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Concerning the Antileukemic Agent Jatrophatrione: The First Total Synthesis of a [5.9.5] Tricyclic Diterpene

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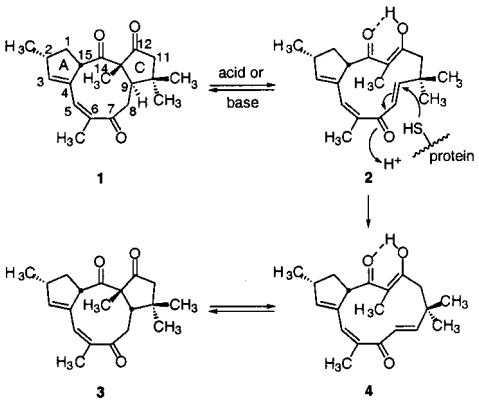
Jatrophatrione (**1**) is an architecturally novel, naturally occurring substance with potent antileukemic activity.[1] Isolated from the roots of *Jatropha macrorhiza*, this synthetically challenging molecule is believed to derive its therapeutic effectiveness via a retrograde Michael process to give **2** (Scheme 1). X-ray crystallography has shown that the dienone chromophore in **1** is not conjugated (torsion angle of 61.0° for C5−C6−C7−O3).[1] The liberation of **2** sets the stage for thiol capture across C8−C9. This innovative mechanistic proposal prompted us to consider initial elaboration of the somewhat more strained C9 epimer **3** (6.5 kcal/mol on the basis of MM2) for the purpose of inducing its ring opening to give **4**.[2,3] Subsequent rotation about the flanking σ bonds in a manner previously used to tactical advantage in our synthesis of taxusin,[4] would lead via **2** to the natural stereoisomer and add credence to this latent mechanism of action.

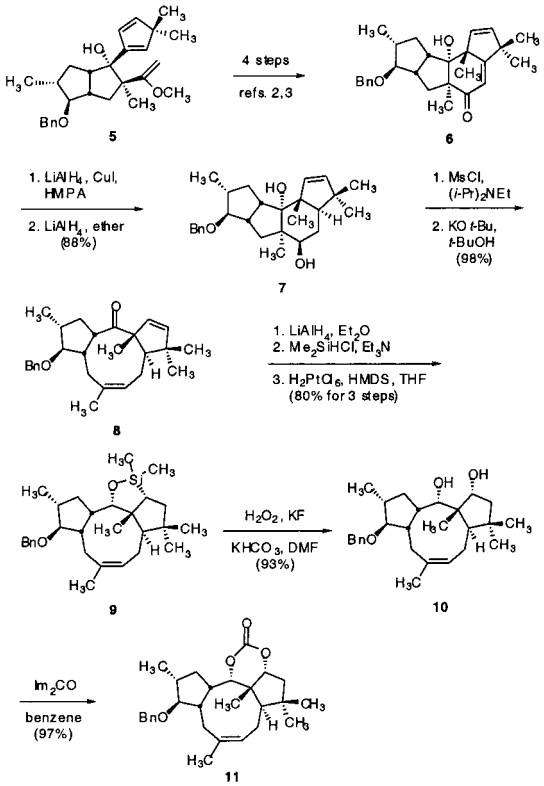
The earlier undertaking alerted us to several relevant issues associated with synthetic operations involving a functionalized [5.9.5] tricyclic framework of this type. These include, but are not limited to, notably facile transannular covalent bonding, exceptional proclivity for reagent capture on the convex surface as a result of the inherent highly folded topography, and the manifestation of kinetic instability following premature introduction of the 1,3-dicarbonyl system at C12 and C14. Herein we describe an efficient route that effectively skirts these complications and leads in highly regio- and stereocontrolled fashion to (±)-jatrophatrione.

In reaching **7**, we took advantage of the ease with which the *O*-methyl analogue of **5** had been found to undergo sequential anionic oxy-Cope rearrangement, α-methylation of the enolate anion so formed, and subsequent transannular ene reaction in a single laboratory operation[2] (Scheme 2). The change to a benzyl-protecting group was an obvious move to facilitate ultimate deblocking. The elaboration of **6** from **5** was likewise based on our recently introduced technology involving two-fold bromination with NBS, generation of a cyclohexenone unit by heating with LiBr and Li_2CO_3 in DMF, and reduction of the bromo oxetane substructure with zinc in methanol.[3] At this point, a key goal was to transmit the chirality associated with the tertiary hydroxyl group to the β-carbon of the conjugated ketone. Since the presence of the cyclopentene double bond rendered hydroxyl-directed hydrogenation[5] unattractive, hydride-reducing agents were selected. For calibration purposes, **6** was first exposed to $LiAlH_4$ in THF−ether (1:4) at −78 °C to room temperature. Four products resulted, with **7** constituting only 14% of the mixture. In contrast, the co-addition of CuI (1 equiv) with THF−HMPA (3:1) as the reaction medium[6] served to convert **6** into the saturated ketone (1,4-reduction, 77%) and **7** (12%). Resubmission of the dihydro ketone to reduction delivered **7** (88% overall), the stereochemistry of which was established by

Scheme 1



Scheme 2



2D NMR methods and direct comparison with the 9β epimer already in hand.

With the discovery of an effective means for establishing the necessary *trans*-B/C ring fusion, it proved an easy matter to carry out the monomesylation of **7** and ensuing Grob fragmentation to furnish **8**. This ketone was amenable to reduction from the β-face,

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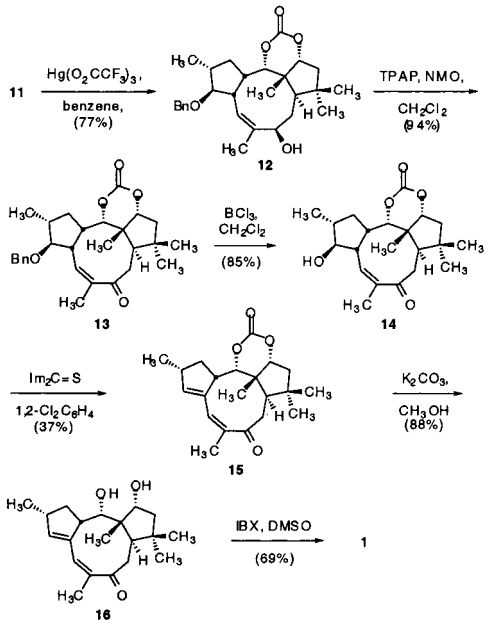
Scheme 3



but not to subsequent regiocontrolled hydroboration of the proximal cyclopentene double bond.[7] Attempts to bring about iodolactonization of the derived *tert*-butyl carbonate[8] were unexpectedly ineffective. In contrast, intramolecular hydrosilylation[9] of the dimethylsilyl ether proceeded smoothly in the presence of a catalytic amount of H_2PtCl_6 to afford **9** in 80% overall yield. It was considered most expedient if oxidative cleavage of the C−Si bond in **9** could be deferred until a late stage of the synthesis. However, subsequent deployment of the Treibs reaction[10] precluded this option. Consequently, peroxide oxidation[11] was performed in advance of the late-stage operations, and diol **10** so formed was protected as the cyclic carbonate.[12]

With construction of the northern rim of jatrophatrione now completed, attention was turned to proper introduction of functionality along the southern sector (Scheme 3). After the examination of several protocols for achieving suitable oxidation, we settled on the use of mercuric trifluoroacetate in refluxing benzene. The transposed allylic alcohol **12** generated in this manner (77%) was oxidized with the perruthenate reagent to make enone **13** readily available.

The last major hurdle involved elimination of the benzyloxy substituent with proper control of regiochemistry. The use of Raney nickel to bring about debenzylation was avoided because of the ease with which the double bond in **13** undergoes catalytic hydrogenation. Instead, we benefited from the selectivity exhibited by BCl_3 [13] in effecting the conversion to **14**. At this juncture, syn elimination of the C3 hydroxyl group was mandated. In the absence of precedent, it was envisioned that the enone fragment might well induce a higher acidity on H4 relative to H2, notwithstanding the nonplanarity of this chromophore. When attempts to prepare a xanthate ester failed (due to existing sensitivity to strongly basic conditions), it was subsequently found that the desired dehydration could be accomplished simply by heating **14** with thiocarbonyldiimidazole in 1,2-dichlorobenzene.[14] Formed alongside **15** (37% isolated) was the $\Delta^{2,3}$ isomer (10%). Hydrolysis of the cyclic carbonate ring in **15** with K_2CO_3 in methanol at room temperature required 3 h to proceed to completion. This reaction time contrasts with the behavior of **12**, where quantitative hydrolysis is complete in less than 5 min. This kinetic difference is construed to be a reflection of increased ring strain in **12**. The final oxidation was accomplished with IBX in DMSO in 69% yield. Synthetic jatrophatrione exhibited a 500 MHz ^{1}H NMR spectrum entirely congruent with that of the natural sample recorded at a lower field strength. Our sample exhibited the following carbon shifts when recorded in $CDCl_3$ at both 100 and 125 MHz (Bruker); 218.0, 215.6, 210.6, 144.5, 138.4, 135.9, 128.1, 64.5, 55.5, 51.4, 51.0, 39.8, 38.3, 37.4, 27.9, 23.6, 20.7, 20.5, 14.0.[15]

The synthesis of jatrophatrione (**1**) described herein is direct, provides a new approach to complex terpenoid frameworks, and constitutes a formal entry into a wide variety of designed analogues for biological evaluation.

Acknowledgment. We thank Dr. Pengli Zhang for some early experiments and Dr. Charles Cottrell for an insightful discussion regarding technicalities involved in the recording of ^{13}C NMR shifts.

Supporting Information Available: Experimental procedures and spectral data for **9**−**16** and synthetic **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Conventional conditions (H_2O_2/KF/$KHCO_3$/THF/MeOH) gave clean product (TLC analysis) but invariably in low yield following requisite prolonged reaction. This complication was resolved by changing the reaction solvent to DMF. Recourse to this polar aprotic solvent shortened the reaction time to 8 h and consistently led to a 97% isolated yield of **10**: (a) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120. (b) Review: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.
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(15) We postulate that the discrepancy observed between "our" ^{13}C shifts and those cited in the literature[1] might be caused by an error in the dwell clock divider chain of their Fourier transform NMR spectrometer. In the digitizer, the dwell clock generates the dwell time which sets the frequency width of the spectrum, and the relationship between them is SW − 1/(2*DW) where SW is the sweep width in Hertz and DW is the dwell time. Because the shift differences between the peaks observed in our spectrum and those of the literature increase the further we go from TMS, we know the discrepancy is not due to a simple referencing problem which would give a constant difference between the peaks of the two spectra. It of course is possible that a temperature or concentration difference could account for these observations, but a plot of the increasing differences shows such a high linear correlation ($\rho = 0.998$) that it seems more likely we are dealing with a systematic error. We have actually observed this dwell time error in our NMR facility on at least two of our older spectrometers which had the same or similar digitizer design. To verify that our values are correct, we ran the spectrum on two different spectrometers and noted the same ppm values.

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