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Tetrahedron Letters 49 (2008) 1741–1744
Tetrahedron Letters

Acid-promoted sequential cationic cyclizations for the synthesis of (±)-taiwaniaquinol B

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Received 14 November 2007; revised 16 January 2008; accepted 18 January 2008
Available online 26 January 2008

Abstract

A formal total synthesis of (±)-taiwaniaquinol B starting from (*E*/*Z*)-citral has been accomplished by sequential cationic cyclizations promoted by acids. The cyclization to an α-cyclogeranyl ketone derivative is promoted by Lewis acid, whereas the use of Brønsted acid promotes an olefin isomerization leading to undesired cyclizations. The final ring formation to give the hydrofluorenone skeleton is promoted by Brønsted acid. Thus, the choice of the acid in each step critically determined the cationic reaction pathways and cyclization outcome.

In the synthetic community, there has been considerable interest in a series of natural diterpenoids and norditerpenoids having unusual 6-5-6 fused tricyclic carboskeletons. There are presently about eighteen natural products having this hydrofluorene skeletal framework. Some members, such as taiwaniaquinol B, were isolated from *Taiwania cryptomerioides*, a Taiwanese pine (Fig. 1).[1] Other members include dichroanal A from *Salvia dichroantha*, a sage found in Turkey,[2] and standishinal from *Thuja standishii*, a genus of cypress.[3] In addition to possessing some promising antitumor and aromatase inhibitory activity,[4,5] the unique carbotricyclic structure of this family of compounds has attracted varied approaches for its assembly.

One synthetic approach has been to begin with the aromatic ring A and a functionalized cyclohexane C, where the main synthetic tasks are the tethering of the two rings and the formation of central ring B. The strategies used for the cyclization of ring B include the Heck reaction, as in the syntheses of a number of taiwaniaquinoids by Banerjee[6] and Node,[7] an aldol reaction in the synthesis of (±)-standishinal by Katoh et al.,[8] and an aromatic

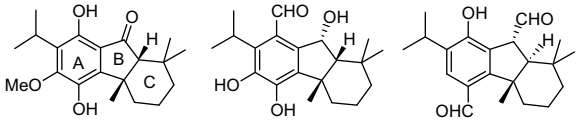

Fig. 1. Representative taiwaniaquinoids.

Nazarov cyclization induced by triflation, as in the synthesis of several taiwaniaquinoids including (±)-**1** by Trauner's group.[9] In a related work, Bhar et al. induced both bond-making events for ring B formation in one pot by a nominal alkylation–cycloacylation domino event promoted by acid.[10]

Another approach that has been successfully implemented is an overall bis-cyclization, in which both rings B and C are formed in the course of the synthesis. Fillion utilized such a strategy in the synthesis of (±)-**1** starting from a aromatic precursor, where a decarboxylative intramolecular Friedel–Crafts acylation–alkylation sequence generated ring B then ring C in a domino fashion.[11] The synthesis of dichroanone by Stoltz et al began with ring C, and enantioselective allylation followed by an aldol reaction produced the BC fused system. Another alkylation-aldol sequence installed ring A which was

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doi:10.1016/j.tetlet.2008.01.084

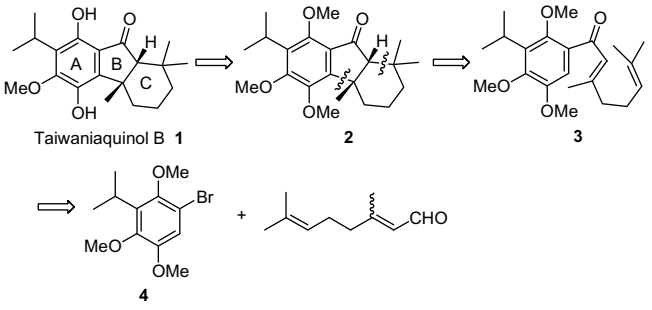
aromatized, and eventually culminated in the only asymmetric synthesis of a taiwaniaquinoid thus far.[12]

We chose to examine a bis-cyclization strategy toward the taiwaniaquioids that would lead to the formation of the B and C rings by a series of carbon–carbon bond formations through sequential or domino cationic cyclizations promoted by acid. There are many precedents of these processes in polyene cyclizations,[13] and Nazarov-initiated polycyclizations[14] catalyzed by Brønsted or Lewis acids.

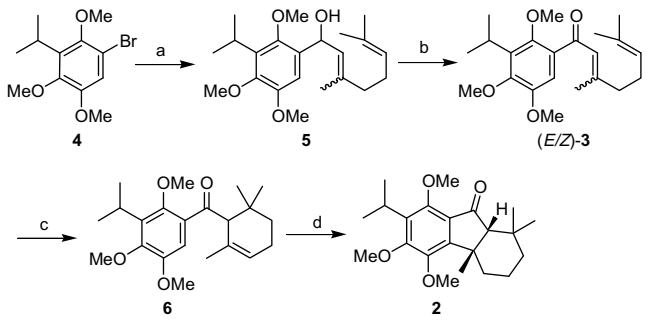
We envisioned trienone **3** as the key cyclization precursor in this synthetic route (Scheme 1). Dienone **3** could in turn be obtained readily from substituted arene **4** and commercially available citral.

Bromoarene **4**, which was prepared from commercially available 1,2,4-trimethoxybenzene, according to Carreño et al,[15] was subjected to bromine–lithium exchange, and added to citral, a 1:1 mixture of geranial (*trans*-isomer) and neral (*cis*-isomer), Scheme 2. The reaction afforded aryl vinyl carbinols (*E*/*Z*)-**5**. Oxidation of these alcohols by MnO_2 yielded the key trienone **3** as a mixture of *cis* and *trans* isomers. To clearly observe the outcome of the ensuing reaction, (*Z*)-**3** and (*E*)-**3** were separated, and their reactions were examined individually.

For (*E*)-**3**, a survey of reaction conditions was conducted as shown in Table 1. When dienone (*E*)-**3** was treated with a Lewis acid, $SnCl_4$ in nitromethane, the anticipated biscyclized product **2** was not formed. Instead, the monocyclic α-cyclogeranyl ketone derivative **6** was obtained in excellent yield (Table 1, entry 1). Notably, compound **6** is deconjugated and is a different precursor than the β-cyclogeranyl aryl ketone substrates used previously in aromatic Nazarov-type cyclizations toward the taiwaniaquinoids.[9] Nevertheless, compound **6** was recognized as an intermediate which can be further cyclized to give hydrofluorenone 2. Prolonged reaction using the same Lewis acid $SnCl_4$, however, failed to promote the desired cyclization (Table 1, entry 2). Eventually, it was found that compound **6** underwent cyclization in the presence of triflic acid, a Brønsted acid, to produce a good yield of desired tricyclic product **2** (Scheme 2).

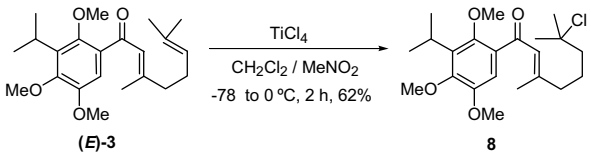


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis and cyclization of Dienone **3**. Reaction conditions: (a) (i) *n*-BuLi, Et_2O, −78 °C, 1 h; (ii) citral, −78 °C to rt, 1 h, 86%; (b) MnO_2, CH_2Cl_2, reflux, 10 h, 78%; (c) $SnCl_4$, CH_3NO_2, rt, 1 h, 89%. (d) TfOH, CH_3NO_2, 100 °C, 1 h, 71%.

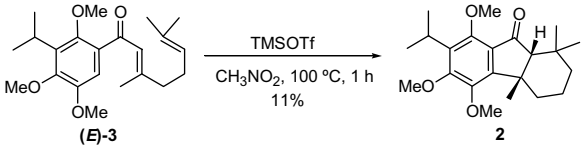
The cyclization promoted by $SnCl_4$ was subsequently applied to (*Z*)-**3**. Under the same conditions, an excellent yield of **6** was obtained (Table 1, entry 3), as was the case for a 1:1 mixture of (*E*/*Z*)-**3** (Table 1, entry 4). Examining other solvents, it was found that the reaction of (*E*)-**3** with $SnCl_4$ in dichloromethane produced **6** in an inferior yield compared to the more polar $MeNO_2$ (Table 1, entry 5). Using AgOTf, compound **6** was produced in a poor yield (Table 1, entry 6). When $TiCl_4$ was used as the Lewis acid, chloride **8** resulting from HCl addition was the only significant product isolated (Eq. 1).



(1)

However, when (*E*)-**3** was treated with Brønsted acids such as TfOH or $HClO_4$, an oxabicyclo[3.3.1]non-3-ene **7** emerged as the major product in 80–90% yield (Table 1, entries 7–8). This compound had been a minor product in the reactions of (*E*)-**3** with $SnCl_4/CH_2Cl_2$, and a major product when AgOTf was used. This cyclization pathway was undesirable and unproductive for the synthesis of the target framework. These studies demonstrate that the choice of acids at various stages of the synthesis is critical to the success of this route.

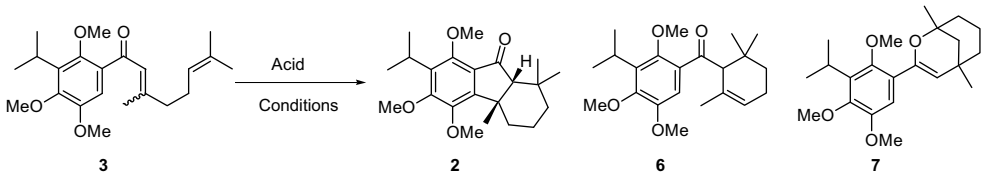
While it would be highly desirable to be able to convert trienone **3** to hydrofluorenone **2** directly by domino cyclizations in one step instead of two, the only reagent that was found to induce a one-pot bis-cyclization was TMSOTf, albeit producing **2** in only 11% yield, the major product being enol ether **7** (Table 1, entry 3 and Eq. 2). Our efforts to further optimize this bis-cyclization using TMSOTf by varying the solvent and the temperature failed to increase the yield of **2**.



(2)

Mechanistically, these divergent results could be rationalized as depicted in Scheme 3. Under strong Brønsted acid conditions, protonation induced the rapid isomeri-

Table 1
Acid-promoted cyclizations of dienone **3**

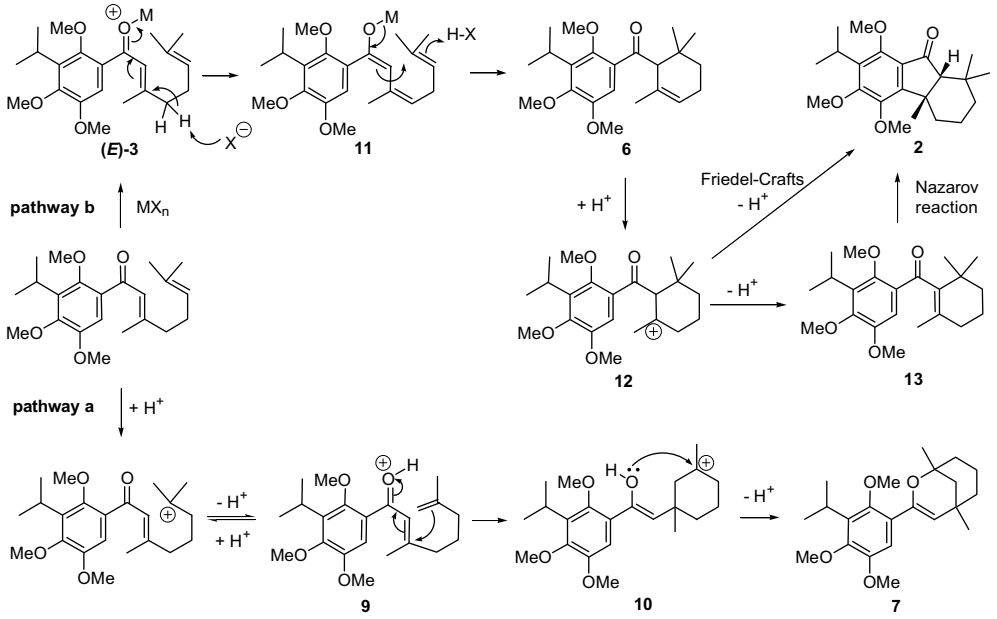


Entry	Substrate	Acid (equiv)	Conditions	Products	Yield (%)
1	(*E*)-**3**	$SnCl_4$ (3.0)	$MeNO_2$, rt, 2 h	**6**	92
2	(*E*)-**3**	$SnCl_4$ (3.0)	$MeNO_2$, rt (1 h), then 100 °C (0.5 h)	Complex mixture	—
3	(*Z*)-**3**	$SnCl_4$ (3.0)	$MeNO_2$, rt, 2 h	**6**	86
4	1:1 (*E*)-**3** + (*Z*)-**3**	$SnCl_4$ (3.0)	$MeNO_2$, rt, 2 h	**6**	89
5	(*E*)-**3**	$SnCl_4$ (3.0)	CH_2Cl_2, rt, 1 h	**6**:**7** = 3.5:1	81
6	(*E*)-**3**	AgOTf (0.3)	$MeNO_2$, 50 °C, 10 h	**6**:**7** = 1:4	73
7	(*E*)-**3**	TfOH (2.0)	$MeNO_2$, 100 °C, 2 h	**7**	83
8	(*E*)-**3**	$HClO_4$ (2.0)	EtOAc, rt, 2 h	**7**	91
9	(*E*)-**3**	TMSOTf (2.0)	$MeNO_2$, 100 °C, 1 h	**2**:**7** = 1:7	71

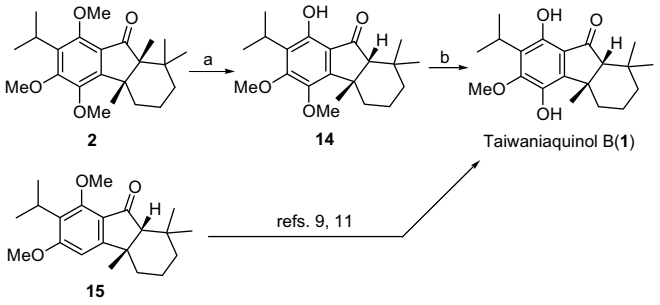
zation of the nucleophilic olefin through a fast protonation and deprotonation to form the terminal alkene **9** (Scheme 3, pathway a). This kind of isomerization has been previously described by Büchi to account for the outcome of the acid-catalyzed cyclization of 4,8-dimethylnona-3,7-dien-2-one.[16] The terminal olefin **9** then intramolecularly attacked the enone activated by protonation. The carbocation **10** thus produced is captured by the enol to afford a six-membered ring enol ether **7**.

Treatment of **3** with the Lewis acid $SnCl_4$ follows pathway b (Scheme 3). Under these conditions, isomerization to terminal olefin **9** is much slower in the absence of a proton source and leads to an alternative reaction pathway. The cyclization to give **6** is well precedented in the acid-promoted cyclization of geranic acid,[17] and pseudodamascone.[18] Several mechanistic rationalizations are possible. Synchronously, this could be regarded as a 1,5-proton transfer to generate **6** directly from activated trienone **3**. Asynchronously, the Lewis acid promotes the transformation of enone **3** into the enolate-like species **11**, which then undergoes intramolecular electrophilic addition and cyclization with the olefin moiety activated by the in situ generated HCl to give rise to **6**. The use of the more polar solvent $MeNO_2$ may favor this pathway by facilitating the formation of the metallated complex **11**.

With subsequent Brønsted acid treatment, **6** reprotonates to give carbocation **12**, which then undergoes an intramolecular Friedel–Crafts alkylation to give **2**, or a deprotonation to give conjugated **13** followed by an aromatic Nazarov cyclization to generate **2**, since both the Friedel–Crafts and electrocyclization pathways generate indistinguishable products.[19] The generation of both compounds **6** and **7** could be due to adventitious moisture leading to the generation of TfOH in the AgOTf-promoted



Scheme 3. Proposed mechanism for the cyclization of dienone **3** to products **2**, **6**, **7**.



Scheme 4. Synthesis of Taiwaniaquinol B (**1**) Reaction conditions: (a) BCl_3, 1 M in CH_2Cl_2, 0 °C, 20 min, 98%; (b) (i) $PhI(OAc)_2$, CH_3CN/H_2O (2:1), rt, 0.5 h, (ii) $Na_2S_2O_3$, rt, 2 h, 85%.

reaction, following both pathways a and b (Table 1, entry 6). The fact that using TMSOTf as a Lewis acid led to the generation of some **2** could be due to the promotion of the reaction by TMSOTf by pathway b, then due to small amounts of TfOH in the reaction, further resulted in tricycle **2** (Table 1, entry 9). The presence of TfOH is also implicated in the substantial yield of **7** in this reaction.

Since compound **2** is a key intermediate in Banerjee's total synthesis[8] of (±)-taiwaniaquinol B and (±)-taiwaniaquinone D, this synthetic route already constitutes a short formal total synthesis of these two natural products. However, we found that the application of an alternative three-step protocol, slightly modified from that reported by Fillion[11] and by Trauner,[9] resulted in a superior yield of taiwaniaquinol B (Scheme 4). The selective and quantitative demethylation of **2** by boron trichloride to give **14**, followed by a mild $PhI(OAc)_2$ oxidation,[20] and a sodium thiosulfate reduction[21] in one-pot afforded (±)-taiwaniaquinol B. Using a less oxidized aromatic precursor **15** (Scheme 4), the final functionalizations to generate **1** by Fillion and Trauner proceeded in 47% and 48% yields, respectively, compared to 83% from **2** in this work.

In conclusion, we have developed an efficient route for the synthesis of the hydrofluorenone carboskeleton by sequential cationic cyclizations promoted by acid. From trienone **3**, cyclization to form ring C is promoted by Lewis acid, while cyclization to give ring B is induced by Brønsted acid. A one-pot domino bis-cyclization to generate the rings B and C is possible through the use of TMSOTf, albeit in low yield. The direct treatment of trienone **3** with Brønsted acid results instead in the formation of a bicyclic enol ether. This route is applicable to the synthesis of other taiwaniaquinoid natural products and analogues with similar skeletons. Efforts to optimize the domino cyclization and establish asymmetric versions of this synthesis are in progress.

Acknowledgments

This research was supported by the University of Hong Kong, the Research Grants Council of Hong Kong SAR (HKU 7017/04P), and the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (Project No. AoE/P-10/01).

Supplementary data

Detailed experimental procedures for the synthesis and characterization of compounds **2**, **3**, **6**–**8**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.084.

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