An enantiospecific route towards taiwaniaquinoids. First synthesis of (–)-taiwaniaquinone H and (–)-dichroanone†

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Received 7th August 2009, Accepted 21st September 2009
First published as an Advance Article on the web 21st October 2009
DOI: 10.1039/b916209g

A new methodology for the enantiospecific synthesis of taiwaniaquinoids, based on a thermal 6π electrocyclization, is reported. Under this procedure, 4a-methylhexahydrofluorene terpenoids bearing an A/B *trans*-configuration has been prepared for the first time. This methodology also makes it feasible to synthesize taiwaniaquinoids with an A/B *cis*-configuration and 4a-methyltetrahydrofluorene terpenoids. Accordingly, the first synthesis of (–)-taiwaniaquinone G, (–)-taiwaniaquinone H and (–)-dichroanone has been achieved.

Introduction

Several rearranged terpenoids possessing the uncommon 4a-methyltetra- (and hexa-)hydrofluorene skeleton have been described during the past decade. These compounds, known as taiwaniaquinoids, were isolated from certain species of East Asian conifers. Among these, let us mention taiwaniaquinones A (**1**),[1a] D (**2**),[1b] G (**3**)[1d] and H (**4**),[1d] and taiwaniaquinols A (**5**),[1a] B (**6**)[1a] and C (**7**),[1a] isolated from *Taiwania cryptomerioides*,[1] dichroanone (**8**), obtained from *Salvia dichroantha*,[2] and standishinal (**9**), found in *Thuja standishii* (Fig. 1).[3] Hexahydrofluorene derivatives with an A/B *trans*-, *e.g.* compounds **1** and **3**, or *cis*-configuration, *e.g.* compound **6**, have been isolated. Moreover, in some cases, one carbon is lost in the course of the biosynthesis to give norditerpenoids, such as compounds **4** and **8**.

Although not much is known about their bioactivities, recent studies have revealed that taiwaniaquinones A (**1**) and D (**2**), and taiwaniaquinols A (**5**) and C (**7**) exhibit cytotoxic activity,[1d] and that standishinal (**9**) is a potential antitumor agent for treating breast cancer due to its aromatase inhibitory activity.[4]

These promising biological activities and the peculiar carbotricyclic structure of this family of compounds have motivated the development of varied synthetic approaches. Four main strategies have been utilized for the construction of the core 6,5,6-ABC tricyclic skeleton of taiwaniaquinoids. An A-AB-ABC approach[5] was used by McFadden and Stoltz for synthesizing (+)-dichroanone (**8**), the antipode of the natural product; the 5-membered B ring was formed *via* a novel asymmetric palladium-catalyzed allylation.[6] The C-ABC strategy, involving a bis-cyclization process, was utilized in the synthesis of

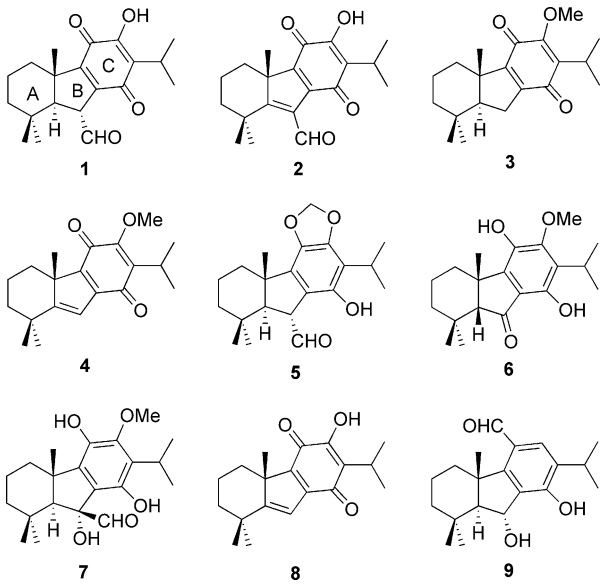

Fig. 1 Some representative taiwaniaquinoids.

(±)-taiwaniaquinol B (**6**) reported by Fillion and Fishlock, through a domino intramolecular acylation carbonyl α-*tert*-alkylation reaction.[7] The same strategy was utilized by Li and Chiu, who synthesized compound **6** *via* an intramolecular acid-promoted sequential cationic cyclization.[8] The AC-ABC approach is currently the most widely utilized strategy for synthesizing this type of terpenoid. The process usually involves the utilization of a monoterpene synthon, such as β-cyclocitral or cyclogeranic acid, together with a phenol derivative to construct the 4a-methyl- (or hexa-)hydrofluorene skeleton. Node *et al.*[9] and Banerjee *et al.*[10] utilized intramolecular Heck reactions to prepare some compounds of this family of metabolites. Trauner *et al.* described an interesting synthetic approach toward taiwaniaquinoids utilizing a Nazarov cyclization.[11] Recently, She *et al.* described the synthesis of compounds **6** and **8** using an acid-promoted Friedel–Crafts acylation/alkylation process, which allows the elaboration of the ABC tricyclic skeleton in one step.[12] Very recently, our group described a very short synthesis of (±)-taiwaniaquinone H (**4**) and

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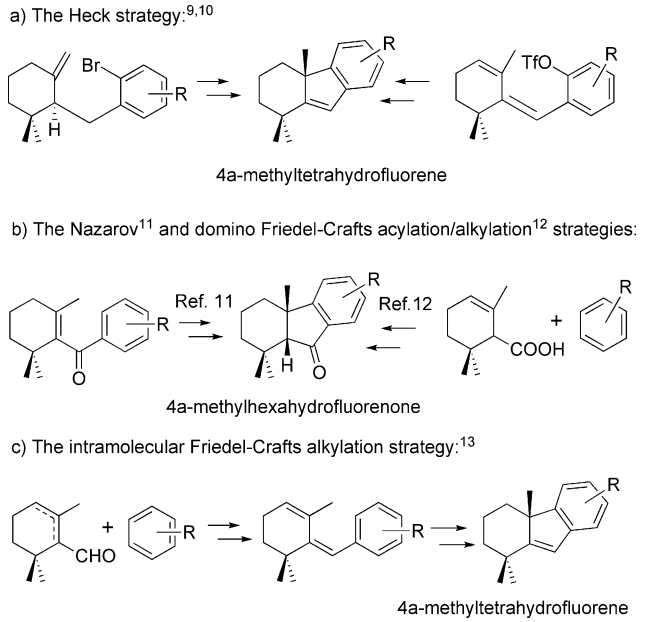
† Electronic supplementary information (ESI) available: Experimental procedures for compounds **17**, **18**, **22**, **28**, **33** and **37**, and copies of ^{1}H and ^{13}C NMR for all novel compounds. See DOI: 10.1039/b916209g

(±)-dichroanone (**8**), through an intramolecular Friedel–Crafts alkylation[13] (Scheme 1).



Scheme 1 Previously reported strategies starting from a monoterpene (AC-ABC approach)

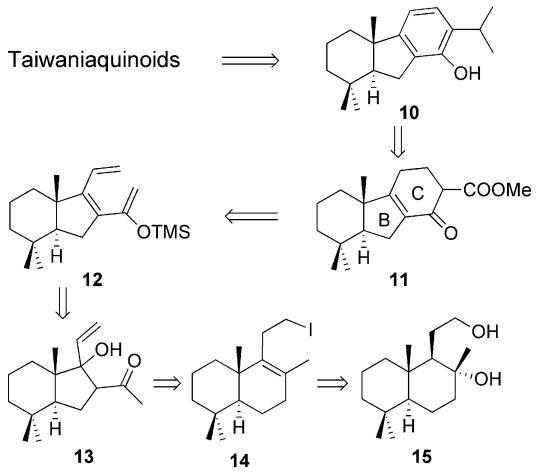
All the previously reported approaches are total syntheses. Moreover, all these methods are restricted to synthesizing compounds with an A/B *cis*-configuration or a cyclopentane double bond, such as compounds **6** and **8**, respectively. Our group recently communicated the first route towards taiwaniaquinoids bearing an A/B *trans*-configuration *via* a thermal 6π electrocyclization; furthermore, this new procedure, which utilizes chiral precursors with the same absolute configuration on the AB junction carbons, makes it feasible to address the enantiospecific synthesis of natural taiwaniaquinoids.[14]

In this paper, we report our studies on the synthesis towards this family of compounds, utilizing the 6π electrocyclization strategy, and its possible application to obtaining different types of taiwaniaquinoids.

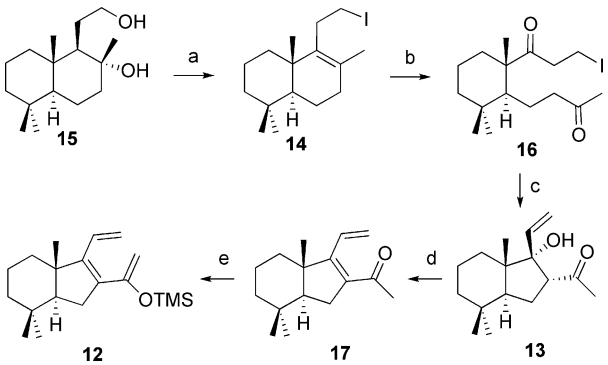
Results and discussion

The synthetic strategy planned is shown in Scheme 2. Phenol **10** is postulated as an adequate precursor for synthesizing the target compounds. The isopropyl group would be introduced utilizing the ester group of methyl salicylate derived from ketoester **11**, which is obtained from the enone resulting from the electrocyclization of silyl enol ether **12**. This will be obtained from the conjugated dienone formed after the dehydration of ketol **13**, resulting from the intramolecular aldol condensation of diketone derived from the oxidative rupture of the homoallylic iodide **14**, which can be easily prepared from diol **15**.

The synthesis of silyl enol ether **12** is depicted in Scheme 3, in which key steps are the transformation of diol **15** into the homoallylic iodide **14** and the intramolecular aldol condensation with simultaneous dehydrohalogenation of diketone **16**, affording the hydroxyketone **13**.



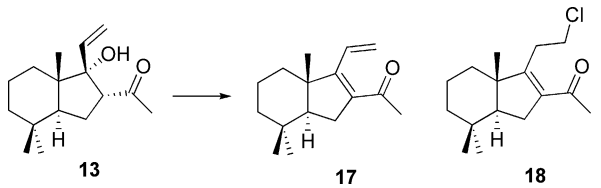
Scheme 2 Retrosynthetic analysis.



Scheme 3 Synthesis of triene **12**. (a) I_2, PPh_3, CH_2Cl_2, rt, 3.5 h (83%). (b) (i) O_3, CH_2Cl_2, −78 °C, 3 h. (ii) Me_2S, −78 °C–rt, 12 h (75%). (c) DBU, benzene, rt, 12 h (90%). (d) H_2SO_4, dioxane, rt, 4 h (73%). (e) TMSOTf, Pr^iNEt_2, CH_2Cl_2, 0 °C, 30 min (quant.).

Diol **15** has previously been obtained by lipase-catalyzed kinetic resolution after the acid cyclization of homofarnesyl acetate (2 steps, 27% overall yield);[15] we have prepared diol **15** in 96% yield after reduction of commercial (+)-sclareolide with KBH_4.[14] Treatment of compound **15** with the I_2–PPh_3 system, following a methodology previously reported by our group,[16] caused the simultaneous regioselective dehydration of tertiary alcohol and the transformation of primary alcohol into the corresponding iodide, giving compound **14**.[17] Ozonolysis of this afforded 1,6-diketone **16** in good yield,[18] which was converted into β-hydroxy ketone **13** by treating it with DBU in benzene. Transformation of hydroxy derivative **13** into dienone **17** was not a trivial task, the dehydration probably being difficult due to the strong hydrogen bond in the molecule. Table 1 shows the most representative attempts to achieve this goal. Treatment with $SOCl_2$ and pyridine in CH_2Cl_2 at −58 °C for 10 min gave chloroketone **18** in 60% yield (entry 2). The same compound results in high yield after treatment with conc. HCl in CH_2Cl_2 at room temperature for 1 h (entry 6). Dienone **17** and chloroketone **18** were obtained in low yield by treating hydroxy derivative **13** with $POCl_3$ and pyridine in CH_2Cl_2 (entry 3). The best result was achieved utilizing conc. H_2SO_4 in dioxane at room temperature, which afforded dienone **17** in 73% yield (entry 4). Chloroketone **18** was completely converted into dienone **17** by treating it with DBU in benzene at room temperature for 1 h.

Table 1 Dehydration of β-hydroxyketone **13**

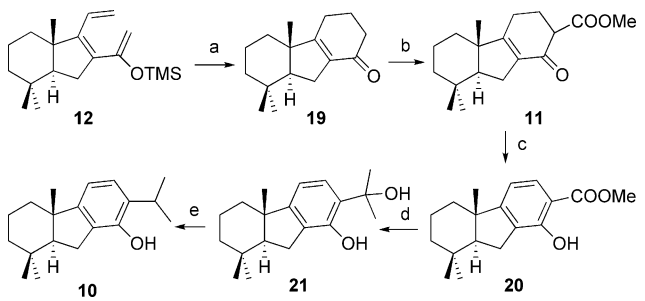


Entry	Reaction conditions	Compound (%)
1	TsOH, benzene, 85 °C, 10 min	Complex mixture
2	$SOCl_2$, pyridine, CH_2Cl_2, –58 °C, 10 min	**18**[a] (60)
3	$POCl_3$, pyridine, CH_2Cl_2, –36 °C–reflux, 10 min	**17** (20), **18**[a] (35)
4	Conc. H_2SO_4, dioxane, rt, 4 h	**17** (73)
5	$BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 5 h	**13**
6	Conc. HCl, CH_2Cl_2, rt, 1 h	**18**[a] (97)

[a] Treatment of chloroketone **18** with DBU in benzene at room temperature for 1 h gave dienone **17** in 95% yield.

Triene **12** was finally obtained in quantitative yield after treatment with TMSOTf and Pr^iNEt_2 in dichloromethane at 0 °C.

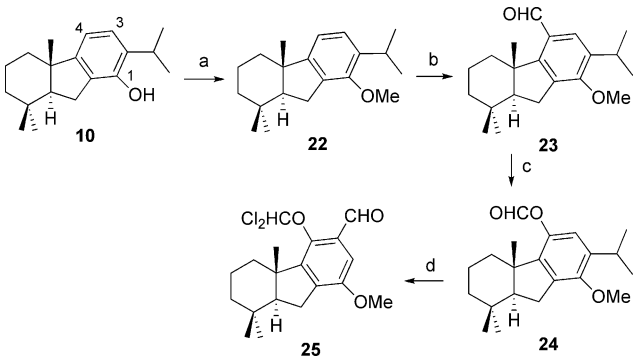
Scheme 4 shows the transformation of silyl enol ether **12** into the tricyclic precursor **10** of taiwaniaquinoids. The key step is the 6π electrocyclization of triene **12** leading to enone **19**, which has a tricyclic system of taiwaniaquinoid. Refluxing triene **12** in xylene for 4 h gave α,β-enone **19**, which when treated with LDA and NCCOOMe in THF afforded β-ketoester **11**, obtained as a 1 : 1 mixture of epimers. Treatment of the latter with DDQ (1.5 equiv.) in dioxane under reflux led to the methyl salicylate **20**, which was then transformed into hydroxyphenol **21** when treated with MeMgBr (4 equiv.). Treatment of this compound with Et_3SiH and CF_3COOH gave the desired phenol **10**.



Scheme 4 Synthesis of intermediate **10** from triene **12**. Reagents and conditions: (a) xylene, reflux, 4 h (92%). (b) (i) LDA, THF, –78 °C. (ii) NCCOOMe, THF, –78 °C—36 °C, 3 h, (97%). (c) DDQ (1.5 eq), dioxane, reflux, 30 min (94%). (d) MeMgBr (4 eq), THF, rt, 13 h (97%). (e) Et_3SiH, CF_3COOH, CH_2Cl_2, –40 °C, 1 h (95%).

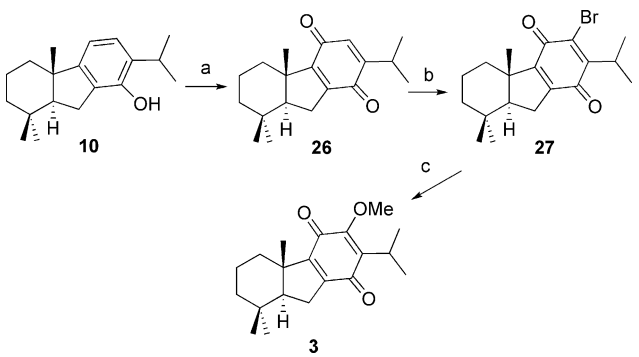
Next, the functionalization of the aromatic C ring was undertaken. We selected taiwaniaquinone G (**3**) as the target compound because it is the most immediate terpenoid bearing an A/B *trans*-configuration and it has not yet been synthesized. All preceding authors have utilized phenolic precursors with a substitution pattern quite different from that of intermediate **10**. Most of them used 1,3-[7,11] or 3,4-dihydroxy[10] derivatives, which were transformed into the final compound after a 2- or 3-step sequence in 45–52% yield. McFadden and Stoltz,[6] and She *et al.*[12] utilized a 3-hydroxy precursor, which afforded quinone **8** in a 3-step sequence (35% overall yield). These precedents forced us to investigate new strategies to achieve the target quinone.

A first approach to compound **3** is depicted in Scheme 5. The sequence involves the introduction of the oxygenated functions on the C ring through successive formylation and Baeyer–Villiger oxidations. Treatment of the methyl ether **22** with Cl_2CHOMe and $TiCl_4$ gave aldehyde **23**, which was converted into formiate **24** by treating it with MCPBA. Further formylation of this compound took place with the simultaneous removal of isopropyl group, affording aldehyde **25**.



Scheme 5 Functionalization of the C ring. Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 17 h (97%). (b) (i) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, –20 °C, 13 h. (ii) H_2O (87%). (c) MCPBA, CH_2Cl_2, 0 °C, 1 h (97%). (d) (i) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, –20 °C, 15 h. (ii) H_2O (87%).

A straightforward transformation of phenol **10** into taiwaniaquinone G (**3**) has been developed (Scheme 6).

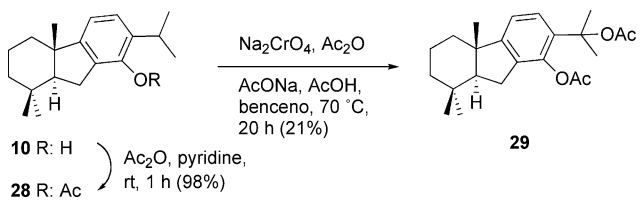


Scheme 6 Synthesis of (–)-taiwaniaquinone G (**3**) from phenol **10**. Reagents and conditions: (a) Fremy's salt, acetone, rt, pH 7 buffer, 15 h (94%). (b) Br_2, AcOH, rt, 5 min (89%). (c) MeONa, MeOH, rt, 30 min (97%).

Treatment of compound **10** with Fremy's salt gave quinone **26** in high yield. The direct introduction of the methoxy group onto the quinone ring under the diverse previously reported conditions, *e.g.* $HgCl_2$, I_2, MeOH[19] or $Fe_2(SO_4)_3$, MeOH,[20] was unsuccessful. Methoxy quinone **3** was finally obtained after treatment of bromoquinone **27** with MeONa in MeOH. In this way, phenol **10** was converted into taiwaniaquinone G (**3**) in a 3-step sequence in 81% overall yield. The optical rotation of synthetic taiwaniaquinone G (**3**) ($[\alpha]_D^{25}$: –91.4°; *c* 1.1, $CHCl_3$) was similar to that reported for the natural product ($[\alpha]_D^{22}$: –120.8°; *c* 0.29, $CHCl_3$); the spectroscopic properties were identical to those previously described.[1d]

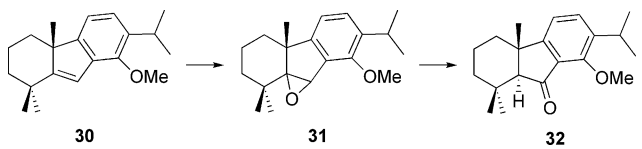
After this, we were interested in exploring the utilization of this new strategy to develop the enantiospecific synthesis of a wider range of taiwaniaquinoids, including A/B *trans*- and *cis*-fused 4a-methylhexahydrofluorene and 4a-methyltetrahydrofluorene derivatives. First, the direct oxidation of A/B *trans*-fused 4a-methylhexahydrofluorene derivatives, such as quinones **26** and **3**, to the corresponding 4a-methyltetrahydrofluorene derivatives was unsuccessfully essayed; thus, compounds **26** and **3** remained unaltered after refluxing for 48 h with DDQ in dioxane.

Next, we investigated the introduction of a functional group into the cyclopentane B ring of A/B *trans*-fused derivatives, which would allow us to synthesize compounds such as **1**, **5**, **7** or **9**. With this purpose in mind, we attempted the preparation of the corresponding oxocyclopentane derivatives. The oxidation of several compounds resulting from the hydroxyl group protection of phenol **10** was then investigated. The unaltered starting material was recovered when the methyl ether derived from **10** was treated with different oxidizing reagents under mild conditions; a complex mixture of compounds resulted when the reaction conditions were forced. Acetoxy derivative **28** exhibited a similar behaviour; however, treatment of this with Na_2CrO_4, Ac_2O, AcONa and AcOH in benzene at 70 °C allowed the isolation of diacetoxy derivative **29** in low yield (Scheme 7). This result revealed that the methyne of the isopropyl group is more easily oxidized than is the cyclopentane methylene.



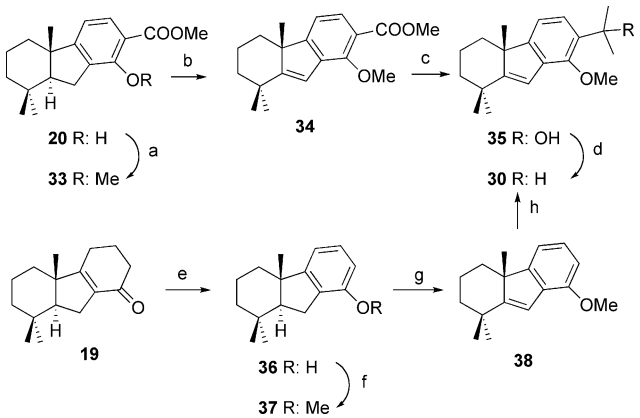
Scheme 7 Oxidation of acetoxy derivative **28** with Na_2CrO_4.

In view of the failure to achieve direct oxidation of the cyclopentane ring, an alternative route towards the oxo derivative **32**, *via* rearrangement of epoxide **31**, derived from the 4a-methyltetrahydrofluorene **30**, was planned (Scheme 7).



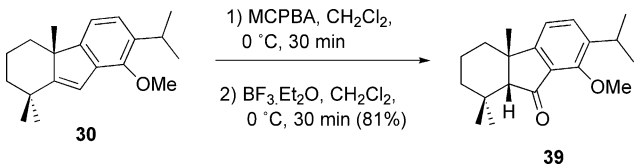
Scheme 8 A possible route towards A/B *trans*-fused oxocyclopentane derivatives.

Then, the synthesis of intermediate **30** was addressed. Scheme 9 shows two alternative procedures developed to synthesize the methoxy derivative **30**. In both sequences, the isopropyl group was introduced after the elaboration of the cyclopentane double bond. The first route started from salicylate **20**; treatment of its *O*-methyl derivative **33** with NBS and Bz_2O_2 in CCl_4 under irradiation followed by refluxing with cationic resin in CH_2Cl_2 gave the 4a-methyltetrahydrofluorene **34** in good yield. The introduction of the isopropyl group to give the desired compound **30** was achieved in a similar way to that commented on above for compound **10**. In the second procedure, the α,β-enone **19** was the starting material. Refluxing this ketone with DDQ in dioxane afforded phenol **36** in almost quantitative yield, which, after methylation, was converted into the 4a-methyltetrahydrofluorene **38** following the same treatment utilized for **33**. The isopropyl group was then introduced by treating the *O*-methyl derivative **38** with n-BuLi and acetone. At this point, it should be noted that, following the same procedure described for quinones **26** and **3**, treatment of compounds **33** and **37** with DDQ in refluxing dioxane did not afford the desired 4a-methyltetrahydrofluorene derivatives, but the starting materials remained unaltered.



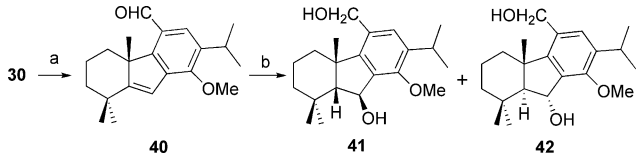
Scheme 9 Synthesis of intermediate **30**. Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux, 8 h (98%). (b) (i) NBS, CCl_4, hν, Bz_2O_2, 60 °C, 30 min. (ii) Amberlyst A-15, CH_2Cl_2, reflux, 1 h (90%). (c) MeMgBr, THF, rt, 15 min (96%). (d) ZnI_2, $NaBH_3CN$, CH_2Cl_2, 0 °C, 2 h (96%). (e) DDQ, dioxane, reflux, 1 h (98%). (f) MeI, K_2CO_3, acetone, reflux, 6 h (96%). (g) (i) NBS, CCl_4, hν, Bz_2O_2, 60 °C, 30 min. (ii) Amberlyst A-15, CH_2Cl_2, reflux, 1 h (93%). (h) (i) n-BuLi, THF, –20 °C, 30 min. (ii) Acetone, HMPA, 0 °C, 3 h (84%).

Next, the preparation of oxocyclopentane **32** following the synthetic proposal depicted in Scheme 8 was tackled. Treatment of methyl ether **30** with MCPBA in CH_2Cl_2 at 0 °C for 30 min and the further treatment of crude epoxide with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C for 30 min led to ketone **39**, with an A/B *cis*-configuration, as revealed by nOe experiments. This compound is a suitable intermediate for the enantiospecific synthesis of A/B *cis*-fused taiwaniaquinoids, such as taiwaniaquinol B (**6**). All attempts to epimerize ketone **39** to the corresponding *trans* isomer **32** were unsuccessful (Scheme 10).



Scheme 10 Synthesis of oxocyclopentane derivative **39**.

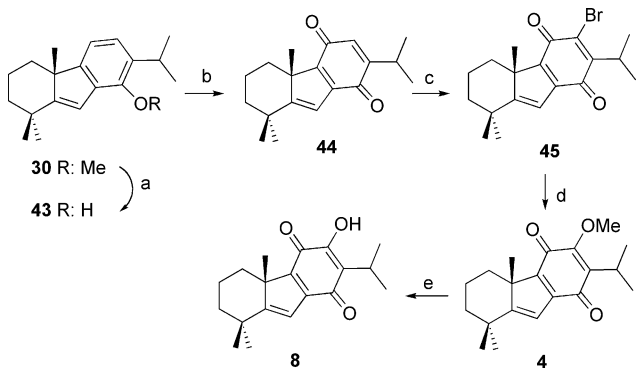
An alternative route towards A/B *trans*-fused taiwaniaquinoids with a functionality in the cyclopentane B ring could be achieved *via* the hydroboration–oxidation of intermediate **30**. The axial angular methyl would direct the α attack of borane, thus providing a cyclopentane substitution pattern similar to that of standishinal (**9**). Under this assumption, we investigated an approach to this taiwaniaquinoid (Scheme 11). Treatment of the methoxy derivative **30** with Cl_2CHOMe and $TiCl_4$ gave aldehyde **40** in high yield;



Scheme 11 Hydroboration of the cyclopentane double bond. Reagents and conditions: (a) (i) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, –30 °C, 10 h. (ii) H_2O (96%). (b) (i) B_2H_6, THF, –78 °C—35 °C, 14 h. (ii) NaOH, H_2O, EtOH, H_2O_2 30%, rt, 8 h (81%, **41** : **42** 4 : 1).

further reaction of this with B_2H_6 followed by alkaline H_2O_2 led to diols **41** and **42** in a 4 : 1 relation. Compound **42** is an immediate precursor of (–)-standishinal (**9**). In obtaining diol **41** and ketone **39**, the considerable stability of the A/B *cis*-fused 4a-methylhexahydrofluorene system was apparent.

Of course, the methoxy derivative **30** is a suitable precursor to synthesize taiwaniaquinoids bearing the 4a-methyltetrahydrofluorene skeleton. Scheme 12 shows the sequence developed to prepare (–)-taiwaniaquinone H (**4**) and (–)-dichroanone (**8**). Phenol **43** was transformed almost quantitatively into quinone **44** by treatment with CAN in CH_2Cl_2 at room temperature for 1 h. Introduction of the methoxy group of compound **4** *via* bromo derivative **45** was carried out in a similar way to that utilized for quinone **26**. Treatment of methoxy derivative **4** with KOH in MeOH at room temperature for 15 h gave (–)-dichroanone (**8**) in 88% yield.[21] This sequence constitutes the first enantiospecific synthesis of (–)-taiwaniaquinone H (**4**) and (–)-dichroanone (**8**). The optical rotations of synthetic **4** ($[\alpha]_D^{25}$: –11.9; *c* 0.56, $CHCl_3$) and **8** ($[\alpha]_D^{25}$: –88.7; *c* 0.79, $CHCl_3$) were similar to those reported for the natural products ($[\alpha]_D^{25}$: –9.0; *c* 0.29, $CHCl_3$[1d] and $[\alpha]_D^{25}$: –99.3; *c* 0.67, dioxane,[2] respectively); their spectroscopic properties were identical to those previously described.[1d,2]



Scheme 12 Synthesis of (–)-taiwaniaquinone H (**4**) and (–)-dichroanone (**8**) from intermediate **30**. Reagents and conditions: (a) BBr_3, CH_2Cl_2, –78–0 °C, 2 h (64%). (b) CAN, CH_2Cl_2, rt, 1 h (96%). (c) Br_2, AcOH, rt, 5 min (82%). (d) MeONa, MeOH, rt, 30 min (95%). (e) KOH, MeOH, rt, 15 h (88%).

Conclusions

In summary, a new synthetic strategy towards taiwaniaquinoids, based on a thermal 6π electrocyclization, is described. This procedure, which enables the preparation of natural enantiomers, is the first reported to synthesize taiwaniaquinoids with an A/B *trans*-configuration; it also allows the synthesis of terpenoids with an A/B *cis*-configuration as well as 4a-methyltetrahydrofluorene derivatives. Utilizing this, the first enantiospecific synthesis of (–)-taiwaniaquinone G (**3**), (–)-taiwaniaquinone H (**4**) and (–)-dichroanone (**8**), and an approach to (–)-standishinal (**9**) have been developed. The elaboration of A/B *trans*-fused taiwaniaquinoids bearing a functionality in the cyclopentane B ring, which presents some difficulties, is currently under study.

Experimental

For the experimental procedure and analytical data concerning compounds **3**, **10–16**, **19–21** and **26–27** see ref. 14.

(4b*S*,8a*S*)-2-Isopropyl-1-methoxy-4b,8,8,-trimethyl-5,6,7,8,8a,9-hexahydro-4b*H*-fluoren-4-carbaldehyde (23)

Cl_2CHOMe (0.5 mL, 5.52 mmol) and $TiCl_4$ (0.3 mL, 2.73 mmol) were added to a solution of compound **22** (320 mg, 1.12 mmol) in CH_2Cl_2 (15 mL) at –20 °C under argon and the mixture was stirred at this temperature for 13 h, at which time TLC showed no starting material. Then, water (5 mL) was added and the mixture was stirred for a further 10 min. It was extracted with ether (2 × 20 mL) and the organic phase was washed with water (5 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude residue was purified by flash chromatography column on silica gel (10% ether/hexanes), affording aldehyde **23** (305 mg, 87%) as a yellow syrup. $[\alpha]_D^{25} = -9.0$ (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (s, 3H), 1.07 (s, 3H), 1.20 (d, $J = 6.9$ Hz, 3H), 1.21 (ddd, $J = 13.6$, 13.6, 4.2 Hz, 1H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.25 (s, 3H), 1.53 (dt, $J = 13.4$, 3.4 Hz, 1H), 1.69 (m, 2H), 1.76 (bd, $J = 12.9$, 6.1 Hz, 1H), 1.88 (qt, $J = 13.5$, 4.0 Hz, 1H), 2.44 (dt, $J = 12.0$, 3.2 Hz, 1H), 2.67 (dd, $J = 14.1$, 12.9 Hz, 1H), 2.85 (dd, $J = 14.1$, 6.1 Hz, 1H), 3.27 (h, $J = 6.9$ Hz, 1H), 3.86 (s, 3H), 7.63 (s, 1H), 10.63 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.1 (CH_2), 21.1 (CH_3), 21.5(CH_3), 23.3 (CH_3), 23.4 (CH_3), 26.9 (CH), 27.2 (CH_2), 33.1 (C), 31.2 (CH_3), 38.6 (CH_2), 40.8 (CH_2), 48.2 (C), 59.4 (OCH_3), 60.4 (CH), 125.4 (CH), 127.7 (C), 134.1 (C), 139.2 (C), 158.1 (C), 159.3 (C), 190.6 (CHO). IR (cm^{-1}) ν: 1684, 1471, 1259; HRMS [FAB, (M + Na)$^+$] *m*/*z*: calcd for $C_{21}H_{30}O_2Na$ 337.2143, found: 337.2156.

8-(4b*S*,8a*S*)-2-Isopropyl-1-methoxy-4b,8,8-trimethyl-5,6,7,8,8a,9-hexahydro-4b*H*-fluoren-4-yl) formate (24)

m-Chloroperoxybenzoic acid (MCPBA, 75%; 123 mg, 0.5 mmol) was added at 0 °C to a stirred solution of **23** (147 mg, 0.468 mmol) in CH_2Cl_2 (10 mL) and the reaction was stirred for 1 h, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq Na_2SO_3 (0.5 mL) and stirred for an additional 10 min. Then, it was poured into ether/water (20 : 7 mL), and the organic phase was washed with sat. aq $NaHCO_3$ (10 × 8 mL) and brine, dried over Na_2SO_4 and concentrated to give **24** (150 mg, 97%) as a colourless oil. $[\alpha]_D^{25} = -23.3$ (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.96 (s, 3H), 1.03 (s, 3H), 1.10 (s, 3H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.18 (ddd, $J = 13.6$, 13.6, 4.2 Hz, 1H), 1.21 (d, $J = 6.9$ Hz, 3H), 1.50 (dt, $J = 13.0$, 3.2 Hz, 1H), 1.55 (dd, $J = 13.1$, 3.9 Hz, 1H), 1.62 (m, 1H), 1.75 (bd, $J = 12.8$, 6.1 Hz, 1H), 1.78 (qt, $J = 13.6$, 4.0 Hz, 1H), 2.16 (dt, $J = 12.4$, 3.1 Hz, 1H), 2.63 (dd, $J = 14.6$, 12.8 Hz, 1H), 2.82 (dd, $J = 14.6$, 6.1 Hz,

1H), 3.26 (h, $J = 6.9$ Hz, 1H), 3.79 (s, 3H), 6.66 (s, 1H), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.8 (CH_3), 19,9 (CH_2), 23.5 (CH_3), 23.8 (CH_3), 26.9 (CH), 27.4 (CH_2), 33.1 (C), 33.2 (CH_3), 36.3 (CH_2), 41.2 (CH_2), 46.6 (C), 59.9 (OCH_3), 60.7 (CH), 118.1 (CH), 135.9 (C), 140.3 (C), 140.7 (C), 144.1 (C), 152.2 (C), 160.3 (OCHO); IR (cm^{-1}) ν: 1742, 1474, 1132; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{21}H_{30}O_3Na$ 353.2093, found: 353.2101.

(4b*S*)-4-(dichloromethoxy)-1-methoxy-4b,8,8,-trimethyl-5,6,7,8,8a,9-hexahydro-4b*H*-fluorene-3-carbaldehyde (25)

Cl_2CHOMe (0.5 mL, 3.31 mmol) and $TiCl_4$ (0.3 mL, 1.82 mmol) were added to a solution of compound **24** (105 mg, 0.318 mmol) in CH_2Cl_2 (15 mL) at –20 °C under argon and the mixture was stirred at this temperature for 15 h, at which time TLC showed no starting material. Then, water (5 mL) was added and the mixture was stirred for a further 10 min. It was extracted with ether (2 × 20 mL) and the organic phase was washed with water (5 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude residue was purified by flash chromatography column on silica gel (10% ether/hexanes), affording aldehyde **25** (305 mg, 87%) as a yellow oil. $[\alpha]_D^{25} = -46.4$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.99 (s, 3H), 1.05 (s, 3H), 1.13 (s, 3H), 1.19 (ddd, $J = 13.7$, 13.7, 4.5 Hz, 1H), 1.53 (dd, $J = 13.4$, 3.0 Hz, 1H), 1.60 (ddd, $J = 12.9$, 12.9, 3.8 Hz, 1H), 1.77 (dd, $J = 12.9$, 6.3 Hz, 1H), 1.79 (qt, $J = 13.9$, 3.8 Hz, 1H), 2.42 (dt, $J = 12.8$, 3.2 Hz, 1H), 2.66 (dd, $J = 14.1$, 13.0 Hz, 1H), 2.88 (dd, $J = 14.7$, 6.2 Hz, 1H), 3.94 (s, 3H), 7.05 (s, 2H), 10.30 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.3 (CH_3), 19,9 (CH_2), 21.1 (CH_3), 27.3 (CH_2), 33.19 (C), 33.22 (CH_3), 35.9 (CH_2), 41.1 (CH_2), 47.7 (C), 59.6 (OCH_3), 62.2 (CH), 112.9 (CH), 127.3 (C), 137.4 (C), 145.9 (C), 153.1 (C), 156.8 (C), 189.0 (CHO). IR (cm^{-1}) ν: 1685, 1601, 1579, 1472, 1412, 1385, 1284, 1251, 1220, 1115, 1091, 1074, 1004, 820, 703; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{22}H_{30}O_3$ Cl_2Na 435.1470, found: 435.1482.

(4b*S*,8a*S*)-2-Isopropyl acetate-4b,8,8-trimethyl-5,6,7,8a,9-hexahydro-4b*H*-fluoren-1-yl acetate (29)

To a solution of **28** (130 mg, 0.41 mmol) in benzene (8 mL) was added sodium chromate (201mg, 1.24 mmol, 3 eq.), sodium acetate (68 mg, 0.82 mmol), acetic acid (1 mL) and acetic anhydride (2 mL), and the mixture was heated at 70 °C for 20 h. Then, water was added to quench the reaction and the mixture was extracted with ether (2 × 20 mL). The organic phase was washed with water (6 × 10 mL), sat. aq $NaHCO_3$ (5 × 10 mL), brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue crude purified by flash silica gel column (10% ether/hexanes), affording 32 mg of diacetate **29** (21%) as a colourless oil. $[\alpha]_D^{25} = -8.0$ (*c* 0.4, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.93 (s, 3H), 1.00 (s, 3H), 1.03 (s, 3H), 1.09–1.20 (m, 2H), 1.37 (ddd, $J = 12.6$, 12.6, 3.9 Hz, 1H), 1.4–1.52 (m, 1H), 1.59 (m, 1H), 1.65 (bd, $J = 10.8$, 8.2 Hz, 1H), 1.79 (s, 3H) 1.80 (s, 3H), 1.95 (s, 3H), 2.98 (dt, $J = 12.7$, 3.2 Hz, 1H), 2.32 (s, 3H), 2.39 (dd, $J = 10.8$, 8.2 Hz, 2H), 6.80 (d, $J = 7.7$ Hz, 1H), 7.13 (d, $J = 7.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.0 (CH_2), 21.0 (CH_3), 21.2 (CH_3), 21.7 (CH_3), 22.1 (CH_3), 26.9 (CH_2), 27.0 (CH_3), 27.8 (CH_3), 33.1 (C), 33.2 (CH_3), 35.5 (CH_2), 41.5 (CH_2), 46.2 (C), 59.6 (CH), 80.8 (C), 117.7 (CH), 125.2 (CH), 133.3 (C), 136.1 (C), 144.5 (C), 156.8 (C), 168.5 (C), 169.6 (C); IR (cm^{-1}) ν: 1763, 1458, 1368, 1246; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{23}H_{32}O_4Na$ 395.2198, found: 395.2203.

(*R*)-Methyl-1-methoxy-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-2-carboxylate (34)

NBS (260 mg, 1.45 mmol) and $(BzO)_2$ (6 mg) was added under an argon atmosphere to a solution of compound **33** (400 mg, 1.32 mmol) in CCl_4 (20 mL) and the mixture was stirred at 60 °C under light irradiation for 30 min, at which time TLC revealed no starting material. The mixture was filtered through a silica gel column (50% ether/hexanes) and the solvent removed affording a crude residue (394 mg). This was dissolved in CH_2Cl_2 (20 mL), Amberlyst A-15 (100 mg) was added, and the mixture was refluxed for 1 h, at which time TLC showed only a product. The solvent was evaporated under vacuum and the crude residue purified by silica gel column (10% ether/hexanes), giving compound **34** (360 mg, 90%) as a colourless oil. $[\alpha]_D^{25} = +18.8$ (*c* 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (ddd, $J = 13.2$, 13,2, 3,5 Hz, 1H), 1.11 (ddd, $J = 13.4$, 13.4, 4.0 Hz, 1H), 1.24 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.60–1.69 (m, 2H), 1.96 (qt, $J = 13.6$, 3.2 Hz, 1H), 2.13 (dd, $J = 12.8$, 1.6 Hz, 1H), 3.90 (s, 3H), 3.96 (s, 3H), 6.51 (s, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ: 19.6 (CH_2), 23.1 (CH_3), 25.2 (CH_3), 31.2 (CH_3), 35.7 (C), 37.7 (CH_2), 42.6 (CH_2), 51.7 (C), 52.0 (OCH_3), 62.3 (OCH_3), 116.5 (CH), 116.7 (CH), 122.2 (C), 127.8 (CH), 135.5 (C), 153.1 (C), 162.0 (C), 164.4 (C), 167.2 (C); IR (cm^{-1}) ν: 1727, 1458, 1291, 1224, 1121; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{19}H_{24}O_3Na$ 323.1623, found: 323.1614.

(*R*)-2-(1-Methoxy-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-2-yl)propan-2-ol (35)

Methyl magnesium bromide (1.4 M in 3 : 1 toluene–THF, 1.3 mL, 1.86 mmol) was added at 0 °C under argon to a solution of compound **34** (280 mg, 0.93 mmol) in anhydrous ether (15 mL), and the mixture was stirred for 15 min, at which time TLC showed no starting material. Then, water (2 mL) was added carefully to quench the reaction and the mixture was extracted with ether (3 × 20 mL). The organic phase was washed with water (2 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. After removing the solvent under vacuum, alcohol **35** (270 mg, 96%) was obtained as a colourless syrup. $[\alpha]_D^{25} = +3.8$ (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (ddd, $J = 13.3$, 13.3, 3.7 Hz, 1H), 1.13 (ddd, $J = 12.9$, 12.9, 3.9 Hz, 1H), 1.25 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.62 (s, 3H), 1.63 (s, 3H), 1.59-1.70 (m, 2H), 1.96 (qt, $J = 13.8$, 3.4 Hz, 1H), 2.13 (dd, $J = 12.8$, 1.8 Hz, 1H), 4.15 (s, 3H), 6.50 (s, 1H), 6.92 (d, $J = 7.8$ Hz, 1H), 7.10 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.7 (CH_2), 23.5 (CH_3), 25.3 (CH_3), 30.9 (CH_3). 31.2 (CH_3), 31.3 (CH_3), 35.7 (C), 38.1 (CH_2), 42.7 (CH_2), 50.7 (C), 61.6 (OCH_3), 73.0 (C), 116.1 (CH), 117.1 (CH), 122.0 (CH), 133.2 (C), 137.3 (C), 151.0 (C), 157.1 (C), 164.0 (C). IR (cm^{-1}) ν: 3527, 1458, 1416, 1367, 1268, 1217, 1055, 1021, 820, 672; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{20}H_{28}O_2Na$ 323.1987, found: 323.1995.

(4b*S*,8a*S*)-4b,8,8-Trimethyl-5,6,7,8,8a,9- hexahydro-4b*H*-fluoren-1-ol (36)

DDQ (2.28 g, 10.05 mmol) was added to a solution of compound **19** (1.6 g, 6.7 mmol) in dioxane (20 mL) and the mixture was stirred under reflux for 1 h, at which time TLC showed no ketone **19**. The solvent was evaporated under vacuum and the crude residue was purified by flash chromatography column on silica gel (20% hexanes/ether), affording phenol **36** (1.55 g, 98%) as a yellow oil. $[\alpha]_D^{25} = -23.7$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.39 (ddd, $J = 12.8$, 3.7 Hz, 1H), 1.47 (dt, $J = 13.6$, 3.1 Hz, 1H), 1.51-1.62 (m, 2H), 1.66 (dd, $J = 12.4$, 6.2 Hz, 1H), 1.76 (qt, $J = 13.4$, 3.5 Hz, 1H), 1.97 (dt, $J = 12.5$, 2.8 Hz, 1H), 2.45 (dd, $J = 14.1$, 12.4 Hz, 1H), 2.62 (dd, $J = 14.1$, 6.2 Hz, 1H), 5.12 (bs, 1H), 6.52 (d, $J = 8.0$ Hz, 1H), 6.59 (d, $J = 7.3$ Hz, 1H), 6.94 (dd, $J = 8.0$, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.9 (CH_2), 20.0 (CH_3), 20.5 (CH_3), 24.3 (CH_2), 32.0 (CH_3), 32.2 (C), 34.7 (CH_2), 40.6 (CH_2), 59.0 (CH), 111.6 (CH), 111.8 (CH), 126.0 (C), 126.8 (CH), 151.0 (C), 156.9 (C).); IR (cm^{-1}) *v*: 3405, 1719, 1586, 1459, 1369, 1263, 1099, 787; HRMS [FAB, $(M + Na)^+$] *m*/*z*: calcd for $C_{16}H_{22}ONa$ 253.1568, found: 253.1580.

(*R*)-8-Methoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (38)

NBS (500 mg, 2.8 mmol, 1.2 eq.) and $(BzO)_2$ (10 mg) was added under argon atmosphere to a solution of compound **37** (570 mg, 2.33 mmol) in CCl_4 (40 mL) and the mixture was stirred at 60 °C under light irradiation for 30 min, after which time TLC revealed the absence of starting material. The mixture was filtered through a silica gel column (10% ether/hexanes) and the solvent removed affording a crude residue. This was dissolved in CH_2Cl_2 (40 mL), Amberlyst A-15 (100 mg) was added, and the mixture was refluxed for 1 h, at which time TLC showed only a product. The solvent was evaporated under vacuum and the residue purified by silica gel column (10% ether/hexanes), giving compound **38** (252 mg, 93%) as a yellow syrup. $[\alpha]_D^{25} = +35.9$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.91 (ddd, $J = 13.2$, 13.2, 3.4 Hz, 1H), 1.03 (ddd, 12.8, 12.8, 3.8 Hz, 1H), 1.16 (s, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.51-1.61 (m, 2H), 1.89 (qt, $J = 13.7$, 3.4 Hz, 1H), 2.60 (dd, $J = 12.9$, 1.8 Hz, 1H), 3.80 (s, 3H), 6.45 (s, 1H), 6.66 (d, $J = 8.1$ Hz, 1H), 6.81 (d, $J = 7.3$ Hz, 1H), 7.03 (bd, $J = 8.1$, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.7 (CH_2), 22.3 (CH_3), 24.3 (CH_3), 30.2 (CH_3), 34.5 (C), 37.0 (CH_2), 41.7 (CH_2), 50.4 (C), 54.3 (OCH_3), 107.3 (CH), 113.0 (CH), 115.5 (CH), 124.2 (CH), 129.2 (C), 151.6 (C), 156.3 (C), 161.6 (C); IR (cm^{-1}) *v*: 3078, 1592, 1573, 1478, 1478, 1439, 1272, 1248, 1076, 1032, 862, 784, 740, 671; HRMS [FAB, $(M + Na)^+$] *m*/*z*: calcd for $C_{17}H_{22}ONa$ 265.1568, found: 265.1549.

(*R*)-2-(1-Methoxy-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-2-yl)propan-2-ol (35) (from 38)

n-BuLi (2.4 M, 1 mL, 2.4 mmol) was added to a solution of compound **38** (420 mg, 1.72 mmol) in anhydrous THF (15 mL) at –20 °C under argon atmosphere, and the mixture was stirred at this temperature for 20 min. Then HMPA (1 mL, 5.73 mmol) was added and the reaction mixture was warmed to 0 °C for 30 min and dry acetone (0.5 mL, 6.81 mmol) was added at 0 °C and the mixture was stirred for a further 3 h, at which time TLC showed no starting material. The mixture was poured into ice (30 mL) and extracted with ether (2 × 20 mL). The organic phase was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent under vacuum afforded a crude residue, which after purification by flash chromatography column on silica gel (10% ether/hexanes) gave compound **35** (437 mg, 84%) as a colourless syrup.

(*R*)-7-Isopropyl-8-methoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (30)

$NaBH_3CN$ (684 mg, 9.4 mmol, 10 eq.) was added at 0 °C under argon to a solution of compound **35** (283 mg, 0.94 mmol) in freshly distilled CH_2Cl_2 (20 mL) and the mixture was stirred for 2 min at this temperature. Then, ZnI_2 (514 mg, 2.82 mmol) was added and the mixture was stirred for a further 2 h, at which time TLC showed no compound **35**. The mixture was filtered through a silica gel column (5% ether/hexanes) and the solvent evaporated to give compound **30** (257 mg, 96%) as a colourless oil. $[\alpha]_D^{25} = +20.0$ (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (ddd, $J = 13.3$, 13.3, 3.7 Hz, 1H), 1.17 (ddd, $J = 12.8$, 12.8, 3.9 Hz, 1H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.26 (s, 3H), 1.27 (d, $J = 6.9$ Hz, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 1.60-1.71 (m, 2H), 1.97 (qt, $J = 13.8$, 3.2 Hz, 1H), 2.13 (bd, $J = 12.8$ Hz, 1H), 3.38 (h, $J = 6.9$ Hz, 1H), 3.86 (s, 3H), 6.51 (s, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.8 (CH_2), 23.6 (CH_3), 23.7 (CH_3), 23.9 (CH_3), 25.4 (CH_3), 26.6 (CH_3), 31.3 (CH_3), 35.6 (C), 38.2 (CH_2), 42.8 (CH_2), 50.9 (C), 61.8 (OCH_3), 116.7 (CH), 117.2 (CH), 122.3 (CH), 133.6 (C), 138.7 (C), 150.6 (C), 155.2 (C), 163.5 (C). IR (cm^{-1}) *v*: 1470, 1249, 1054, 1023, 814, 671; HRMS [FAB, $(M + Na)^+$] *m*/*z*: calcd for $C_{20}H_{28}ONa$ 307.2038, found: 307.2045.

(4a*S*,9a*R*)-7-Isopropyl-8-methoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluoren-9(9a*H*)-one (39)

m-Chloroperoxybenzoic acid (MCPBA, 75%; 114 mg, 0.49 mmol) was added at 0 °C to a stirred suspension of **30** (93 mg, 0.327 mmol) and solid $NaHCO_3$ (84 mg, 1 mmol) in CH_2Cl_2 (12 mL), and the reaction was stirred for 30 min, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq Na_2SO_3 (2 mL) and stirred for an additional 10 min. Then, it was poured into ether/water (20 : 7 mL), and the phases were shaken and separated; the organic phase was washed with sat. aq $NaHCO_3$ (10 × 7 mL) and brine, dried over Na_2SO_4 and concentrated to give a crude product as a mixture of epoxide derivatives.

A solution of this crude product (89 mg) in CH_2Cl_2 (8 mL) was added at 0 °C $BF_3{\cdot}Et_2O$ (45%, 0.1 mL, 0.788 mmol) and the mixture was stirred for 30 min, at which time TLC showed no **30**. Water (1 mL) was added and the mixture was stirred for an additional 15 min, then it was extracted with ether (2 × 10 mL), the organic phase was washed with water, sat. aq $NaHCO_3$ (2 × 7 mL), brine, dried over Na_2SO_4 and concentrated to give the ketone **39** (79 mg, 81%) as a yellow oil. $[\alpha]_D^{25} = -68$ (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.67 (s, 3H), 1.20 (d, $J = 6.9$ Hz, 6H), 1.21 (s, 3H), 1.24 (s, 3H), 1.28–1.37 (m, 2H), 1.44 (m, 1H), 1.55–1.65 (m, 2H), 2.10 (m, 1H), 2.14 (s, 1H), 3.38 (h, $J = 6.9$ Hz, 1H), 3.95 (s, 3H), 7.08 (d, $J = 7.8$ Hz, 1H), 7.44 (d, $J = 7.8$ Hz,

1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.4 (CH_2), 23.57 (CH_3), 23.64 (CH_3), 24.7 (CH_3), 26.3 (CH_3), 32.4 (CH_3), 33.5 (CH_2), 33.9 (C), 34.8 (CH_2), 38.7 (CH_2), 41.5 (C), 62.2 (OCH_3), 66.1 (CH), 117.2 (CH), 127.8 (C), 133.1 (CH), 140.3 (C), 155.1 (C), 161.9 (C), 206.6 (C). IR (cm^{-1}) ν: 1704, 1595, 1474, 1409, 1291, 1247, 1175, 1026, 827; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{20}H_{28}O_2Na$ 323.1987, found: 323.1998.

(*S*)-2-Isopropyl-1-methoxy-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-4-carbaldehyde (40)

Cl_2CHOMe (0.7 mL, 7.7 mmol, 10 eq.) and $TiCl_4$ (0.43 mL, 3.85 mmol, 5 eq.) were added to a solution of compound **30** (220 mg, 0.77 mmol) in CH_2Cl_2 (20 mL) at -30 °C under argon and the mixture was stirred at this temperature for 10 h, at which time TLC showed no starting material. Then, water (5 mL) was added and the mixture was stirred for a further 10 min. It was extracted with ether (2 × 20 mL) and the organic phase was washed with water (5 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude residue was purified by flash chromatography column on silica gel (10% ether/hexanes), affording aldehyde **40** (231 mg, 96%) as a yellow syrup. $[\alpha]_D^{25} = +9.5$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.92 (ddd, J = 13.2, 13.2, 3.4 Hz, 1H), 1.05 (ddd, J = 12.8, 12.8, 3.8 Hz, 1H), 1.18 (s, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.31 (d, J = 6.9 Hz, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.56 (dt, J = 13.2, 3.1 Hz, 1H), 1.61 (brd, J = 12.4 Hz, 1H), 1.89 (qt, J = 13.8, 2.9 Hz, 1H), 2.11(bd, J = 12.4 Hz, 1H), 3.83 (s, 3H), 3.65 (h, J = 6.9 Hz, 1H), 6.44 (s, 1H), 7.49 (s, 1H), 10.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.6 (CH_2), 23.2 (CH_3), 23.4 (CH_3), 23.5 (CH_3), 25.1 (CH_3), 25.8 (CH_3), 31.1 (CH), 36.1 (C), 37.9 (CH_2), 42.6 (CH_2), 51.5 (C), 61.9 (OCH_3), 117.5 (CH), 118.0 (CH), 134.6 (C), 140.4 (C), 142.0 (C), 152.2, 154.9 (C), 169.1 (C), 192.0 (CHO); IR (cm^{-1}) ν: 1684, 1603, 1450, 1274; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{21}H_{28}O_2Na$ 335.1987, found: 335.1972.

(4a*S*,9*S*,9a*R*)-5-(Hydroxymethyl)-7-isopropyl-8-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluoren-9-ol (41) and (4a*S*,9*R*,9a*S*)-5-(hydroxymethyl)-7-isopropyl-8-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluoren-9-ol (42)

1M B_2H_6–THF (1.27 mL, 0.7 mmol) was added to a solution of compound **40** (100 mg, 0.32 mmol) in anhydrous THF (10 mL) at –78 °C, under argon, and the temperature was raised to –35 °C for 14 h, at which time TLC showed no starting material. Then, EtOH (0.6 mL), 4 M NaOH in EtOH (0.3 mL) and 30% H_2O_2 1 mL) were added and the mixture was stirred at room temperature for 8 h. The solvent was evaporated and ether (20 mL) was added. The organic phase was washed with water (3 × 6 mL), brine (2 × 5 mL) and dried over anhydrous Na_2SO_4. After removing the solvent under vacuum the crude residue was purified by flash chromatography column on silica gel (20% ether/hexanes), affording the mixture of diols **41–42** (86 mg, 81%), in a 4 : 1 proportion, as a yellow syrup. $[\alpha]_D^{25} = +45.0$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: Assignable signals to isomer **41**: 1.00 (ddd, J = 13.7, 13.7 Hz, 1H), 1.15 (s, 3H), 1.19 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.36 (d, J = 6.9 Hz, 3H), 1.38-1.44 (m, 1H), 1.46 (s, 3H), 1.53-1.68 (m, 4H), 1.77 (d, J = 7.8 Hz, 1H), 2.88 (d, J = 2.9 Hz, 1H), 3.34 (h, J = 6.9 Hz, 1H), 3.87 (s, 3H), 4.71 (d, J = 4.9 Hz, 2H), 5.25 (dd, J = 7.8, 2.9 Hz, 1H), 6.90 (s, 1H). Assignable signals to isomer **42**: 1.16 (s, 3H), 1.20 (s, 3H), 1.82 (br d, J = 8.8 Hz, 1H), 1.94 (brd, J = 13.7 Hz, 1H), 3.28 (h, J = 6.9 Hz, 1H), 3.47 (bs, 1H), 3.82 (s, 3H), 4.75 (dd, J = 4.9, 3.9 Hz, 2H), 5.17 (bs, 1H), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.7 (CH_2), 22.2 (CH_3), 22.5 (CH_3), 25.9 (CH_3), 29.7 (CH), 29.8 (CH_3), 31.9 (C), 32.0 (CH_3), 36.5 (CH_2), 39.3 (CH_2), 44.1 (C), 59.7 (CH), 64.3 (CH_2), 66.0 (OCH_3), 75.1 (CH), 117.7 (CH), 128 (C), 133.4 (C), 136.8 (C), 139.8 (C), 153.1 (C); IR (cm^{-1}) ν: 3421, 1459, 1224, 1031, 757; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{21}H_{32}O_3Na$ 355.2249, found: 355.2249.

(*R*)-Isopropyl-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-1-ol (43)

BBr_3 (0.25 mL, 2.08 mmol) was added at –78 °C to a solution of compound **30** (150 mg, 0.53 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred at 0 °C for 2 h, at which time TLC showed no starting material. The mixture was poured onto ice (10 g) and extracted with ether (30 mL). The organic phase was washed with water (5 × 10 mL), brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude residue was purified by flash chromatography column on silica gel (10% ether/hexanes) affording phenol **43** (92 mg, 64%) as a colourless oil. $[\alpha]_D^{25} = +12.0$ (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.93 (ddd, J = 13.2, 13.2, 3.4 Hz, 1H), 1.04 (ddd, J = 12.8, 12.8, 3.6 Hz, 1H), 1.12 (s, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.51-1.56 (dt, J = 13.2, 3.1 Hz, 1H), 1.58 (bd, J = 12.8 Hz, 1H), 1.88 (qt, J = 13.7, 3.3 Hz, 1H), 2.04 (bd, J = 12.8, 1.5 Hz, 1H), 3.13 (h, J = 6.9 Hz, 1H), 4.60 (s, 1H), 6.37 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ: 19.7 (CH_2), 22.9 (CH_3), 22.9 (CH_3), 23.5 (CH_3), 25.3 (CH_3), 26.9 (CH), 31.2 (CH_3), 35.6 (C), 38.1 (CH_2), 42.7 (CH_2), 51.3 (C), 113.8 (CH), 115.2 (CH), 122.2 (CH), 128.3 (C), 131.9 (C), 145.5 (C), 154.6 (C), 163.2 (C); IR (cm^{-1}) ν: 3473, 1718, 1576, 1459, 1295, 807. HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{19}H_{26}ONa$ 293.1881, found: 293.1873.

(*S*)-2-Isopropyl-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-1,4-dione (44)

CAN (350.6 mg, 0.64 mmol) was added to a solution of compound **43** (87 mg, 0.32 mmol) in CH_2Cl_2 (10 ml) and the mixture was stirred at room temperature for 1 h, at which time TLC showed no starting material. The mixture was extracted with ether (20 mL) and the organic phase was washed with water (4 × 10 mL), brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvent, the crude residue was purified on silica gel (10% ether/hexanes) affording quinone **44** (88 mg, 96%) as a red syrup. $[\alpha]_D^{25} = -16.8$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.98–1.04 (m, 2H), 1.05 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.16 (s, 3H), 1.21 (s, 3H), 1.37 (s, 3H), 1.54 (dd, J = 13.7, 3.3 Hz, 1H), 1.62 (dd, J = 13.5, 2.4 Hz, 1H), 1.86 (qt, J = 13.8, 3.4 Hz, 1H), 2.34 (dd, J = 13.0, 2.0 Hz, 1H), 2.99 (h, J = 6.9 Hz, 1H), 6.27 (bs, 1H), 6.32 (s, 1H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ: 18.0 (CH_2), 19.0 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 23.8 (CH_3), 25.3 (CH), 29.3 (CH_3), 35.3 (C), 36.1 (CH_2), 42.3 (CH_2), 54.5 (C), 115.4 (CH), 130.8 (CH), 144.4 (C), 151.4 (C), 152.0 (C), 173.9 (C), 182.5 (C),

184.6 (C); IR (cm^{-1}) ν: 2962, 2933, 2872, 1685, 1653; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{19}H_{24}O_2Na$ 307.1674, found: 307.1690.

(*S*)-3-Bromo-2-isopropyl-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluoren-1,4-dione (45)

Bromine (0,10 ml, 1.95 mmol) was added to a solution of quinone **44** (82 mg, 0.28 mmol) in acetic acid (5 mL) and the mixture was stirred at room temperature for 5 min, at which time TLC showed no quinone **44**. Then, 5% $NaHSO_3$ (1 mL) was added and the mixture was stirred for a further 5 min, and extracted with ether (25 mL). The organic phase was washed with water (5 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the resulting crude residue was purified by flash chromatography on silica gel (10% ether/hexanes) giving the bromo derivative **45** (84 mg, 82%) as a yellow syrup; $[\alpha]_D^{25} = -19.1$ (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.96–1.07 (m, 2H), 1.16 (s, 3H), 1.21 (s, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.38 (s, 3H), 1.55 (dt, J = 13.7, 3.3 Hz, 1H), 1.64 (dd, J = 13.5, 2.3 Hz, 1H), 1.86 (qt, J = 13.8, 3.4 Hz, 1H), 2.36 (dd, J = 13.4, 2.5 Hz, 1H), 3.39 (h, J = 6.9 Hz, 1H), 6.31 (s, 1H), 7.19 (s, 1H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ: 18.0 (CH_2), 18.93 (CH_3), 18.96 (CH_3), 19,1 (CH_3), 23.8 (CH_3), 29.8 (CH), 33.0 (CH_3), 35.7 (C), 36.1 (CH_2), 42.3 (CH_2), 55.3 (C), 115.4 (CH), 137.0 (C), 145.0 (C), 149.0 (C), 150.0 (C), 173.2 (C), 175.4 (C), 181.3 (C); IR (cm^{-1}) ν: 2960, 2925, 2851, 1687, 1656, 1533, 1459, 1255, 1086, 1037, 802, 666; HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{19}H_{23}O_2BrNa$ 385.0779, found: 385.0791.

(–)-Taiwaniaquinone H (4)

Sodium methoxide (68 mg, 1.26 mmol) was added to a solution of bromide **45** (78 mg, 0.21 mmol) in methanol (8 mL) and the mixture was stirred at room temperature for 30 min. The mixture was diluted with ether (20 mL) and the organic phase was washed with water (2 × 6 mL), brine (6 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent under vacuum gave compound **4** (63 mg, 95%) as a red syrup. $[\alpha]_D^{25} = -11.9$ (*c* 0.56, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.05–1.14 (m, 2H), 1.21 (s, 3H), 1.220 (d, J = 7.0 Hz, 3H), 1.223 (d, J = 7.0 Hz, 3H), 1.27 (s, 3H), 1.45 (s, 3H), 1.62 (m, 1H), 1.69 (ddd, J = 13.1, 5.4, 2.5 Hz, 1H), 1.93 (qt, J = 13.9, 3.4 Hz, 1H), 2.41 (ddd, J = 10.1, 4.9, 2.9 Hz, 1H), 3.26 (h, J = 7.0 Hz, 1H), 3.99 (s, 3H), 6.38 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.2 (CH_2), 20.2 (CH_3), 20.77 (CH_3), 20.79 (CH_3), 24.6 (CH_3), 24.9 (CH_3), 31.0 (CH), 36.7 (C), 37.3 (CH_2), 43.5 (CH_2), 55.8 (C), 61.4 (CH_3), 116.8 (CH), 136.2 (C), 145.9 (C), 150.7 (C), 157.4 (C), 175.7 (C), 178.9 (C), 186.3 (C). IR (cm^{-1}) ν: 1644, 1538, 1451, 1058, 864. HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{20}H_{26}O_3Na$ 337.1780, found: 337.1793.

(–)-Dichroanone (8)

2 N KOH in MeOH (3 mL) was added to a solution of (–)-Taiwaniaquinone H (**4**) (55 mg, 0.175 mmol) in MeOH (5 mL) and the mixture was stirred at room temperature for 15 h. Then, 2 N HCl (3 mL) was added slowly and the mixture was diluted with ether (20 mL). The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to afford quinone **8** (46 mg, 88%) as a red syrup. $[\alpha]_D^{25} = -88.7$; *c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.04–1.17 (m, 2H), 1.231 (s, 3H), 1.234 (d, J = 7.0 Hz, 3H), 1.238 (d, J = 7.0 Hz, 3H), 1.25 (s, 3H), 1.46 (s, 3H), 1.62 (m, 2H), 1.70 (ddd, J = 13.2, 5.4, 2.4 Hz, 1H), 1.91 (qt, J = 13.9, 3.5 Hz, 1H), 2.36 (ddd, J = 12.4, 4.9, 2.1 Hz, 1H), 3.21 (h, J = 7.0 Hz, 1H), 6.43 (s, 1H), 7.31 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.1 (CH_2), 20.1 (CH_3), 20.11 (CH_3), 20.2 (CH_3), 24.0 (CH_3), 24.8 (CH_3), 31.0 (CH), 37.1 (C), 37.4 (CH_2), 43.5 (CH_2), 55.4 (C), 118.1 (CH), 122.8 (C), 147.8 (C), 148.9 (C), 152.5 (C), 177.1 (C), 178.3 (C), 185.8 (C). IR (cm^{-1}) ν: 3350, 1638, 1528, 1455, 1367, 1318, 966. HRMS [FAB, $(M + Na)^+$] m/z: calcd for $C_{19}H_{24}O_3Na$ 323.1623, found: 323.1609.

Acknowledgements

The authors thank the Spanish Ministry of Science and Innovation (Project CTQ2006-12697) and the Regional Government of Andalucia (Project P07-FQM-03101 and aids to the group FQM-348) for financial support.

References

1 (*a*) W. Lin, J. Fang and Y. Chang, *Phytochemistry*, 1995, **40**, 871–873; (*b*) W. Lin, J. Fang and Y. Cheng, *Phytochemistry*, 1996, **42**, 1657–1663; (*c*) C. Chang, S. Chien, S. Lee and Y. Kuo, *Chem. Pharm. Bull.*, 2003, **51**, 1420–1422; (*d*) C.-I. Chang, J.-Y. Chang, C.-C. Kuo, W.-Y. Pan and Y.-H. Kuo, *Planta Med.*, 2005, **71**, 72–76.
2 K. Kawazoe, M. Yamamoto, Y. Takaishi, G. Honda, T. Fujita and E. Sezik, *Phytochemistry*, 1999, **50**, 493–497.
3 H. Ohtsu, M. Iwamoto, U. Ohishi, S. Matsunaga and R. Tanaka, *Tetrahedron Lett.*, 1999, **40**, 6419–6422.
4 (*a*) M. Iwamoto, H. Ohtsu, H. Tokuda, H. Nishino, S. Matsunaga and R. Tanaka, *Bioorg. Med. Chem.*, 2001, **9**, 1911–1921; (*b*) T. Minami, M. Iwamoto, H. Ohtsu, H. Ohishi, R. Tanaka and A. Yoshitake, *Planta Med.*, 2002, **68**, 742–745.
5 This classification of the different synthetic approaches has been utilized for some polycyclic terpenoids. See: K. Kawada, M. Kim and D. S. Watt, *Org. Prep. Proced. Int.*, 1989, **21**, 521–618.
6 R. M. McFadden and B. M. Stoltz, *J. Am. Chem. Soc.*, 2006, **128**, 7738–7739.
7 E. Fillion and D. Fishlock, *J. Am. Chem. Soc.*, 2005, **127**, 13144–13145.
8 S. Li and P. Chiu, P., *Tetrahedron Lett.*, 2008, **49**, 1741–1744.
9 L. Planas, M. Mogi, H. Takita, T. Ajimoto and M. Node, *J. Org. Chem.*, 2006, **71**, 2896–2898.
10 M. Banerjee, R. Mukhopadhyay, B. Achari and A. K. Banerjee, *Org. Lett.*, 2003, **5**, 3931–3933; M. Banerjee, R. Mukhopadhyay, B. Achari and A. K. Banerjee, *J. Org. Chem.*, 2006, **71**, 2787–2796.
11 G. Liang, Y. Xu, I. B. Sciple and D. Trauner, *J. Am. Chem. Soc.*, 2006, **128**, 11022–11023.
12 S. Tang, Y. Xu, J. He, J. Zheng, X. Pan and X. She, *Org. Lett.*, 2008, **10**, 1855–1858.
13 E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, R. Alvarez-Manzaneda, R. Meneses, H. Es-Samti and A. Fernández, *J. Org. Chem.*, 2009, **74**, 3384–3388.
14 E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, M. Hmammouchi and H. Es-Samti, *Chem. Commun.*, 2009, 592–594.
15 H. Tanimoto and T. Oritani, *Tetrahedron: Asymmetry*, 1996, **7**, 1695–1704.
16 E. J. Alvarez-Manzaneda, R. Chahboun, E. Cabrera Torres, E. Alvarez, R. Alvarez-Manzaneda, A. Haidour and J. M. Ramos, *Tetrahedron Lett.*, 2004, **45**, 4453–4455, and references cited therein.
17 Synthesis of compound **14** has also been reported by Hagiwara *et al*. These authors prepared this homoallylic iodide from a Wieland–Miescher ketone analogue, after an 11-step sequence (21% overall yield). See: (*a*) H. Hagiwara, F. Takeuchi, M. Nozawa, T. Hoshi and T. Suzuki, *Tetrahedron*, 2004, **60**, 1983–1989; (*b*) H. Hagiwara, H. Nagatomo, S. Kazayama, H. Sakai, T. Hoshi, T. Suzuki and M. Ando,

J. Chem. Soc., Perkin Trans. 1, 1999, 457–460; (*c*) H. Hagiwara and H. Uda, *J. Org. Chem.*, 1988, **53**, 2308–2311.
18 Ozonolysis of compound **14** to give diketone **16** has also been accomplished by Hagiwara's group (ref. 17*a*). However, these authors reported low yields for this transformation, probably due to the small quantity of starting material they utilized.
19 G. A. Kraus and I. Kim, *J. Org. Chem.*, 2003, **68**, 4517–4518.
20 G. A. Kraus and N. Zhang, *Tetrahedron Lett.*, 2002, **43**, 9597–9599.
21 E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, J. L. Romera, M. A. Escobar and I. Messouri, *Synthesis*, 2008, 4019–4027.