Reviews

The Taiwaniaquinoids: A Review[†,‡]

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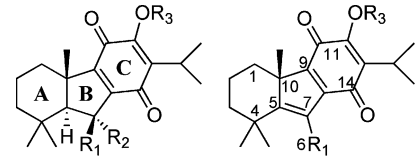
A comprehensive overview of the taiwaniaquinoid family of natural products is presented. A summary of the isolation, biosynthesis, and biological activity of these compounds is followed by a discussion of various synthetic strategies to the skeletal framework and a detailed discussion of 12 published syntheses of members of this family. This review covers the literature from the discovery of the first taiwaniaquinoid in 1995 until June 2009.

Isolation

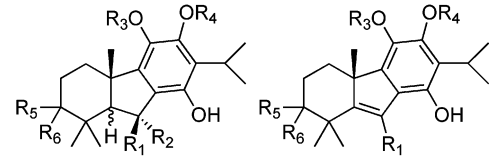
Taiwania cryptomerioides Hayata (Taxodiaceae) is an economically important, decay-resistant evergreen tree indigenous to the central mountains of Taiwan. Extensive studies over the last half-century of the chemical constituents in the heartwood, bark, and leaves (largely by researchers at National Taiwan University) have yielded many new sesquiterpenes, diterpenes, lignans, and biflavones.[1] In 1995, while continuing their investigation of the leaf extracts, Cheng et al. discovered[2a] a new family of diterpenoids (four diterpenes and one norditerpene) possessing a [6,5,6]-*abeo*-abietane skeleton[3] previously unknown in nature.[4] They named the compounds taiwaniaquinones A (**1**), B (**2**), and C (**3**) and taiwaniaquinols A (**4**) and B (**5**) (Figure 1) according to their botanical origin, C-ring functionality, and order of isolation, respectively. Cheng's continued work expanded this family in 1996, when the leaf extract yielded taiwaniaquinones D (**6**) and E (**7**).[2b]

A similar skeleton was soon discovered in other families of abietane-rich plants. In 1999, Kawazoe et al. reported the isolation of three structurally similar compounds (Figure 2) from the roots of *Salvia dichroantha* Stapf (Lamiaceae), a Turkish flowering sage. These new compounds were named dichroanals A (**8**) and B (**9**) and dichroanone (**10**).[5] Tanaka's group isolated the compound designated standishinal (**11**) from the bark of *Thuja standishii* (Cupressaceae), a Japanese conifer, in the same year.[6] Meanwhile, Kuo et al. reinvestigated the bark extracts from *T. cryptomerioides*, and the structures of taiwaniaquinone F (**12**) and taiwaniaquinols C (**13**) and D (**14**) were reported in 2003.[7a] Further study of the bark extract resulted in the 2005 report of taiwaniaquinones G (**15**) and H (**16**) and taiwaniaquinols E (**17**) and F (**18**).[7b] No related *abeo*-abietane diterpenes have been reported since 2005.

It should be noted that Cheng's second report included several compounds that represented [4+2]-cycloaddition reactions between taiwaniaquinol A and myrcene or *trans*-ozic acid.[2b] Although the cycloadducts were dismissed warily by the authors as artifacts, the reference cited in support of this position appears to have been misunderstood, being in direct opposition to their conclusion.[8] The strong similarity between the adducts and compounds such as salvadiol[9] also gives support to their legitimacy as natural metabolites.



	R_1	R_2	R_3	-one
1	H	CHO	H	A
2	OH	CHO	H	B
3	CHO	OH	H	C
6	CHO	--	H	D
7	H	CO_2Me	H	E
12	H	CHO	CH_3	F
15	H	H	CH_3	G
16	H	--	CH_3	H



	H	R_1	R_2	R_3	R_4	$R_{5,6}$	-ol
4	α	H	CHO	$+R_4$	CH_2	H	A
5	β	$+R_2$	O	H	CH_3	H	B
13	α	CHO	H	H	CH_3	H	C
14	--	CHO	--	H	CH_3	H	D
17	α	$+R_2$	O	H	CH_3	H	E
18	β	$+R_2$	O	H	CH_3	O	F

Figure 1. *abeo*-Abietanes (taiwaniaquinones and taiwaniaquinols) from *Taiwania cryptomerioides.*

Biosynthesis and Classification

Cheng postulated that the *abeo*-abietanes found in *T. cryptomerioides* arise from a pinacol-type rearrangement of 6,7-dihydroxyferruginol (**19**), possibly derived from 6,7-dehydroferruginol (**20**), which is also found in the leaves of *T. cryptomerioides* (Scheme 1).[2a] This kind of rearrangement gives rise to the 5(6→7)*abeo*-

[†] Taken in part from the Ph.D. dissertation of Joel M. Shimkus, University of Georgia, Athens, GA (2009).

[‡] Dedicated to Professor Paul A. Grieco on the occasion of his 65th birthday.

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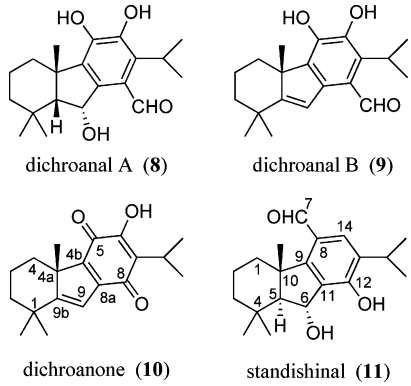
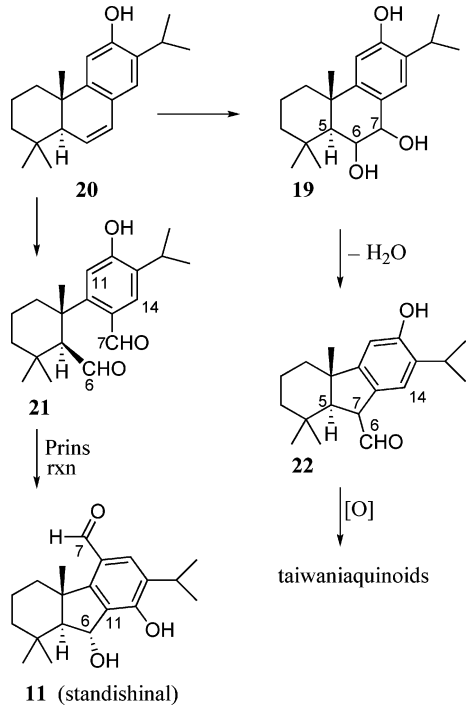


Figure 2. [6,5,6]-Compounds isolated from *Salvia dichroantha* and *Thuja standishii.*

abietanes (**1**−**4**, **6**, **7**, **12**−**14**) or, if a carbon is lost during or after rearrangement, the 6-*nor*-5(6→7)*abeo*-abietanes (**5**, **15**−**18**). No work has been done to verify this conjecture.

Scheme 1. Proposed Biosyntheses of the Taiwaniaquinoids and Standishinal



Standishinal (**11**), a 6(7→11)*abeo*-abietane, was isolated along with 12-hydroxy-6,7-*seco*-abieta-8,11,13-triene-6,7-dial (**21**), which was hypothesized as the penultimate intermediate in the biosynthesis of standishinal. Tanaka gave credence to this idea by smoothly converting **21** into standishinal.[6] It is interesting to note that while **21** is also found in *T. cryptomerioides* (likely derived from **20**), standishinal is not, which highlights the phytochemical difference in the production of these compounds. A similarity in biosynthesis is expected, as *T. cryptomerioides* and *Th. standishii* are cypress-family conifers.

Table 1. Percent Inhibition (%) of EBV-EA by Standishinal (**11**) and Its Diacetate

	concentration (μM)			
	32	16	3.2	0.32
standishinal (**11**)	85.9	32.0	16.7	0
standishinal diacetate	84.5	30.5	11.1	0
labdane	92.3	51.9	22.2	4.5
β-carotene[a]	91.0	66.0	18.0	0

[a] positive control.

Table 2. Aromatase Inhibition by Standishinal (**11**) and Its Diacetate versus Steroidal Inhibitors

	concentration (μM)	inhibition (%)
standishinal	1.0	50.2
standishinal $(OAc)_2$	1.0	38.6
formestane[a]	0.6	63.7

[a] Positive control.

Table 3. Aromatase Inhibition (%) by Standishinal (**11**) versus Nonsteroidal Inhibitors

	concentration (μM)			
	10	3	1	0.3
standishinal	23.7	6.7	10.3	1.1
ketoconazole	87.9	87.5	84.2	81.7
letrozole	92.5	83.8	91.1	89.3

A biosynthetic pathway has not been proposed for the [6,5,6]-products found in *S. dichroantha*. If dichroanals A (**8**) and B (**9**) are derived from the abietane skeleton, the installation of the C-14 formyl group requires a more complex rearrangement process than either of the two shown in Scheme 1, wherein migration of either C-6 or C-7 would also have to occur (cf. **21** and **22**). Moreover, none of the other compounds obtained in this isolation study provide any insight into the mechanism of the rearrangement. Dichroanone (**10**) is probably the result of a *nor*-process associated with this rearrangement, since a common biosynthesis with its congeners is more likely than its formation through the 6-*nor*-5(6→7) rearrangement process, in close analogy with taiwaniaquinone H (**16**). The

Table 4. Cytotoxicity of Some Taiwaniaquinoids against KB Epidermoid Carcinoma Cells

compound	EC_{50} (μM)
etoposide[a]	1.1
taiwaniaquinone A (**1**)	6.9
taiwaniaquinone D (**6**)	7.2
taiwaniaquinone E (**7**)	>10
taiwaniaquinone F (**12**)	4.4
taiwaniaquinone G (**15**)	>10
taiwaniaquinone H (**16**)	>10
taiwaniaquinol A (**4**)	8.3
taiwaniaquinol B (**5**)	>10
taiwaniaquinol C (**13**)	8.1
taiwaniaquinol D (**14**)	3.5
taiwaniaquinol E (**17**)	>10
taiwaniaquinol F (**18**)	>10

[a] Positive control.

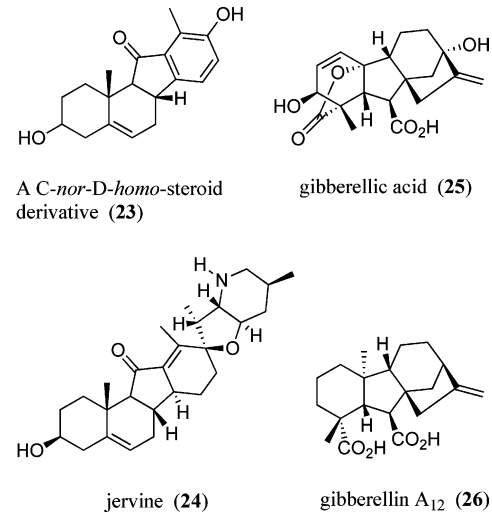
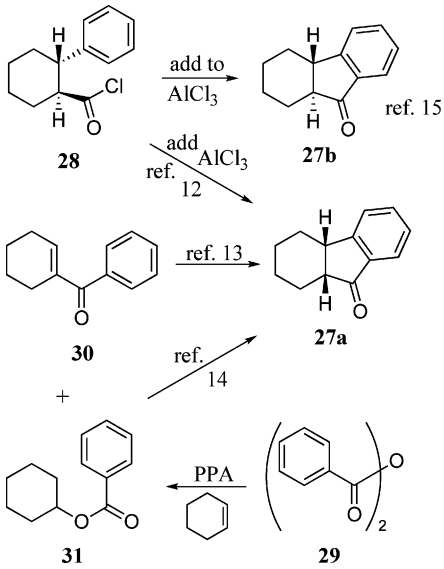


Figure 3. Other natural products containing the [6,5,6]-system.

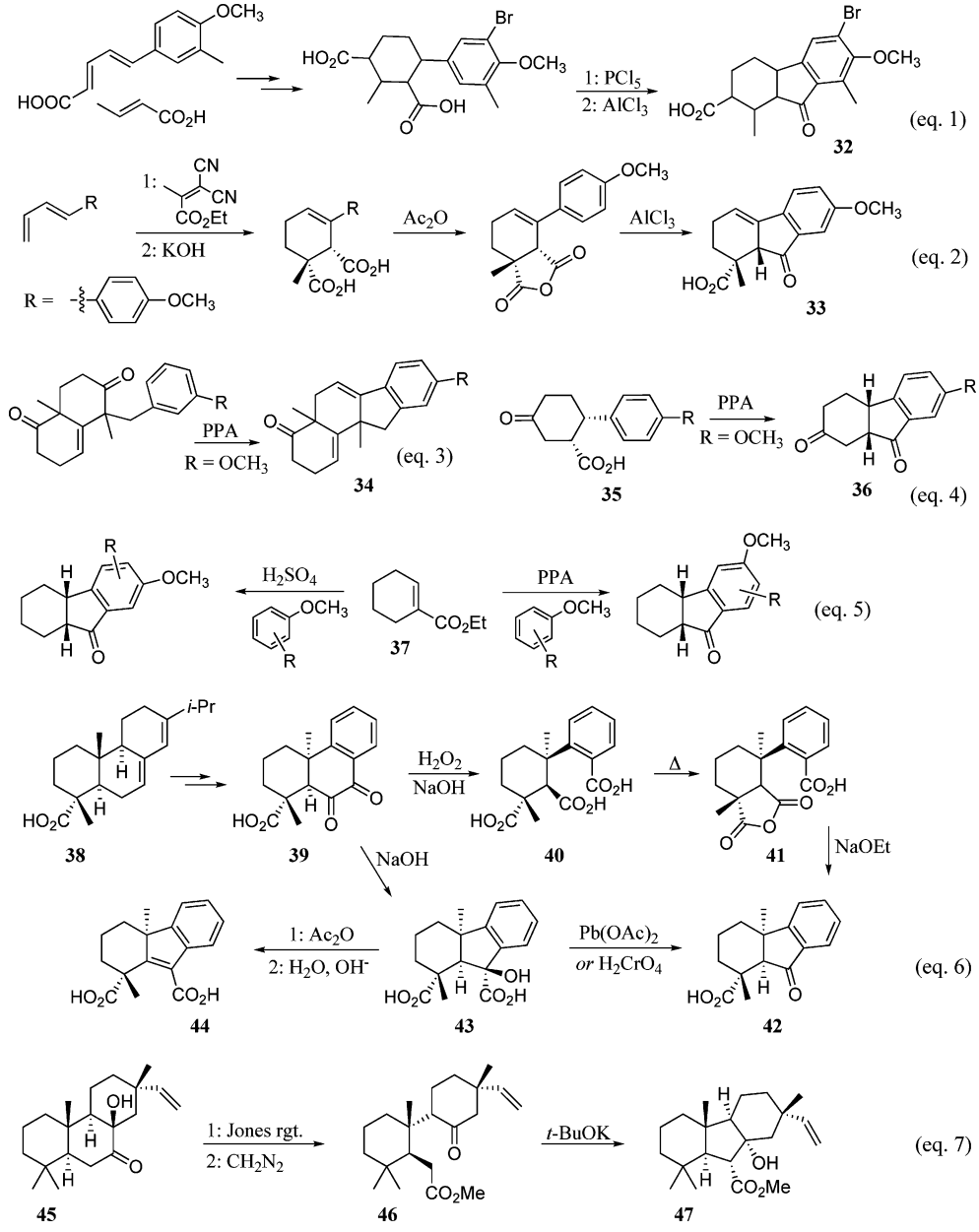
Scheme 2. Fundamental Methods of Basic Hexahydrofluorenone Formation



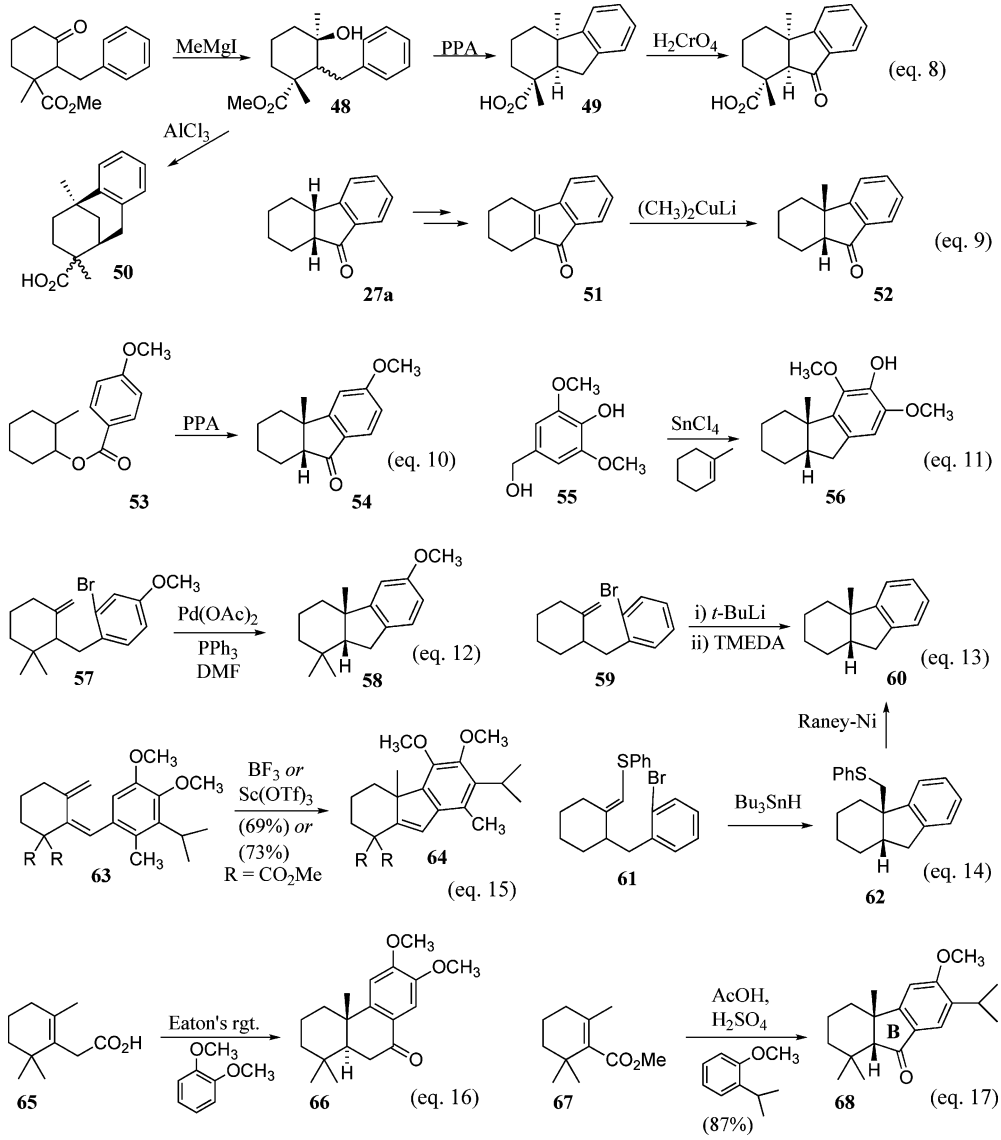
fact that dichroanone has not yet been found in *T. cryptomerioides* supports this position, although it is important to remember that these *S. dichroantha* metabolites were found in the roots, while the isolates from *T. cryptomerioides* were from the leaves or bark. Also, *S. dichroantha* is highly disparate from the cypress family.

Although Cheng recognized the rearranged abietane core of **1**−**5**, no emphasis was placed on naming or classification.[2a] Kawazoe also reported compounds **8**−**10** as rearranged abietanes, but he named them as hexa- and tetrahydrofluorenes; whether or not this is due to the unclear nature of the rearrangement process is unknown.[5] Despite Tanaka's proper classification of standishinal (**11**)[6] and Kuo's emphasis on the use of formal nomenclature,[7] most publications refer to these compounds as 4a-methylhydrofluorene derivatives. This label allows the grouping of all representatives from the three species by highlighting the shared trimethyl, isopropyl-substituted tricyclic core. Unfortunately, it requires a cumbersome system of nomenclature (which skirts the problem of naming the *S. dichroantha* products as abietanes) and detracts from the recognition of the biogenetic process. The general, inclusive term "taiwaniaquinoid" has gained some popularity in the literature.[10] While it is technically correct only when referring to those

Scheme 3. Synthetic Strategies toward Substituted Hydrofluoren(on)es



Scheme 4. Strategies for Constructing 4a-Methylhydrofluoren(on)es



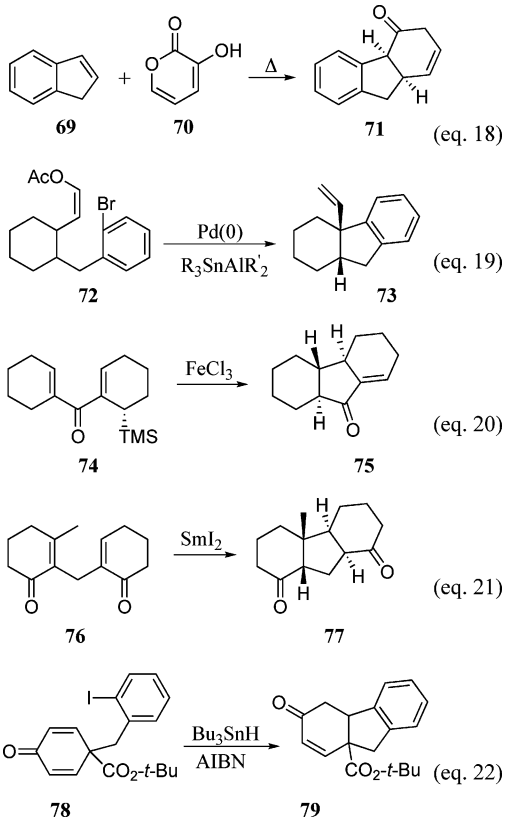
structures found in *T. cryptomerioides*, the preponderance of examples from that source and their close association with those from *S. dichroantha* and *Th. standishii* throughout the literature make it more instinctive and specific than the 4a-methylhydrofluorene label when referencing these compounds. While the subtle differences in biogenesis make generic labeling difficult, the fact that these compounds belong together in a separate structural class cannot be denied. For simplicity, the 5(6→7)*abeo*-abietane numbering system is used when referencing substituent locations throughout the body of the text.

Biological Activity

Relatively little is known about the biological activity of the taiwaniaquinoids. Standishinal (**11**) has received the most attention, as Tanaka was investigating *Th. standishii* in the search for biologically active constituents found in the waste from conifers processed by the local forestry industry.[11a] Standishinal (**11**) and its diacetate derivative were first examined in 2001 for Epstein−Barr virus early antigen (EBV-EA) inhibition along with several labdane and abietane diterpenoids from the same source; in order to obtain a direct comparison with known terpenoid EBV-EA inhibitors, β-carotene was used as the standard. Unfortunately, standishinal (**11**) and its diacetate were among the worst performers in the in vitro study, faring better than only one of the synthetic labdane derivatives (Table 1), and they were not used in the subsequent in vivo investigation.[11b] They were then tested for aromatase inhibition, an established therapeutic strategy for the treatment of breast cancer. A 2001 study compared the labdanes and abietanes used in the EBV-EA inhibition study with formestane, the most potent steroidal aromatase inhibitor. Standishinal performed the best in this study, being 50% as effective as formestane in vitro (Table 2).[11c]

A synthesis of racemic standishinal was reported in 2007, accompanied by the in vitro comparison of standishinal and several synthetic precursors to clinically used nonsteroidal aromatase inhibitors.[11d] While the clinical drugs performed consistently over a range of concentrations, standishinal at the highest concentration reached only 25% of their effectiveness (Table 3). Interestingly, the synthetic precursors possessing the unnatural *cis*-configuration on the A-ring outperformed the selected *trans*-precursors. The activity differences in Tables 2 and 3 are a result of the differing assay methods used in the studies. Kuo's 2005 isolation report[7b] also included an in vitro study of compounds **1**, **4**−**7**, and **12**−**18** against human oral epidermoid carcinoma KB cells, employing the clinically used chemotherapeutic drug etoposide as a positive control (Table 4). Taiwaniaquinol D (**14**) and taiwaniaquinone F (**12**) were the most active, being one-third and one-fourth as effective as etoposide, respectively. Compounds **1**, **4**, **6**, and **13** exhibited weak

Scheme 5. Generic Strategies for [6,5,6]-Polycyclic Skeletons



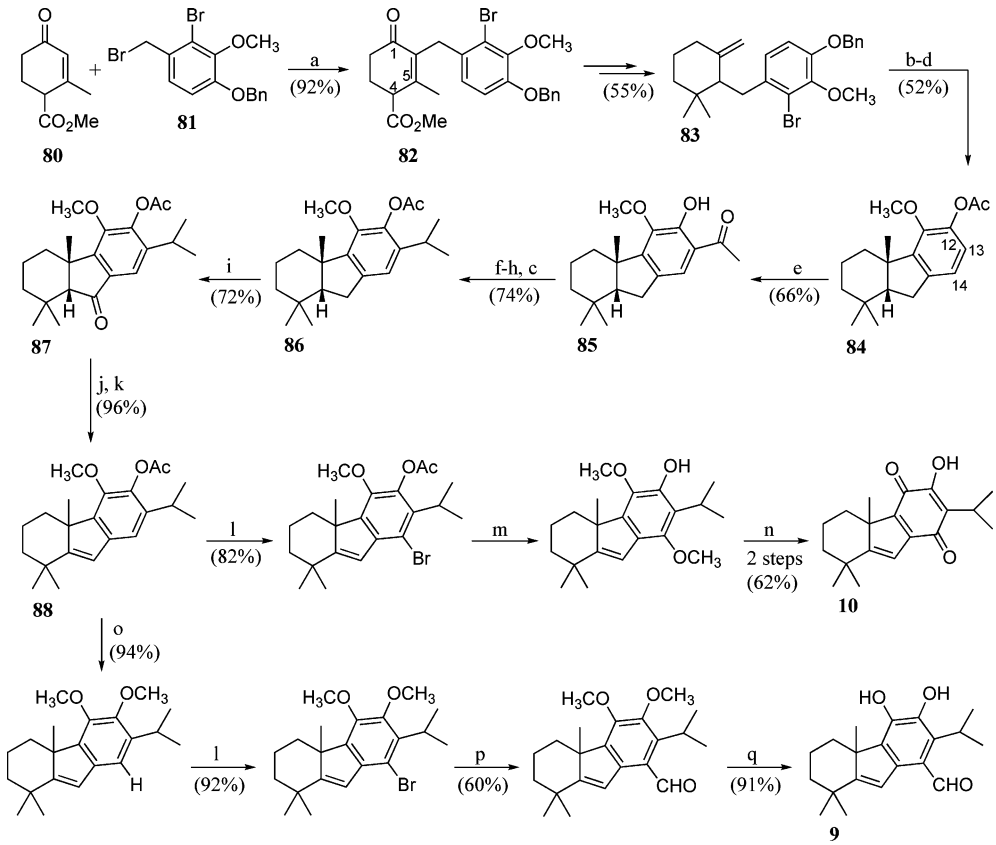
activity, and the rest were inactive. This study correlated the activity of the compounds to the structures where a formyl substituent occurs at C-6. This work suggests that the claims of promise of standishial (**11**) as a drug lead are overstated. Ironically, the fact that the taiwaniaquinoids performed better than **11** against their respective standards has received almost no attention. Additional biological activity studies of these compounds is warranted.

Synthetic Approaches

Even the most cursory examination finds the literature replete with strategies for preparing various [6,5,6]-carbocyclic systems. The work directed toward the C-*nor*-D-*homo*-steroids (e.g., **23**), jervine (**24**), and the gibberellins (e.g., **25** and **26**), which contain this motif within a tetracyclic core, is particularly applicable (Figure 3). Special value has been given to reports dealing specifically with the installation of the angular methyl group, as it is one of the key features of the taiwaniaquinoid skeleton. As a full review of these methods would detract from the focus of this work, only a representative selection is provided. This information is presented topically in an effort to best show the relationships among the methods, and chronology is preserved wherever possible.

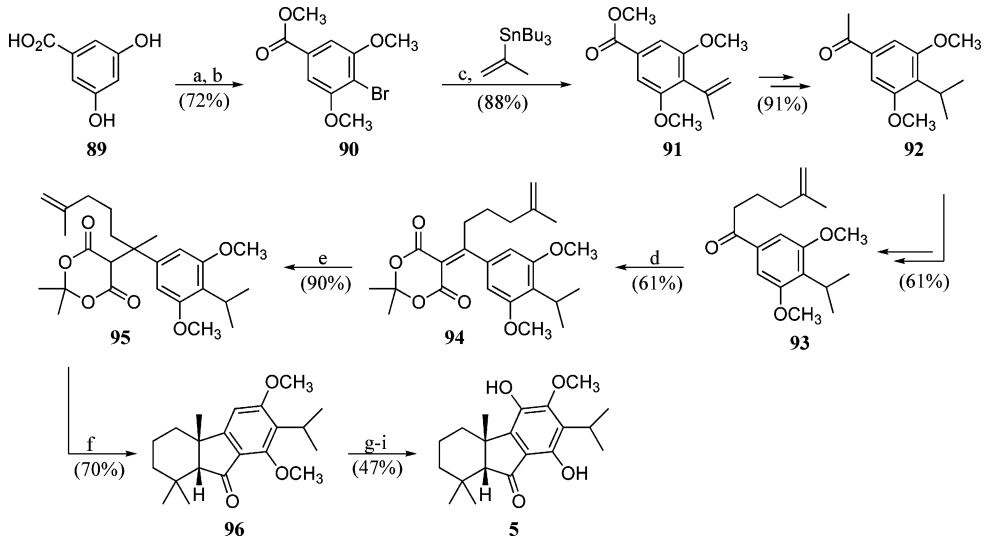
In 1936, Cook and Hewett prepared the simple hexahydrofluorenone **27a** by the intramolecular Friedel−Crafts cyclization of acid chloride **28** (Scheme 2).[12] Nearly twenty years later, Dev prepared **27a** by reacting cyclohexene and benzoic anhydride (**29**) in polyphosphoric acid (PPA) and asserted that the reaction proceeds through cyclohexenyl phenyl ketone **30**.[13] Dev also reported that cyclohexyl benzoate was obtained, which prompted Conia to study the possible cyclization of related esters.[14] House et al. determined that both the *cis*- and the *trans*-fused isomers of ketone **27** could be obtained merely by reversing the order of the addition of $AlCl_3$ to acid chloride **28**.[15a] They also found that the Nazarov cyclization

Scheme 6. Banerjee's Syntheses of (±)-Dichroanone and (±)-Dichroanal B[a]



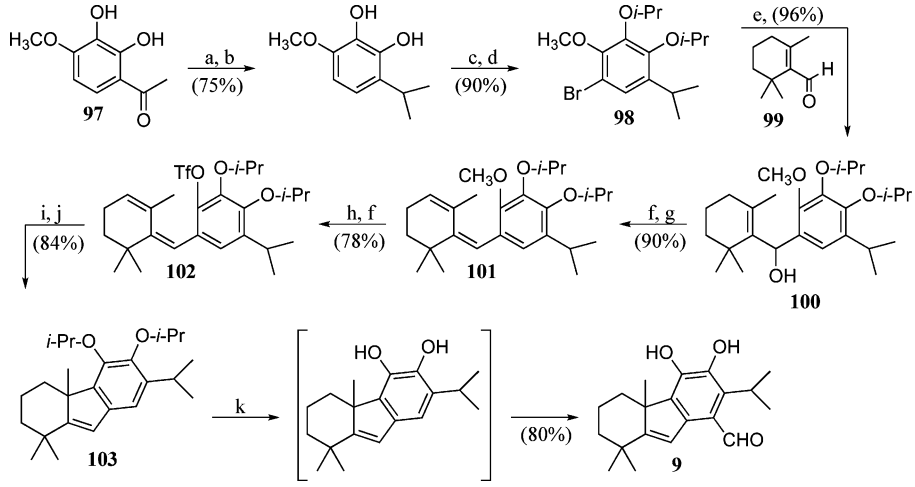
[a] Reagents and conditions: (a) *t*-BuOK; (b) $Pd(PPh_3)_4$; (c) H_2, Pd/C; (d) Ac_2O; (e) $AlCl_3$, $PhNO_2$; (f) MeLi; (g) SiO_2, Δ; (h) Ac_2O; (i) PCC; (j) $NaBH_4$; (k) $SOCl_2$/Py; (l) NBS; (m) NaOMe, CuI; (n) CAN; (o) K_2CO_3, MeI; (p) *n*-BuLi, DMF; (q) PhSH, K_2CO_3, NMP, Δ.

Scheme 7. Fillion and Fishlock's Total Synthesis of (±)-Taiwaniaquinol B[a]



[a] Reagents and conditions: (a) Br_2; (b) $(MeO)_2SO_2$; (c) $Pd(P(t\text{-}Bu)_3)_2$; (d) Meldrum's acid, $TiCl_4$, Py; (e) MeMgBr; (f) TMSOTf, CH_3NO_2; (g) BCl_3; (h) CAN; (i) H_2, Pd/C.

Scheme 8. Node's Synthesis of (±)-Dichroanal B[a]



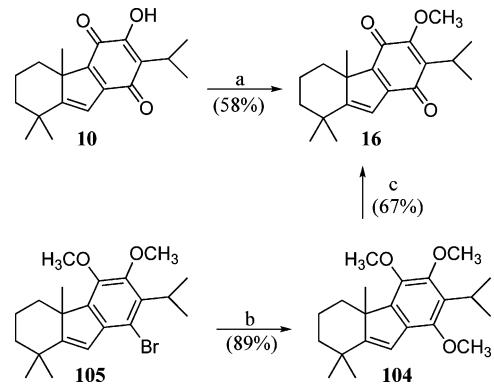
[a] Reagents and conditions: (a) MeMgBr; (b) BF_3-Et_2O, Et_3SiH; (c) *i*-PrBr, Cs_2CO_3; (d) NBS; (e) *n*-BuLi; (f) Tf_2O, Py; (g) DABCO; (h) DodSNa; (i) $Pd(OAc)_2$, dppp; (j) H_2, $RhCl(PPh_3)_3$; (k) BCl_3, $MeOCHCl_2$.

of **30** proceeded well in neat H_2SO_4.[15b] House and co-workers applied these methods to the synthesis of the degradation products of gibberellic acid.

Scheme 3 presents five synthetic strategies for the preparation of substituted hydrofluoren(on)es and two examples showing the derivation of these frameworks from natural precursors. Gerber[16] and Nakanishi[17] used similar strategies to create the highly functionalized fluorenone systems of **32** and **33** aimed at jervine (eq 1) and the gibberellins (eq 2). Los et al. found the PPA cyclization of 2-benzyl-cyclohexanones to be effective in their synthesis of 8β-methyl-D-homo-B-*nor*-estranes (cf. **34**, eq 3).[18] Ziegler and Condon used the PPA cyclization of phenylcyclohexanecarboxylic acid derivatives to construct their gibbane synthons (**35** → **36**, eq 4).[19] Ramana extended the methodology of Dev, Rand, and Conia by reacting ethyl cyclohexene-1-carboxylate (**37**) with variously substituted methoxylated arenes under acidic conditions (eq 5).[20] Interestingly, Ramana found that the use of H_2SO_4 caused Michael addition to occur first, followed by intramolecular Friedel–Crafts acylation, whereas the use of PPA caused 1,2-addition to the ester to take place, followed by a Nazorov cyclization.

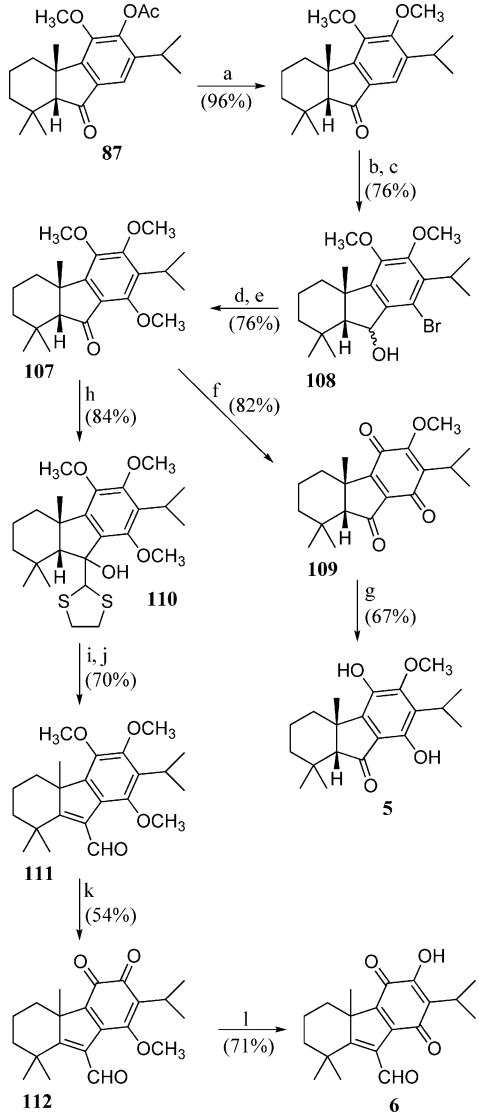
Ohta,[21] Grove,[22] and Tahara[23] approached the [6,5,6]-core, as found in the gibberellins, by manipulation of readily available

Scheme 9. Banerjee's Syntheses of (±)-Taiwaniaquinone H[a]



[a] Reagents and conditions: (a) K_2CO_3, MeI, acetone–MeOH; (b) NaOMe, CuI; (c) AgO, HNO_3.

Scheme 10. Banerjee's Syntheses of (±)-Taiwaniaquinol B and (±)-Taiwaniaquinone D[a]

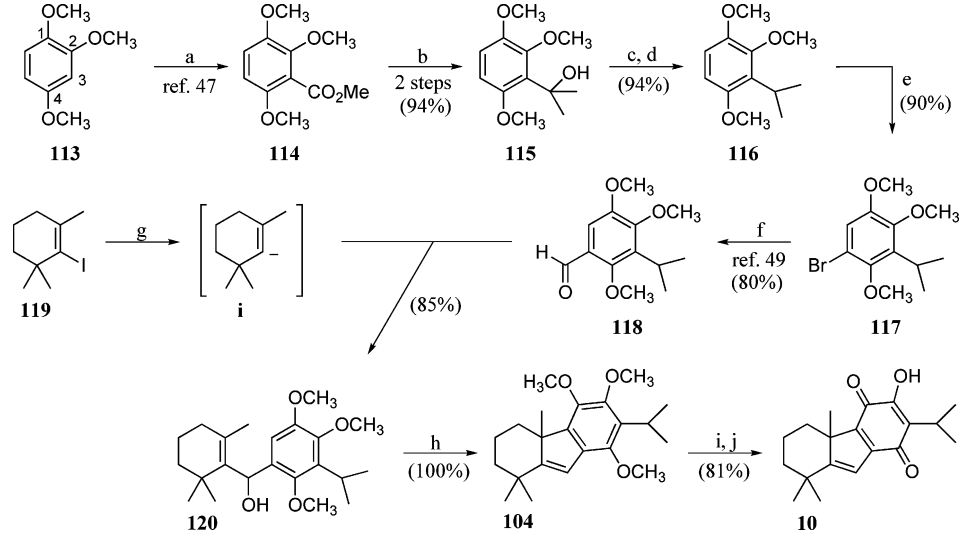


[a] Reagents and conditions: (a) K_2CO_3, MeI; (b) $NaBH_4$; (c) NBS; (d) Jones rgt.; (e) NaOMe, CuI; (f) AgO, HNO_3; (g) $Na_2S_2O_4$; (h) 1,3-dithiane, *n*-BuLi; (i) MeI, (j) CH_3CN-H_2O; $KHSO_4$, 205 °C; (k) CAN; (l) TMSI.

abietic acid (**38**) into podocarpate **39** (Scheme 3, eq 6). Ohta employed oxidative cleavage of **39** to obtain triacid **40**; conversion to anhydride **41** allowed base-induced cyclization to keto-acid **42**. Grove and Tahara used a benzilic acid rearrangement to contract **39** into diacid **43**. Choice of oxidation or elimination allowed the formation of either **42** or conjugated acid **44**, respectively. Pinto et al. also used a naturally available precursor (**45**) in their synthesis of the *ent*-gibberellanes (eq 7).[24] The transformation started, as before, with the oxidative opening of the B-ring, resulting in keto-ester **46**. This difference in functionality allowed the formation of **47** through an intramolecular Claisen reaction.

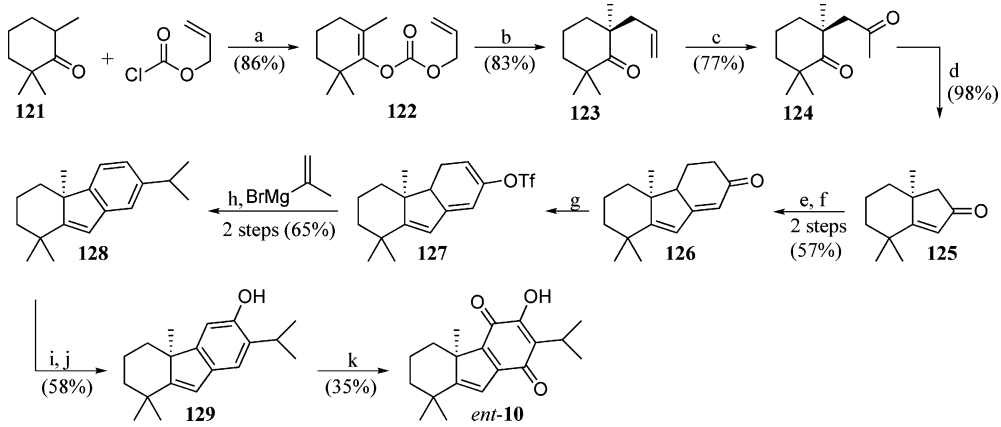
Scheme 4 summarizes nine strategies used to construct various substituted 4a-methylhydrofluoren(on)e skeletons. Ghatak and co-workers employed PPA cyclization of 2-benzylcyclohexanols to afford 4a-methylhydrofluorenes as a means of accessing this type of gibberellane from synthetic intermediates (eq 8).[25] They investigated this process extensively and found that while PPA cyclization of **48** produced hydrofluorene **49**, using $AlCl_3$ resulted in rearranged bicyclo[3.3.1]nonane **50**. Parham and Czuba,[26] in their studies toward angularly substituted octahydrophenanthrenes (eq 9), showed that conjugate addition of lithium dimethylcuprate to enone **51**, derived from **27a**, proceeded efficiently to form **52**. Woodgate et al. extended Conia's basic formation of **27a** to include 4a-methyl and C-ring methoxy derivatives (**53** → **54**, eq 10).[27] In work focused on dihydroindene synthesis, Angle formed 4a-methylhydrofluorene **56** via formal [3+2]-cycloaddition of 1-methylcyclohexene to the benzylic carbocation derived from alcohol **55** (eq 11).[28] Ghatak's work on hydroanthracene derivatives led him to investigate intramolecular Heck reactions of exo-olefins such as **57** (eq 12). These were converted exclusively to 4a-methylhydrofluorenes (e.g., **58**), offering a flexible and direct approach to this framework.[29] In contrast, Bailey studied the formation of 4a-methylhydrofluorenes by anionic attack of aryllithiums tethered to substituents bearing an exomethylene (e.g., **59** → **60**, eq 13).[30] Ishibashi and co-workers,[31] while investigating factors controlling endo- versus exo-selection in radical cyclizations, showed that exo vinyl sulfide **61** gave only exo-cyclization to **62**; the thio group was removed with Raney-nickel to give **60** (eq 14). Balme et al. were the first to study the formation of the hydrofluorene nucleus as found in the taiwaniaquinoids.[32] This group used BF_3-Et_2O or $Sc(OTf)_3$ to induce the Friedel−Crafts reaction of bis-exocyclic diene **63** to generate the angular methyl group in **64** (eq 15). Bhar and Ramana[33] used Eaton's reagent, which is P_2O_5 in neat methanesulfonic acid (MSA), to effect domino alkylation−cyclization

Scheme 11. Majetich's Synthesis of (±)-Dichroanone[a]



[a] Reagents and conditions: (a) *n*-BuLi, $ClCO_2Me$; (b) MeMgI, Et_2O; (c) *p*-TsOH, benzene; (d) H_2, Pd/C; (e) NBS, CH_3CN; (f) Mg/THF, DMF; (g) *t*-BuLi; (h) BF_3-Et_2O, CH_2Cl_2; (i) BBr_3, CH_2Cl_2; (j) SiO_2.

Scheme 12. Stoltz's Approach to (+)-Dichroanone[a]



[a] Reagents and conditions: (a) LiHMDS; (b) $Pd_2(dba)_3$, (*S*)-*t*Bu-PHOX; (c) O_2, $PdCl_2$, $Cu(OAc)_2$; (d) KOH; (e) LiHMDS, MVK; (f) KOH, xylenes, Dean−Stark; (g) LDA, $PhN(Tf)_2$; (h) $Pd(PPh_3)_4$; (i) $TiCl_4$, $MeOCHCl_2$; (j) H^+, H_2O_2; (k) IBX, C_6H_5SH, O_2, NaOH.

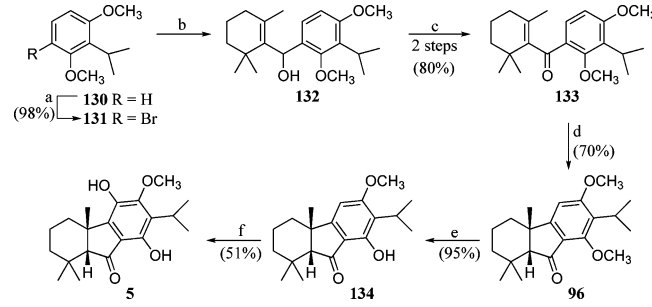
reactions (**65** → **66**, eq 16) in the total syntheses of several natural abietanes in a modified version of their previous strategy (cf. eq 5).[20] While abietanes containing the A/B *cis*-fusion could not be directly obtained by this cyclization strategy, applying it to the *nor-abeo*-abietane core resulted in the desired ring junction. This methodology provided an avenue to not only this specific class but, after expansion of the B-ring, the *cis*-fused abietane products as well (**67** → **68**, eq 17). Interestingly, ketone **68** later served as a precursor for dichroanone (**10**) (see Scheme 17).

Scheme 5 shows some additional methods that form nonspecific [6,5,6]-tricyclic frameworks. Middlemiss employed a Diels−Alder reaction with indene (**69**) and pyrone **70** to annulate the C-ring of ketone **71** (eq 18).[34] In 1987, Trost and Walchli used a palladium-mediated reaction of aryl bromide **72** to produce adduct **73** (eq 19).[35] Denmark[36a] and Handy[36b] independently reported the Nazarov cyclization of substrates **74** and **76** (eqs 20 and 21, respectively) to assemble the [6,5,6]-frameworks of **75** and **77**. In 2007, Clive and Sunasee reported the formation of a [6,5,6]-system from the radical-induced cyclization of an aryl iodide to a tethered enone (**78** → **79**, eq 22).[37] While these example would require significant modification before any meaningful application to the syntheses of the taiwaniaquinoids, they show the breadth of synthetic strategies available for consideration.

Published Syntheses

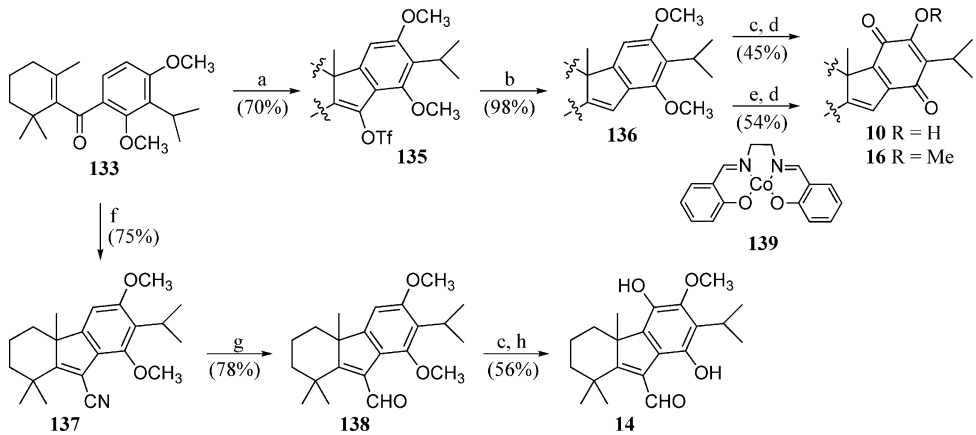
This taiwaniaquinoids went unnoticed by the synthetic community until Banerjee reported the first total synthesis of (±)-dichroanone and (±)-dichroanal B in 2003.[38] In the past six years the taiwaniaquinoids have been the focus of considerable attention. Banerjee elected to construct the 4a-methylhydrofluorene core by Ghatak's palladium-mediated cyclization strategy (Scheme 4, eq 12), with the overall goal of creating a common intermediate from which several taiwaniaquinoids could be derived. As shown in Scheme 6, the cyclization precursor **82** was prepared by coupling benzyl bromide **81** (derived from vanillin)[39] to Hagemann's ester (**80**),[40] followed by hydrolytic decarboxylation of the C-4 ester,

Scheme 13. Trauner's Nazarov Cyclization Approach to (±)-Taiwaniaquinol B[a]



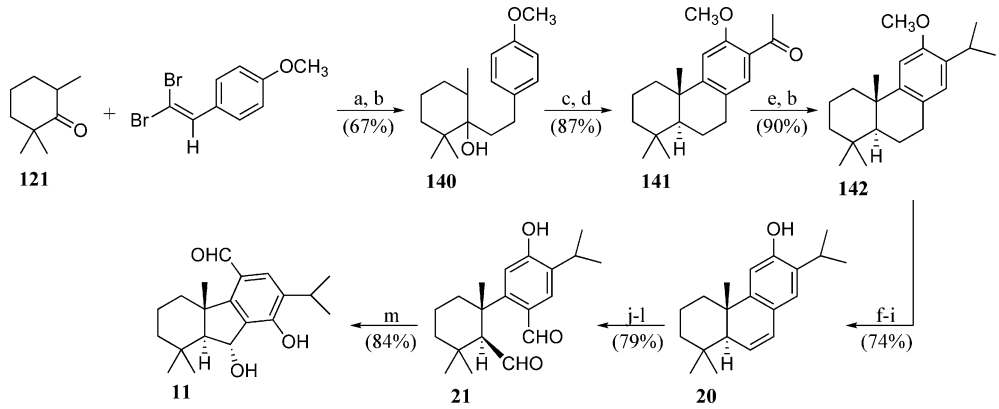
[a] Reagents and conditions: (a) NBS; (b) *n*-BuLi, *β*-cyclocitral (99); (c) Dess−Martin periodinane, Py; (d) TMSOTf, CH_3NO_2; (e) BCl_3; (f) (i) CAN, (ii) $Na_2S_2O_4$.

Scheme 14. Trauner's Endgame Strategies for (±)-Dichroanone, (±)-Taiwaniaquninone H, and (±)-Taiwaniaquinol D[a]



[a] Reagents and conditions: (a) Tf_2O, CH_3NO_2; (b) $Pd(OAc)_2$, HCO_2NH_4; (c) BBr_3; (d) O_2, 139; (e) BBr_3−SMe_2; (f) $Pd(OAc)_2$, TMSCN; (g) DIBAH; (h) (i) CAN, (ii) $Na_2S_2O_4$.

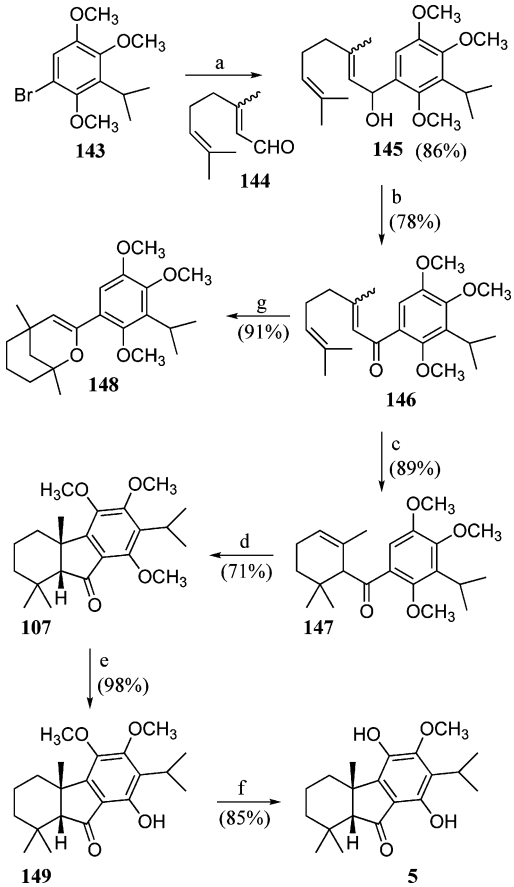
Scheme 15. Node and Tanaka's Synthesis of (±)-Standishinal[a]



[a] Reagents and conditions: (a) *n*-BuLi; (b) H_2, Pd/C; (c) Eaton's rgt.; (d) AcCl, $AlCl_3$; (e) MeMgBr; (f) CrO_3; (g) $NaBH_4$; (h) TsOH; (i) DodSLi; (j) TBSCl; (k) O_3; (l) TBAF; (m) camphorsulfonic acid.

conjugate addition of a methyl group to C-5, and olefination of the C-1 carbonyl. This sequence is also similar to Ghatak's synthetic strategy.[29] After cyclization of **83** to **84**, the C-12 benzyl group was replaced with an acetyl moiety, followed by a Fries rearrangement to install an acyl moiety at C-13 (**84** → **85**). Completion of the isopropyl unit and reprotection to form **86** required four transformations. Oxidation of C-7 with pyridinium chlorochromate (PCC) gave ketone **87**, which was converted into tetrahydrofluorene **88**. From here the routes diverged: placing a bromine atom at C-14 allowed transformations culminating in either dichroanone (**10**) or dichroanal B (**9**). The strategy for cyclization and isopropyl installation limited the complexity of the starting materials and put heavy manipulative constraints on the synthesis, which resulted in a 23-step synthesis of intermediate **88**. However, alkene **88** is only three steps removed from dichroanone (**10**) and four steps away from dichroanal B (**9**), as shown.

Scheme 16. Chiu's Consecutive-Cyclization Synthesis of (±)-Taiwaniaquinol B[a]



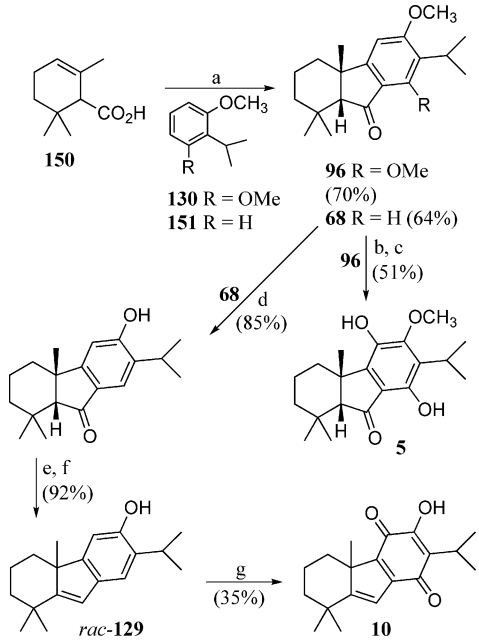
[a] Reagents and conditions: (a) *n*-BuLi; (b) MnO_2, CH_2Cl_2; (c) $SnCl_4$, CH_3NO_2; (d) TfOH, CH_3NO_2; (e) BCl_3; (f) (i) $PhI(OAc)_2$, (ii) $Na_2S_2O_3$; (g) "H^+".

Nearly two years after Banerjee's pioneering report, Fillion and Fishlock reported the first total synthesis of (±)-taiwaniaquinol B (**5**) (Scheme 7).[41] This target was a logical extension of their use of Meldrum's acid to prepare indanones. Acid **89** was brominated and permethylated in preparation for the introduction of the isopropyl group via Stille coupling (**90** → **91**). Ester **91** was converted to acetophenone **92** over three steps, allowing the synthesis of ketone **93** through a modified acetoacetic ester protocol. Meldrum's acid was condensed with ketone **93**, and conjugate addition of methylmagnesium bromide to **94** generated the methyl-substituted quaternary center (cf. **95**). Domino acylation/cycloalkylation was achieved using stoichiometric trimethylsilyl triflate (TMSOTf) in refluxing CH_3NO_2 (**95** → **96**); substoichiometric amounts resulted in acylation of the B-ring without concomitant closure of the C-ring. Deprotection of **96** and ceric ammonium nitrate (CAN) oxidation of the resulting resorcinol derivative, followed by hydrogenation, afforded (±)-taiwaniaquinol B in 15 steps. The use of Meldrum's acid is quite effective, as it allows the facile introduction of the quaternary methyl group, essentially creating a masked geranoyl system substituted at the C-3 position.

In March 2006, Node et al. published a concise synthesis of dichroanal B (**9**), as shown in Scheme 8.[42] They also utilized a Heck-type reaction, but through an endocyclic olefin, which facilitated the more judicious choice of starting materials. Commercially available acetophenone **97** was transformed over four steps into bromide **98**, which was subjected to metal−halogen exchange and coupled with β-cyclocitral (**99**) to form alcohol **100**. Alcohol **100** was converted into diene **101**, and protecting group manipulation gave cyclization precursor **102**. Cyclization proceeded smoothly, and **103** was produced by selective hydrogenation of the resulting C-1, C-2 double bond. One-pot deprotection/formylation of **103** completed the 12-step synthesis of (±)-dichroanal B. The use of advanced commercial synthons resulted in a significant reduction in the number of steps required. Surprisingly, key intermediate **103** was not converted into (±)-dichroanone (**10**) and (±)-taiwaniaquinone H (**16**).

Banerjee et al., concurrent with Node's publication, reported an extension of their prior work to (±)-taiwaniaquinol B (**5**), (±)-taiwaniaquinone D (**6**), and (±)-taiwaniaquinone H (**16**).[43] They first completed the synthesis of (±)-taiwaniaquinone H, which was not isolated at the time of their first report, by the methylation of dichroanone (cf. **10** → **16**, Scheme 9). Bromide **105** was then used

Scheme 17. She's Syntheses of (±)-Taiwaniaquinol B and (±)-Dichroanone[a]



[a] Reagents and conditions: (a) Eaton's rgt.; (b) BCl_3; (c) (i) CAN, (ii) $Na_2S_2O_4$; (d) BBr_3; (e) $NaBH_4$; (f) $SOCl_2$, Py; (g) IBX, C_6F_5SH, O_2, NaOH.

to prepare alkene **104**, which also permitted the synthesis of (±)-taiwaniaquinone H.

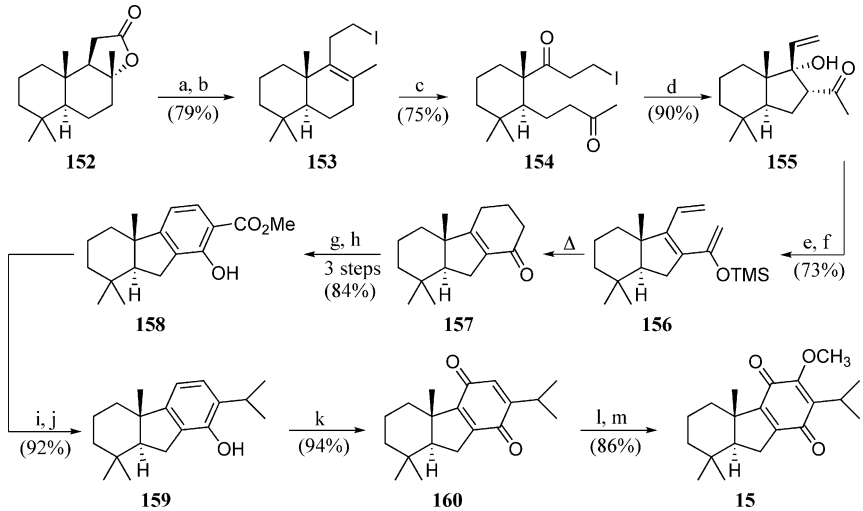
Banerjee's synthesis of (±)-taiwaniaquinol B began with ketone **87** (Scheme 10). Implementation of their previous closing steps yielded the trimethoxy ketone **107**. The selective introduction of a bromide at C-14 (cf. **108**) required prior reduction of the C-7 carbonyl. Their synthesis of (±)-taiwaniaquinol B was completed via intermediate **107** in a manner similar to Fillion and Fishlock:[41] acidic AgO oxidation to benzoquinone **109**, followed by dithionite reduction.

Banerjee's route to prepare (±)-taiwaniaquinone D diverged from that of (±)-taiwaniaquinol B at ketone **107** (Scheme 10). Addition of the anion of 1,3-dithiane to the C-7 carbonyl of **107** gave alcohol **110**. The aldehyde was unmasked, and the resulting aldol was dehydrated with hot, fused $KHSO_4$ to yield enal **111**. Oxidation of **111** with CAN and reaction of *o*-quinone **112** with trimethylsilyl iodide (TMSI) furnished (±)-taiwaniaquinone D. Banerjee and coworkers ultimately derived each of their targets from ketone **87**, demonstrating the utility of this approach. The syntheses of (±)-taiwaniaquinol B and (±)-taiwaniaquinone D were completed from this common intermediate in seven and 10 steps, respectively.

In April 2006, Majetich and Shimkus synthesized (±)-dichroanone[44] using an A + C → ABC Friedel−Crafts-based strategy to prepare the carbocyclic skeleton.[45] The C-ring was prepared as shown in Scheme 11.[46,47] Deprotonation of 1,2,4-trimethoxybenzene (**113**) with *n*-butyllithium occurs at C-3. Quenching this anion with methyl chloroformate gave ester **114**, and subsequent reaction with excess methylmagnesium iodide produced alcohol **115**. Although **115** could be converted directly to isopropyl derivative **116** by hydrogenation in the presence of H_2SO_4,[48] hydrogenation proceeded faster if the alkene was formed first. Azeotropic disillation of a benzene solution of **115** and catalytic *p*-TsOH performed this transformation in high efficiency. Arene **116** was selectively brominated by NBS. The Grignard reagent derived from bromide **117** reacted with DMF to produce aldehyde **118** in good yield.[49] Vinyl iodide **119**[50] was smoothly lithiated and then coupled with aldehyde **118** to form alcohol **120** in 85% yield. The anticipated intramolecular Friedel−Crafts alkylation was effected by treating **120** with BF_3−Et_2O at 0 °C to yield tricyclic alkene **104** in quantitative yield. Heating **104** with excess BBr_3, followed by aqueous workup and chromatography on SiO_2, gave (±)-dichroanone (**10**) in 81% yield.

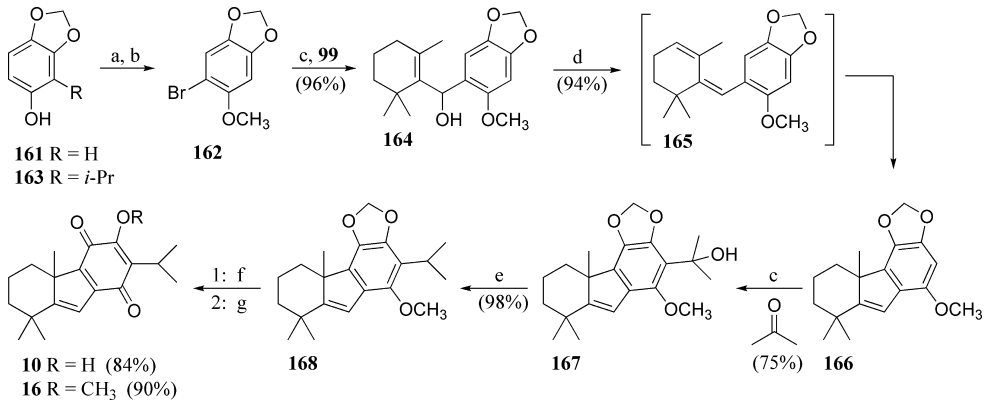
In June 2006, Stoltz and Mcfadden published the synthesis of (+)-dichroanone based on an asymmetric Tsuji allylation (Scheme 12).[51a] They targeted the (+)-enantiomer because the *tert*-butylphosphinooxazoline ligand required to generate (−)-dichroanone was "reasonably expensive". 2,2,6-Trimethylcyclohexanone (**121**) was used to prepare carbonate **122**; Tsuji allylation (cf. **123**), followed by Wacker oxidation, formed diketone **124**. Aldol condensation of **124** gave enone **125**, and Robinson annulation of **125** gave tricyclic ketone **126**. The requisite isopropyl unit was installed via Kumada coupling (**127** → **128**).[52] Alkene **128** was formylated and subjected to a Baeyer−Villager oxidation to produce phenol **129**, which was further oxidized into quinone *ent*-**10** by a novel oxidation. This was the first enantiospecific synthesis directed at the taiwaniaquinoids and contained several novel methods that drew the interest of the synthetic chemistry community.[51b] While the emphasis on procedural novelty definitely warrants attention, the 11-step sequence is palladium intensive, and the final oxidation, albeit novel, proceeds in low yield.

Scheme 18. Alvarez-Manzaneda's Enantiospecific Synthesis of (−)-Taiwaniaquinone G[a]



[a] Reagents and conditions: (a) KBH_4; (b) I_2, PPh_3; (c) O_3; (d) DBU; (e) H_2SO_4; (f) TMSOTf; (g) LDA, $NCCO_2Me$; (h) DDQ; (i) MeMgBr; (j) Et_3SiH, TFA; (k) Fremy's salt; (l) Br_2; (m) NaOMe.

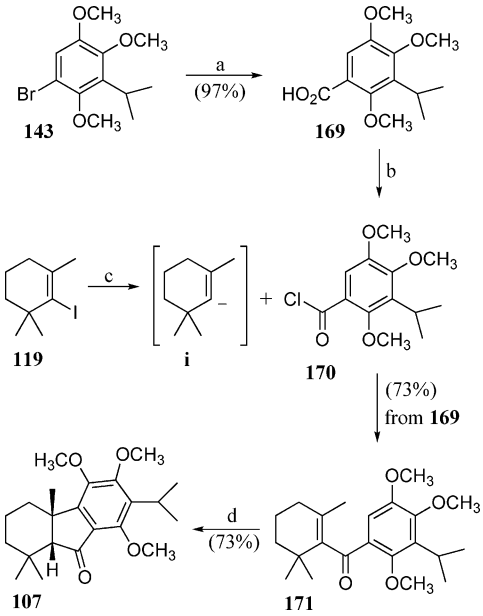
Scheme 19. Alvarez-Manzaneda's Syntheses of (±)-Dichroanone and (±)-Taiwaniaquinone H[a]



[a] Reagents and conditions: (a) "CH_3"; (b) NBS; (c) *n*-BuLi; (d) $SnCl_4$; (e) ZnI_2, $NaBH_3CN$, (f) DDQ, *p*-TsOH, Δ; (g) Me_2SO_4, K_2CO_3, acetone.

Trauner et al., the first to use the term "taiwaniaquinoid" in the literature, reported the syntheses of (±)-taiwaniaquinol B, (±)-dichroanone, (±)-taiwaniaquinone D, and (±)-taiwaniaquinone H, in August 2006.[53] Enone **133**, which served as a common intermediate for all three targets, was generated from bromide **131** and *β*-cyclocitral (cf. Scheme 8), followed by Dess−Martin periodinane oxidation in the presence of pyridine (Scheme 13). Trauner ultimately found that Nazarov cyclization of **133** to **96** could be carried out in TMSOTf in CH_3NO_2, as reported by Fillion and Fishlock.[41] The conversion of **96** to (±)-taiwaniaquinol B was similar to Fillion's strategy, but the reduction of the quinone derived from **133** was achieved with $Na_2S_2O_4$, giving a total of six steps from **130**. Switching from TMSOTf to Tf_2O in the cyclization process resulted in vinyl triflate **135**, shown in Scheme 14. Treating **135** with $Pd(OAc)_2$ and ammonium formate gave alkene **136**, whereas using $Pd(OAc)_2$ and trimethylsilyl cyanide produced nitrile **137**. Selective demethylation of **136**, followed by oxidation, yielded (±)-dichroanone and (±)-taiwaniaquinone H, in seven steps for each route. Nitrile **137** was converted to aldehyde **138** with DIBAl-H. The same endgame strategy used for (±)-taiwaniaquinol B furnished (±)-taiwaniaquinol D in eight steps. Trauner's observation that the polarity of CH_3NO_2 was necessary for cyclization to occur had an immediate impact on the study of the taiwaniaquinoids.

Scheme 20. Majetich's Formal Synthesis of (±)-Taiwaniaquinol B[a]

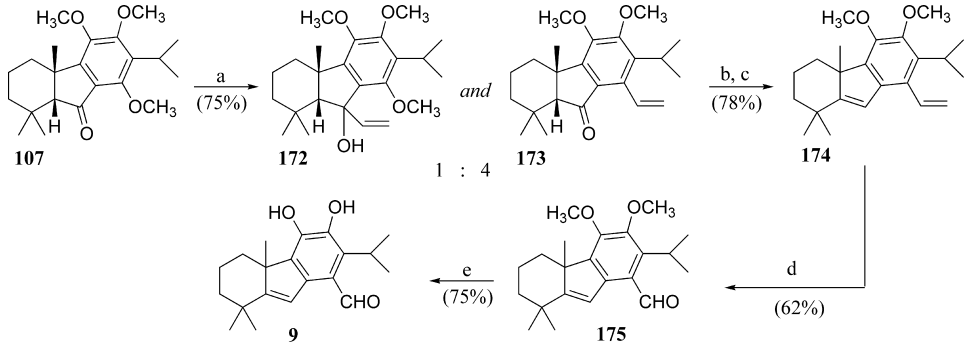


[a] Reagents and conditions: (a) (i) *n*-BuLi, (ii) CO_2; (b) $SOCl_2$, $CHCl_3$; (c) *t*-BuLi; (d) methanesulfonic acid.

Ramana's[33] strategy for constructing *cis*-fused abietanes appeared shortly after Trauner's publication. Although it was not mentioned, a formal synthesis of (±)-taiwaniaquinol B is contained in the paper, intermediate **104** being generated by the process shown in Scheme 4 (eq 17).

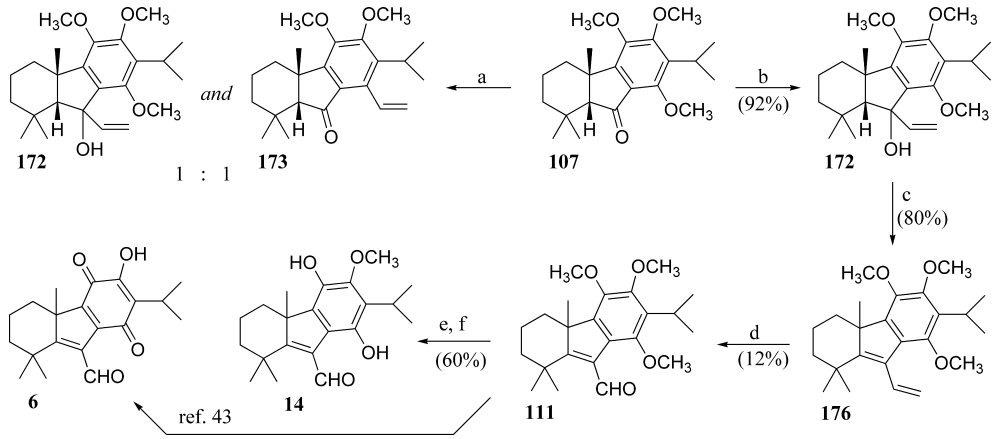
In early 2007, Node and Tanaka[11d] reported their efforts to synthesize standishinal (Scheme 15). In order to achieve the A/B *trans*- fusion, the proposed biosynthetic cyclization process was employed (cf. Scheme 1). Other noteworthy transformations include the use of 2,2,6-trimethylcyclohexanone (**121**) as a precursor for the A-ring and the formation of the B-ring (cf. **141**) from alcohol

Scheme 21. Majetich's Formal Synthesis of (±)-Dichroanal B[a]



[a] Reagents and conditions: (a) vinylmagnesium bromide, toluene, 0 °C; (b) LAH, Et_2O; (c) TFA, CH_2Cl_2; (d) 3.5 mol % $RuCl_3$, 2 equiv $NaIO_4$, 6:1 CH_3CN/H_2O, 0 °C; (e) 3 equiv PhSH, 0.5 equiv K_2CO_3, NMP, 160 °C.

Scheme 22. Majetich's Formal Synthesis of (±)-Taiwaniaquinone D and Total Synthesis of (±)-Taiwaniaquinol D[a]



[a] Reagents and conditions: (a) vinylmagnesium bromide, 0.5 LiBr, Et_2O, −78 °C; (b) vinyllithium, Et_2O, −78 °C; (c) *p*-TsOH, cyclohexane; (d) 3.5 mol % $RuCl_3$, 2 equiv $NaIO_4$, 5:1 CH_3CN/EtOAc/H_2O; (e) BCl_3; (f) (i) CAN, (ii) $Na_2S_2O_4$.

140 with Eaton's reagent. The installation of the C-13 isopropyl moiety was accomplished by simply hydrogenating the alcohol resulting from methyl Grignard addition to **141** (cf. **141** → **142**). It is interesting that Brønsted acids were superior to Lewis acids in promoting the Prins reaction of dialdehyde **21**.

Chiu and Li[54] synthesized (±)-taiwaniaquinol B using a domino-cyclization strategy[55] similar to Fillion and Fishlock's (cf. Scheme 7), but with the C-ring attached to the geranoyl system at C-1 instead of at C-3. Coupling bromide **143** with citral (**144**) afforded alcohol **145**, which was oxidized to ketone **146** with MnO_2 (Scheme 16). However, only A + C coupled ketone **147** was produced on treatment with $SnCl_4$ in CH_3NO_2. Further study revealed that TMSOTf induced the domino-formation of the B-ring, but in very poor yield. Interestingly, treating **146** with Brønsted acids produced bridged bicycle **148**, analogous to Ghatak's work (Scheme 4, eq 8). Ultimately, nonconjugated ketone **147** was cyclized to **107** with triflic acid in CH_3NO_2. Chiu and Li first used BCl_3 to prepare phenol **149**, then completed the oxidation/reduction sequence required for the C-ring using $PhI(OAc)_2$ and $Na_2S_2O_3$ instead of CAN and $Na_2S_2O_4$. These conditions proved more efficient, allowing an 85% yield in the final step, a total of six steps from **143**.

Shortly thereafter, She et al. applied Bhar and Ramana's method[33] in a domino Friedel−Crafts acylation/alkylation of cyclogeranic acid (**150**) and an appropriately substituted isopropylanisole promoted by Eaton's reagent.[56] As shown in Scheme 17, anisole derivatives **130** and **151** were reacted with cyclogeranic acid to yield **96** and **68**, respectively. Ketone **96** yielded (±)-taiwaniaquinol B through Trauner's protocol, while its congener was converted into *rac*-**129** in the manner of Banerjee and then into (±)-dichroanone by using Stoltz's conditions. It is interesting to note that although they reference both of Ramana's reports[33] in applying the H_2SO_4/AcOH system in their cyclization attempts, no reference is made to the related application of Eaton's reagent, which is the primary feature of their strategy.

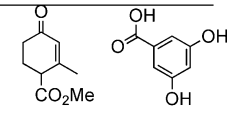
Alvarez-Manzaneda et al. published their enantiospecific synthesis of taiwaniaquinone G in January 2009.[57a] They addressed the difficult A/B *trans*-fusion by starting with an available asymmetric [6,6]-system already containing this characteristic, reminiscent of the gibberellin syntheses. Commercial (+)-sclareolide (**152**) was transformed into iodide **153**, which was cleaved to yield diketone **154**, and an intramolecular aldol reaction formed the B-ring of **155** (Scheme 18). Elimination of the alcohol and converting the ketone into a silyl enol-ether gave triene **156**, which underwent 6π-electrocyclization to form the C-ring. The enolate of **157** was reacted with Mander's reagent to introduce an ester moiety at C-13, and the C-ring was aromatized to phenol **158**. The C-13 ester was converted to the isopropyl group by standard procedures, and oxidation of phenol **159** with Fremy's salt furnished quinone **160**. A bromination/methoxylation sequence introduced the requisite C-12 methoxy group, which completed the synthesis of (−)-taiwaniaquinone G. This 13-step sequence is high yielding and unique for the thermal-cyclization construction of the C-ring and simple transformation to the final quinone.

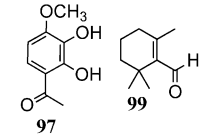
Three months later, Alvarez-Manzaneda et al. also reported a synthesis of (±)-dichroanone and (±)-taiwaniaquinone H.[57b] They theorized that aryl diene **165** would easily undergo Friedel−Crafts alkylation to construct the 4a-methyltetrahydrofluorene core and used β-cyclocitral (**99**) and sesamol (**161**) as the A- and C-ring synthons. As shown in Scheme 19, protection and bromination of sesamol gave **162**, which was lithiated and coupled with β-cyclocitral to give alcohol **164**. Dehydration of **164** to diene **165** with $SnCl_4$ at 0 °C was followed by the formation of the central cyclopentane ring, which also occurred rapidly under these conditions. In contrast, dehydration with acidic resins gave only diene **165**. *ortho*-Lithiation of **166** and subsequent reaction with acetone produced **167**, which was reduced to **168** with ZnI_2 and $NaBH_3CN$. (±)-Dichroanone was produced using their previously reported deprotection−oxidation system comprised of TfOH and DDQ in dioxane.[57c] Methylation of (±)-dichroanone to (±)-taiwaniaquinone H proceeded efficiently with K_2CO_3/Me_2SO_4 in acetone. Installation of the isopropyl moiety prior to coupling was also examined by converting **161** to **163** by the same methods shown, and comparable results were obtained. While the formation of alcohol **164** is similar to previous reports, the overall strategy is to date the most efficient due to its straightforward cyclization and the use of a readily transformable C-ring. The optimized conversion of (±)-dichroanone to (±)-taiwaniaquinone H is superior to prior syntheses.

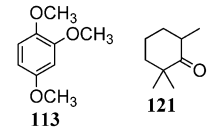
In February 2009, Majetich and Shimkus reported a formal synthesis of (±)-taiwaniaquinol B en route to the total synthesis of (±)-dichroanal B and the formal synthesis of (±)-taiwaniaquinone D.[58] As shown in Scheme 20, aryl bromide **143** was converted into carboxylic acid **169**, followed by conversion into acid chloride **170**. Enone **171** was prepared by adding a solution of the vinyl anion (**i**), derived from iodide **119**, to **170**. Warming enone **171** in neat methanesulfonic acid produced ketone **107**. Ketone **107** can be converted into (±)-taiwaniaquinol B, using the transformations reported by Li and Chiu,[54] and served as a common intermediate for the syntheses of (±)-dichroanal B and (±)-taiwaniaquinone D. Addition of vinylmagnesium bromide to ketone **107** produced a mixture of tertiary alcohol **172** and ketone **173** (Scheme 21). The choice of solvent and reaction temperature influenced the preference for vinyl addition at C-7 or C-14, and dichroanal B precursor **173** was obtained as a 4:1 mixture with **172** by treating ketone **107** with the Grignard reagent in toluene at 0 °C.[59] The reduction of

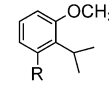
Table 5. Summary of the Overall Efficiency of Reported Taiwaniaquinoid Syntheses

Target/Author	A-Ring	C-Ring	Reported steps	Overall yield
dichroanal B (**9**)				
Node	**99**	**97**	12	30.5%
Majetich	**121**	**113**	14	9.0%
Banerjee	**80**	**177**	27	3.0%
dichroanone (**10**)				
Alvarez-Manzaneda	**99**	**161**	7	55.7% (from step 3)
Majetich	**121**	**113**	11	43.8%
Trauner	**99**	**130**	7	24.2%
She	**150**	**151**	5	17.5%
Stoltz	**121**	--	10	4.1%
standishinal (**11**)				
Node	**121**	**178**	15	26.1%
taiwaniaquinol B (**5**)				
She	**150**	**130**	3	35.7%
Chiu	**144**	**113**	10	35.5% (from step 5)
Trauner	**99**	**130**	6	26.6%
Fillion	**89**	--	15	6.4%
Banerjee	**80**	**177**	28	2.0%
taiwaniaquinol D (**14**)				
Trauner	**99**	**130**	8	25.7%
Majetich	**121**	**113**	14	2.2%
taiwaniaquinone D (**6**)				
Banerjee	**80**	**177**	31	0.83%
taiwaniaquinone H (**10**)				
Alvarez-Manzaneda	**99**	**161**	8	50.1% (from step 3)
Trauner	**99**	**130**	7	29.1%
Banerjee$_2$	**80**	**177**	27	3.3%
Banerjee$_1$	**80**	**177**	27	1.9%
taiwaniaquinone G (**15**)				
Alvarez-Manzaneda	**152**		13	24.3%

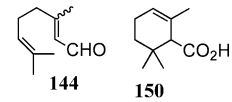


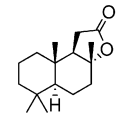


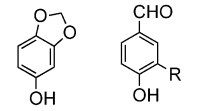




130 R = OCH_3
151 R = H







177 R = OCH_3
178 R = H

ketone **173** with LAH, followed by dehydration with trifluoroacetic acid, produced diene **174**. The selective cleavage of the vinyl group in the presence of the C-5, C-7 double bond was achieved using ruthenium chloride and $NaIO_4$.[60] The deprotection of **175** to give (±)-dichroanal B was effected with a catalytic amount of thiophenolate anion,[61] identical to Banerjee's approach.

The route to (±)-taiwaniaquinone D followed a nearly identical sequence (Scheme 22). Slowly warming an ethereal mixture of LiBr,[62] Grignard reagent, and ketone **107** from −78 °C to room temperature produced a 1:1 ratio of adducts **172** and **173**, whereas the use of vinyllithium resulted in the selective formation of **172**. Treatment of tertiary alcohol **172** with six equivalents of methanesulfonyl chloride in refluxing CH_2Cl_2 furnished diene **176**; it was subsequently found that using *p*-TsOH in warm cyclohexane provided superior results. The oxidative cleavage of the vinyl moiety was accomplished using $RuCl_3$ and $NaIO_4$ to furnish aldehyde **111**, an intermediate in Banerjee's synthesis[43] of (±)-taiwaniaquinone D. This intermediate was later converted into (±)-taiwaniaquinol D through Trauner's oxidation/reduction protocol.[53] The syntheses demonstrate the versatility of ketone **107** as an intermediate to several taiwaniaquinoids, but suffer from the poor to moderate yields obtained from oxidative cleavage of the vinyl moiety.

Conclusions

The biological role of the taiwaniaquinoids has yet to be reported. This knowledge would be useful in screening these products for therapeutic applications. While such studies are currently few in number, the taiwaniaquinoids' known potential for activity and the synthetic availability of several members should serve as an invitation for their inclusion in broader studies.

Table 5 compares the overall efficiencies of the synthetic strategies for the taiwaniaquinoids reported herein (descending order based on overall yield). Many of the methods used to construct the tricyclic core of the taiwaniaquinoids were known in connection with other synthetic targets. The A + C → ABC annulation strategy is the most commonly employed, and the unexpected need for a very polar medium for this transformation (first expressed by Trauner) must be recognized. Only eight out of the 18 known taiwaniaquinoids have been synthesized, with dichroanone (**10**) and taiwaniaquinol B (**5**) receiving the most attention. All of the natural products containing the C-5, C-7 double bond have been made. Future taiwaniaquinoid syntheses will be asymmetric and will undoubtedly focus on improving how the substituents at C-5 and C-7 are introduced. Given the synthetic challenge of these novel structures and their promising biological

activity, we expect that these natural products will continue to be the focus of considerable attention.

References and Notes

(1) (a) Cheng, Y. S.; Kuo, Y. H.; Lin, Y. T. *J. Chem. Soc., Chem. Commun.* **1967**, 565–566. (b) Lin, Y. T.; Cheng, Y. S.; Kuo, Y. H. *Tetrahedron Lett.* **1968**, 3881–3882. (c) Kuo, Y. H.; Cheng, Y. S.; Lin, Y. T. *Tetrahedron Lett.* **1969**, 2375–2377. (d) Kuo, Y. H.; Shih, J. S.; Lin, Y. T.; Lin, Y. T. *J. Chin. Chem. Soc.* **1979**, *26*, 71–73. (e) Kuo, Y. H.; Lin, Y. T.; Lin, Y. T. *J. Chin. Chem. Soc.* **1985**, *32*, 381–383. (f) Su, W. C.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1993**, *34*, 779–782. (g) Su, W. C.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1994**, *35*, 1279–1284. (h) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1997**, *46*, 169–173. (i) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1998**, *48*, 1391–1397. (j) Kuo, Y. H.; Chang, C. I.; Lee, C. K. *Chem. Pharm. Bull.* **2000**, *48*, 597–599. (k) Kuo, Y. H.; Chang, C. I. *J. Nat. Prod.* **2000**, *63*, 650–652. (l) Kuo, Y. H.; Chien, S. C. *Chem. Pharm. Bull.* **2001**, *49*, 1033–1035. (m) Kuo, Y. H.; Chien, S. C.; Huang, S. L. *Chem. Pharm. Bull.* **2002**, *50*, 544–546. (n) Kuo, Y. H.; Chien, S. C.; Kuo, C. C. *Planta Med.* **2002**, *68*, 1020–1023.

(2) (a) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871–873. (b) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657–1663.

(3) Cheng recognized the rearranged abietane core, but only referred to it as "the uncommon skeleton of fused 6−5−6 rings". See the section titled "Biosynthesis and Classification".

(4) Although Cheng claims to have "the first report of compounds having the uncommon 6−5−6 rings in nature", this is only valid in reference to the *abeo*-abietane skeleton, as several natural fluorenones had been discovered several decades earlier. The gibberellins also contain a fused [6,5,6]-system as part of their tetracyclic core and predate the aforementioned fluorenones by several decades. For a review on this historically important class, see: Mander, L. N. *Nat. Prod. Rep.* **2003**, *20*, 49–69, and references therein.

(5) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sesik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493–497.

(6) Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419–6422.

(7) (a) Chang, C. I.; Chien, S. C.; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420–1422. (b) Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72–76.

(8) Oikawa, H.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1321–1322.

(9) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Choudhary, M. I.; Akhtar, F.; Ali, Z.; Iqbal, M. Z. *Tetrahedron Lett.* **1999**, *40*, 7561–7564.

(10) This term has been used in the literature only by Trauner, Alvarez-Manzaneda, and Majetich.

(11) (a) Tanaka, R.; Ohtsu, H.; Iwamoto, M.; Minami, T.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Yoshitaka, A. *Cancer Lett.* **2000**, *161*, 165–170. (b) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg, Med. Chem.* **2001**, *9*, 1911–1921. (c) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742–745. (d) Katoh, T.; Akagi, T.; Noguchi, C.; Kajimoto, T.; Node, M.; Tanaka, R.; Nishizawa, M.; Ohtsu, H.; Suzuki, N.; Saito, K. *Bioorg. Med. Chem.* **2007**, *15*, 2736–2748.

(12) Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1936**, 62–71.

(13) Dev, S. *J. Indian Chem. Soc.* **1957**, *34*, 169.

(14) Conia, J. M.; Leriverend, M. L. *Tetrahedron Lett.* **1968**, 2101–2104.

(15) (a) House, H. O.; Paragamian, V.; Ro, R. S.; Wluka, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1457–1462. (b) House, H. O.; Paragamian, V.; Wluka, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 2561–2565.

(16) (a) Gerber, N. N. *J. Am. Chem. Soc.* **1960**, *82*, 5216–5218. (b) Barnes, R. A.; Gerber, N. N. *J. Org. Chem.* **1961**, *26*, 4540–4543.

(17) Hori, T.; Nakanishi, K. *Chem. Commun.* **1969**, 528–529.

(18) France, D. J.; Hand, J. J.; Los, M. *Tetrahedron* **1969**, *25*, 4011–4022.

(19) Ziegler, F. E.; Condon, M. E. *J. Org. Chem.* **1971**, *36*, 3707–3714.

(20) Ramana, M. M. V.; Potnis, P. V. *Synthesis* **1993**, 575–576.

(21) Ohta, M. *Chem. Pharm. Bull.* **1957**, *5*, 256–260.

(22) Grove, J. F.; Riley, B. J. *J. Chem. Soc.* **1961**, 1105–1112.

(23) (a) Tahara, A. *Chem. Pharm. Bull.* **1961**, *9*, 252–253. (b) Tahara, A.; Hoshino, O. *Tetrahedron Lett.* **1966**, 5031–5035.

(24) Pinto, A. C.; Epifanio, R.; Camargo, W. *Tetrahedron* **1993**, *49*, 5039–5046.

(25) (a) Ghatak, U. R.; Chakravarty, J.; Banerjee, A. K. *Tetrahedron Lett.* **1965**, 3145–3150. (b) Ghatak, U. R.; Chakravarty, J. *Tetrahedron Lett.* **1966**, 2449–2458. (c) Ghatak, U. R.; Chakravarty, J.; Banerjee, A. K. *Tetrahedron* **1968**, *24*, 1577–1593. (d) Ghatak, U. R.; Chakravarty, J.; Dasgupta, R.; Chakraborti, P. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2438–2445. (e) Chakraborti, P. C.; Ghosh, S.; Kanjilal, P. R.; Satyanarayana, G. O. S. V.; Ghatak, U. R. *Indian J. Chem.* **1979**, *18B*, 183–185.

(26) Parham, W. E.; Czuba, L. J. *J. Org. Chem.* **1969**, *34*, 1899–1904.

(27) Ng, K. S.; Roberts, J. L.; Rutledge, P. S.; Wilson, M. A.; Woodgate, P. D. *Aust. J. Chem.* **1976**, *29*, 2683–2692.

(28) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5937−5947. For a nearly identical study see: Kim, S.; Kitano, Y.; Tada, M.; Chiba, K. *Tetrahedron Lett.* **2000**, *41*, 7079–7083.

(29) Mukhopadhyaya, J. K.; Pal, S.; Ghatak, U. R. *Synth. Commun.* **1995**, *25*, 1641–1657.

(30) Bailey, W. F.; Daskapan, T.; Rampalli, S. *J. Org. Chem.* **2003**, *68*, 1334–1338.

(31) (a) Ishibashi, H.; Kobayashi, T.; Takamasu, D. *Synlett* **1999**, 1286–1288. (b) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem.* **2000**, *65*, 9022–9027.

(32) Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055–2057.

(33) (a) Bhar, S. S.; Ramana, M. M. V. *J. Org. Chem.* **2004**, *69*, 8935–8937. (b) Bhar, S. S.; Ramana, M. M. V. *Tetrahedron Lett.* **2006**, *47*, 7805–7807.

(34) (a) Middlemiss, D. *Synthesis* **1979**, 987–988. For a related Diels-Alder strategy, see: (b) Minuti, L.; Selvaggi, R.; Taticchi, A. *Tetrahedron* **1993**, *49*, 1071–1078.

(35) (a) Trost, B. M.; Walchli, R. *J. Am. Chem. Soc.* **1987**, *109*, 3847–3488. For non-palladium-mediated reactions of aryl bromides with stannanes leading to related products, see: (b) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972–2976.

(36) (a) Denmark, S. E.; Wallace, M. E.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543–5545. (b) Handy, S. T.; Omune, D. *Org. Lett.* **2005**, *7*, 1553–1555.

(37) Clive, D. L. J.; Sunasee, R. *Org. Lett.* **2007**, *9*, 2677–2680.

(38) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *Org. Lett.* **2003**, *5*, 3931–3933.

(39) Burger, A. P. N.; Brandt, E. V.; Roux, D. G. *Phytochemistry* **1983**, *22*, 2813–2817.

(40) Hagemann, C. *Ber.* **1893**, *26*, 2300.

(41) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144–13145.

(42) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896–2898.

(43) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *J. Org. Chem.* **2006**, *71*, 2787–2796.

(44) Shimkus, J. M.; Majetich, G. *58th Southeastern Regional Meeting of the American Chemical Society*, Augusta, GA, November 1−4, 2006. Abstract # SRM06-633.

(45) (a) Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979–4980. (b) Majetich, G.; Wang, Y.; Li, Y.; Vohs, J. K.; Robinson, G. H. *Org. Lett.* **2003**, *5*, 3847–3850. (c) Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217–225. (d) Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227–235.

(46) Majetich, G.; Liu, S. *Synth. Commun.* **1993**, *23*, 2331–2335.

(47) (a) Carreño, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328–5331. (b) Carreño, M. C.; Ruano, J. L. G.; Toledo, M. A.; Urbano, A. *Tetrahedron: Asymmetry* **1997**, *8*, 913–921.

(48) Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189–192.

(49) Burnell, R. H.; Caron, S. *Can. J. Chem.* **1992**, *70*, 1446–1454.

(50) (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147–162. (b) Pazos, Y.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **2001**, *66*, 8483–8489. (c) Törmäkangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskinen, A. M. P. *Tetrahedron* **2002**, *58*, 2175–2181. (d) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989–4992.

(51) (a) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (b) This report was one of the most online-accessed *J. Am. Chem. Soc.* communications and was cited as a research highlight in *Nature* **2006**, *441*, 708.

(52) For a summary of this reaction see: Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: New York, 2005.

(53) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022–11023.

(54) Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741–1744.

(55) Professor Chiu revealed to us in a personal communication that Trauner's report was nearly identical to their unpublished work, which forced a change in their strategy.

(56) Tang, S.; Xu, Y.; He, J.; He, Y.; Zheng, J.; Pan, X.; She, X. *Org. Lett.* **2008**, *10*, 1855–1858.

(57) (a) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortéz, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181–15208. (b) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592–594. (c) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Alvarez-Manzaneda, R.; Meneses, R.; Es-Samti, H.; Fernández, A. *J. Org. Chem.* **2009**, *74*, 3384–3388.

(58) Majetich, G.; Shimkus, J. M. *Tetrahedron Lett.* **2009**, *50*, 3311–3313.
(59) Kojima, T.; Ohishi, T.; Yamamoto, I.; Matsuoka, T.; Kotsuki, H. *Tetrahedron Lett.* **2001**, *42*, 1709–1712.
(60) (a) Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814–4818. (b) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116–1124.
(61) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1997**, *38*, 8749–8752.
(62) Carreira, E. M.; DuBois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825−10826.

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