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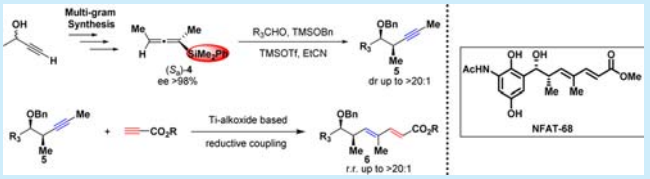
Total Synthesis of Nuclear Factor of Activated T-Cells-68 (NFAT-68): Sequential Use of Chiral Allenylsilane and Titanium Alkoxide-Mediated Reductive Coupling Bond Construction

Bin Cai, Ryan W. Evans,[†] Jie Wu,[‡] and James S. Panek*

Department of Chemistry, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: Highly enantioenriched chiral allenylsilanes **4** were prepared in high yield through a scalable synthetic sequence, employing a modified copper-catalyzed S_N2' reaction. These reagents were used for the production of enantioenriched homopropargylic ethers **5**, which were subjected to titanium alkoxide-mediated reductive coupling with acetylenic esters to produce (*E*,*E*)-dienes **6** bearing $\alpha,\beta,\gamma,\delta$-unsaturated esters. Both enantiomers of nuclear factor of activated T-cells-68 (NFAT-68) were synthesized in five steps with the sequential use of the two methods.



Immunosuppressant drugs such as cyclosporine A and fujimycin target the inhibition of T-cell activation by preventing the activation of the nuclear factor of activated T-cells (NFAT-68) transcription factor.[1] In 1995, the New Lead Discovery group from AbbVie (formally Abbott Laboratories) isolated a new polyketide natural product NFAT-68 (Figure 1)

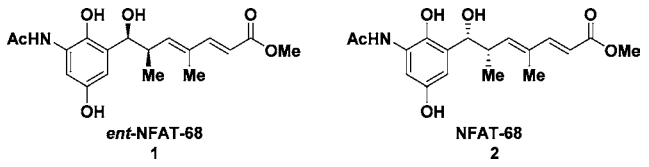


Figure 1. Enantiomers of NFAT-68.

from the broth and mycelia of two *Streptomyces* sp. fermentations.[2] That molecule displayed potent in vitro immunosuppressive activity with an IC_{50} concentration <1 μg/mL and no cytotoxicity observed at that concentration. In the original isolation paper, neither the absolute nor the relative stereochemistry of the C6 methyl group and the C7 hydroxyl group was established. Recently, the Yang group[3] reported the first synthesis of both enantiomers of NFAT-68 utilizing a chelation-controlled vinylogous Mukaiyama aldol reaction originally developed by the Kobayashi group,[4] which resulted in the elucidation of a *syn* stereochemical relationship between the C6 methyl group and the C7 hydroxyl group.

We have had a longstanding interest in developing and utilizing organosilane reagents as versatile carbon nucleophiles in natural product and diversity-oriented synthesis.[5] In that context, chiral allenylsilanes[6] have proven to be useful carbon nucleophiles in acyclic stereocontrol to produce homopropargylic alcohols,[7] ethers,[6a] and sulfonamides[6b] with complete transfer of axial chirality to point chirality and moderate to high *syn* selectivity. In this report, we described the use of chiral allenylsilanes (S_a)-**4** (Figure 2) and its enantiomer (R_a)-**4** (not

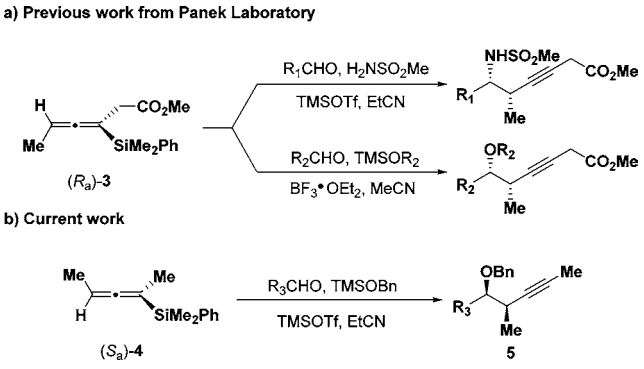


Figure 2. Complementary chiral allenylsilane reagents.

shown), evaluated their reactivity in additions to in situ generated oxonium ions for the direct formation of stereochemically well-defined homopropargylic ethers, and applied the allenes as chiral nucleophiles in the synthesis of both enantiomers of NFAT-68.

Recently, titanium-mediated alkyne−alkyne reductive coupling emerged as a useful method for the construction of stereodefined (*E*,*E*)-diene embedded in natural products and pharmaceutically important targets.[8] In particular, the Micalizio group[9] and our group[5h,i] demonstrated the utility of such chemistry in several complex molecule syntheses, featuring highly convergent approaches without the need to generate preactivated and/or prefunctionalized coupling partners. However, the reductive coupling between internal alkynes bearing

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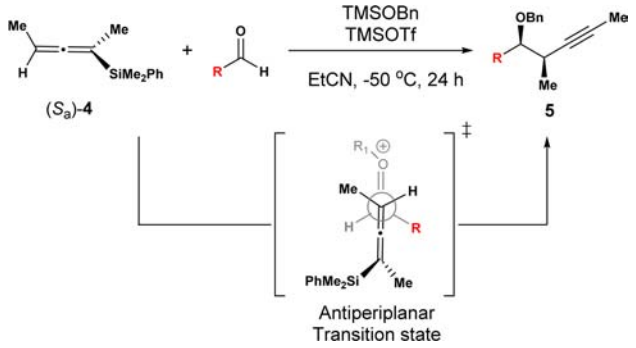
sterically encumbered environments and electronically activated terminal alkynes bearing acetylenic esters has not been explored in the context of reactivity, reaction regioselectivity, and application in natural product synthesis.[10]

Herein, we report the results of our investigation of titanium-mediated reductive coupling between functionalized internal alkynes and acetylenic esters and application of newly generated allenylsilanes, in the context of the total synthesis of both enantiomers of NFAT-68.

The study was initiated by establishing the reactivity and selectivity of chiral allenylsilane (S_a)-**4** in asymmetric three-component propargylation reactions. Taking advantage of our previous synthesis of (R_a)-**3**[6a] and a modified S_N2' addition reaction,[11] we were able to obtain multigram quantities (>30 g prepared in one synthetic sequence) of (S_a)-**4** and (R_a)-**4** in a four-step sequence with high yield and >98% ee (see Supporting Information for details). With multigram quantities of (S_a)-**4** in hand, we proceeded to evaluate the asymmetric three-component propargylation reactions between (S_a)-**4**, aldehydes, and (benzyloxy)trimethylsilane. A screen of the combination of Lewis acid, solvent, and stoichiometry of Lewis acid identified 0.5 equiv of TMSOTf and propionitrile as the optimal combination of reagents. Once the conditions were determined, a range of aldehydes were evaluated to probe the reaction scope (Table 1).

Table 1. Asymmetric Three-Component Propargylation with (S_a)-4



entry	aldehyde	5	yield (%)[a]	dr[b]
1	benzaldehyde	**5a**	75	3.5:1
2	3-bromobenzaldehyde	**5b**	85	3.3:1
3	2-bromobenzaldehyde	**5c**	81	4.0:1 (10:1)[c]
4	4-fluorobenzaldehyde	**5d**	52	4.0:1
5	2,5-dimethoxybenzaldehyde	**5e**	78	3.0:1
6	*o*-tolualdehyde	**5f**	51[d]	>20:1
7	cyclohexanecarbaldehyde	**5g**	86	>20:1
8	isobutyraldehyde	**5h**	75	>20:1
9	isovaleraldehyde	**5i**	66	3.0:1
10	pentanal	**5j**	65	2.0:1

[a]Isolated yields after chromatographic purification over silica gel. [b]Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis on crude material. [c]Diastereomeric ratio after column chromatography purification over silica gel. [d]Reaction performed with 1 equiv of TMSOTf at −40 °C.

As anticipated, *syn* products were produced as the major diastereomer with moderate to high levels of diastereoselectivities and yields, consistent with the well-documented antiperiplanar transition state,[6a] where the destabilizing interaction between the R group on the oxonium ion and the methylene groups of the allene is minimized. In general, aromatic aldehydes with either activating or deactivating substituents afforded products with good yields but moderate diastereoselectivities (Table 1, entries 1−5), with the exception for *o*-tolualdehyde, with which *syn* product **5f** was obtained as the single diastereomer. On the other hand, reactions with aliphatic aldehydes afforded products with good yields and more predictable diastereoselectivies (Table 1, entries 7−10). Tertiary aliphatic aldehydes delivered **5g** with good yields and complete diastereoselectivity (Table 1, entries 7 and 8). As the tertiary center moved one carbon away, the diastereoselectivity dropped significantly with slightly lower yield (Table 1, entry 9). When the substrate was a straight chain aliphatic aldehyde, the diastereoselectivity decreased further (Table 1, entry 10).

As the three-component propargylation reaction with (S_a)-**4** was established, we next sought to investigate the titanium-mediated reductive coupling between the propargylation products and acetylenic esters with the anticipation that it would be used in a successful synthesis of NFAT-68. At the outset, we anticipated that the reductive coupling with electronically activated acetylenic esters would exhibit reactivity very different than that with electronically neutral terminal alkynes. Indeed, after extensive reaction optimization, it was found that lower reaction temperature and prolonged reaction time (a modification of Micalizio's conditions for alkyne−alkyne reductive coupling[11b,12]) were essential for efficient generation of the presumed titanocyclopropene complex and subsequent coupling with acetylenic ester. With the optimized conditions, we then explored the internal alkyne substrate scope. Generally, moderate yields and moderate to excellent regioselectivities were achieved with slightly higher yields and cleaner reactions for internal alkynes bearing aliphatic substituents (Scheme 1, entries 6−9). The yields were moderate presumably due to the instability and/or incomplete formation of the metallacycle intermediate. Interestingly, the observed regioselectivity with aromatic and aliphatic terminal alkynes exhibited an interesting dependence on the substitution patterns of the aromatic reaction partners (Scheme 1, entries 1−5) and the steric bulk near the reacting centers for aliphatic reaction partners (Scheme 1, entries 6−9). Notably, the *para*-fluoro substrate afforded homopropargylic ether **6e** with high regioselectivity (Scheme 1, entry 5), which was only observed for Ti-based alkyne−alkyne reductive coupling reactions employing alkoxide as a directing group[13] or TMS[10] as a bulky substituent to influence the regiochemical course. In addition, aliphatic substrates bearing tertiary carbons rendered products **6h** and **6i** with complete regioselectivity (Scheme 1, entries 8 and 9). Lastly, variation on the steric bulk of the ester group on the terminal alkyne was also explored, and the regioselectivity also appeared to depend on the steric environment of the terminal alkyne. Changing from a methyl ester to an ethyl ester group exhibited a 2-fold enhancement of selectivity, while the substitution with a *t*-butyl group led to complete conversion to a single regioisomer (Scheme 1, entries 10 and 11).

The observed steric effects on the regiochemical course of Ti-based reductive coupling reactions may be rationalized by the empirical models depicted in Figure 3. Exposure of internal alkyne to Ti(II) species, generated in situ by reduction of $ClTi(OiPr)_3$ by cC_5H_9MgCl, leads to the presumed titanocyclopropene complex **I**.[8a,12] A classic Newman projection maybe utilized to aid in analysis by viewing down the C4−C5 bond of metallacycle **I**, where the $A^{1,3}$ strain is minimized and the lowest energy conformation is presented by minimizing gauche interactions between the C4 and C5 substituents. Importantly, this open transition state analysis results in the position of the R

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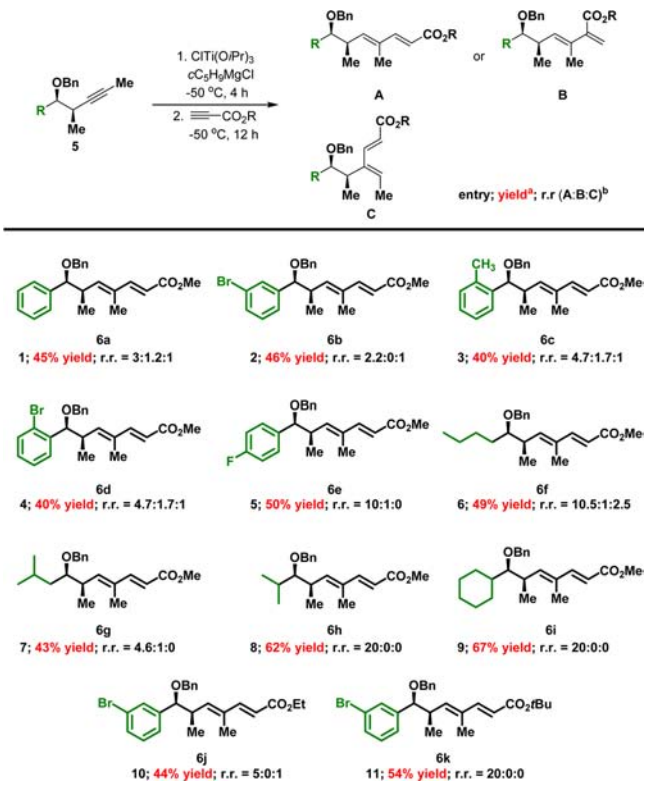
Scheme 1. Alkyne−Alkyne Reductive Coupling with Acetylenic Esters



[a]Combined yields of all regioiosmers after chromatographic purification over silica gel. [b]Regioselectivity was based on the analysis of the crude ^{1}H NMR spectra; r.r. = ratio of regioselectivity.

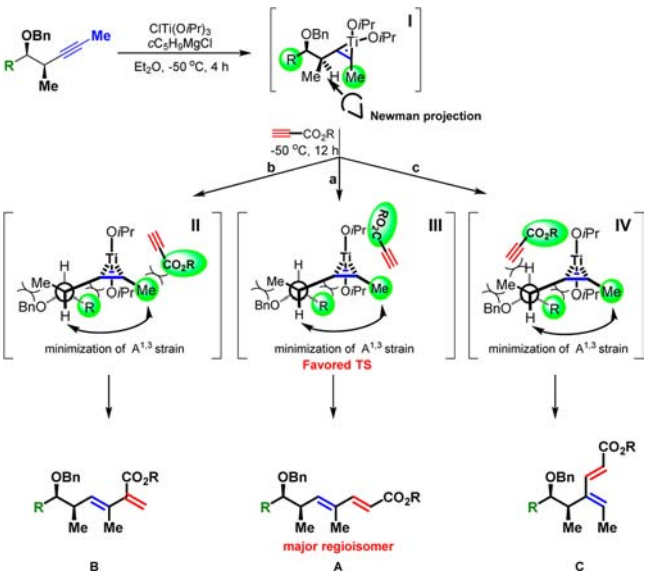
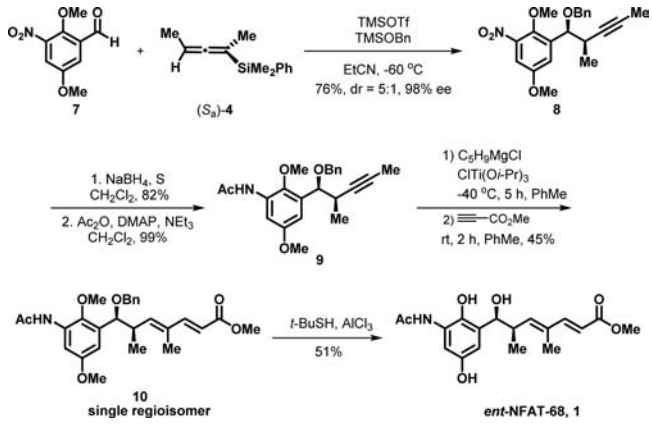


Figure 3. Empirical transition state models for regiochemical course of reductive coupling.

group from an internal alkyne in proximity to the titanium reaction center, and thus the steric bulk or the position of substituent on the aryl ring of the R group could potentially affect the steric environment of the titanium reaction center. Subsequent intermolecular carbometalation between metallacycle **I** and acetylenic ester is anticipated to proceed through three distinct pathways (Figure 3, A, B, and C), resulting in three transition states (Figure 3, II, III, and IV), and deliver three titanocyclopentene complexes (not shown),[8a] which upon hydrolytic quench form three regioisomers. In the present case, regiosiomer **A** is formed as the major isomer because transition state III has the fewest destabilizing steric interactions and thus is energetically favored.

With both the propargylation and reductive coupling reactions established, we applied the two methods to the total synthesis of both enantiomers of NFAT-68 (Scheme 2). The three-

Scheme 2. Total Synthesis of NFAT-68



component propargylation reaction between aldehyde **7**, (benzyloxy)trimethylsilane, and chiral allenylsilane (S_a)-**4** produced internal alkyne **8** with good yield and diastereoselectivity. The ee of alkyne **8** was determined to be 98% by chiral HPLC analysis (see Supporting Information for details). The arylnitro group of alkyne **8** was reduced by in situ generated sulfurated borohydride $NaBH_2S_3$ to afford alkynyl aniline **8a** (not shown here),[14] which was subsequently *N*-acylated to yield alkyne **9**. Originally, we adopted the above optimized condition for reductive coupling between **9** and methyl propiolate. However, to our surprise, we did not obtain the desired coupled product. After considerable effort, we learned that excess Grignard reagent (6 equiv) was essential for the efficient generation of a titanocyclopropene complex and increased temperature (room temperature) was required to drive the intermolecular carbometalation process to completion. Thus, a solution of alkyne **9**, $ClTi(OiPr)_3$ (2 equiv), and cC_5H_9MgCl (6 equiv) in toluene was subjected to −40 °C for 5 h to generate the metallacycle complex, after which methyl propiolate was added, and the mixture was warmed to room temperature, at which time the reaction proceeded for another 2 h before being stopped. This experiment showed that the coupled product **10** was formed as a single regioisomer with moderate yield. Subsequent global deprotection[3] of diene **10** afforded *ent*-NFAT-68 cleanly with a 51% isolated yield. NFAT-68 was synthesized starting from chiral allenylsilane (R_a)-**4** in the same manner. In summary, both enantiomers of NFAT-68 were synthesized in five steps with a 14% overall yield starting from chiral allenylsilanes (S_a)-**4**.

In conclusion, highly enantioenriched chiral allenylsilanes (S_a)-**4** and (R_a)-**4**, generated in scalable four-step and five-step sequences, respectively, have been applied in the asymmetric three-component propargylation to give access to *syn* homopropargylic ethers **5**. The reactivity and selectivity of the titanium-mediated alkyne−alkyne reductive coupling between these internal alkynes and electronically activated acetylenic esters were studied to expand the scope of this bond

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construction. Accordingly, the convergent total synthesis of both enantiomers of NFAT-68 was achieved in five steps with a 14% overall yield. In addition, the diene products from Scheme 1 may be suitable for a future SAR study of NFAT-68 with respect to its immunosuppressive activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02052.

Experimental procedures and spectroscopic data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: panek@bu.edu.

Present Addresses

†Department of Chemistry, Princeton University, Princeton, NJ 08544.

‡Department of Chemistry, National University of Singapore, Block S15, Level 5, 15-05-02, 3 Science Drive 2, Singapore, 117543.

Notes

The authors declare no competing financial interest.

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