JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Synthesis of Fijiolide A via an Atropselective Paracyclophane Formation

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Supporting Information

ABSTRACT: Fijiolide A is a secondary metabolite isolated from a marine-derived actinomycete and displays inhibitory activity against TNF-α-induced activation of NFκB, an important transcription factor and a potential target for the treatment of different cancers and inflammation related diseases. Fijiolide A is a glycosylated complex paracyclophane, which is structurally closely related to the Bergman-aromatization product of enediyne C-1027. We report an enantioselective synthesis of fijiolide A demonstrating the power of fully intermolecular ruthenium-catalyzed [2 + 2 + 2]-cyclotrimerizations with three different alkynes to assemble the heavily substituted central arene core. The characteristic strained [2.6]-paracyclophane structure is accessed by a templated atropselective macroetherification reaction.

Rapid acting primary transcription factors are first responders to harmful cellular stimuli. Nuclear factor kappa B (NFκB) is an important transcription factor regulating the expression of over 400 different genes.[1] In this respect, NFκB is a relevant therapeutic drug target for the treatment of different types of cancer[2] and inflammation related diseases.[3] Hence, the discovery of inhibitors and elucidation of their mode of action is an important endeavor. The natural products fijiolide A (**1**) and B (Figure 1) have been shown to inhibit the TNF-α-induced activation of NFκB.[4] Both are secondary metabolites isolated from a marine-derived actinomycete of the genus *Nocardiopsis*, collected from the Beqa Lagoon, Fiji. Structurally, **1** is closely related to the Bergman-cyclization product of the antitumor antibiotic enediyne C-1027.[5,6] This suggests a common biosynthetic origin from a putative enediyne precursor prefijiolide A (**2**).[7] The biradical Bergman cyclization intermediate **3** could then be trapped in an ionic fashion,[8] analogous to the monochlorinated arene moieties of the sporolides[9] and cyanosporasides.[10] In contrast to many related Bergman-cyclization products of highly bioactive enediynes losing their biological activity upon cyclization,[11] the fijiolides possess significant NFκB inhibitory properties, making them an attractive synthetic target. Moreover, the different potencies of fijiolide A and B may allow for tuning of the activities. To the best of our knowledge, no previous synthesis or approaches have been reported. Fijiolide A bears several different synthetic challenges. In particular, **1** features a rotationally restricted [2.6]-paracyclophane moiety. This strained structural feature[12] originates from the [12]paracyclophane formed during the Bergman cyclization of **2**. Moreover, it possesses a glycosylated cyclopentadieneol unit. A synthesis would require the challenging installation of an amino sugar at a hindered tertiary alcohol.

Our envisioned synthetic strategy features a late stage elimination reaction to access the cyclopentadiene unit and a β-selective glycosylation with Schmidt donor **5**[13] of the tertiary alcohol of a suitable precursor **4** (Scheme 1). The central [2.6]paracyclophane unit of **4** could be constructed by a cyclization building the phenol ether linkage rather than the more usual macrolactonization strategy. We hypothesized that this option may allow improved atropselectivity control during cyclization as the relevant groups are in closer proximity to the

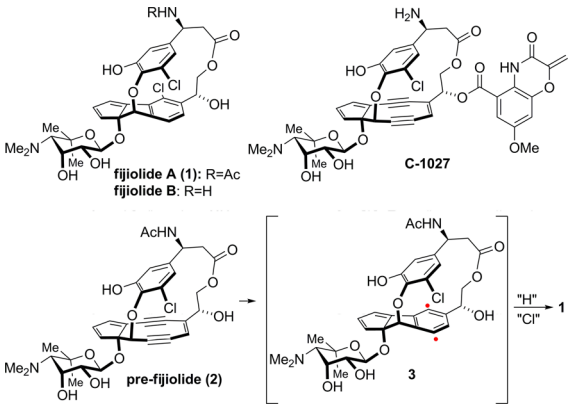
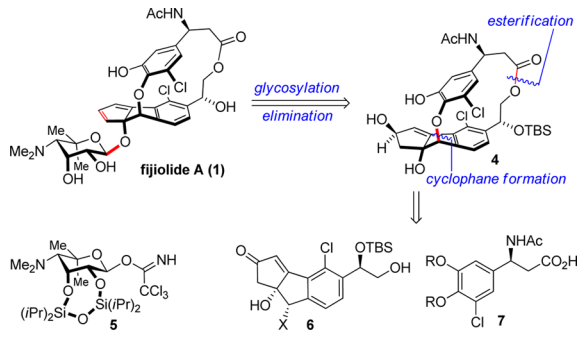


Figure 1. Fijiolide A and related structures.

Scheme 1. Synthetic Strategy for Fijiolide A



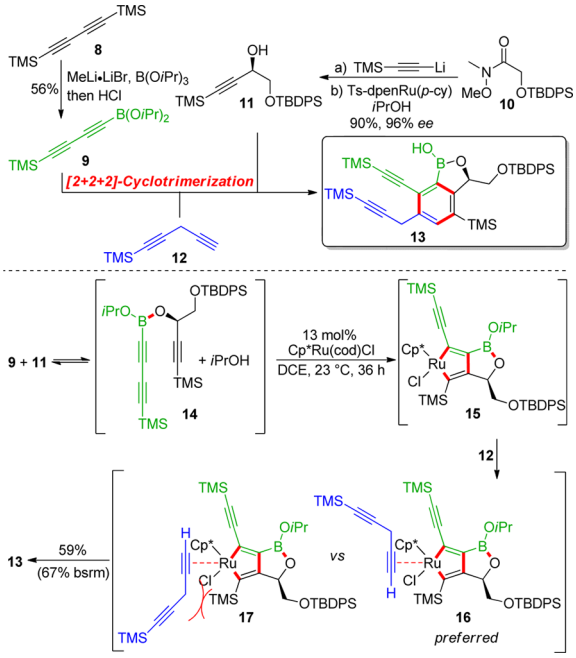
Received: July 29, 2015
Published: August 24, 2015

DOI: 10.1021/jacs.5b07964
J. Am. Chem. Soc. 2015, 137, 11278−11281

reaction site. In turn, **4** could be available from β-amino acid fragment **7** and indanyl cyclopentenone **6**.

We envisioned a [2 + 2 + 2] cyclotrimerization key step for the assembly of the tetra-substituted arene moiety of carbocyclic fragment **6** (Scheme 2). Fully intermolecular cyclotrimerizations

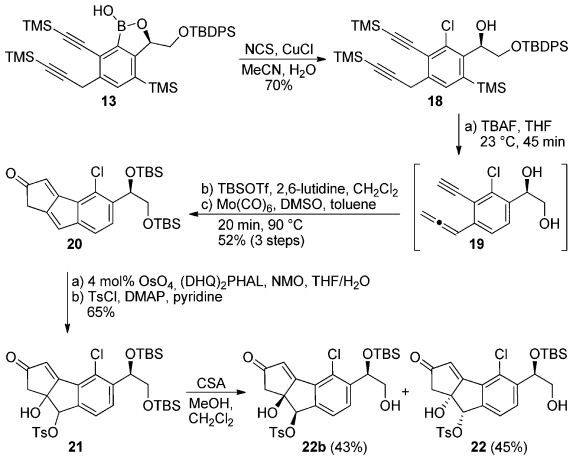
Scheme 2. [2 + 2 + 2]-Cyclotrimerization for the Arene Core



provide a very steep increase in molecular complexity, but demand in the same time a high reaction control.[14] The substituents of the three different alkyne reactants need to be carefully selected to obtain the desired regioselectivity for the heterotrimerization, while still maintaining suitable reactivity and reducing parasitic homotrimerization. Cp*Ru(cod)Cl is the catalyst of choice for demanding cyclotrimerizations,[15a−c] and careful tuning of the electronic and steric properties of the participating alkynes allows for impressive selectivities.

For our synthesis, the [2 + 2 + 2] cyclotrimerization required a completely selective reaction of alkyne **9**, **11**, and **12** forming **13**. The TMS group of commercial methylenediyne **12** serves two purposes: slowing a rapid homotrimerization of this least hindered alkyne reactant down and serving as a masked allene in the later arene for a subsequent allenic Pauson−Khand reaction. Diynylboronate **9** was prepared from TMS acetylene dimer **8** according to a modified literature procedure.[16] The boronic ester moiety of **9** serves both as dynamic temporary tether[15d−f] and as a chlorine synthon in the later arene. The chiral propargylic alcohol **11** was synthesized from Weinreb amide **10**.[17] Addition of lithium trimethylsilyl acetylide and subsequent transfer hydrogenation with Noyori's Ts-dpen-ruthenium catalyst gave **11** in 96% *ee* and 90% overall yield.[18] Mixing of diynylboronate **9** with secondary propargyl alcohol **11** should lead to a boronate ester exchange giving **14** and isopropanol. Triyne **14** should now be a competent substrate for the initial ruthenacyclopentadiene formation providing **15**. With the bulky trimethylsilyl group adjacent to the ruthenium atom, terminal alkynes should coordinate selectively and react in productive manner. An orientation of **12** away from this guiding TMS-group (**16** preferred over **17**) would ensure the required regioselective insertion of the third alkyne component. Indeed, the addition of **12** and Cp*Ru(cod)Cl to a premixed solution of **9** and **11** in dichloroethane provided 59% isolated yield (67% brsm of **11**) of arene **13** as single regioisomer. The boronic acid handle of **13** was subsequently oxidized with CuCl and NCS installing the required chlorine substituent (Scheme 3).[19] Treatment of **18**

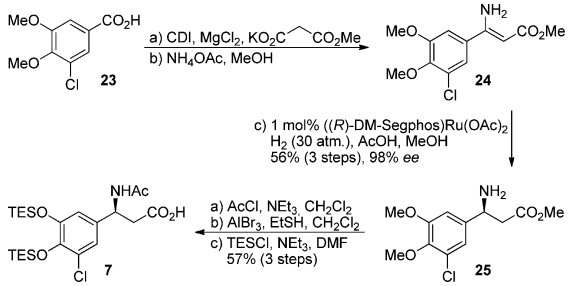
Scheme 3. Completion of Carbocyclic Fragment 22



with excess of TBAF removed all silyl groups and triggered the expected rearrangement of the propargyl group into the terminal allene.[20] Allene-yne **19** is rather unstable and protection of the hydroxyl groups gave a better efficiency in the subsequent allenic Pauson−Khand reaction.[21] Brief exposure of the silylated diol of **19** to $Mo(CO)_6$ gave indenylcyclopentenone **20**. Sharpless dihydroxylation highly selectively dihydroxylated the indenyl double bond in good yields; however with almost no facial selectivity.[22,23] The obtained diol was subsequently monotosylated at the secondary benzylic hydroxyl group giving **21**. Selective removal of the primary TBS group under acidic conditions provided carbocyclic fragment **22**, separated at this stage from its diastereomer **22b**.

The preparation of the required β-amino acid fragment **7** proceeded smoothly, starting from substituted benzoic acid **23** (Scheme 4). Conversion to the corresponding β-keto ester and

Scheme 4. Synthesis of the β-Amino Acid Building Block 7



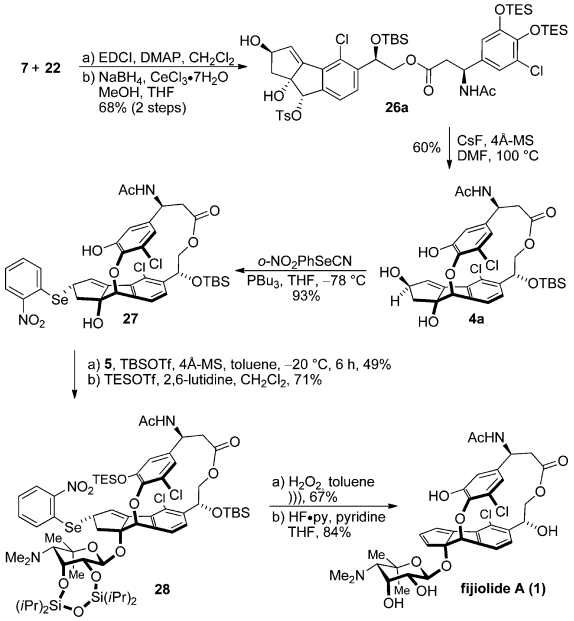
subsequent treatment with ammonia gave enamine **24** in virtually quantitative yield. Direct enantioselective reduction of unprotected **24** was achieved using ((*R*)-DM-Segphos)Ru(OAc)$_2$ and provided β-amino ester **25** in 98% *ee*.[24] Acetylation, followed by global methyl group removal with $AlBr_3$/EtSH[25] and silylation of the intermediate catechol gave β-amino acid fragment **7**.

EDCI mediated coupling of alcohol **22** and β-amino acid **7**, followed by a directed diastereoselective reduction of the enone

DOI: 10.1021/jacs.5b07964
J. Am. Chem. Soc. 2015, 137, 11278−11281

moiety to the secondary allylic alcohol yielded the macrocyclization precursor **26a** (Scheme 5). Subsequent exposure of

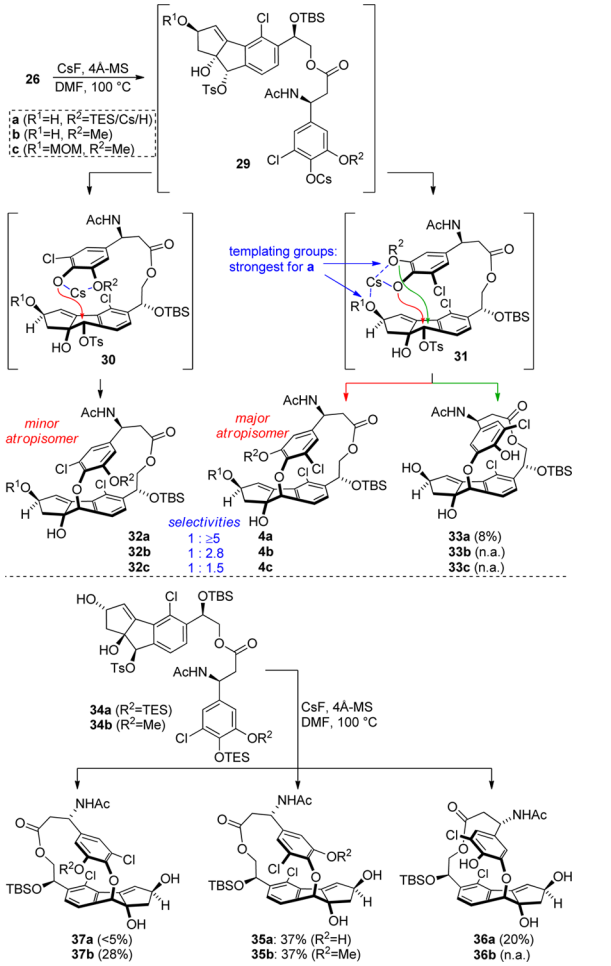
Scheme 5. Fragment Assembly and Completion of the Synthesis



26a to cesium fluoride in DMF at 100 °C cleaved at first both phenolic TES groups and induced then an intramolecular cyclization to give the desired cyclophane **4a** in 60% isolated yield. Notably, **4a** is formed in an atrop- and regioselective manner.[12] We engineered this selectivity in the [2.6]-paracyclophane formation with both free hydroxyl groups that are not involved in the S_N2 displacement event. The free allylic and phenolic hydroxyl groups are believed to coordinate the cesium cation leading to a preorganized intermediate, thus facilitating cyclization (*vide infra*, Scheme 6). Such favorable interaction would be absent for the formation of undesired atropisomer **32** via intermediate **30**. We were not able to isolate **32a**. However, the corresponding [2.6]metacyclophane **33a** was found as a minor byproduct in 8% yield with a catechol orientation arising from the same template effect during cyclization.

For the completion of the synthesis, various elimination attempts of the secondary allylic hydroxyl group of **4a** to provide the cyclopentadieneol functionality were not fruitful (Scheme 5). Additional results from model systems pointed toward the free tertiary hydroxyl group as the major issue causing the poor stability. In consequence, fijiolide A aglycon or another glycosyl acceptor with a cyclopentadieneol moiety might not be sufficiently stable for the glycosylation. A stepwise procedure turned out to be feasible. First, the most reactive allylic hydroxyl group was substituted by an *o*-nitrophenyl selenide for a later Grieco elimination providing **27**. The remaining hindered tertiary alcohol could be now glycosylated with the required Schmidt donor **5**.[13] We found that **5** has significantly higher stability (and shelf life) in toluene than in more commonly employed solvents such as ether or dichloromethane. However, the classical activation with TMSOTf led to silylation of the tertiary alcohol. This outcome was attributed to the amino sugar **5**, carrying a built-in base. Neither glycosylated product nor any silylation of the free phenolic hydroxyl group was observed. We

Scheme 6. Studies of the Templated Atropselective [2.6]Paracyclophane Formation



anticipated that the unprotected phenol moiety would be tolerated. Executing the glycosylation reaction with TBSOTf instead of TMSOTf as activating Lewis acid completely suppressed the parasitic silylation reaction, while still efficiently activating the glycosyl donor. With these conditions, glycosylated compound **28** was obtained exclusively as the desired β-anomer. With the blocked tertiary hydroxyl group, the Grieco elimination was attempted next.[26] Typically allylic selenoxides undergo seleno-Mislow-Evans [2,3]-sigmatropic rearrangements to provide allylic alcohols.[27] Indeed, this behavior was observed with the common oxidation/solvent systems, giving at best a 1:1 mixture of the desired elimination product and material tentatively assigned as the corresponding allylic alcohol. However, a biphasic reaction mixture (toluene/30% H_2O_2) mitigated the rearrangement pathway and selectively promoted elimination. Neither oxidation of the dimethylaminogroup nor the formation of the allylic alcohol was detected. Global desilylation proceeded with HF·pyridine. In its protonated form as the TFA salt, synthetic **1** matched the spectra obtained by Fenical et al. for natural fijiolide A.[4,28]

To obtain further insights on the origin and magnitude on the observed template effect for the atropselective cyclophane formation, substrates related to **26a** were evaluated under similar conditions (Scheme 6). Blocking the nonreacting phenolate as methyl ether (**26b**), less coordination of the cesium cation would be expected. Indeed, although the cyclization proceeded well, a

DOI: 10.1021/jacs.5b07964
J. Am. Chem. Soc. 2015, 137, 11278–11281

modest atropselectivity (**4b**/**32b** = 2.8:1) was observed. Moreover, additional protection of the allylic hydroxyl group as MOM ether (**26c**) reduced the atropselectivity further (**4c**/**32c** = 1.5:1). The influence of the stereogenic centers of the tether on the atropselectivity was investigated as well with diastereomers **34a** (R = TES/H) and **34b** (R = Me). Both underwent macroetherification under similar conditions. For **34a**, predisposed for the cation templated cyclization, the anticipated atropisomer paracyclophane **35a** (37%) was formed along with metacyclophane **36a** (20%), again as the expected atropisomer. The other atropisomer **37a** could not be isolated. In contrast, **34b** with a blocked phenolic OH group cyclized with a poor atropselectivity of 1.3:1 (**35b**/**37b**).

In summary, we report here an enantioselective synthesis of fijiolide A in 18 steps in the longest linear sequence and 36 total steps including the 11 steps for the preparation of the glycosyl donor. The synthesis showcases the power of ruthenium-catalyzed intermolecular cyclotrimerizations to selectively construct heavily substituted arenes. Another salient feature is the demonstration of controlled atropselective macroetherification reaction to access the strained paracyclophane core of fijiolide A. The modular synthesis strategy allows now accessing analogues to further explore the biological activities of this substance class.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07964.

Synthetic procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Professor William Fenical for sharing the NMR FID data of fijiolide A. We thank the Ecole Polytechnique Fédérale de Lausanne for supporting this work and Guillaume Magnin for help in the preparation of **7** and **20**.

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DOI: 10.1021/jacs.5b07964
J. Am. Chem. Soc. 2015, 137, 11278−11281