that for many other QHS derivatives we have tested before, presumably due to the significantly increased hydrophobic interaction and/or the steric bulk associated with the naphthyl group. Four major products were isolated from this reaction and characterized (Scheme 3). The most abundant product **6** has no precedents in our earlier experiments. This

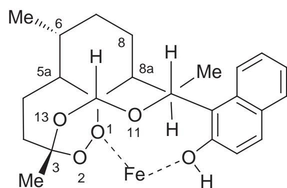
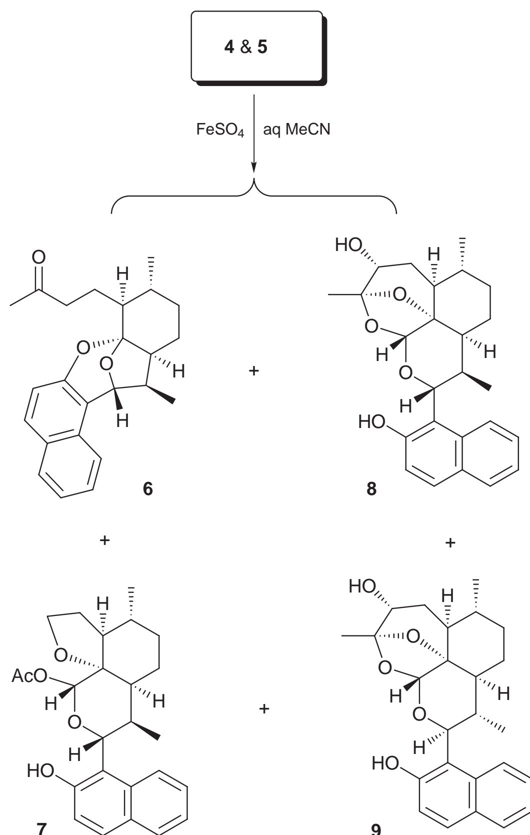


Fig. 2 The origin of the relatively high reactivity (compared with **5**) and the preference for the O-2 radical route.



Scheme 3

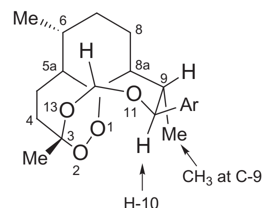
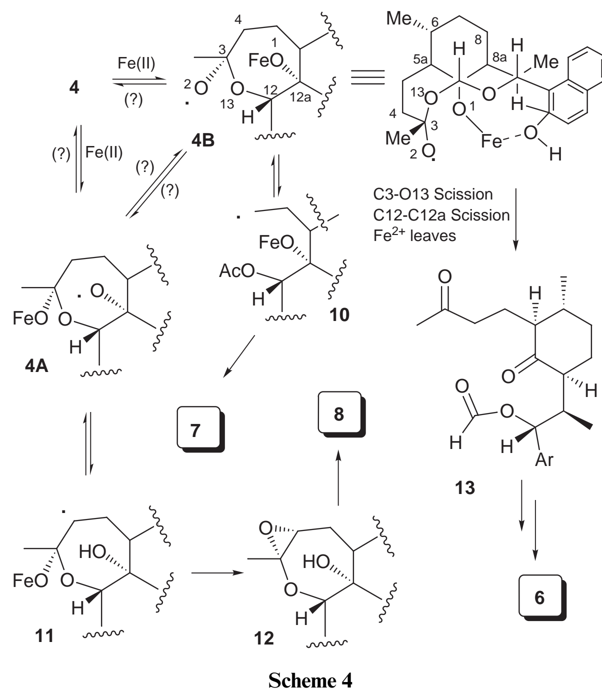


Fig. 3 The CH_3 at C-9 and the H-10 in **5** are all in close vicinity to the peroxy bridge. They effectively fend off the attack of the Fe^{II} ion and thus greatly reduce the cleavage rate.



Scheme 4

compound has the same polarity as **4** and **5** on TLC. Therefore its separation can be realized only after treating the mixture with acetic anhydride, which converts **4** and **5** into the corresponding acetates but has no effects on **6**.

The product distribution pattern of this reaction is very interesting. It shows that the two diastereomers react at highly different rates. Each isomer has its own preferred mechanistic route. Compound **4**, the isomer that retains the original stereochemistries of the QHS framework at C-9 and C-10, shows significantly higher reactivity towards the Fe^{II} ion than does **5**. After 3 days of reaction, almost all **4** has been consumed. It appears that the reductive cleavage by Fe^{II} occurs almost exclusively at O-1, generating an 'O-2' radical. After careful inspection of the molecular model, we believe that this unusually high selectivity is most likely due to the participation of the phenolic OH as shown in Fig. 2. The resulting O-2 radical evolves further along two different sub-paths (Scheme 4); one leading to the C-4 primary radical **10**, and the other to **13**. The radical substitution at O-1 leading to **7** is probably slower than without the participation of the phenolic OH, providing enough time for the less common sequential scissions to manifest. The resulting **13** soon loses the formyl group and forms cyclic ketal **6** in the acidic reaction medium.

Compound **5** is much less reactive than **4**. The recovered starting material is almost exclusively **5** as shown by ^1H NMR. This lower reactivity is now attributed to the steric congestion around the peroxy bridge (Fig. 3), especially near the O-1 atom. The CH_3 at C-9 and the H-10 are in close vicinity to O-1, which blocks the way for Fe^{II} to attack O-1. The relatively less hindered electron transfer from Fe^{II} to O-2 can result only in the O-1 radical (which leads to **9**). This explains why no normal 'O-2' products were formed.

To confirm the configuration assignments of C-9 and C-10 in the products **6** and **7** and the unusual composition of the product mixture, the pure substrate **5** recovered from the aforementioned 'kinetic resolution' of the diastereomeric mixture of **4** and **5** was subjected to the same reaction conditions again. This time the starting material was consumed at a much lower rate than when starting with a mixture of **4** and **5**, and neither **6** and/or **7** nor their diastereomers were detected, confirming that the compounds **6** and **7** were indeed formed from **4** and that their configurations at C-9 and C-10 were as depicted above.

Model systems were first introduced to help to clarify the situations in complex physiological systems. This function can be clearly seen from Posner's[9] demonstration of the iron-mediated degradation of qinghaosu in 1992 and the subsequent[4,9,10] studies on model systems, which played an indispensable role in establishing the radical nature of the process in the erythrocytes. The results of model studies were also used to rationalize the variations in antimalarial potency caused by structural modification. There have been some attempts[11] to evaluate the role of each individual carbon-centred radical generated in the course of the cleavage in the antimalarial mechanism. Although conclusions from these endeavors are still open to reconsideration, this approach did inspire further investigations to pinpoint the main lethal entity. The present work may be of great value to studies along this line, as it is the very first case ever recorded where one of the

Table 1 The ED_{50}- and ED_{90}-values against *Plasmodium berghei* K173 strain (administered orally to mice as suspensions in Tween 80)

Cmpd	ED_{50} (mg kg^{-1})	ED_{90} (mg kg^{-1})
4	0.58	1.73
5	7.08	60.99
Artemether	1.00	3.10

two cleavage routes ('O-1' and 'O-2' routes, see ref. 5) predominates over another to such an overwhelming extent.

The successful 'tuning' of the reaction path as illustrated in this work may open up a new dimension for structure–activity relationship studies. Indeed, up to now almost all the efforts in this aspect have been limited to simply relating the structural changes of the starting trioxane to the *in vitro* antimalarial efficacy without paying any attention to the corresponding changes in the cleavage route and the reactive intermediates. Many previously puzzling[12] results can, in fact, be easily understood in terms of steric as well as electronic effects if using three-dimensional structures instead of the commonly employed two-dimensional drawings (the latter can be very much misleading in the present context due to the unique method of ring junction in the QHS framework) as long as one has gained enough knowledge of the iron(II)-induced cleavage process. Introduction of the notion of 'route-tuning' (*i.e.*, directing the radical evolution to a particular route) and evaluating the influence of the substituents using three-dimensional models may greatly improve our understanding of the variation in the antimalarial efficacy associated with the structural alterations, and facilitate the rational design of more potent 1,2,4-trioxane antimalarial agents.

The isomer **4**, which has the 'normal' configuration (*i.e.*, the same configuration as in QHS) at C-9, showed high antimalarial efficacy in the preliminary *in vivo* test on mice against *Plasmodium berghei* K173 strain. The ED_{50}- and ED_{90}-values are listed in Table 1, with the corresponding data for artemether shown as references. The 'abnormal' isomer **5** is obviously much less potent than **4**. It should be noted that although many trioxanes have been subjected to the cleavage conditions in model systems and many have been tested for their antimalarial efficacy (either *in vitro* or *in vivo*), the cleavage results and antimalarial efficacy of such a pair of molecules differing from each other only in the configuration at C-9 (and C-10) have never been available before. The present work represents the first piece of experimental evidence that shows the ease with which the peroxide bond is cleaved may directly be related to the antimalarial potency of the trioxane.

Experimental

All 2D NMR experiments were performed on a Varian Inova spectrometer operating at 600 MHz for proton. The mixing time used in the NOESY spectra was 1.000 s. Detailed signal assignments in ^{13}C and ^{1}H NMR are based on the DQF-COSY, HMQC, and NOESY spectra. Column chromatography was performed on silica gel (300–400 mesh). P.E. stands for petroleum ether (distillation range 60–90 °C). Reagents (C.P. or A.R.) were used as received without further purification. Mps were measured on a ZMD-2 apparatus and are uncorrected.

DihydroQHS acetate 3[7]

DihydroQHS **2**[6] (1.37 g, 4.82 mmol) was dissolved in dry dichloromethane (65 cm^3). To this solution were added pyridine (0.6 cm^3, 7.46 mmol), acetic anhydride (0.8 cm^3, 8.48 mmol) and DMAP. The mixture was stirred at 25 °C until TLC showed the disappearance of the starting material. The solution was washed successively with 1 M HCl and saturated aq. salt, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (7:1 P.E.–EtOAc) to give the product **3** (1.36 g, 87%); δ_H (300 MHz, $CDCl_3$) 5.78 (d, 1H, *J* 9.9 Hz, H-10), 5.44 (s, H-12), 2.58 (m, 1H, H-9), 2.33 (m, 2H), 2.12 (s, 3H, AcO), 1.43 (s, 3H, CH_3 at C-3), 0.91 (d, 3H, *J* 5.9 Hz, CH_3 at C-6), 0.84 (d, 3H, *J* 7.1 Hz, CH_3 at C-9).

Compounds 4 and 5

Acetyl-dihydroQHS (**3**, 2.0 g, 6.0 mmol) and 2-naphthol (1.04 g, 7.2 mmol) were dissolved in dry dichloromethane (100 cm^3). To this mixture (at 0 °C) was added boron trifluoride–diethyl ether (0.08 cm^3). The mixture was stirred at 0 °C for 2 h before the temperature was raised to 25 °C. After 7 h the reaction was quenched with distilled water (10 cm^3) and the resultant mixture was washed in turn with aq. $NaHCO_3$ and brine. The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The resultant oil was purified by column chromatography (P.E.–EtOAc 15:1) to provide an almost 1:1 mixture of **4** and **5** (1.68 g, 68%). Physical and spectroscopic data for compound **4**: Colorless scales, mp 162–165 °C (Found: C, 73.00; H, 7.42. $C_{25}H_{30}O_5$ requires C, 73.15; H, 7.37%); $[\alpha]_D^{22}$ +224.2 (*c* 1.07, $CHCl_3$); δ_C (150 MHz, $CDCl_3$) 154.46 (q, C-2′), 132.50 (q), 129.76 (C-4′), 128.78 (C-5′), 128.53 (q), 126.10 (C-7′), 122.51 (C-6′), 121.60 (C-8′), 120.37 (C-3′), 115.75 (q), 105.21 (q, C-3), 92.15 (C-12), 81.22 (q, C-12a), 73.11 (C-10), 51.58 (C-5a), 45.88 (C-8a), 37.59 (C-6), 35.99 (C-4), 34.19 (C-7), 31.32 (C-9), 25.97 (CH_3 at C-3), 24.91 (C-5), 21.26 (C-8), 20.22 (CH_3 at C-6), 14.20 (CH_3 at C-9); δ_H (600 MHz, $CDCl_3$) 8.90 (s, 1H, OH), 7.78 (d, 1H, *J* 8.9 Hz, H-8′), 7.78 (d, 1H, *J* 10.6 Hz, H-5′), 7.70 (d, 1H, *J* 8.9 Hz, H-4′), 7.41 (t, 1H, *J* 7.4 Hz, H-7′), 7.28 (t, 1H, *J* 7.6 Hz, H-6′), 7.18 (t, 1H, *J* 8.8 Hz, H-3′), 5.58 (d, 1H, *J* 11.3 Hz, H-10), 5.54 (s, 1H, H-12), 3.11 (m, 1H, H-9), 2.48 (dt, 1H, *J* 14.2, 4.3 Hz, H^{β}-4), 2.08 (m, 1H, H^{α}-4), 1.96 (m, 1H, H^{α}-5), 1.93 (m, 1H, H^{α}-8), 1.83 (m, 1H, H^{β}-7), 1.78–1.65 (m, 2H, H^{β}-8 and H-8a), 1.57 (m, 1H, H^{β}-5), 1.48 (s, 3H, CH_3 at C-3), 1.47 (m, 1H, H-6), 1.40 (m, 1H, H-5a), 1.12 (m, 1H, H^{α}-7), 1.01 (d, 3H, *J* 5.9 Hz, CH_3 at C-6), 0.60 (d, 3H, *J* 7.2 Hz, CH_3 at C-9); ν_{max}(KBr)/cm^{-1} 3352, 1622, 1600, 1522, 1100, 880, 820; *m/z* 410 (M^+, 8.7%), 364 (5.3), 195 (35.6), 182 (100), 165 (19.5), 43 (59.0).

Physical and spectroscopic data for **5**: colorless needles, mp 168–175 °C (from hexane-ethyl acetate). (Found: C, 73.13; H, 7.56%); $[\alpha]_D^{22}$ +85.8 (*c* 1.20, $CHCl_3$); δ_C (150 MHz, $CDCl_3$) 154.24 (q, C-2′), 133.00 (q), 129.85 (C-4′), 128.70 (q), 128.52 (C-5′), 126.43 (C-7′), 122.80 (C-6′), 122.44 (C-8′), 119.70 (C-3′), 117.23 (q), 102.76 (q, C-3), 90.85 (C-12), 82.03 (q, C-12a), 73.55 (C-10), 51.50 (C-5a), 47.47 (C-8a), 41.35 (C-9), 37.42 (C-6), 36.50 (C-4), 34.08 (C-7), 32.13 (C-8), 25.72 (CH_3 at C-3), 24.83 (C-5), 20.16 (CH_3 at C-9), 19.83 (CH_3 at C-6); δ_H (600 MHz, $CDCl_3$) 8.17 (s, 1H, OH), 8.02 (d, 1H, *J* 8.7 Hz, H-8′), 7.75 (d, 1H, *J* 9.4 Hz, H-5′), 7.72 (d, 1H, *J* 9.3 Hz, H-4′), 7.46 (t, 1H, *J* 7.5 Hz, H-7′), 7.30 (t, 1H, *J* 7.5 Hz, H-6′), 7.15 (d, 1H, *J* 8.8 Hz, H-3′), 6.36 (d, 1H, *J* 11.0 Hz, H-10), 5.71 (s, 1H, H-12), 2.40 (dt, 1H, *J* 14, 3.7 Hz, H^{α}-4), 2.09 (m, 1H, H^{β}-4), 2.05 (m, 1H, H-9), 2.02 (m, 1H, H^{α}-5), 1.84 (m, 1H, H^{α}-8), 1.68 (m, 1H, H^{β}-7), 1.59 (m, 1H, H-8a), 1.48 (m, 1H, H^{β}-8), 1.44 (m, 1H, H^{β}-5), 1.43 (s, 3H, CH_3 at C-3), 1.38 (m, 2H, H-5a and H-6), 1.09 (m, 1H, H^{α}-7), 1.01 (d, 3H, *J* 5.3 Hz, CH_3 at C-6), 0.93 (d, 3H, *J* 7.0 Hz, CH_3 at C-9); ν_{max}(KBr)/cm^{-1} 3362, 1622, 1599, 1523, 1008; *m/z* 410 (M^+, 64.9%), 195 (69.1), 184 (81.5), 183 (66.9), 182 (100), 43 (53.1).

The reaction of 4 and 5 with ferrous [iron(II)] sulfate

A mixture of **4** and **5** (1.68 g, 4.1 mmol) was dissolved in MeCN (40 cm^3). A solution of $FeSO_4 \cdot 7H_2O$ (1.71 g, 6.1 mmol) in water (40 cm^3) was added slowly. The mixture was stirred at 37 °C under a nitrogen atmosphere for 3 days. The precipitates were filtered off. The filtrate was concentrated under reduced pressure to remove MeCN. The residue was extracted with ethyl

acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (15:1–2:1 P.E.–EtOAc) to give recovered starting material that contained only **5** (448 mg, 1.09 mmol) as shown by ^{1}H NMR, a mixture of **4** (only traces as shown later by separation as acetate), **5**, and **6** (768 mg, <2.1 mmol), **7** (200 mg, 0.49 mmol), and a mixture **8** (minor) and **9** (100 mg altogether, 0.24 mmol), which were very difficult to separate from each other. Very careful chromatography plus partial crystallization provided some pure **8** and pure **9** for analyses. The mixture of **4**, **5** and **6** was treated with acetic anhydride to give pure **6** (550 mg, 1.51 mmol), acetate of **4** (traces), and acetate of **5**.

Physical and spectroscopic data for compound **6**: A sticky gum (Found: C, 78.97; H, 7.99. $C_{24}H_{28}O_3$ requires C, 79.09; H, 7.74%); $[\alpha]_D^{22}$ +64.3 (*c* 1.14, $CHCl_3$); δ_C (75 MHz, $CDCl_3$, assigned on the basis of DEPT experiments) 211.20 (q), 150.76 (q), 132.56 (q), 130.70 (CH), 130.37 (CH), 129.87 (q), 128.29 (CH), 124.74 (CH), 122.83 (CH), 119.37 (CH), 117.83 (q), 112.44 (q), 78.70 (CH), 56.39 (CH), 51.19 (CH), 48.70 (CH), 44.02 (CH_2), 34.63 (CH), 32.37 (CH_2), 31.59 (CH_3), 31.06 (CH_2), 24.07 (CH_2), 23.20 (CH_3), 16.10 (CH_3); δ_H (300 MHz, $CDCl_3$) δ 7.73 (d, 1H, *J* 8.1 Hz, ArH), 7.66 (d, 1H, *J* 9.1 Hz, ArH), 7.63 (d, 1H, *J* 10.3 Hz, ArH), 7.43 (dt, 1H, *J* 6.9, 1.2 Hz, ArH), 7.28 (t, 1H, *J* 7.9 Hz, ArH), 6.97 (d, 1H, *J* 8.8 Hz, ArH), 5.68 (d. 1H, *J* 6.7 Hz, 10-H), 2.70 (m, 1H), 2.57 (m, 1H), 2.49 (m, 1H), 2.02 (s, 3H, $CH_3C{=}O$), 1.08 (d, 3H, *J* 6.5 Hz, CH_3 at C-6), 0.75 (d, 3H, *J* 7.0 Hz, CH_3 at C-9); ν_{max}(KBr)/cm^{-1} 1715, 1625, 1598, 1518; *m/z* 364 (M^+, 36.3%), 346 (27.4), 195 (33.4), 183 (46.7), 182 (100), 181 (35.8), 157 (21.3), 43 (35.1).

Physical and spectroscopic data for compound **7**: Colorless crystals; mp 105–110 °C (Found: C, 73.38; H, 7.77. $C_{25}H_{30}O_5$ requires C, 73.15; H, 7.37%); $[\alpha]_D^{22}$ +97.4 (*c* 1.13, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.79 (d, 1H, *J* 8.6 Hz), 7.74 (d, 1H, *J* 8.1 Hz), 7.70 (d, 1H, *J* 8.9 Hz), 7.42 (dt, 1H, *J* 6.9, 1.2 Hz), 7.28 (t, 1H, *J* 7.5 Hz), 7.17 (d, 1H, *J* 9.0 Hz), 6.33 (s, 1H), 5.62 (d, 1H, *J* 11.4 Hz), 4.33 (dt, 1H, *J* 8.63, 2.0 Hz), 4.03 (m, 1H), 2.87 (m, 1H), 2.10 (s, 3H), 0.98 (d, 3H, *J* 6.1 Hz), 0.66 (d, 3H, *J* 7.1 Hz); ν_{max}(KBr)/cm^{-1} 3378, 1760, 1622, 1601, 1523; *m/z* 410 (M^+, 5.6%), 350 (43.8), 195 (36.5), 184 (100), 183 (64.1), 169 (47.8), 165 (86.7), 138 (39.3), 43 (33.5).

Physical and spectroscopic data for compound **8**: HRMS Found: M^+, 410.2068. $C_{25}H_{30}O_5$ requires *M*, 410.2093; $[\alpha]_D^{22}$ +51.1 (*c* 0.98, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 8.75 (s, 1H, OH), 7.70 (m, 3H), 7.40 (t, 1H, *J* 7.6 Hz), 7.27 (t, 1H, *J* 7.2 Hz), 7.15 (d, 1H, *J* 8.8 Hz), 5.67 (d, 1H, *J* 10.9 Hz), 5.46 (s, 1H) 3.63 (d, 1H, *J* 2.1 Hz), 1.70 (s, 3H), 0.92 (d, 3H, *J* 6.1 Hz), 0.54 (d, 3H, *J* 7.2 Hz); ν_{max}(KBr)/cm^{-1} 3587, 3323, 1622, 1600, 1523; *m/z* 410 (M^+, 73.7%), 409 (71.9), 391 (10.3), 312 (16.6), 289 (13.5), 221 (21.3), 195 (58.9), 184 (100), 169 (57.0), 157 (40.0), 43 (65.1).

Physical and spectroscopic data for compound **9**: (Found: C, 72.95; H, 7.35. $C_{25}H_{30}O_5$ requires C, 73.15; H, 7.37%); δ_H (300 MHz, $CDCl_3$) 7.95 (s, 1H, OH), 7.86 (d, 1H, *J* 8.5 Hz), 7.76 (d, 1H, *J* 8.5 Hz), 7.73 (d, 1H, *J* 11.1 Hz), 7.47 (t, 1H, *J* 7.7 Hz), 7.31 (t, 1H, *J* 7.4 Hz), 7.16 (d, 1H, *J* 8.8 Hz), 5.81 (d, 1H, *J* 10.6 Hz), 5.52 (s, 1H), 3.65 (s, 1H), 1.77 (s, 3H), 0.98 (d, 3H, *J* 10.0 Hz), 0.93 (d, 3H, *J* 6.2 Hz); ν_{max}(KBr)/cm^{-1} 3501, 3409, 1622, 1601, 1523 cm^{-1}; *m/z* 410 (M^+, 87.1%), 195 (39.1), 184 (92.1), 183 (68.0), 174 (39.1), 169 (82.1), 157 (46.5), 43 (100).

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