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Total Synthesis and Bioactivity Studies of Fungal Metabolite (−)-TAN-2483B

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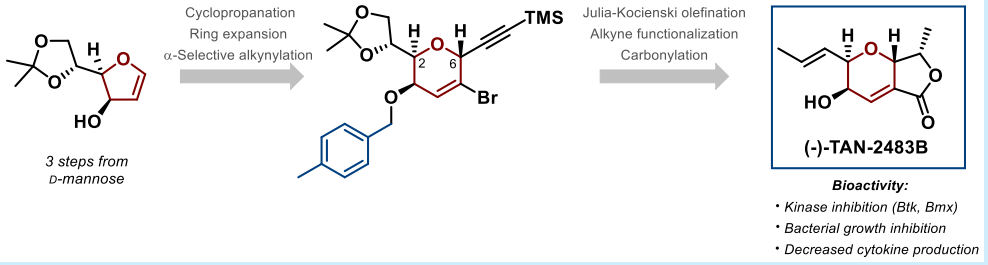

ABSTRACT: The first total synthesis of (−)-TAN-2483B, a fungal metabolite possessing a densely functionalized furo[3,4-*b*]pyran-5-one framework, is achieved in 14 steps from D-mannose. Generation of the 2,6-*trans*-pyran is by cyclopropane ring expansion followed by α-selective alkynylation. Julia−Kocienski olefination introduces the *E*-propenyl side chain. Alkyne functionalization and carbonylation stereoselectively establish the bicyclic core of (−)-TAN-2483B. Inhibition of kinases Btk and Bmx, bacterial priority pathogens, and cytokine production in splenocytes indicates promising therapeutic potential.

The furo[3,4-*b*]pyran-5-one natural product (−)-TAN-2483B (**1**) was discovered in fungal fermentation cultures in conjunction with its epimer, (−)-TAN-2483A [**2** (Figure 1)].[1,2] TAN-2483A was reported to inhibit *c*-Src kinase and

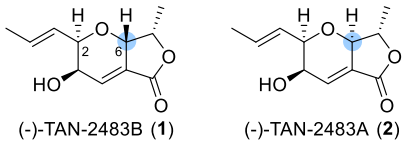

Figure 1. Structures of (−)-TAN-2483B (**1**) and (−)-TAN-2483A (**2**).

PTH-induced bone resorption,[1] while a 3:1 mixture of TAN-2483A and TAN-2483B exhibited bacterial inhibitory and immunomodulatory activity.[2] Related fungal natural products, including the scirpyranes, thiessenolactones, waols, massarilactones, isoaigilones, and fusidilactones,[3−8] display various biological activities, including antitumor, anti-inflammatory, and antibacterial properties. No bioactivity has been recorded for pure (−)-TAN-2483B (**1**).

An aldol-based synthetic approach to several of these compounds has been developed by Snider and co-workers,[9] and the furo[3,4-*b*]pyran-5-one ring system has also been constructed by [2+2] reactions of dihydropyrans, including glycals, with ketenes,[10] and by multicomponent couplings.[11] Related fungal natural products, the dinemasones,[12] containing a pyrano[4,3-*b*]pyran-5-one scaffold, have also been synthesized.[13] The unusual 2,6-*trans*-configured pyran of (−)-TAN-2483B has made the previous synthetic methods unsuitable for gaining access to this natural product, and its total synthesis has remained elusive. We have reported the application of cyclopropane approaches to the syntheses of the natural product core[14] and side-chain analogues[15] of (−)-TAN-2483B. However, our previous efforts to install the *E*-propenyl side chain of the natural product proved to be unfruitful.[15] We now disclose our successful completion of the first total synthesis of (−)-TAN-2483B and initial studies of its biological activity.

Our synthetic approach relies upon ring expansion of a cyclopropyl carbohydrate, formed from D-mannose-derived glycal **3**,[16] α-selective alkynylation, and carbonylative lactonization to generate the furo[3,4-*b*]pyran-5-one core (Scheme 1). While Wittig, Takai, and Julia−Kocienski olefinations previously failed to install the *E*-propenyl side chain,[15] extensive optimization efforts with the latter method have recently led to success in appending the side chain. The protection strategy also proved to be challenging, because a robust protecting group was necessary during the synthetic

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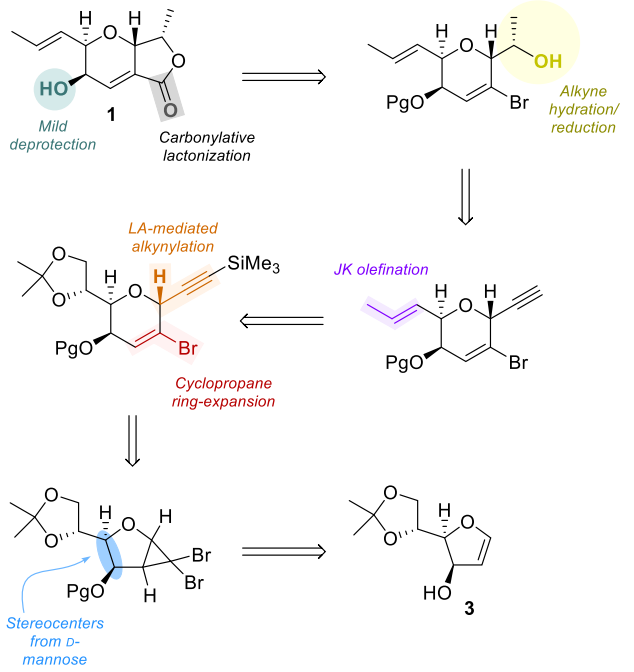
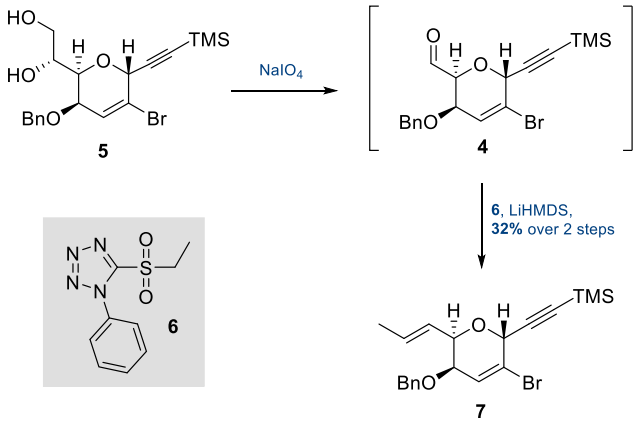
Scheme 1. Retrosynthetic Strategy for (−)-TAN-2483B (1)



route, yet the final product was highly sensitive to many deprotection conditions. This Letter documents these challenges and the successful culmination of efforts to address them.

Construction of the *E*-propenyl side chain of the natural product (−)-TAN-2483B had previously evaded us.[15] Attempts to perform Julia−Kocienski reactions with aldehyde **4**, obtained by periodate cleavage of diol **5** (Scheme 2),[15] using

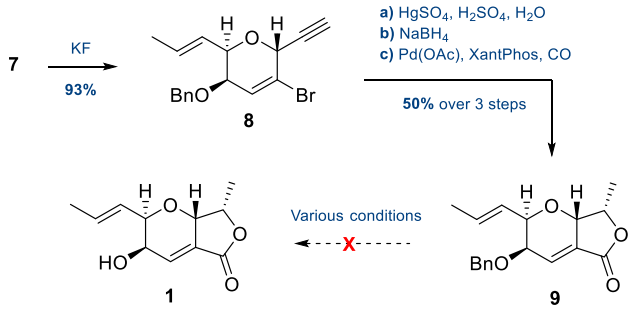
Scheme 2. Attachment of the *E*-Propenyl Side Chain



ethyl 1-phenyl-1*H*-tetrazol-5-yl sulfone (**6**) and LiHMDS or KHMDS in THF led to degradation and mixtures from which neither the desired product nor recovered starting material could be obtained. Likewise, Wittig reactions with ethyltriphenylphosphonium iodide were unsuccessful. A Takai−Utimoto reaction involving 1,1-diiodoethane and $CrCl_2$ led to a mixture of compounds containing *E*- and *Z*-propenyl side chains, according to NMR spectroscopy (Figure S1), but useful quantities of the desired *E*-olefin **7** could not be obtained. Eventually, extensive exploration of the Julia−Kocienski reaction (Tables S1−S3) revealed conditions that minimized base-induced degradation and isomerization of the enyne, thus reliably affording product **7** in satisfactory amounts. Ultimately, the best method involved slow addition of LiHMDS to a dilute solution of aldehyde **4** and sulfone **6** in DMF, which favored olefin formation over the base-mediated degradation that had previously made the reaction problematic, affording product **7** in a moderate yield.

Following desilylation of alkyne **7**, the alkyne moiety in **8** was converted into lactone **9** in a manner identical to that used in our synthesis of TAN-2483B side-chain analogues (Scheme 3).[15] Specifically, alkyne **8** underwent oxymercuration to afford

Scheme 3. Attempted Synthesis of (−)-TAN-2483B Using a Benzyl Protecting Group



the corresponding methyl ketone (54% yield). As in our previous studies with alternative side chains,[15] ketone reduction with sodium borohydride was stereoselective. On the basis of the spectral similarities of the analogues, it was determined that the reduction proceeded with substrate control corresponding to nucleophilic attack according to the polar Felkin−Ahn model.[17] The resulting alcohol engaged in a palladium-catalyzed carbonylation to deliver lactone **9** in 93% yield over two steps from the ketone. The deprotection of the benzyl ether, however, was not facile. Surprisingly, the Lewis acid method that proved to be successful with the analogues, viz., use of $TiCl_4$,[15] gave none of the anticipated product but caused degradation. An attempt to remove the benzyl protecting group with Raney nickel caused rapid reduction of the internal alkene, while a dissolving metal reduction (Na, naphthalene) caused extensive degradation. Oxidative cleavage of benzyl ethers using DDQ is notably sluggish compared to that with substituted variants such as *p*-methoxybenzyl ethers.[18] Nonetheless, this was attempted several times, and signals consistent with the structure of the desired product were observed in the NMR spectra of the crude reaction mixtures. Unfortunately, significant degradation also occurred over the unavoidably long reaction times, so pure TAN-2483B could not be isolated in sufficient quantities for follow-up.

At this point, it became evident that an alternative protecting group strategy was necessary to obtain the natural product (−)-TAN-2483B in reasonable amounts and high purity. Major considerations were the necessity for the protecting group to be stable in the basic cyclopropanation conditions, the Lewis and Bronsted acidic conditions of the alkynylation and oxymercuration, and the fluoride-promoted desilylation of the alkyne. A recent report of *p*-methylbenzyl (MBn) ethers as orthogonal variants of benzyl ethers caught our attention.[19] In particular, the observed rapidity of MBn cleavage by DDQ compared with that with benzyl ethers persuaded us that a change to this protecting group should enable more efficient deprotection while retaining the requisite stability under the

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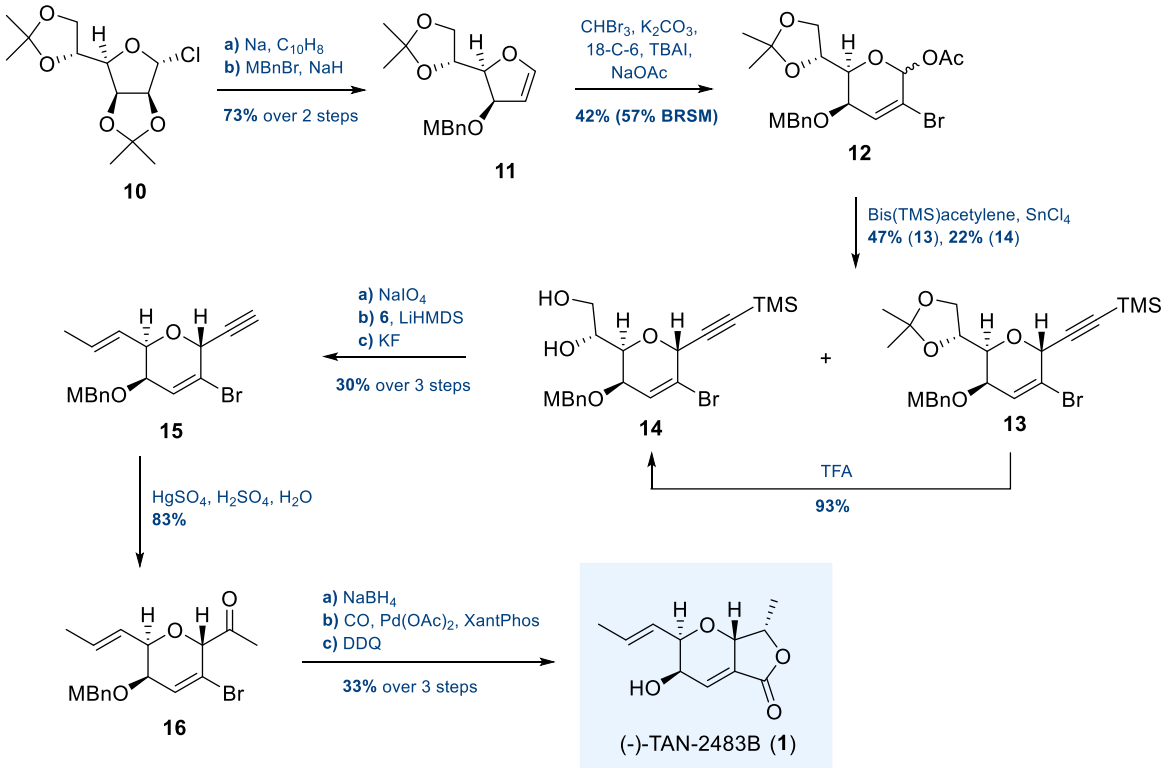
Scheme 4. Total Synthesis of (−)-TAN-2483B (1) Using a *p*-Methylbenzyl Protecting Group



diversity of conditions to which the protected intermediates would be exposed.

Accordingly, chloride **10**, which can be obtained in two steps from D-mannose,[16] was converted into MBn-protected glycal **11** in a manner similar to that used for the Bn-protected series[15] (Scheme 4). Cyclopropanation of **11** under conditions that allowed *in situ* ring expansion and nucleophilic attack by an acetate anion afforded glycosyl acetate **12** as a 7:3 mixture of anomers. Alkynylation of **12** according to the method of Isobe et al.[20] selectively provided the α-*C*-glycoside as a mixture of acetonide **13** (47%) and diol **14** (22%), with the α-configuration at the pseudoanomeric center assigned on the basis of spectral homology with the benzyl series.[15] Acetonide **13** was converted into diol **14** in high yield through acid-promoted deprotection. Oxidative cleavage of the diol produced an aldehyde, which was immediately subjected to a Julia−Kocienski reaction with **6** under the previously optimized conditions to append the propenyl side chain with high *E*-selectivity. The crude material was desilylated to afford terminal alkyne **15** in reasonable yield over three steps. Alkyne **15** then underwent oxymercuration to afford methyl ketone **16**. As before with the benzyl-protected material, reduction of the ketone with sodium borohydride was stereoselective for the *S*-isomer, based on spectral consistency with the earlier variants.[15] The resulting alcohol participated in a palladium-catalyzed carbonylative lactonization to afford MBn-protected TAN-2483B. Finally, DDQ-promoted deprotection delivered (−)-TAN-2483B (**1**) cleanly in 65% isolated yield. The spectroscopic and spectrometric data obtained from this material are consistent with the proposed structure and match those reported for the natural product. Namely, the specific rotation value obtained [−156 (*c* 0.09, $CHCl_3$)] was comparable with that reported [−135 (*c* 1.1, $CHCl_3$)];[1] the mass spectrum showed a molecular ion at *m*/*z* 228.1225 [calculated for $[M + NH_4]^+$, 228.1230 (Δ = 2.43 ppm)], and the ^{13}C NMR shifts matched those reported (Table S4).[1] The ^1H and ^{13}C NMR spectra obtained from our synthetic material match those of natural TAN-2483B (**1**), both from the original isolation[1,21] and from a mixture of **1** and **2**.[2,22]

No biological data have been reported previously for (−)-TAN-2483B, except as the minor component of a mixture with its epimer, (−)-TAN-2483A,[2] so analysis of its bioactivity remains a topic of interest. The synthetic sample of (−)-TAN-2483B (**1**) was subjected to a full kinome assay using the ThermoFisher SelectScreen assay with a panel of 485 human disease-relevant kinases (Tables S5−S8). At 10 μM, the only kinases inhibited by >50% were the highly homologous Btk (Bruton's tyrosine kinase, 74% inhibition, IC_{50} of 5.1 μM) and Bmx (bone marrow tyrosine kinase on chromosome X, 74% inhibition, IC_{50} of 2.7 μM), indicating potential applications in inflammatory and oncological disorders.[23] These kinases, among others, were also inhibited by our side-chain analogues of (−)-TAN-2483B.[15] No inhibition of Src by **1** was observed at 10 μM, which contrasts with the reported[1] inhibition of this kinase by (−)-TAN-2483A and indicates distinct selectivity profiles for these epimeric natural products.

A 3:1 mixture of (−)-TAN-2483A and (−)-TAN-2483B was previously found to be active against Gram-negative *Escherichia coli* but not Gram-positive *Staphylococcus aureus*.[2] Effective antibiotics against Gram-negative pathogens are needed,[24] so our sample of pure (−)-TAN-2483B (**1**) was tested in this context. The previous study[2] used a *tolC* mutant (*E. coli* MB 5746); TolC-mediated efflux is a primary defense mechanism for Gram-negative bacteria,[25] imparting up to four logs of protection against otherwise promising drug candidates.[26] Therefore, the activity of **1** toward several *E. coli* strains was measured, specifically a *tolC* knockout (93% growth inhibition at 200 μM), wild-type *E. coli* BW25113 (73% inhibition), and a

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drug resistant clinical isolate *E. coli* ARL 06/624 (47% inhibition) (Figure 2). These results demonstrate that TolC

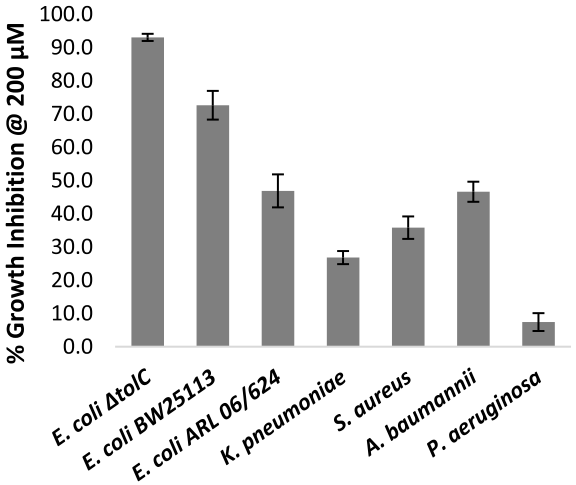

Figure 2. Growth inhibition of ESKAPE pathogens by (−)-TAN-2483B.

imparts at most marginal protection against **1**, while the clinical isolate is also sensitive to **1**, albeit less so than the lab strains. IC_{50} assays across a 2-fold dilution series confirmed the inhibition of these *E. coli* strains by (−)-TAN-2483B (Table 1). Further antibacterial effects were assessed by testing

Table 1. Inhibition of *E. coli* Strains by (−)-TAN-2483B (IC_{50} data)

bacterium	IC_{50} (μM)
E. coli BW25113 Δ*tolC*	61 ± 10
E. coli BW25113	140 ± 20
E. coli ARL 06/624	210 ± 16

compound **1** against Gram-negative ESKAPE pathogens that the World Health Organization views with particular concern,[27] with Gram-positive *S. aureus* included for comparison. At 200 μM, modest inhibitory activity by compound **1** was observed. *Acinetobacter baumannii* growth inhibition (47%) was similar to that of the *E. coli* clinical isolate (Figure 2). Some inhibition of *S. aureus* growth (36%) by compound **1** was also noted, whereas the mixture of **1** and **2** had previously not inhibited its growth;[2] this may reflect a differential activity by the stereoisomers toward this Gram-positive bacterium, combined with the small proportion of **1** present in the mixture of the earlier study.[2]

A 3:1 mixture of TAN-2483A and TAN-2483B was previously shown to inhibit NO production in LPS-stimulated mouse macrophages (IC_{50} of 2.26 μM), indicating anti-inflammatory potential.[2] In our studies, to determine the effects on primary immune cells (T and B lymphocytes), mouse splenocytes were stimulated for 48 h with concanavalin A (ConA; T cell mitogen) or LPS (B cell mitogen) or left unstimulated. Incubation of these cell populations with TAN-2483B (**1**) showed that compound **1** is toxic to splenocytes (stimulated or not) with IC_{50} values of 3.5−4.4 μM as assessed by the MTT assay (Table 2 and the Supporting Information).[28] Interleukin (IL)-6, interferon (IFN)-γ, and nitric oxide (NO) production was measured in the supernatants of ConA-stimulated splenocyte cultures[28,29] and showed inhibition by

Table 2. Effect of TAN-2483B on the Viability of Primary Immune Cells and Production of IL-6, IFN-γ, and NO

	inhibition by TAN-2483B [IC_{50} (μM)]			
	cell viability	IL-6 production	IFN-γ production	NO production
unstimulated	3.5			
ConA-stimulated	4.4	0.99	0.73	0.42
LPS-stimulated	4.2			

TAN-2483B at concentrations (IC_{50} of 0.99−0.42 μM) well below those found to be cytotoxic.

The conjugated unsaturated lactone of TAN-2483B may implicate broad-spectrum Michael acceptor activity.[9b] Indeed, from the preliminary results described herein, and also with our side-chain analogues,[15] cytotoxicity is evident. Nevertheless, the variable activity between bacterial strains and the selectivity in kinase inhibition indicate modulation of bioactivity that may preclude a pan-assay reactive feature.

In summary, the first total synthesis of the fungal metabolite (−)-TAN-2483B (**1**) has been achieved in 12 steps from chloride **10**. The synthetic strategy relies on a cyclopropyl ring expansion to create the pyran ring, stereoselective alkynylation of a glycoside, a Julia−Kocienski reaction to append the side chain, and carbonylative lactonization to form the furanone ring. Key to the success of our synthesis were application of the 4-methylbenzyl protecting group and its ready deprotection with DDQ, which avoids the orthogonality issues with hydrogenolytic and acid-promoted methods required to remove the corresponding benzyl ether. A preliminary biological profile has been generated. (−)-TAN-2483B is found to selectively inhibit the structurally homologous kinases Btk and Bmx. Modest inhibitory activity against Gram-negative pathogens, with little susceptibility to TolC-mediated drug efflux and resistance, is noted. TAN-2483B inhibits IL-6, IFN-γ, and NO production in primary immune cells.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03303.

FAIR data, including the primary NMR FID files, for compounds **1** and **11**−**16** (ZIP)

Experimental details for chemical reactions and biological assays, characterization data and NMR spectra for all new compounds, and kinase and immune assay results (PDF)

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Author Contributions

Experimental chemistry work was performed by J.A.J.M., K.K.S., and C.L.O. Biological assays were conducted by K.R.H., E.-R.G., and A.C.L.F. Synthetic strategy development was by J.E.H., K.K.S., J.A.J.M., and R.J.H. The manuscript was written by J.E.H. and J.A.J.M., with contributions from K.R.H., D.F.A., and A.C.L.F. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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