Pergamon

Tetrahedron Letters 40 (1999) 3313–3316

TETRAHEDRON LETTERS

A Remarkable Pyranose to Furanose Isomerization Mediated by an "Anomeric" Silyloxy Function

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Received 27 January 1999; revised 26 February 1999; accepted 1 March 1999

Abstract: *The conversion of* **3** *to* **6** *is accomplished in high yields in three steps. The sequence greatly simplifies access to eleutherobin* **1**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *antitumor compounds, eleutherobin, isomerization, rearrangements.*

We have recently disclosed [1,2] our total synthesis of the marine natural product, eleutherobin (**1**), which possesses cytotoxic activity and has a mechanism of action similar to paclitaxel, epothilones and discodermolide.[3]

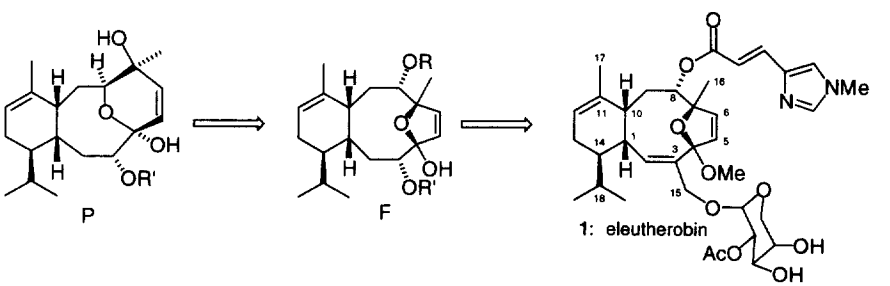
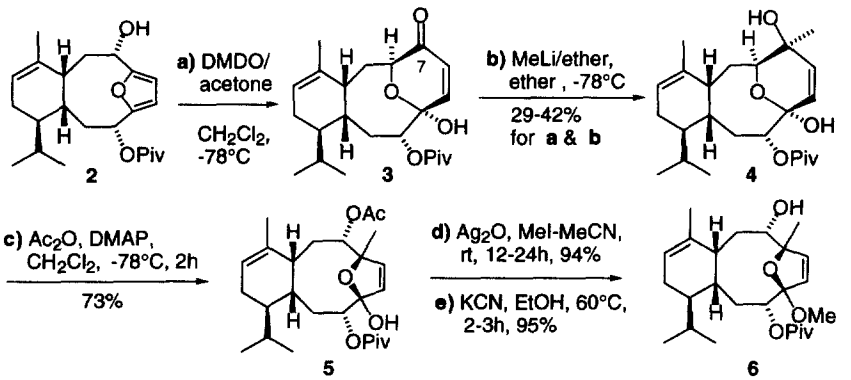


Figure 1

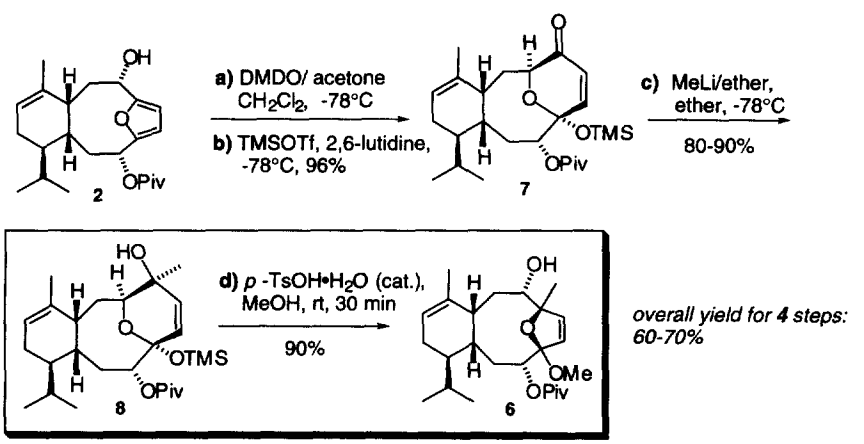
An important phase in our published route to eleutherobin involved a pyranose (P)→furanose (F) rearrangement, which unveiled the 2,5-dihydrofuran ring of the target (**Figure 1**). Thus, as depicted in **Scheme 1**, reaction of a lactol-enone **3** with methyllithium paved the way for incorporation of the C16 methyl group. The tertiary alcohol **4** then underwent rearrangement upon exposure to acetic anhydride. This reaction is no doubt driven by the selective trapping of the secondary alcohol at C8 via acetylation. While we obtained a single isomer in the nucleophilic addition of the methyl group, the overall scheme was plagued by low yields. Thus, advancing from **3** to **6** in the lengthy sequence shown was difficult.

PII: S0040-4039(99)00499-2



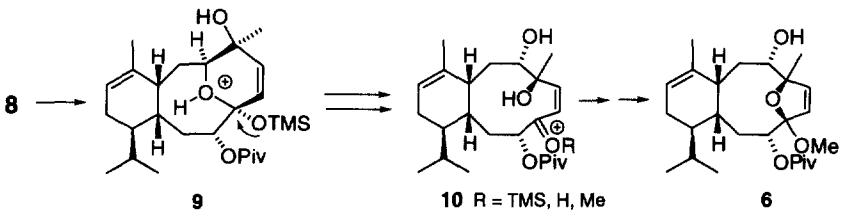
Scheme 1

We describe herein an alternate solution which is both concise and novel. We hoped to explore the consequences of protecting the tertiary "anomeric - like" hydroxyl group of **3**. Indeed, in the opening step, a trimethylsilyl (TMS) group was efficiently installed at this center (see compound **7**, **Scheme 2**). The nucleophilic methylation now worked extremely well providing **8** in ~80-90% yield.[4] Even more important was the ease with which this compound could be advanced toward eleutherobin. Thus, simple exposure of **8** to the action of catalytic *p*-TsOH•H_2O in methanol led directly to **6** in excellent yields. This was a particularly valuable result in that it obviated the need for a separate methylation step. Thus, the required C4 methoxy group has been derived from methanolysis rather than methylation.



Scheme 2

A plausible general mechanism for the important conversion of **8→6** is suggested in **Scheme 3**. Thus ring opening of protonated **8** would lead to oxonium ion **10**. The latter can proceed to **6** by any of several obvious, but difficultly distinguishable pathways.



Scheme 3

At the time of our initial report,[1] the representation of the relationship of the bridgehead substituents as *out-out* as shown in the pyranose systems **3** and **7** was necessarily tentative.[5] This arrangement corresponded to the presumed thermodynamically most stable configuration (Macromodel v 5.5 calculations).[6] Spectroscopically however, it was difficult to obtain persuasive proof regarding this stereochemical question due to the conformational fluxionality of the ring system. This resulted in broadening of signals in the proton NMR spectrum. Sharpening of peaks could be observed only at temperatures around 220K. In the first level of analysis, low temperature COSY and 1D-NOESY experiments might have been construed to suggest an *in-out* assignment for the TMS protected compound **7**. However, the matter was unclear. Eventually, some crystals of the lactol-enone were obtained. Crystallographic analysis (**Figure 2**)[7] indeed established the *out-out* formulation shown in **3**.

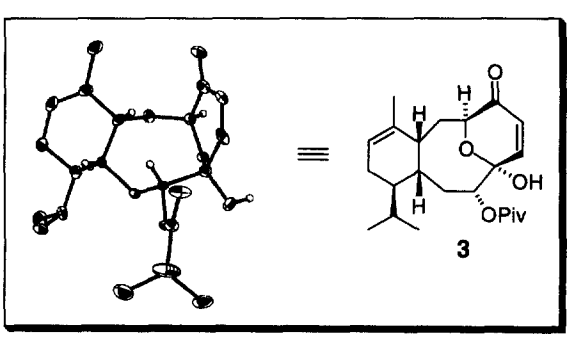


Figure 2

In conclusion, the overall yield for the 4-step route from **3** to **6** is 60-70%. A key element is the siloxy-mediated valence isomerization accompanied by methanolysis (see **8→6**). The modified route described herein, corresponds to a three-fold improvement over the previous route to eleutherobin and has made a very favorable impact on material throughput. Indeed, we were able to synthesize ample amounts of fully synthetic eleutherobin (**1**) for both *in vitro* and *in vivo* studies. These very interesting investigations will be reported shortly.

Acknowledgments: The work was supported by the National Institutes of Health (Grant Numbers: HL25848 (S.J.D.) and CA-08748 (SKI Core Grant). We thank Mr. T. Hascall, Dr. B. Bridgewater and Professor G. Parkin for an expeditious X-Ray crystallographic determination.

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[4] Almost 10 equivalents of the organometallic reagent were necessitated to drive the reaction to completion. As long as the temperature remained at ~-78°C and the reaction was quenched at the same low temperature, only the desired product was obtained.

[5] For a discussion on *out-out* and *in-out* arrangements in bridged compounds see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic compounds*, Wiley, New York, 1994, pp. 791-793.

[6] Macromodel v 5.5 calculations on **7**: E_{rel} (kcal/mol) = 0 (*out-out*), 12.35 (H *in*-OTMS *out*), 14.33 (H *out*-OTMS *in*).

[7] Although good diffraction patterns were obtained from the crystals, the structure could not be refined beyond an *R* factor of 0.15.