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Tandem Diels–Alder/Fragmentation Approach to the Synthesis of Eleutherobin

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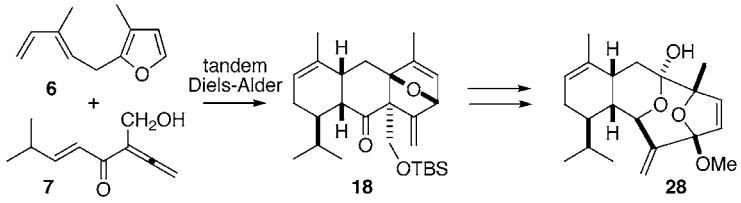
ABSTRACT



A synthesis of 28, the carbon framework of the eleutherobin aglycone, is reported in a 15-step sequence from readily available starting materials. The tandem Diels–Alder reaction of 6 and 7 to produce 18, in which three new rings and six new stereocenters are formed, is a key step in the reaction sequence.

The antitumor activity of eleutherobin, **1** (Scheme 1), a structurally complex diterpene glycoside first isolated in low yield (0.01−0.02%) from a rare alcyonacean coral *Eleutherobia* sp.,[1] compares favorably to that of Taxol, the most widely used cancer chemotherapeutic agent in the United States. Eleutherobin competes with Taxol for binding to microtubules, inhibiting their depolymerization and thereby preventing division of cancer cells.[2] Eleutherobin displays an in vitro cytotoxicity of 10−15 nM against a diverse panel of NIH tumor cell lines and a ca. 10^2-fold increased selectivity relative to that of Taxol.[1a]

The structural complexity, biological significance, and limited availability of **1** have attracted the interest of synthetic laboratories around the world,[3] culminating in the total syntheses of eleutherobin by the laboratories of Nicolaou[4] and Danishefsky.[5] We describe herein a conceptually novel approach to the synthesis of the tricyclic framework of **1**,

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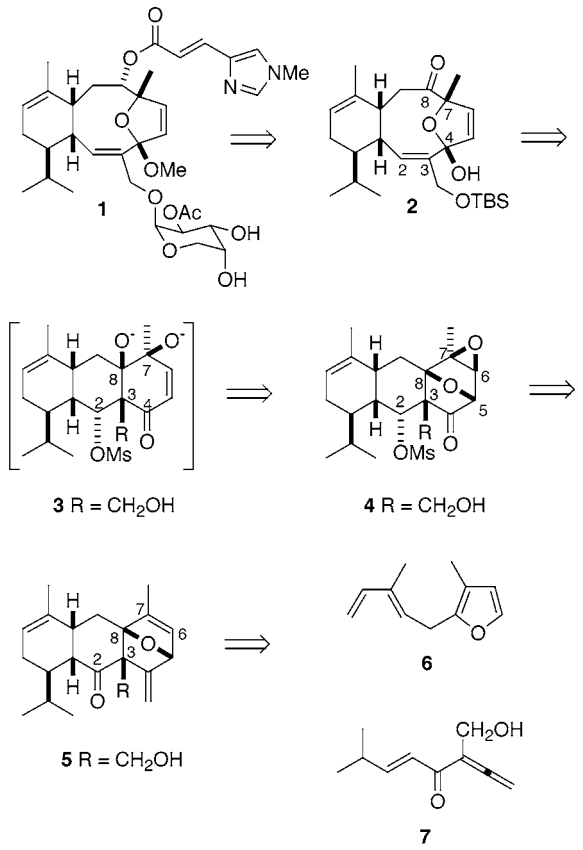
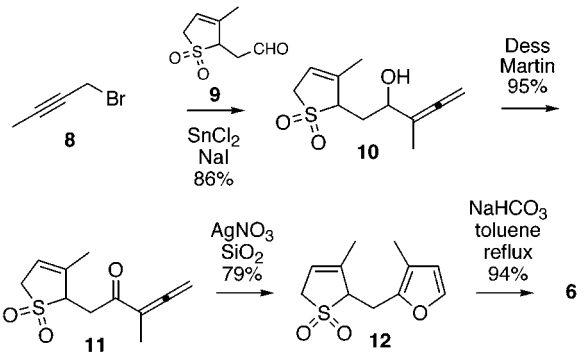
Scheme 1. Retrosynthetic Analysis for the Synthesis of Eleutherobin **1**



which highlights the high degree of convergence and efficiency that is possible using the tandem Diels−Alder cycloaddition reaction.[6]

The key retrosynthetic step involves the recognition that the carbocyclic bicyclo[8.4.0]tetradecane ring system of eleutherobin, **2**, could be constructed, in the synthetic direction, by cleavage of the C_3-C_8 σ-bond of pentacyclic ketone **4**, which in turn could be prepared from **5**, the product of tandem Diels−Alder reaction of bis-diene **6** and bis-dienophile **7**. We envisioned that two-electron reduction of epoxyketone **4** would effect both fragmentation of the oxanorbornane ether bridge and epoxide opening to give dianion **3**, which on Grob fragmentation and hemiketalization would generate **2** and establish the ring system of eleutherobin.[7] The correct (*Z*)-geometry of the $\Delta^{2,3}$ alkene would be expected as a result of the relationship between the C-2 and C-3 stereocenters and the stereoelectronics of the Grob fragmentation.[8]

Scheme 2. Synthesis of Bis-diene **6**



The synthesis of bis-diene **6** is outlined in Scheme 2. Following the protocol of Mukaiyama and Harada,[9] the organostannane derived from **8** was added to sulfolene aldehyde **9**[10] to give allenic alcohol **10** as an inseparable mixture of diastereomers in 86% yield. Dess−Martin oxidation of **10** provided allenic ketone **11** in 95% yield, which on exposure to silver nitrate provided furan **12**, based on the work of Marshall.[11] Heating **12** in toluene led to the extrusion of SO_2 and the formation of the requisite bis-diene **6** in 94% yield. This sequence provides an efficient four-step sequence for the generation of bis-diene **6** from **9** in 61% overall yield.

The preparation of bis-dienophile **7** and its tandem Diels−Alder reaction with bis-diene **6** is outlined in Scheme 3. Addition of the organostannane derived from propargyl bromide **13**[12] to aldehyde **14** led to the formation of hydroxyallenoate **15** in 72% yield. DIBAL-H reduction of **15** then gave 77% yield of allenic diol **16**, which was regioselectively oxidized with $BaMnO_4$[13] to provide bis-dienophile **7**. Warming the neat mixture of **6** and **7** to 50 °C resulted in tandem Diels−Alder cycloaddition, and in situ protection of the adduct **18a** as the corresponding TBS ether gave tetracycle **18b**. This remarkable sequence of oxidation/tandem cycloaddition/protection involves four distinct chemical reactions and leads to the generation a single stereoisomeric product, in which three new rings and six new stereogenic centers have been created, in 51% overall yield (85% average yield per step). Careful analysis of NMR data indicated that **18b** had the epimeric stereochemistry at the C-3 quaternary center relative to that shown in **5 (**Scheme 1), which was later confirmed unambiguously by single-crystal X-ray analysis of **18a**. The C3 stereochemistry of **18** would lead, on Grob fragmentation, to the establishment of the (*E*)-$\Delta^{2,3}$ alkene. However, the remarkably efficient

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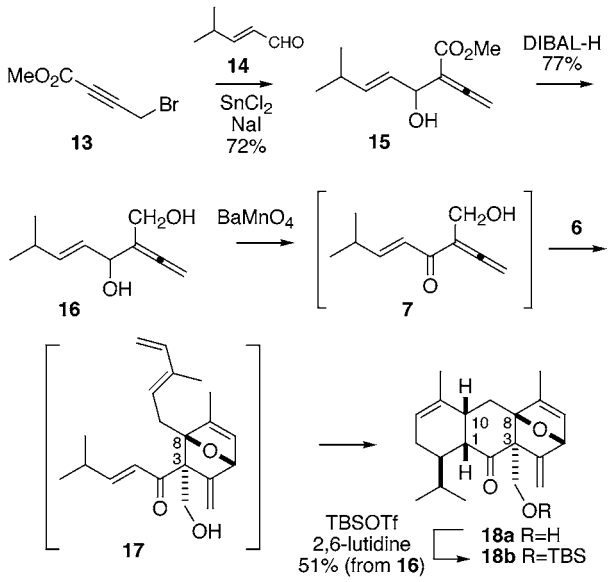
Scheme 3. Synthesis of **18** via Tandem Diels−Alder Cycloaddition

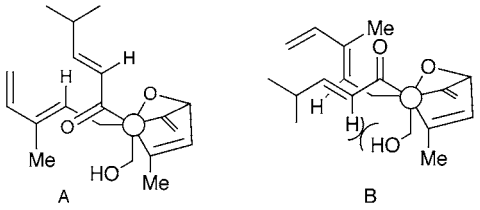


preparation of **18** led us to pursue this synthetic pathway, even though isomerization of the $\Delta^{2,3}$ alkene would be required at some point in the synthetic sequence.

The high *exo*-selectivity observed in the first, intermolecular cycloaddition is consistent with the proclivity of *endo*-oriented furan Diels−Alder adducts to undergo retro-Diels−Alder reaction faster than the corresponding *exo* adducts,[14] leading to the establishment of the C_3-C_8 stereochemistry shown in intermediate **17**. The highly *endo*-selective intramolecular Diels−Alder reaction of **17** generates the C_1-C_{10} relative stereochemistry shown in **18**. The communication of stereochemical information between the two six-membered rings, i.e., the establishment of the C_8-C_{10} relative stereochemistry in **18**, can be explained by examination of conformers A and B, in both of which the dienophile adopts the preferred s-cis conformation.[15] Reaction of A, which avoids the unfavorable steric interaction shown in B, leads to the formation of **18**.[16]

The conversion of **18b** to a substrate suitable for the key fragmentation reaction (analogous to **4→2** in Scheme 1) is outlined in Scheme 5. Oxidation of the exocyclic methylene in **18b** to the corresponding ketone in the presence of the endocyclic alkenes could not be achieved. However, selective oxidation of the exocyclic methylene could be accomplished via the C-2α alcohol **19**, which was prepared by selective

Scheme 4. Conformations for the Cycloaddition of **17**



addition of DIBAL-H from the sterically less hindered β-face of **18b**. Treatment of **19** with catalytic $VO(acac)_2$ in the presence of *t*-BuOOH selectively produced epoxide **20**, in which the C-2α hydroxyl directs the epoxidation exclusively to the β-face of the C-4 olefin.[17] Epoxide **20** was converted to the requisite C-4 ketone by epoxide hydrolysis under strongly basic conditions (with concomitant TBS removal) and subsequent oxidative cleavage of the resulting 1,2-diol with $NaIO_4$ to afford **21** in 51% yield over three steps.

Selective activation of the C-2 hydroxyl moiety in **21**, the next requirement for the implementation of our fragmentation strategy, proved to be exceedingly difficult. While selective silylation of the primary hydroxyl in **21** was easily achieved, mesylation of the C-2 alcohol only proceeded under forcing conditions and gave poor yields of the desired mesylate due to competitive retro-aldol cleavage of the C_2-C_3 bond. We therefore examined a stepwise approach to the fragmentation cascade. Reduction of the oxanorbornene proceeded smoothly using SmI_2/NiI_2[18,19] to deliver the desired tertiary alcohol **22** in 72% yield. As observed for **21**, selective silylation of the primary hydroxyl in **22** was successful; however, it was not possible to effect mesylation of the C-2 hydroxyl of the primary silyl ether derived from **22**, even under forcing conditions. Ultimately, activation of the C-2 hydroxyl could be achieved only in an "intramolecular" sense by reaction of diol **22** with phosgene to give cyclic carbonate **23** (79% yield), in which both the primary and secondary hydroxyl moieties of **22** have been converted to leaving groups.

In contrast to the retrosynthetic route presented in Scheme 1, the concomitant activation of both the C_2-O and $C_{20}-O$ bonds in **23** (Scheme 5) leads to the possibility of two competing Grob fragmentation pathways. MM2 analysis of the lowest energy conformation of **23** reveals that both the C_2 and C_{20} carbon−oxygen bonds have the requisite antiperiplanar relationship with the C_3-C_8 σ-bond for the Grob fragmentation.[8] Preparation of Grob fragmentation substrate **24** was achieved by directed epoxidation[17] of the $\Delta^{6,7}$ alkene of **23** to give the intermediate β-epoxide (not shown), establishing the requisite C-7 oxygen stereochemistry. Ex-

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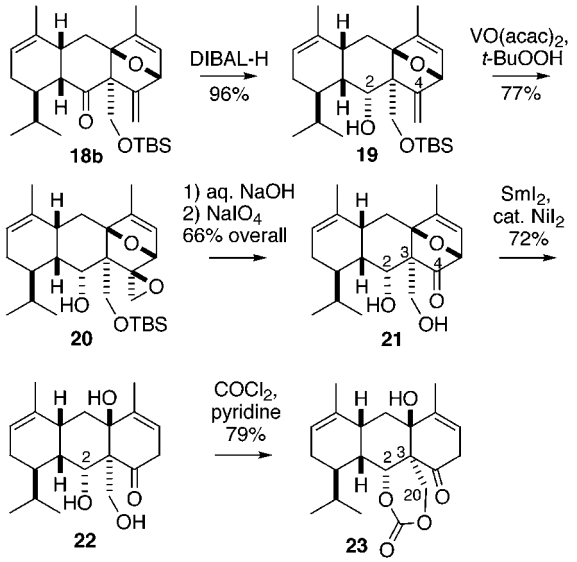
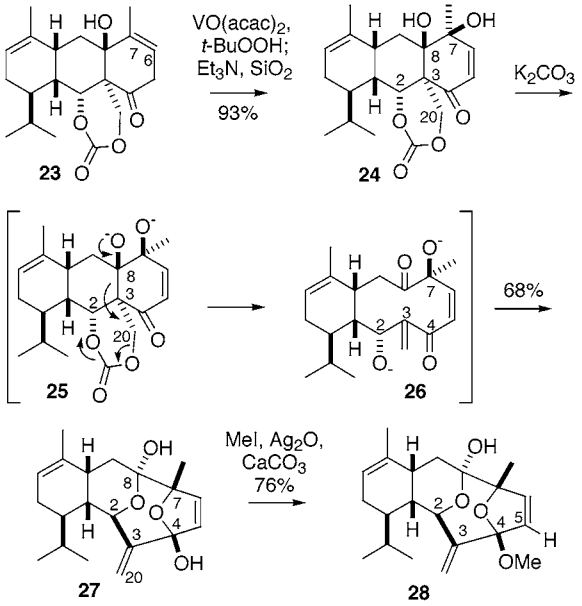
Scheme 5. Preparation of Fragmentation Substrate **23**



Scheme 6. Synthesis of **28** via Grob Fragmentation



posure of the labile ketoepoxide to triethylamine and silica gel induced β-elimination, providing **24** in 93% yield. The transformations of **21** to **22** and **23** to **24** constitute the successful stepwise execution of the first two steps in the originally proposed fragmentation cascade (**4**→**2**, Scheme 1).

The overall feasibility of our approach would depend on the successful cleavage of the C_3-C_8 bond in the third step of the proposed reaction sequence. In the event, heating a DMF solution of **24** to 75 °C in the presence of potassium carbonate provided a single product, **27**, in 68% yield.

The formation of **27** is presumed to occur via the intermediacy of dianion **26**, the product of fragmentation of the undesired $C_{20}-O$ bond and subsequent loss of carbon dioxide. Bis-hemiketalization under the reaction conditions then afforded **27**, the structure of which was confirmed by X-ray crystallographic analysis. While fragmentation of **24** did not produce the desired $\Delta^{2,3}$ olefin via C_2-O bond cleavage, we were pleased by the high degree of regioselectivity in the formation of **27**.

Moreover, the conversion of **23** to **27** marks the realization of the third part of the proposed fragmentation cascade and validates this approach to the synthesis of eleutherobin. Finally, differentiation of the two hemiketal functionalities in **27** was readily achieved by exposure of **27** to MeI with Ag_2O and $CaCO_3$[20] at 25 °C in the absence of light to produce **28** in 76% yield. The selective formation of the C-4 methyl ketal **28** was established by NOESY correlation between the C-4 methoxy and the C-5 vinyl proton. This remarkably efficient sequence provides the eleutherobin framework **28** in 15 linear steps from readily available starting materials and underscores the high degrees of convergence and efficiency that can be achieved using the tandem Diels−Alder reaction. Studies directed toward the isomerization of the C-3 *exo*-methylene in **28** to the $\Delta^{2,3}$ alkene present in eleutherobin are currently underway, and our results will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds **6**, **10**−**12**, **15**, **16**, **18**−**24**, **27**, and **28**, and X-ray data for **18** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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