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Total Synthesis of Fijiolide A‡

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§SCS-DSM Award for best poster presentation in Organic Chemistry

Abstract: Fijiolide A is a secondary metabolite isolated from a marine-derived actinomycete of the genus *Nocardiopsis*. It was found to significantly reduce the TNF-α induced activity of the transcription factor NFκB, which is considered a promising target for the treatment of cancer and inflammation-related diseases. We disclose an enantioselective synthesis of fijiolide A enabled by a fully intermolecular, yet regioselective cyclotrimerization of three unsymmetrical alkynes to construct its tetra-substituted arene core. An atropselective macroetherification enables the assembly of the strained [2.6]paracyclophane motif. A late-stage glycosylation of the macrocyclic aglycone at its tertiary alcohol position allowed for the first total synthesis of fijiolide A.

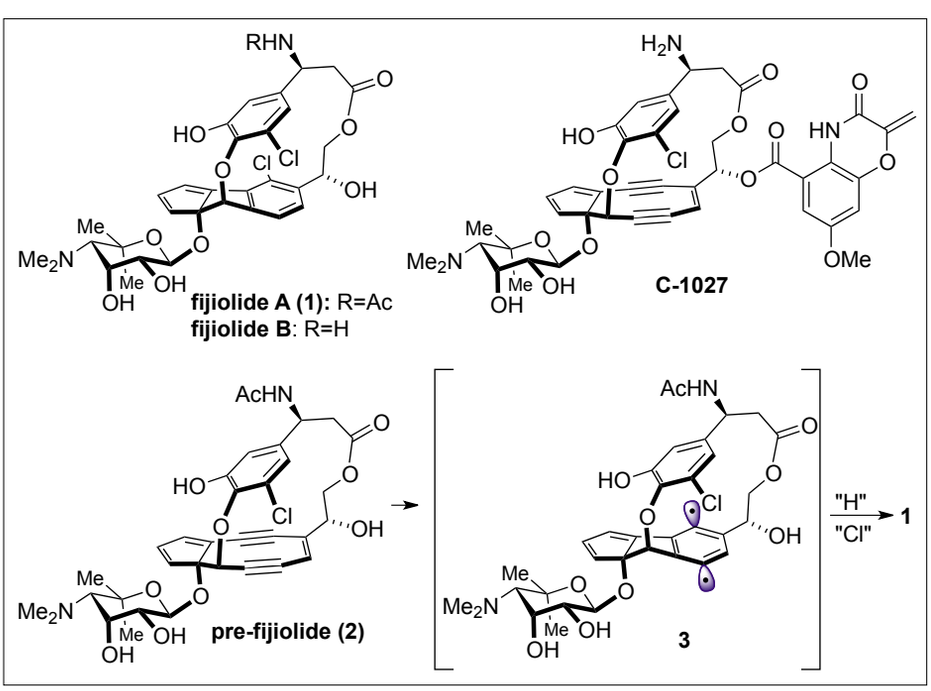
Keywords: [2+2+2] Cycloaddition · Fijiolide · Glycosylation · Paracyclophane formation · Total synthesis

Fijiolides A (**1**) and B were first isolated in 2010 by Fenical and coworkers from a marine-derived actinomycete of the genus *Nocardiopsis*, discovered in a sediment sample of the Beqa Lagoon, Fiji.[1] Both secondary metabolites display inhibitory activity against TNF-α induced activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). Due to its pivotal role in immunological processes, NFκB has been termed 'central mediator of the human immune response'.[2] As a rapid acting primary transcription factor, it regulates the expression of nearly 500 genes,[3] many of whom encode tumorigenesis and inflammation-relevant proteins including cyclooxygenase (COX-2), matrix metalloproteinase (MMP-9), inducible nitric oxide synthase (iNOS) or anti-apoptotic proteins bcl-2 and bcl-xl.[4]

The structures of fijiolides A and B bear close resemblance to the Bergman-cyclization product of the enediyne C-1027 (Scheme 1).[5,6] Consequently, a common biosynthetic origin from the 9-membered enediyne precursor pre-fijiolide (**2**) has been suggested.[7] Recently, a supporting piece of evidence has been provided by Oh *et al.* who reported the isolation of fijiolides A and B together with the cycloaromatized C-1027 chromophore from an actinomycete strain, collected at the East Siberian continental margin.[8] In analogy to the sporolides and cyanosporasides,[9,10] the exclusively mono-chlorinated cyclopenta[*a*]indene core of the fijiolides is believed to result from a regioselective ionic trapping of the intermediate *p*-benzyne biradical species **3**.[11]

The inhibitory properties of fijiolide A with respect to the TNF-α induced NFκB activity renders **1** of pharmacological interest. Concomitant with an intriguing molecular architecture, fijiolide A represents a formidable target for total synthesis. From a synthetic point of view, **1** appears particularly challenging due to its rotationally restricted [2.6]paracyclophane core giving rise to planar chirality and non-biaryl atropisomerism. The strained structural motif is embedded into the fijiolide A aglycone which is glycosylated at its cyclopentadieneol moiety. A synthesis of **1** requires the challenging installation of an amino ribopyranose unit at a hindered tertiary alcohol.

Retrosynthetically, fijiolide A was envisioned to be accessed from precursor **4** *via* a late-stage elimination of an allylic alcohol to install the cyclopentadienyl motif and a glycosylation of the tertiary allylic alcohol with the known Schmidt donor **5** (Scheme 2).[12] An atropselective assembly of the rotationally restricted [2.6]paracyclophane core could be realized by a cyclization reaction forming the phenol ether bond rather than a more obvious macrolactonization approach. An additional strategic fission of the six-atom paracyclophane bridge at the ester functionality dis-



Scheme 1. Structures of fijiolide A and B and related enediyne natural products.

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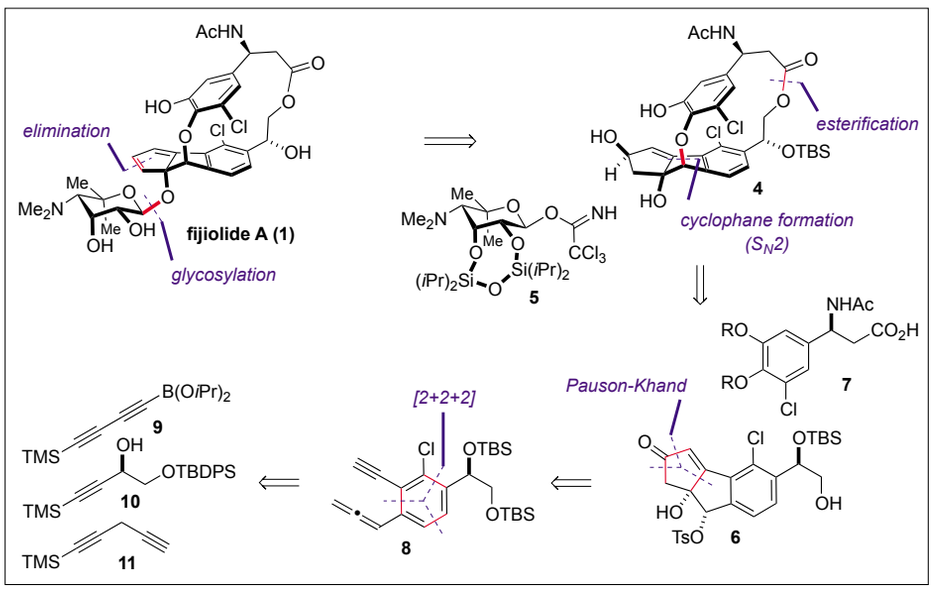
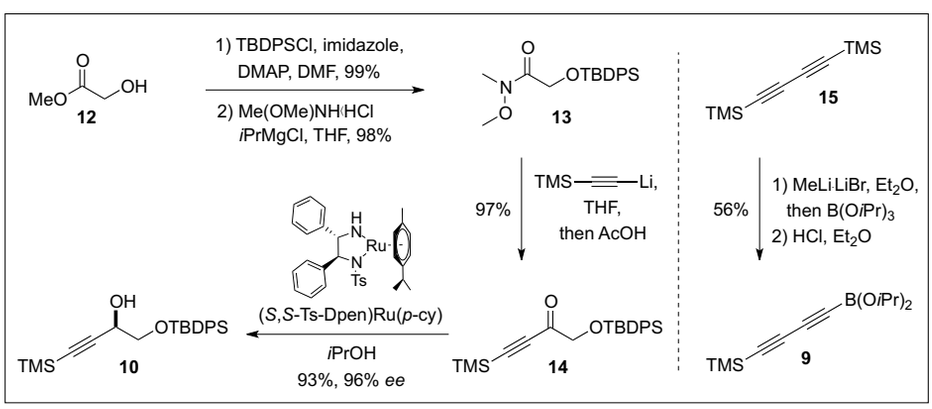
assembles **4** into indanyl cyclopentenone **6** and β-amino acid fragment **7**. In turn, the carbocyclic skeleton of **6** was envisaged to result from a Pauson-Khand reaction of allene-yne **8**. The *de novo* synthesis of benzene derivative **8** from alkynes **9**, **10** and **11** *via* an intermolecular [2+2+2] cycloaddition was considered to provide a higher step-economy than more conventional arene functionalizations.

Our synthesis of fijiolide A commenced with the preparation of enantioenriched propargylic alcohol **10** *via* Weinreb amide **13** (Scheme 3).[13,14] Although commercially available, **13** was prepared in two steps and excellent yield by TBDPS-protection of methyl glycolate, followed by treatment with *N*-methoxy-*N*-methylamide hydrochloride in the presence of *i*PrMgCl. In turn, treatment of **13** with lithium trimethylsilylacetylide afforded ynone **14**. Noteworthy, quenching the reaction with acetic acid turned out to be key for high purity of **14**, and thus for direct employment of the crude product in the ensuing transfer hydrogenation step. Other work-up procedures, *e.g.* the addition of aqueous ammonium chloride led to partial silyl cleavage. The terminal ynone, thus formed, proved to be a strong poison of Noyori's (Ts-Dpen) Ru(*p*-cymene) catalyst.[15] The acetic acid quench furnished a clean ynone **14** and allowed for the direct asymmetric reduction to propargyl alcohol **10** in 93% yield and 96% *ee*. Diynylboronate **9** was synthesized from TMS acetylene dimer **15** according to a modified literature procedure involving isolation of the intermediate lithium triisopropoxydiynylborate.[16]

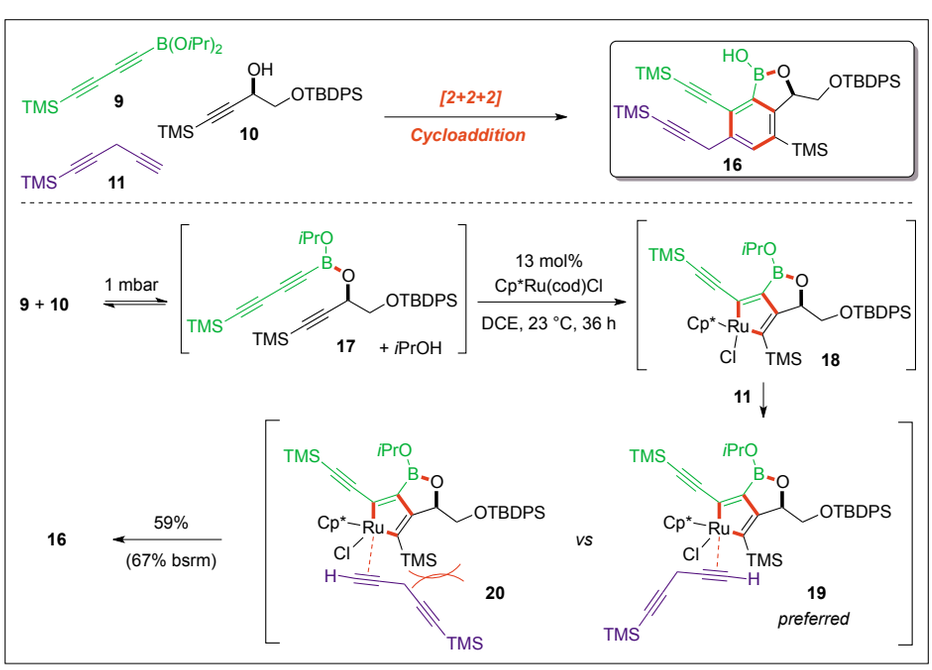
With **9** and **10** in hand, realization of the envisioned [2+2+2] cycloaddition became the paramount synthetic endeavor (Scheme 4). Intermolecular cyclotrimerizations of unsymmetrical alkynes allow for the rapid construction of highly substituted benzene derivatives. However, the difficulty in attaining satisfactory levels of chemo- and regioselectivity to produce a single isomer strongly limits its application in organic synthesis.[17] In 2004, Yamamoto and coworkers reported a ruthenium-catalyzed regioselective cyclotrimerization enabled by a dynamic temporary boron tether between an alkynylboronate species and a propargylic alcohol component.[18] Accordingly, alkynes **9** and **10** were mixed *in vacuo* in order to remove the released isopropanol and shift the equilibrium to the transesterified boronate **17**. Upon addition of Cp*Ru(cod)Cl in DCE, the tethered 1,6-diyne moiety of **17** acts as a competent substrate for oxidative cyclization, giving ruthenacycle **18**. Coordination of terminal alkyne **11** to the metal center occurs preferentially with an orientation avoiding steric repulsion between its silylated propargyl moiety and the bulky, yet removable TMS group adjacent to the ruthenium atom (**19** preferred over **20**). Thus, insertion of the third alkyne proceeds in a productive manner and allows for isolation of desired arylboronic acid derivative **16** in 59% yield (67% brsm of **10**) as a single regioisomer.



Scheme 2. Retrosynthetic analysis of fijiolide A.

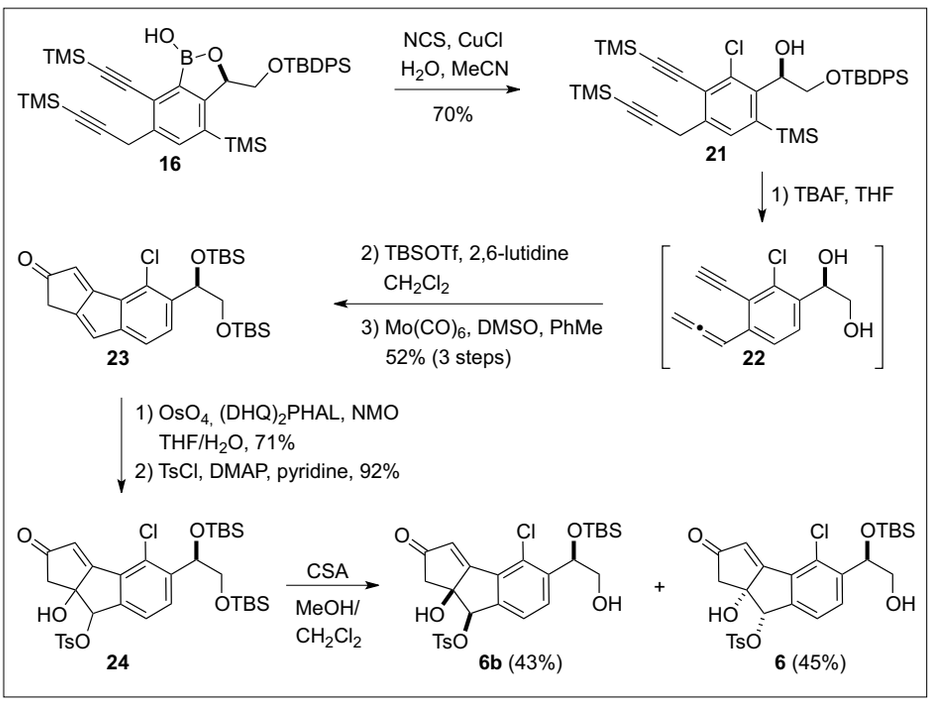


Scheme 3. Synthesis of propargyl alcohol **10** and diynylboronate **9**.



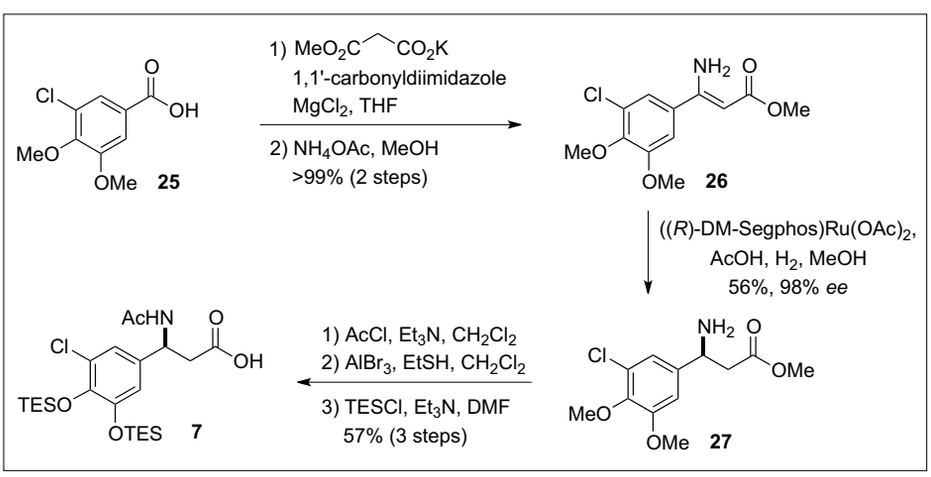
Scheme 4. Intermolecular [2+2+2] cycloaddition to assemble the fijiolide arene core.

Taking further advantage of the dynamic boron substituent as a chlorine atom synthon, oxidative halodeboronation of **16** could be realized in the presence of NCS/CuCl.[19] Subsequent exposure of **21** to excess TBAF resulted in global desilylation and triggered the anticipated isomerization of the propargyl group, generating the required terminal allene.[20] Intermediate diol **22** was protected as its corresponding *bis*-TBS ether. Ensuing subjection to a $Mo(CO)_6$ mediated allenic Pauson-Khand reaction afforded indenyl cyclopentenone **23**.[21] Due to its inherent base-sensitivity, dihydroxylation of **23** could not be performed under classical Sharpless conditions (AD-mix).[22] Consequently, a modified dihydroxylation procedure was employed proceeding with high chemoselectivity for the more electron-rich indenyl double bond. However, almost no facial selectivity could be attained. Selective activation of the secondary benzylic hydroxyl group with TsCl (**24**) over the tertiary alcohol, and cleavage of the primary TBS ether under acidic conditions (CSA) provided fragment **6** (Scheme 5). The separation of the desired diastereomer **6** was conveniently realized at this stage by flash chromatography.



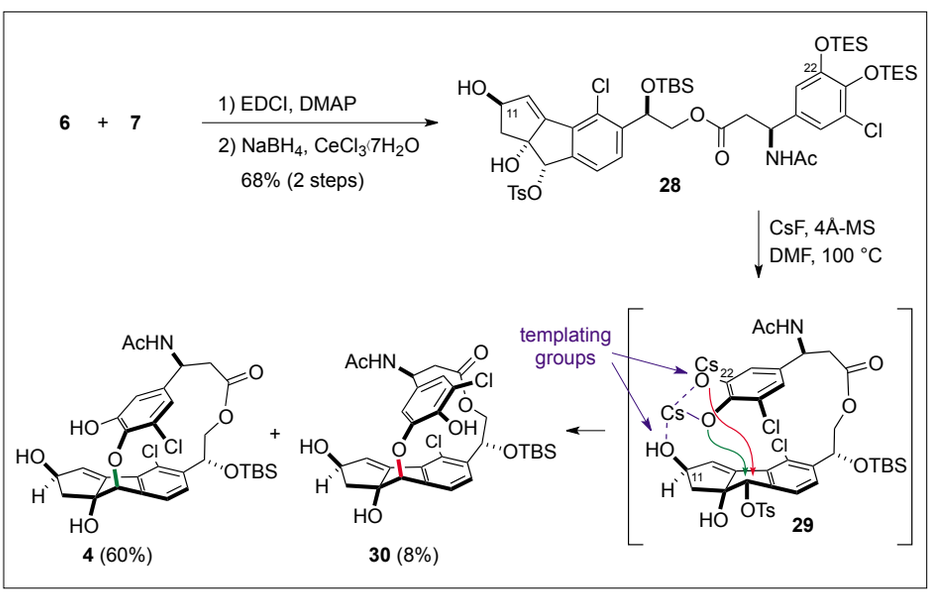
Scheme 5. Completion of carbocyclic fragment **6**.

The synthesis of the second building block, β-amino acid **7**, proceeded smoothly starting from 5-chloroveratric acid (**25**) (Scheme 6). A decarboxylative Claisen condensation afforded the corresponding β-keto ester,[23] which was further converted into enamine **26** by treatment with ammonium acetate. Subsequent enantioselective enamine reduction in the presence of ((*R*)-DM-Segphos)$RuOAc_2$ produced β-amino ester **27** in 98% *ee*.[24] Acetylation, followed by global demethylation with $AlBr_3$/EtSH,[25] and TES protection of the intermediate catechol moiety furnished β-amino acid **7** in a total of six steps.



Scheme 6. Synthesis of β-amino acid **7**.

Ester formation of building blocks **6** and **7** was performed using EDCI (Scheme 7). The enone was diastereoselectively reduced to the secondary alcohol **28** under Luche conditions.[26] Subsequent exposure of **28** to CsF in DMF at ambient temperature cleaved first both phenolic silyl groups. Heating the reaction mixture to 100 °C then enabled an ensuing macrocyclization *via* intramolecular nucleophilic displacement. Remarkably, the macroetherification proceeded in an atrop- and regioselective manner, allowing for isolation of desired [2.6]paracyclophane **4** in 60% yield. We attained this selectivity in the paracyclophane formation step by using an unprotected C(11) hydroxyl group and an *in situ* deprotected C(22) phenolic hydroxyl group. These groups are assumed to coordinate the cesium cation, resulting in preorganized intermediate **29**. The fa-



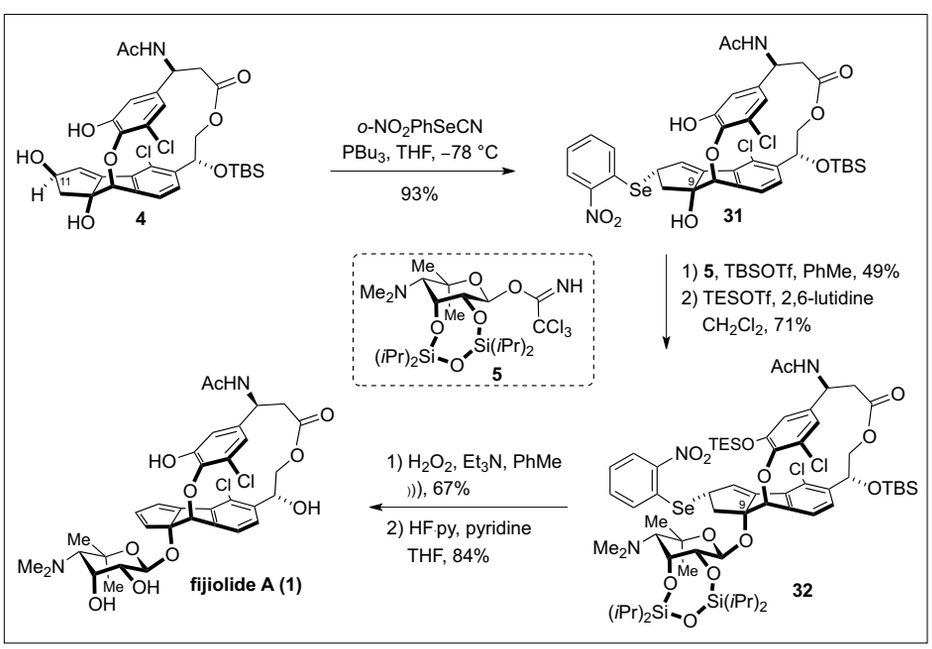
Scheme 7. Regio-and atropselective synthesis of the fijiolide [2.6]paracyclophane core.

vorable templating interactions in **29** are believed to facilitate nucleophilic substitution of the tosylate by the proximate phenolate, resulting in formation of the desired atrop- and regioisomer **4**.

Having overcome the crucial macrocyclization hurdle, our focus shifted towards installation of the cyclopentadiene moiety by elimination of C(11)-OH. Of the numerous dehydration reagents examined, only methyltriphenoxyphosphonium iodide (MTPI)[27] allowed for isolation of the targeted unstable cyclopentadiene, although in unsatisfactory and non-reproducible yields. In accordance with additional model studies, the free cyclopentadienol moiety was identified as the main cause for the poor stability, particularly towards acid conditions. Therefore, glycosylation of any cyclopentadienol containing precursor with trichloroacetimidate **5** under common Schmidt conditions (TMSOTf/BF_3·OEt_2) was deemed inauspicious. Consequently, we built on a stepwise dehydration approach comprising a selective Mitsunobu-type substitution of the secondary allylic hydroxyl group by an *o*-nitrophenyl selenide to produce **31** (Scheme 8). From the outset, late-stage glycosylation of the sterically encumbered tertiary C(9) hydroxyl group was considered a key challenge and was expected to necessitate a preceding protection of the free phenol. However, silylation of **31** (TBSOTf, 2,6-lutidine, CH_2Cl_2) was found to occur selectively at C(9)-OH without the expected silyl aryl ether being formed. The observed reluctance of the phenol to engage in the silylation reaction prompted us to employ **31** directly as the glycosyl acceptor. Initial attempts on glycosylation with Schmidt donor **5** under standard conditions (TMSOTf/CH_2Cl_2) predominantly led to silylation of the tertiary alcohol. This result was attributed to glycosyl donor **5**, carrying a basic amino group. In order to suppress the parasitic C(9)-OH silylation various solvents and Lewis acidic glycosylation promotors were screened. TBSOTf in toluene was found to efficiently activate the glycosyl donor, whereas the undesired silylation reaction could be entirely suppressed. The glycosylation proceeded with complete selectivity for the desired β-anomer and in a remarkable yield of 49% considering the complexity and steric hindrance of the glycosyl acceptor.

With the blocked C(9) hydroxyl group, installation of the cyclopentadiene motif was re-investigated. Direct exposure of the glycosylation product to H_2O_2/Et_3N in THF afforded a 1:1 mixture of the Grieco elimination product[28] and a compound tentatively assigned as the seleno-Mislow-Evans [2,3]-sigmatropic rearranged allylic alcohol.[29] TES protection of the free phenolic hydroxyl group solved this issue. Thus, treatment of **32** with a biphasic mixture of H_2O_2/Et_3N and toluene in a sonicator afforded the desired cyclopentadiene in 67% yield. Finally, global desilylation with HF·py proceeded smoothly and provided targeted fijiolide A in 84% isolated yield.

In summary, we disclose an enantio- and atropselective first total synthesis of fijiolide A. Our strategy encompasses a ruthenium-catalyzed cycloaddition of three unsymmetrical alkynes to construct the heavily substituted arene core with complete regioselectivity. An atropselective macroetherification gives access to the strained paracyclophane framework and is followed by glycosylation of a sterically encumbered tertiary alcohol to assemble the entire carbon backbone. Our concise synthesis of fijiolide A in only 18 steps in the longest linear sequence allows now for the synthesis of analogues and their biological evaluation, which is a current subject of research in our laboratory.



Scheme 8. Completion of the synthesis.

Acknowledgments

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