Communication

# Asymmetric Synthesis of the Antiviral Diterpene Wickerol A

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# Asymmetric Synthesis of the Antiviral Diterpene Wickerol A

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*Supporting Information Placeholder*

**ABSTRACT:** Wickerol A (**1**) is an unusual diterpene with remarkable activity against H1N1 influenza virus. Its tetracyclic skeleton contains three quaternary carbons and is marked by several *syn*-pentane interactions which force a six-membered ring into a twist-boat conformation. We present an asymmetric synthesis of wickerol A (**1**) that is based on a Jung Diels–Alder reaction, an intramolecular alkylation to complete the 6-5-6-6 ring system, and a conjugate addition, all of which overcome considerable steric strain. During the synthesis, we isolated an unexpected cyclopropane that presumably stems from a carbonium ion intermediate.

Terpenes continue to challenge synthetic chemists with the complexity of their hydrocarbon scaffolds,[1] which are often highly strained. This strain can be photochemical in origin but usually stems from to the ability of terpene cyclases to bend linear cyclization precursors into high-energy conformations and promote hydride and carbon-carbon bond shifts that are otherwise unlikely to proceed.[2] A case in point are the wickerols, two bioactive diterpenes isolated from the fungus *Trichoderma atroviride* FKI-3849 by Ōmura and Shiomi (Fig. 1).[3] Wickerol A (**1**) proved to be highly active against the type A/H1N1 influenza virus with an $IC_{50}$ of 0.07 μg/mL, whereas wickerol B (**2**), which differs from its congener only by hydroxylation at C8, was significantly less potent ($IC_{50}$ of 5.0 μg/mL). Wickerol B (**2**) turned out to be identical with the previously reported natural product trichodermanine A (**2**).[4] Both natural products feature a unique tetracyclic carbon skeleton that comprises two adjacent quaternary carbons and seven stereocenters, two of which are quaternary as well. Although the 6-5-6-6 skeleton of the wickerols contains only five and six-membered primary rings, the molecules are remarkably strained due to numerous *syn*-pentane interactions. These primarily involve the angular methyl group at C10a which force the D-ring into a boat conformation, as confirmed by X-ray analysis.[3] The corresponding strain was estimated to be in the range of 60-70 kJ/mol (see the Supporting Information for DFT calculations on isomers of Wickerol A).

Despite the formidable challenge posed by the wickerols, only a single synthetic study has been disclosed to date.[5] We now report an asymmetric synthesis of wickerol A (**1**) that is a testament to the power of catalysis in cycloadditions and the many pleasant and unpleasant surprises that one encounters when working with complex, sterically congested molecules.

Our synthetic strategy toward the wickerols is shown in Scheme 1. We envisioned that both could be derived from a diketone of type **3** *via* conjugate reduction and addition of a methyl group. Disconnection of the C-ring would lead to a *spiro* tricycle of type **4**. In the forward direction, the ring would be closed through an intramolecular alkylation.

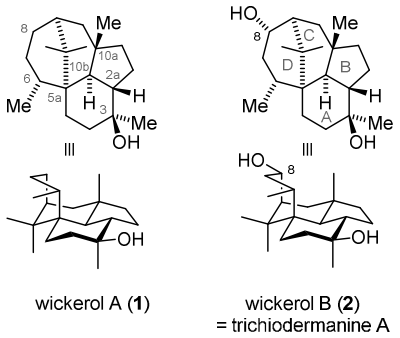
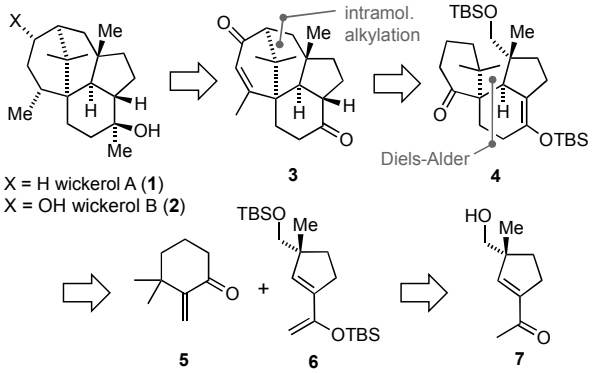


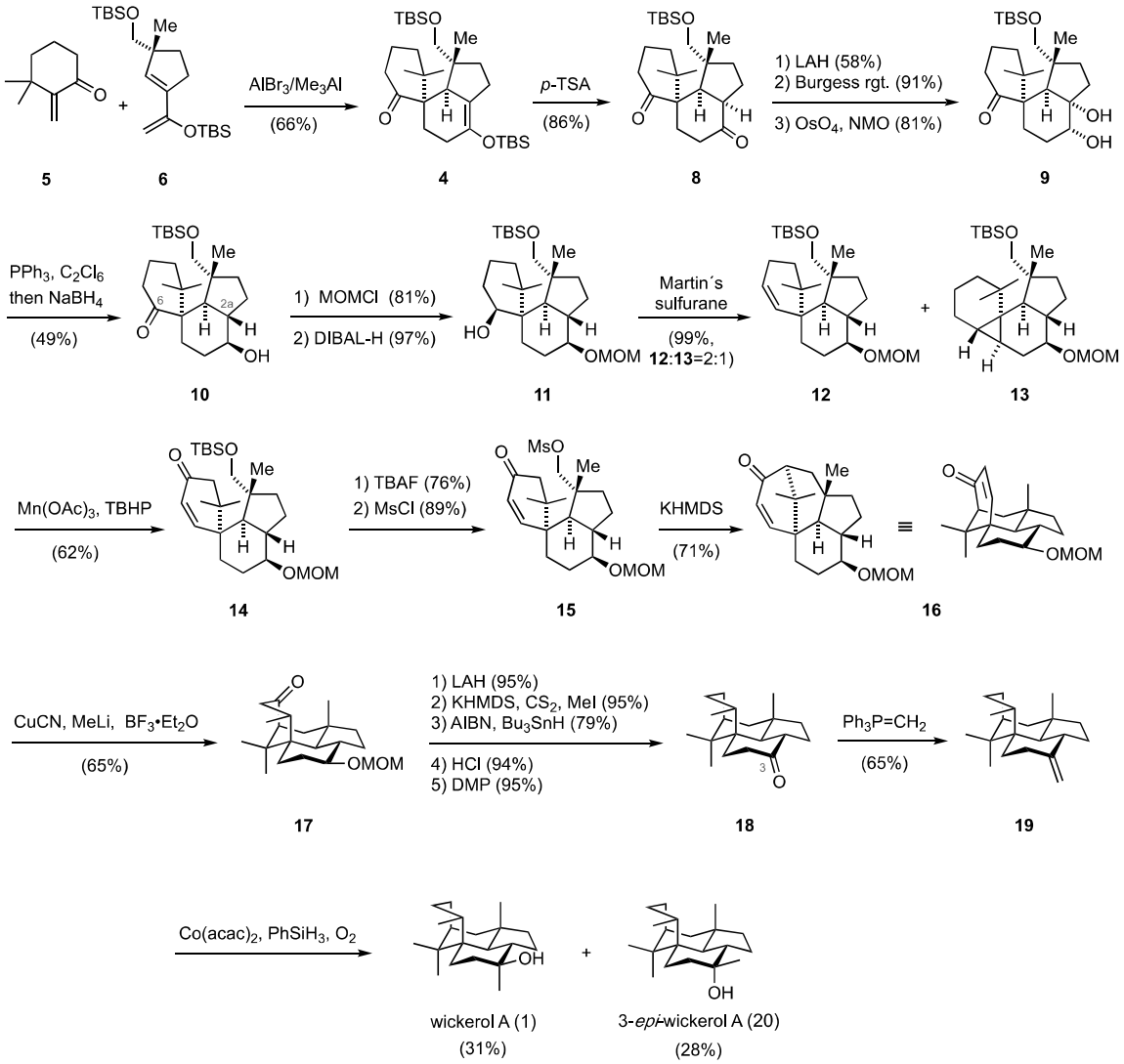

**Figure 1**. Structure of wickerol A (**1**) and B (**2**).




**Scheme 1. Retrosynthetic analysis of the wickerols.**

Key intermediate **4**, which contains all carbons of the wickerols save two, could be accessed with a Diels–Alder addition[6] of known enone **5**[7] to diene **6**. The latter in turn, would be derived from known ketone **7**, which is readily accessible from geraniol *via* Sharpless-epoxidation, Yamamoto-rearrangement[8] and carbonyl–ene cyclization.[9]

Our actual synthesis commenced with the Diels–Alder addition[10] of the achiral enone **5** to the chiral diene **6**, which could be procured from **7**[9] in two steps (see Supporting Information). The intermolecular cycloaddition represented a major challenge since both partners, though electronically matched, are sterically very hindered. Initially, we explored thermal or high pressure conditions,[11] but all our efforts in this regard proved to be unsuccessful.




**Scheme 2. Synthesis of wickerol A (1).**

We then focused our attention on Lewis and Brønsted acid activation and found that commonly used Lewis acids such as $BF_3{\cdot}Et_2O$, $BCl_3$, $TiCl_4$, $SnCl_4$, $Tf_2NH$,[12] $Me_2AlNTf_2$,[13] $Me_2AlCl$, $Et_2AlCl$ or $AlCl_3$ resulted in desilylation of **6**, dimerization of **5** *via* hetero-Diels–Alder reaction, or Mukaiyama–Michael addition without ring closure. However, Jung's conditions, which employ a mixture of $AlBr_3/AlMe_3$ as a catalyst, gave the desired *endo*-product **4** as a single diastereomer.[14] Both the quaternary and the neopentylic stereocenters were set with the correct simple and induced diastereoselectivity. Presumably, the enone approaches the diene *via* an *endo*-transition state and the methyl group provides less steric hindrance than the silyloxy methyl moiety.

With three of the four rings of wickerol A (**1**) established, we set out to prepare the requisite precursor for the intramolecular alkylation. For that purpose, a 1,3-transpostion of the carbonyl group in **4** was necessary, which we envisioned to achieve through 1,2-methyl addition, elimination of the resulting tertiary alcohol and allylic oxidation. Unfortunately, all attempts to add an organometallic reagent[15] to **4** or perform an olefination[16] failed, presumably due to the extreme steric hindrance of the carbonyl group or its competing enolization. We hypothesized that establishing the correct configuration at the A,B-ring junction would lead to a conformational change that would make the ketone more accessible. Upon hydrolysis of Diels–Alder product **4**, however, we obtained unwanted *cis*-hydrindanone **8** as the sole product. Notably, the corresponding *cis*-fused isomer of wickerol A is less stable than the *trans*-fused isomer (see Supporting Information for DFT calculations). Epimerization to the desired *trans* hydrindanone under a variety of conditions proved unsuccessful, reflecting a thermodynamic preference of ca. 14 kJ/mol for the *cis* fusion (see Supporting information).[17] To solve this problem, we turned to the Grainger method, which has proven to be very useful in the synthesis of *trans*-hydrindanes.[18] Thus, we selectively reduced one of the carbonyl groups in **8**, eliminated the resultant secondary alcohol regioselectively using Burgess reagent,[19] and dihydroxylated[20] the resultant alkene from the more accessible face, which yielded diol **9**. Treatment of **9** under Grainger's[18b] conditions indeed afforded the desired *trans*-fused hydrindanone via stereospecific hydride shift. To prevent epimerization during workup, we reduced the carbonyl group *in situ*, which gave alcohol **10**. The desired A,B-ring *trans* junction was confirmed by X-ray structure analysis of diol **21**, obtained through TBS-deprotection of the primary hydroxyl group (Figure 2 and Supporting Information).

Having set the correct configuration at C2a, we turned to the modification of ring D. Again, the carbonyl group at C6 proved to be unreactive toward methyl addition or methylenation. Therefore, we protected the secondary alcohol as a MOM ether and reduced the resultant ketone with DIBAL-H, which gave alcohol **11** in excellent yield. Subsequent elimination could only be achieved by exposure to Martin's sulfurane.[21] This gave alkene **12**, albeit together with an inseparable side product in a 2:1 ratio. Since all attempts at improving this ratio were unsuccessful, we subjected the mixture to a $Mn(OAc)_3$-mediated allylic oxidation,[22] which provided enone **14**. The unreacted side product could be separated at this stage. It was identified as cyclopropane **13** through NMR and X-ray structure analysis of a derivative, diol **22** (Figure 2 and Supporting

Information). Presumably, **13** is formed *via* a carbonium ion, which nicely corresponds to the biosynthesis of terpenoid cyclopropanes.[23]

To set the stage for the crucial intramolecular ring closure, the primary alcohol function in **14** was deprotected and mesylated, giving rise to the key intermediate **15**. To our delight, treatment of **15** with KHMDS gave the desired tetracycle **16**, of which a X-ray crystal structure could be obtained (Fig. 2). The ease with which this intramolecular alkylation proceeded was surprising considering the *syn*-pentane strain built up in its course and the conformational changes that are necessary for the two ends to meet.[24] Interestingly, the reaction showed a strong counterion effect, with the yield significantly decreasing when NaHMDS or LiHMDS were employed.

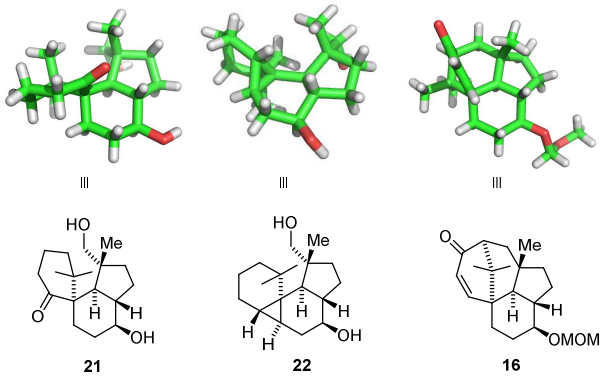



**Figure 2.** X-ray structures of **21**, **22** and **16**.

With the ring system of wickerol A (**1**) complete, we turned to the introduction of the missing methyl groups. The methyl group on the D ring could be added with complete diastereoselectivity by exposure of **16** to methyl lithiocyanocuprate in the presence of $BF_3{\cdot}Et_2O$.[25] Given the steric hindrance at the neopentylic β-position and the introduction of additional *syn*-pentane strain, it is remarkable that this reaction proceeded at all.

Next, we attempted the removal of the carbonyl group in the resultant ketone **17** *via* Wolff-Kishner[26] or Mozingo reduction.[27] Since these failed, we developed a reliable three-step sequence involving hydride reduction, xanthate formation and Barton–McCombie deoxygenation.[28] Deprotection of the MOM ether and oxidation with DMP then afforded ketone **18**.

The final challenge of the synthesis was provided by the methyl addition to **18** to afford wickerol A (**1**). Addition of a methyl Grignard or methyllithium species to ketone **18** gave 3-*epi*-wickerol A (**20**) as the sole product. In the presence of the Lewis acid MAD,[29] which is known to invert the stereoselectivity of nucleophilic attacks to cyclohexanones, we obtained a 1:4 mixture of wickerol A (**1**) and its C3-epimer. Since we were not able to overcome the strong substrate bias with additives,[30] we subjected ketone **18** to Wittig olefination. A subsequent Mukaiyama hydration[31] gave wickerol A (**1**) together with 3-*epi*-wickerol A (**20**) as an almost equimolar mixture, which could be separated by chromatography.

The $^1H$ and $^{13}C$ NMR data of our synthetic wickerol A (**1**) are identical in all respects to those reported by Shiomi and coworkers. All other data also match with the exception of the optical rotation, which was reported as $[\alpha]_D = -2.8$ (c = 0.1, MeOH).[3] We were unable to dissolve wickerol A (**1**) in methanol, as originally reported, but obtained a positive value in chloroform ($[\alpha]_D = +21.7$, c = 0.23, $CHCl_3$). This suggests that natural wickerol A (**1**) has the opposite absolute configuration of our synthetic product. In principle, (–)-wickerol A (**1**) could be accessed from *ent*-**5**, which in turn could be prepared from geraniol using a Sharpless epoxidation with (–)-DIPT.[9, 32]

In summary, we have developed the first total synthesis of a wickerol. Our convergent strategy allowed for the rapid assembly of the complex carbon framework but encountered problems with steric hindrance and unexpected thermodynamic and kinetic preferences, which could be successfully overcome. Salient features of our synthesis are a powerful Diels–Alder reaction to provide most of the rings and carbons, a stereospecific hydride shift to install the challenging C,D-ring *trans* junction, and an intramolecular alkylation to close a bond between two neopentylic carbons. Also of note are a stereoselective conjugate addition to a sterically hindered enone and a final Mukaiyama hydration to establish the tertiary alcohol. The isolation of cyclopropane **13** is another example of the unexpected results that make the total synthesis of complex natural products so rewarding.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information contains detailed experimental procedures, spectral data and X-ray crystallography (PDF). CCDC 1550221, CCDC 1550223, CCDC 1550222 contain the supplementary crystallographic data for **21**, **22**, **16** and can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

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### Notes

The authors declare no competing financial interests.

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