Natural Products

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Structure Elucidation and Total Synthesis of Kulkenon**

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Abstract: *The impressive biological profile of secondary metabolites isolated from strains of Sorangium cellulosum prompted us to initiate synthetic studies on kulkenon, also isolated from Sorangium cellulosum. The synthesis features a syn-selective vinylogous Kobayashi aldol reaction, recently developed by us, and a ring-closing intramolecular Heck reaction as the pivotal transformations. Comparison of the NMR spectra of the authentic and synthetic material revealed that the proposed configuration had to be revised. A combination of molecular modeling and NOE experiments was used to propose the revised configuration, which was confirmed by a new synthesis.*

In 1996 and 2001 Höfle reported the isolation of sulfangolides and kulkenon from different strains of *Sorangium cellulosum* by screening myxobacteria at the Helmholtz Centre for Infection Research (HZI).[1] In 2012, Müller and co-workers reported the relative configuration of sulfangolide C (**1**) on the basis of 1D and 2D NMR spectroscopic data as well as molecular modeling studies.[2] We became interested in kulkenon and the sulfangolides and their biological potential as these natural products were observed as by-products during the isolation of the highly active natural products chivosazol,[3] disorazol,[4] and soraphen.[5]

Even though the structure elucidation was performed only for sulfangolide C, we anticipated that the same configuration would hold true for kulkenon and was consequently used as the hypothetical configuration of our synthetic target **2** (Figure 1). Our retrosynthesis disconnects kulkenon between C5 and C6 and between C20 and C21. These bonds can be constructed in the synthesis through an intramolecular Heck reaction[6] and by means of a Horner–Wadsworth–Emmons (HWE) olefination, respectively.[7] We envisaged that the *syn* configuration between C24 and C25 could be generated through the *syn*-selective Kobayashi aldol reaction, recently developed in our group (Scheme 1).[8]

For the synthesis of the "eastern" fragment **4** we employed our *syn*-selective variation of Kobayashi's vinylogous Mukaiyama aldol reaction. The transformation of isovaleraldehyde (**6**) with *Z*-N,O-keteneacetal **5** provided alcohol **7** in 82% yield and d.r. 20:1 (Scheme 2). Next, the Evans auxiliary was removed with lithium borohydride, the accrued primary hydroxy group protected as its TBS ether, and the secondary alcohol transformed to the corresponding phosphonate **9**. The subsequent HWE olefination with aldehyde **10**, which was prepared in a three-step sequence starting from propargylic alcohol,[9] gave the desired product as a single isomer (92%). Deprotection with TBAF, allylic oxidation, and tin–iodide exchange then completed the synthesis of "eastern" fragment **4** (Scheme 2).

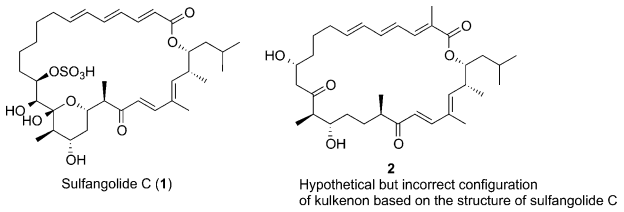
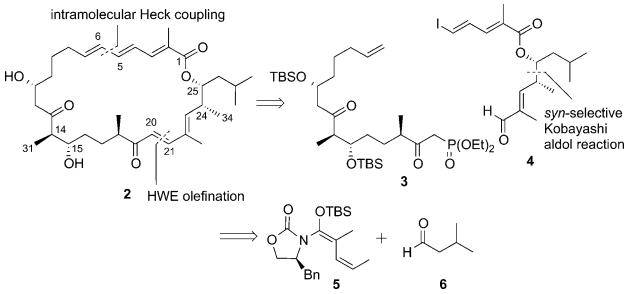
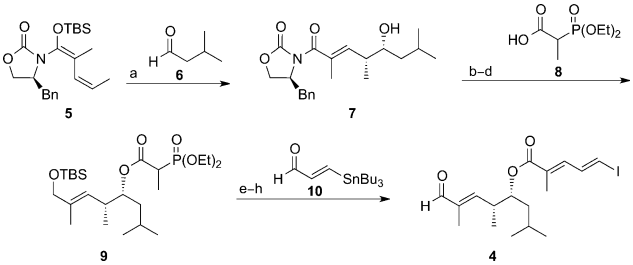


Figure 1. Proposed configurations of sulfangolide C and kulkenon.



Scheme 1. Retrosynthetic synthesis of kulkenon.



Scheme 2. Synthesis of the "eastern" fragment. a) **6**, $TiCl_4$, CH_2Cl_2, −78 °C, 84%, d.r. > 20:1; b) $LiBH_4$, MeOH, THF, 0 °C→RT, 95%; c) TBSCl, imidazole, CH_2Cl_2, RT, 82%; d) **8**, DCC, 4-DMAP, CH_2Cl_2, 0 °C→RT, 90%; e) **10**, NaH, THF, 0 °C→RT, 95%; f) TBAF, THF, 0 °C→RT, 88%; g) MnO_2, CH_2Cl_2, RT, 95%; h) I_2, CH_2Cl_2, RT, 88%. TBSCl = *tert*-butyl(chloro)dimethylsilane, DCC = *N*,*N*′-dicyclohexylcarbodiimide, 4-DMAP = 4-(dimethylamino)pyridine, THF = tetrahydrofuran, TBAF = tetrabutylammonium fluoride.

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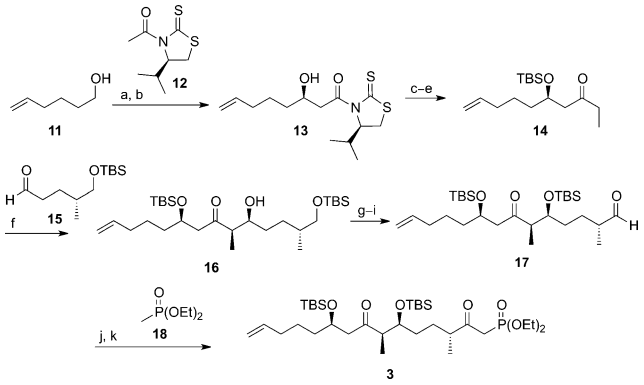


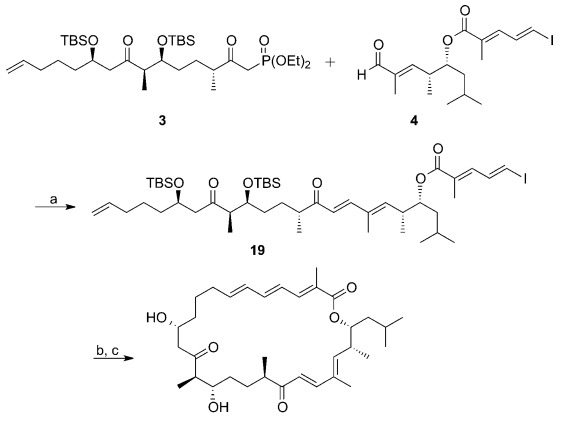
Scheme 3. Synthesis of the "western" fragment. a) PCC, CH_2Cl_2, RT; b) **12**, $TiCl_4$, *i*Pr_2NEt, CH_2Cl_2, −50 °C, 80% over two steps, d.r. 10:1; c) MeO(Me)NH·HCl, Me_3Al, CH_2Cl_2, −20 °C→RT, 90%; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 92%; e) EtMgBr, Et_2O, −78 °C→RT, 86%; f) (+)-Ipc_2BOTf, *i*Pr_2NEt, CH_2Cl_2, −78 °C→−20 °C, 54%, d.r. 12:1; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 92%; h) CSA, MeOH, CH_2Cl_2, −20 °C, 69%; i) DMP, $NaHCO_3$, CH_2Cl_2, RT, 92%; j) **18**, *n*BuLi, THF, −78 °C, 79%; k) DMP, $NaHCO_3$, CH_2Cl_2, RT, 95%. PCC = pyridinium chlorochromate, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, (+)-Ipc_2BOTf = (+)-diisopinocampheylborane trifluoromethanesulfonate, CSA = camphor sulfonic acid, DMP = Dess–Martin periodinane.

The "western" fragment **3** was constructed by joining together ketone **14** and aldehyde **15** through an Ipc_2BOTf-mediated aldol reaction (Scheme 3).[10] To achieve this, alcohol **11** was oxidized with PCC and directly used in a Nagao aldol reaction, which provided **13** in 80% yield over two steps. Subsequent transformation to the corresponding Weinreb amide, TBS protection of the secondary hydroxy group, and a Grignard reaction with EtMgBr gave ketone **14**. Aldehyde **15** was synthesized according to a four-step sequence reported by Paterson et al.[11]

Ketone **14** and aldehyde **15** could now be joined through an aldol reaction with (+)-Ipc_2BOTf, which provided **16** in 54% yield and a diastereomeric ratio of 12:1. Furthermore, the undesired isomers could be separated by column chromatography. The newly generated secondary hydroxy group was protected as a TBS ether, the primary TBS group cleaved with CSA, and subsequently oxidized using DMP to yield aldehyde **17**. Finally, treatment with lithiated **18** and oxidation gave "western" fragment **3**.

The endgame of kulkenon started with a HWE olefination[7] of the "western" and the "eastern" segment with $Ba(OH)_2$ as the base, and provided the precursor for the subsequent Heck reaction[6] (Scheme 4). Finally, the intramolecular Heck reaction provided the macrocyclic backbone of kulkenone. After removal of the TBS protecting groups with TAS-F, compound **2** was isolated in 25% yield over two steps.

Unfortunately, after completion of its synthesis, the NMR spectra of the authentic and the synthetic material were not identical and exhibited significant differences, so we had to conclude that at least one configuration was not correctly installed (see the Supporting Information). After careful inspection of all our stereoselective transformations and confirmation of the stereochemical outcome even of established transformations, it became apparent that we had to determine the configuration of kulkenon independently. Unfortunately, neither of the gene clusters for the kulkenon and the sufangolide C biosynthesis were available and we, therefore, had to rely solely on NMR data in combination with computational methods.



Scheme 4. Endgame of the kulkenon synthesis. a) $Ba(OH)_2$, THF, RT, 73%, *E*/*Z* > 20:1; b) $Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF, 60 °C; c) TAS-F, DMF, RT, 22% over two steps. DMF = dimethylformamide, TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

We employed the Murata method to confirm the relative configuration of C14 and C15 as well as of C24 and C25.[12] The measurement of the required heteronuclear coupling constants ($^{2,3}J_{C,H}$) relied on the analysis of HSQC-HECADE spectra. The homo- and heteronuclear coupling constants for the two respective regions of kulkenon are shown in Figure 2.

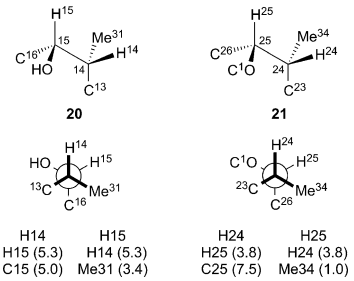


Figure 2. Conformations and configurations determined for the C14/C15 subunit (**20**) and the C24/C25 subunit (**21**) of kulkenon; coupling constants $^3J_{H,H}$ and $^{2,3}J_{H,C}$ [Hz] in parentheses.

A rather small $^3J_{H,H}$ coupling constant between H14 and H15 indicates a gauche conformation of these protons. A large $^2J_{C,H}$ coupling constant between H14 and C15 and a small $^3J_{C,H}$ coupling constant between H15 and C31 also support the gauche conformation. These results lead to configuration **20** and confirmed the *syn*-configuration between the methyl group at C14 and the hydroxy group at C15. The small $^3J_{H,H}$ coupling constant between H24 and H25 supports a gauche conformation of these two protons. A large $^2J_{C,H}$ coupling constant between H24 and C25 and a small $^3J_{C,H}$ coupling constant between H25 and C34 also support a gauche

conformation for each case. Overall, this results in a *syn* configuration for the methyl group at C24 and the ester oxygen atom at C25, as shown in structure **21** (Figure 2).

Consequently, we concluded that the relative configuration at C14 and C15 as well as of C25 and C26 was identical to that proposed for sufangolide C (**1**). Unfortunately, the different clusters of chiral centers cannot be correlated with each other by the Murata method. On the other hand, inspection of the NMR data of authentic kulkenon and compound **2** clearly showed different but indicative NOESY correlations (Figure 3). Both molecules exhibit a transannular

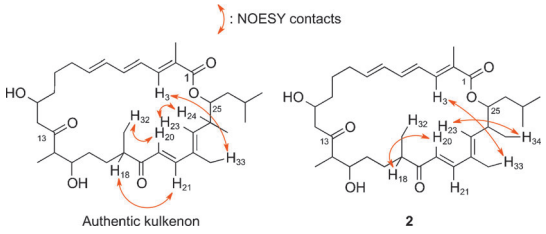


Figure 3. Significant NOESY correlations for authentic kulkenon and compound **2**.

NOESY contact between H3 and H33. However, different NOE interactions were identified in the C18 to C25 region. For authentic kulkenon, we observed NOE interactions between H18 and H21, H20 and H32, as well as between H23 and H24. These NOESY contacts were not detected for compound **2**. On the other hand, **2** exhibited NOESY correlations between H18 and H20 as well as between H23 and H34.

With the knowledge of a *syn* configuration for C14/C15 and C24/C25, the complexity of the configurational assignment was reduced to only four independent regions and a total of eight possible diastereomers. A Monte Carlo search using MacroModel (version 9.9) was performed for all eight diastereomers (see the Supporting Information). The so-obtained conformations were then inspected to identify those that were in accordance with the experimentally observed NOESY correlations. Remarkably, only isomer **22** exhibited a conformation that would be consistent with the NMR data of authentic kulkenon. The opposite configuration at C24 and C25 in isomer **22**, compared to the originally proposed configuration, leads to a conformational change in the C18 to C24 region of kulkenon (Figure 4) and provides a rationale for the observed NOE contacts.

With this knowledge, we aimed at a revised synthesis of kulkenon, in which only the configuration of the two chiral centers established in the vinylogous Mukaiyama aldol reaction had been changed (Scheme 5). In contrast to the synthesis of the non-natural diastereomer **2**, the final TBS deprotection was achieved with $3\,HF{\cdot}NEt_3$, since TAS-F led to significant decomposition of the starting material. After completion of the second synthesis, we gratifyingly realized that the spectroscopic data were identical with the data originating from the authentic sample.

In summary, we used a combination of computational and NMR experiments to propose the configuration of kulkenon.

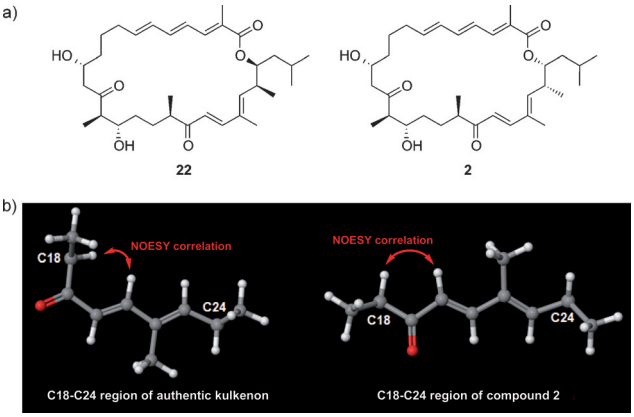
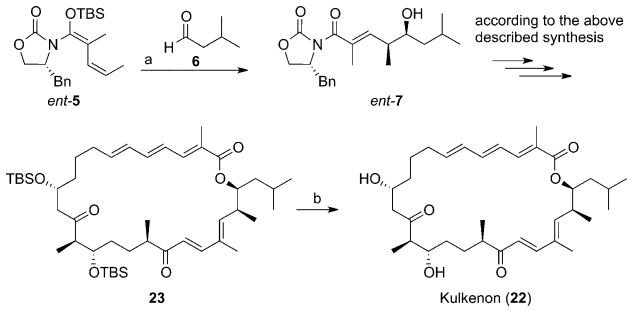


Figure 4. C18–C24 region of authentic kulkenon (**22**) and compound **2**.



Scheme 5. Revised synthesis of kulkenon. a) **6**, $TiCl_4$, CH_2Cl_2, −78 °C, 82 %, >20:1 d.r.; b) $3\,HF{\cdot}NEt_3$, MeCN, 40 °C, 25 % over two steps. DMF = dimethylformamide.

The subsequent total synthesis finally confirmed the proposed absolute and relative configuration. The pivotal transformations used in this synthesis are a *syn*-selective vinylogous Kobayashi aldol reaction and an intramolecular Heck reaction, which serves as a valuable alternative to established cyclization strategies. Our efforts to also confirm the proposed configuration of sulfangolide C will be reported in due course.

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