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Total Synthesis of Taiwaniadducts B, C, and D

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Supporting Information

ABSTRACT: The first total syntheses of taiwaniadducts B, C, and D have been accomplished. Two diterpenoid segments were prepared with high enantiopurity, both through Ir-catalyzed asymmetric polyene cyclization. A sterically demanding intermolecular Diels–Alder reaction promoted by $Er(fod)_3$ assembled the scaffold of taiwaniadducts B and C. A carbonyl-ene cyclization forged the cage motif of taiwaniadduct D at a late stage, providing over 200 mg of this compound.

Taiwaniaquinoids are a class of terpenoids with impressive biological activities isolated from the endangered species *Taiwania cryptomerioides*,[1] which have attracted remarkable attention from a synthetic perspective.[1,2] A few members of this family, namely taiwaniadducts A–J,[3] possess a characteristic Diels–Alder cycloadduct scaffold. From a biosynthetic perspective, taiwaniadduct D (**1**, Figure 1), the most complex molecule among them, could be derived from taiwaniadduct B (**2**) through a carbonyl-ene cyclization, and **2** may arise from an intermolecular Diels–Alder reaction between naturally occurring taiwaniaquinone A or F (**3** or **4**)[3] and *trans*-ozic acid (**5**).[4] Taiwaniadduct C (**6**) is presumably the regioisomer of **3** from the Diels–Alder reaction.[5,6] Herein, we report the total synthesis of taiwaniadducts B, C, and D based on the above biosynthetic hypothesis.

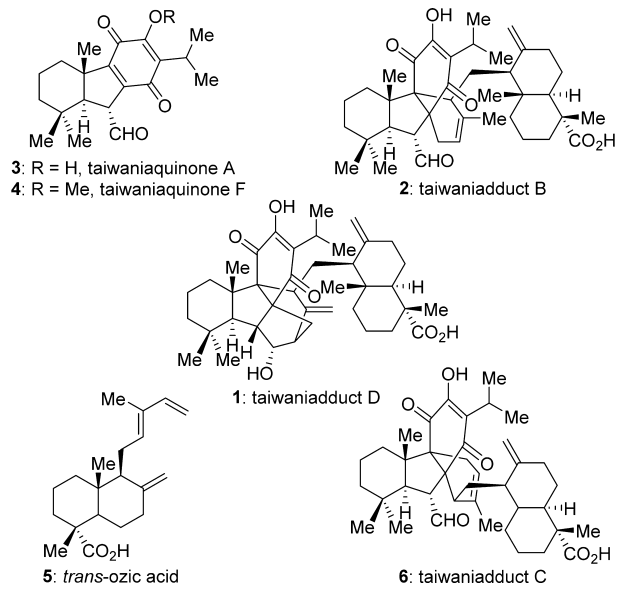
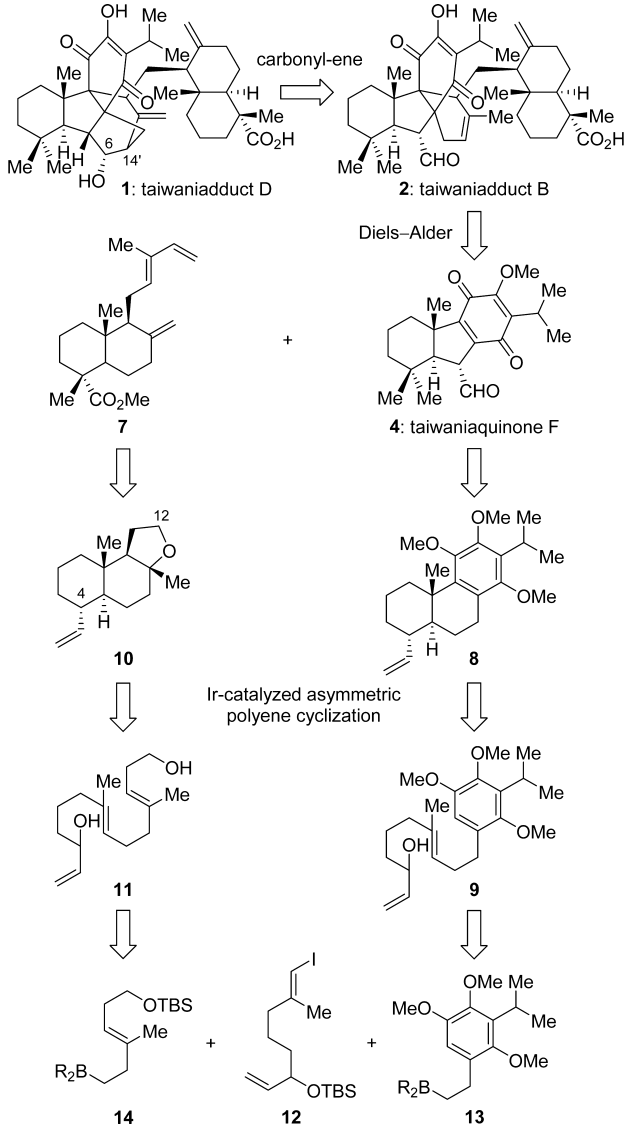


Figure 1. Taiwaniadducts B, C, and D, taiwaniaquinones A and F, and *trans*-ozic acid.

We first undertook a retrosynthetic analysis of taiwaniadduct D (**1**), as illustrated in Scheme 1. The initial disconnection

Scheme 1. Retrosynthetic Analysis



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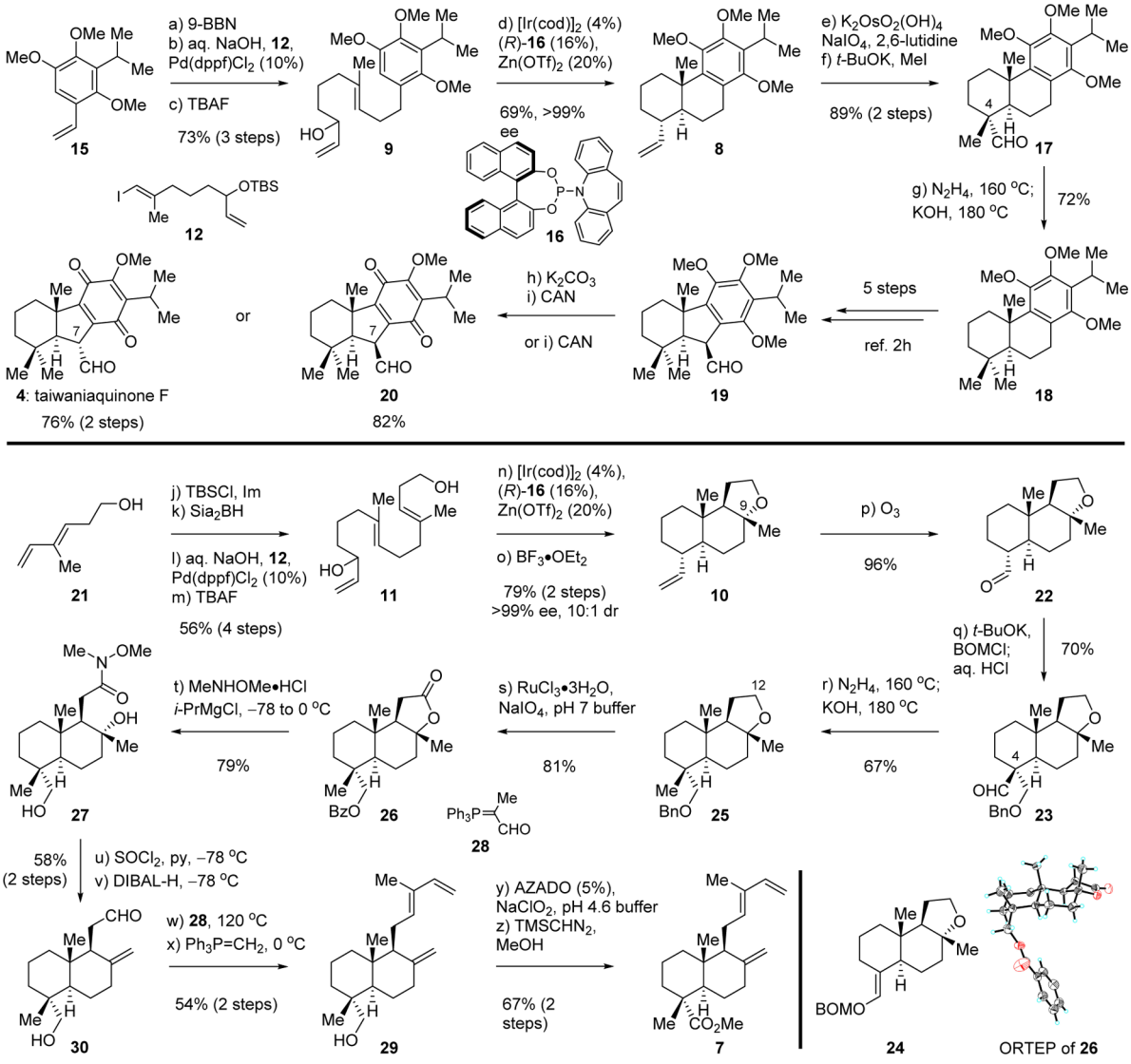
Scheme 2. Synthesis of the Dienophile and Diene through Ir-Catalyzed Asymmetric Polyene Cyclization



takes place at the C6−C14′ bond to provide taiwaniadduct B (**2**) as a carbonyl-ene substrate, which could be further disassembled in a retro-Diels−Alder fashion to give taiwaniaquinone F (**4**) and *trans*-ozic acid methyl ester (**7**). It should be noted that both fragments need to be prepared in the enantioenriched forms, to avoid the diastereomerically mismatched Diels−Alder reactions. Having noticed the inherent similarity between **3** and **7**, we consider the Ir-catalyzed asymmetric polyene cyclization[7] elegantly developed by Carreira and co-workers as a general tool to construct the carbon skeleton of both compounds. Based on the ring-contraction strategy reported by us previously,[2h] **2** could be directly simplified to an optically active 6,6,6-tricycle **8**, which is further traced back to the substrate for the polyene cyclization, allylic alcohol **9**. In parallel, the synthesis of **7** may exploit an enantioenriched 6,6,5-tricycle **10**; modifications at C4 and C12 would install the carboxylate and diene functionalities, respectively. This intermediate is anticipated to arise from dienyl alcohol **11**, through a mechanistically similar Ir-mediated cyclization, despite few precedents of heteroatom trapping.[7,8] The linear precursors **9** and **11** could be prepared by cross-coupling of known iodide **12**[7a] with alkylboranes **13** and **14**, respectively.

The synthesis commenced with the enantioselective constructions of the two segments **4** and **7** (Scheme 2). Hydroboration of styrene **15** with 9-BBN gave a **13**-type alkylborane, which underwent Suzuki−Miyaura coupling [cat. $Pd(dppf)Cl_2$, aq. NaOH][2h,7a] with **12** and subsequent desilylation to afford alcohol **9** in 73% overall yield, setting the stage for the Ir-catalyzed asymmetric polyene cyclization. Thus, **9** was subjected to Carreira's catalyst system {$[Ir(cod)Cl]_2$, (*R*)-**16**, $Zn(OTf)_2$}[7,8] to yield the desired tricycle **8** (69%) with an excellent level of stereoselectivity (>99% ee, a single detectable diastereomer). Notably, this reaction was successfully carried out on the 15 g scale with consistent efficiency and selectivity. Olefin cleavage (OsO_4, $NaIO_4$) followed by *C*-methylation (KO*t*-Bu, MeI) of the resulting aldehyde furnished compound **17** in 89% yield as a single diastereomer at C4, which was converted to tricycle **18** (72% yield) under Wolff−Kishner−Huang conditions ($N_2H_4{\cdot}H_2O$, KOH, 180 °C).[9] This compound entered a five-step sequence involving Wolff ring contraction developed by us previously to reach 6,5,6-tricylic aldehyde **19**; treatment with K_2CO_3/EtOH provided its epimer

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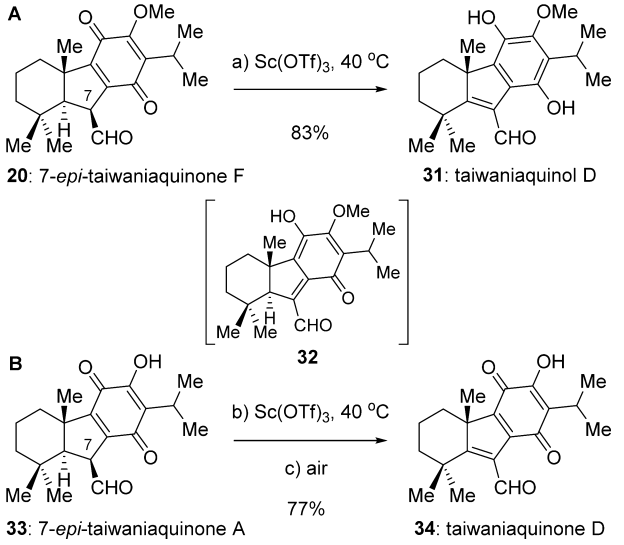
at C7.[2h] Both aldehydes were oxidized by CAN to generate essentially enantiopure taiwaniaquinone F (**4**) and its C7-epimer **20**, respectively, which served as the dienophiles for the devised Diels–Alder reaction.

The synthesis of the diene fragment **7** also took advantage of the Ir chemistry (Scheme 2). Silylation of known dienyl alcohol **21**[10] followed by selective hydroboration of the monosubstituted C=C bond with Sia_2BH afforded a **14**-type alkylborane,[7b] which was subjected to a similar Suzuki–Miyaura coupling/desilylation sequence to furnish diol **11**. This compound turned out to be a suitable substrate for the expected heteroatom-terminating Ir-catalyzed cyclization; 6,6,5-tricycle **10** was obtained in 59% yield and >99% ee under the standard conditions. Notably, a high level of diastereoselectivity at C9 (ca. 10:1) was also achieved, making this chemistry applicable to the synthesis of the framework of a wide range of terpenoids. Monocyclization products (an olefin mixture)[7a] were isolated in 25% yield, which were readily converted to **10** (80% yield) by exposure to $BF_3{\cdot}OEt_2$. Thus, the overall yield of **10** from **11** reached 79%. These transformations were easily amplified to the 5 g scale. With **10** in hand, we introduced the carboxylate and diene functionalities to its scaffold. Similar to the sequence used for the dienophile synthesis, double bond cleavage by ozonolysis gave aldehyde **22** (96% yield), and subsequent alkylation with BOMCl generated compound **23** in 70% yield as a single diastereomer at C4. The byproduct **24** that resulted from *O*-alkylation was hydrolyzed during acid workup, leading to 26% of recovered **22**. Aldehyde **23** underwent Wolff–Kishner–Huang reduction to afford compound **25** (67% yield). Treatment of **25** with $RuCl_3/NaIO_4$ resulted in the C12–H oxidation,[11] providing lactone **26** in 81% yield, the structure of which was confirmed by X-ray crystallographic analysis (Scheme 2). Under these conditions, the benzyl was also oxidized to a benzoyl for convenient removal. Lactone opening (MeNHOMe·HCl, *i*-PrMgCl)[12] formed amide **27** (79% yield) with the primary hydroxyl released. Dehydration ($SOCl_2$, py)[12,13] and DIBAL-H reduction, followed by two Wittig olefinations (with reagent **28** and methylenetriphenylphosphorane, respectively), gave 1,3-diene **29** with the intermediacy of aldehyde **30**. Finally, oxidation (AZADO, $NaClO_2$)[14] followed by esterification ($TMSCHN_2$, MeOH) rendered *trans*-ozic acid methyl ester (**7**) in an essentially enantiopure form.

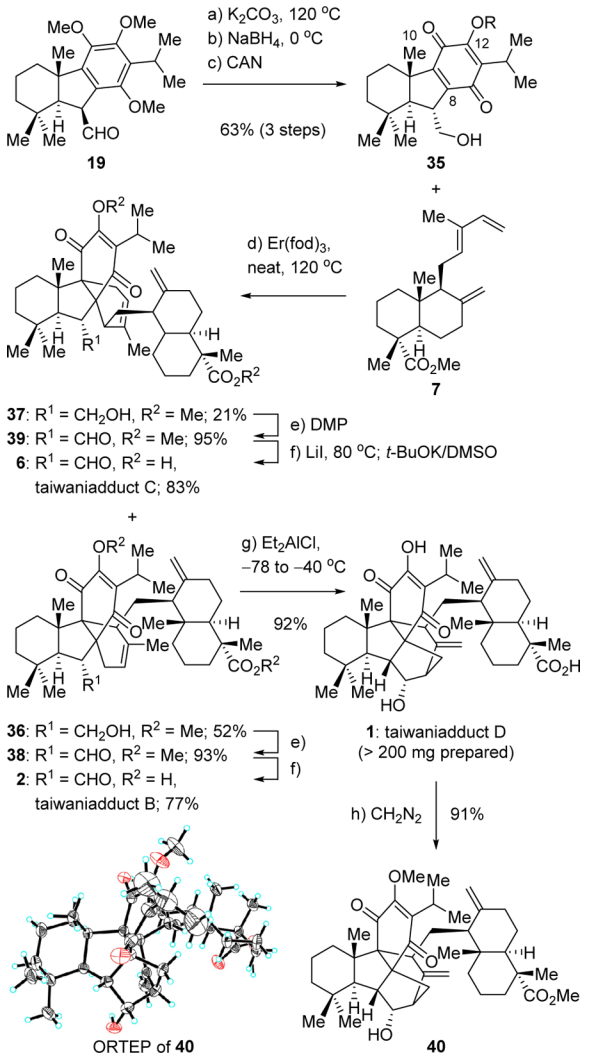
With both diene and dienophile in hand, we investigated the intermolecular Diels–Alder reaction. Unfortunately, a variety of conventional conditions, such as thermal, acidic, neat, and high-pressure conditions,[15] failed to effect the cycloaddition. The instability of both taiwaniaquinone F (**4**) and its alternative 7-*epi*-taiwaniaquinone F (**20**) under forcing conditions was found to be a severe problem. The undesired reaction of **20** was depicted in Scheme 3; exposure to $Sc(OTf)_3$ gave a naturally occurring taiwaniaquinoid, namely taiwaniaquinol D (**31**),[1,2i,3] presumably through a double tautomerization process with the intermediacy of **32**. 7-*epi*-Taiwaniaquinone A (**33**) underwent a similar sequence followed by spontaneous aerobic oxidation to arrive at another natural product taiwaniaquinone D (**34**).[1,2i,3] Distinct from its 7-epimer, taiwaniaquinone F (**4**) underwent a much slower but more complicated decomposition. These observations suggest a plausible biosynthetic model of **31** and **32** and imply the fate of 7-*epi*-taiwaniaquinones A and F which have not been isolated as natural products.

At this point, we directed our attention to the dienophiles more stable against acidic and thermal conditions (Scheme 4).

Scheme 3. Unexpected Reactions of 7-*epi*-Taiwaniaquinones A and F under Acidic Conditions



Scheme 4. Intermolecular Diels–Alder Reaction and Completion of the Total Synthesis of Taiwaniadducts B, C, and D



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Alcohol **35**, which is readily available from aldehyde **19** and secured from the tautomerization observed before, was considered as such an alternative. This compound was prepared on the 4 g scale and used for extensive examinations of Diels–Alder conditions. To our delight, $Er(fod)_3$ turned out to be a effective promoter,[16] despite few precedents of utilizing it in Diels–Alder reactions to our knowledge. Neat conditions and elevated temperature were also required. **35** (1.0 equiv) and **7** (1.2 equiv) reacted under these optimized conditions to afford cycloadduct **36** (52% yield) and its regioisomer **37** (21% yield), and no other positional or diastereomeric isomers were detected. The site selectivity toward the C8-olefin over the C12-olefin may be attributable to the bulky isopropyl and the electron-donating methoxyl that make the latter olefin a worse dienophile. The facial selectivity may arise from the steric effect of the axial C20 methyl group (see the single crystal structure in ref 2h for information). The homodimeric cycloaddition of **7** was not observed either, presumably due to its poor dienophilicity.[17] Both cycloadducts were subjected to a three-step sequence of oxidation (DMP) and demethylations (LiI and then *t*-BuOK/DMSO),[18,19] to furnish taiwaniadducts B and C (**2** and **6**) via the intermediacy of **38** and **39**, respectively. Treatment of **2** with Me_2AlCl realized the final carbonyl-ene cyclization to render taiwaniadduct D (**1**) in 91% yield; over 200 mg of **1** were prepared. The structure of the bis-methylated derivative of **1** (compound **40**) was verified by X-ray crystallographic analysis (Scheme 4). The synthetic samples display identical spectral and physical properties with those of authentic samples (Supporting Information).

In summary, we have accomplished the first total synthesis of taiwaniadducts B, C, and D (**2**, **6**, and **1**). Ir-catalyzed asymmetric polyene cyclization was exploited to construct the scaffolds of both the diene and dienenophile. $Er(fod)_3$ promoted intermolecular Diels–Alder and Me_2AlCl mediated carbonyl-ene reactions forged the core of **1**. The chemistry may find further applications in terpenoid synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization (cif, pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

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†J.D. and S.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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