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EFFICIENT STEREOCONTROLLED SYNTHESIS OF THE ABC SUBUNIT OF DUMSIN

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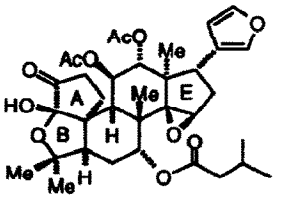
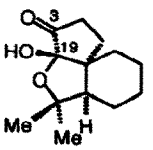
Abstract: The oxygenated ABC network of the potent insect antifeedant dumsin has been expediently assembled in a totally stereocontrolled manner by exploiting the acylation of a lactone carbonyl with a masked keto anion equivalent.

The widely distributed East African plant known in Swahili as "Msinduzi" has long been considered by the native population to possess medicinal properties. The principal uses of its roots are to alleviate stomach aches and to offset the symptoms of the common cold.[1] More recent screening of extracts of the bitter rootbark by Kubo's group[2] led to the identification of a tetranortriterpenoid possessing remarkably potent insect antifeedant activity. The structurally complex features of this constituent were secured on the basis of detailed spectroscopic analysis and ultimately a single-crystal X-ray determination performed by Clardy.[2] The unusual molecular network contained in dumsin is represented by formula **1**, which also correctly depicts its absolute configuration. Central to the uniqueness of this plant metabolite are the ester substituents in rings C and D, a 3-substituted furan linked to the epoxycyclopentane that serves as ring E, and the unprecedented internal hemiacetal of an α-diketone embedded within the ABC subunit. Herein, we describe a short and efficient means for elaborating the oxygenated dumsin part-structure **2** in stereocontrolled fashion.



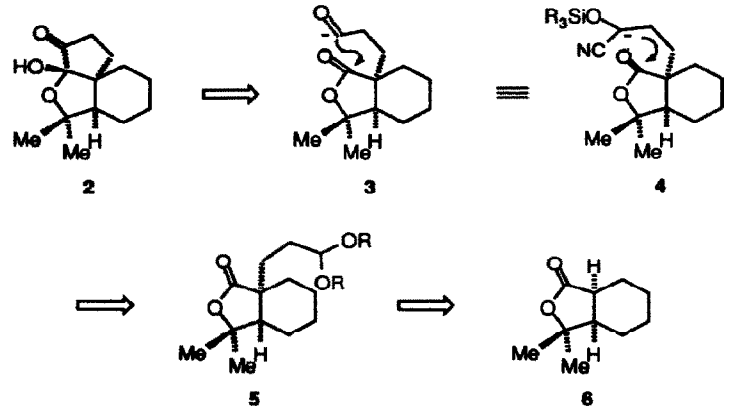
1



2

Our overall goal was the development of a synthetic pathway that would involve few steps, yet be amenable to producing structural analogs of biological interest. For retrosynthetic purposes, the tricyclic system was fragmented across the C-3/C-19 bond (dumsin numbering; see **2**) with an eye to

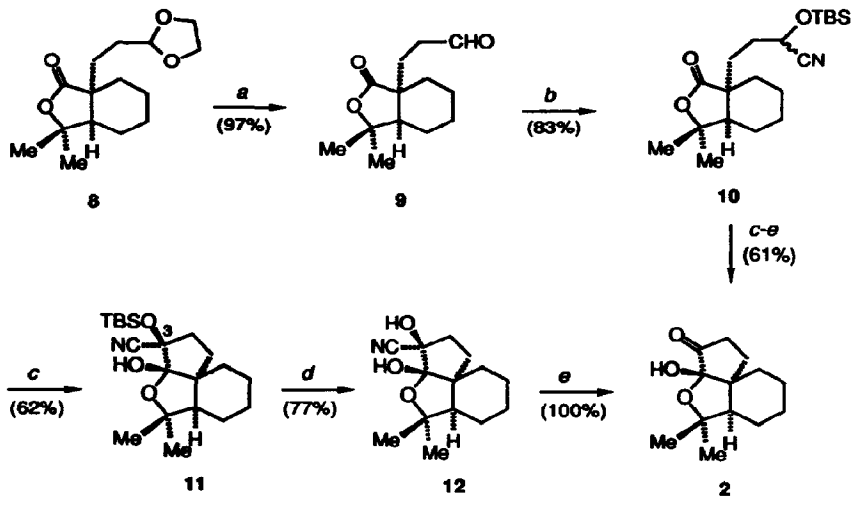
Scheme 1. Retrosynthetic Plan for the Construction of **2**.



its reconstruction as shown in Scheme 1. Direct union of the two carbonyl groups in **3** is, of course, not possible and recourse to a silylated cyanohydrin exemplified by **4** was projected. Methodology based on this principle has proven to be a powerful synthetic tool[3a] and has been extensively applied in an intramolecular alkylation mode for accessing various polycyclic natural products.[3b] However, we have found no precedent involving the application of this umpolung strategy to nucleophilic attack on a lactone.[4]

The synthesis was initiated with an examination of the reactivity of the enolate of known lactone **6**[5] toward an appropriate electrophilic partner. Sequential treatment of **6** with LDA in THF at -78 °C followed by the introduction of 2-(2-bromoethyl)-1,3-dioxolane (**7**)[6,7] according to standard conditions[8] only returned unreacted **6**, a likely reflection of the limited solubility of **6** at this temperature. The use of HMPA as a co-solvent ameliorated this problem and gave **8** in 77% yield (Scheme 2). Subsequent Lewis acid-catalyzed condensation of the derived aldehyde **9**[9] with TBSCl and KCN in acetonitrile[10] led efficiently to **10**. To our delight, dropwise treatment of a cold (-78 °C) THF solution of **10** with 1.1 equiv of potassium hexamethyldisilazide (0.5 M in toluene) led with high diastereoselectivitiy to **11**. No contamination with a second diastereomer could be discerned. Although attempts to elucidate the relative configuration of C-3 in **11** by means of NOE measurements proved not to be definitive, we tentatively projected the larger substituent to the exo surface of the developing five-membered ring in order to minimize steric crowding in the cyclization transition state.

Scheme 2. Preparation of **2**.



[a] *p*-TsOH, wet acetone, rt, 3 days. [b] TBSCl, KCN, ZnI_2 (cat), rt, 12 h. [c] $KN(SiMe_3)_2$ (1.1 equiv), THF, -78 °C, 30 min; H_2O, -78 °C → rt. [d] TBAF, THF, rt, 30 min. [e] 1N NaOH, ether, rt, 30 min.

Despite some reservations, the deprotection of **11** to the cyanohydrin level as in **12** proceeded smoothly and without observable cleavage of the C-3/C-19 bond. The highly crystalline nature of **12** made possible the determination of its stereochemistry by X-ray methods.[11] As seen in Figure 1, the pair of hydroxyl groups are indeed syn related, as expected from earlier considerations. Mere recourse to stirring an ethereal solution of **12** in 1N NaOH at room temperature for 30 min[12] produced

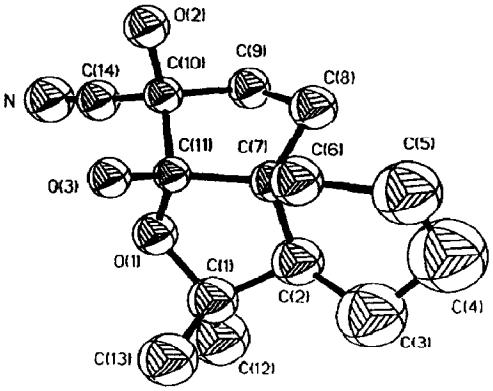


Figure 1. Computer-generated perspective drawing of **12** as determined by X-ray crystallography.

our target compound **2** as a colorless solid in quantitative yield.[13,14] Advantageously, the last three steps in Scheme 2 can be performed without the purification of individual intermediates. Under these circumstances, the overall yield for the three-step conversion of **10** to **2** is a satisfying 61%.

In summary, we have developed a potentially general route to an uncommon ring system recognized to be central to the unique structural features of dumsin (**1**).

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References and Notes

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11. We thank Professor Robin D. Rogers (Northern Illinois University) for this determination.
12. Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth. Coll. Vol. VII* **1990**, 381.
13. The structure assigned to each new compound was in accord with its infrared, 300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, and high resolution mass spectra. In addition, satisfactory combustion analyses were obtained for **2**, **8**, **9**, and **11**.
14. IR (neat, cm^{-1}) 3432, 1755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 1 H), 2.67 (m, 1 H), 2.28 (ddd, J = 18.0, 8.1, 3.4 Hz, 1 H), 2.05 (ddd, J = 18.0, 8.1, 3.4 Hz, 1 H), 1.89 (m, 2 H), 1.75-1.46 (series of m, 6H), 1.39-1.37 (m, 2 H), 1.34 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.0, 104.3, 87.0, 53.6, 50.8, 32.5, 32.0, 30.0, 29.3, 26.1, 22.3, 21.4, 19.8; HRMS *m/z* (M^+) calcd 224.1412, obsd 224.1381.

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