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Total Synthesis of (±)-Hibiscone C

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Abstract

A total synthesis of (±)-hibiscone C, one member of the furanosteroid family of natural products that also includes viridin and wortmannin, is reported. Two new pathways for formation of the key diacyl furan subunit are described.

Keywords

Furanosteroid; Hibiscone C; Oxidative aromatization; Total synthesis

The sesquiterpene furanosteroid family of natural products includes hibiscone C, viridin, wortmannin, and halenaquinone.¹ The key structural similarity shared by each member of this family is a furan ring flanked by two conjugated carbonyl groups. The electrophilicity of such diacylheteroaryl systems coupled with the ring strain caused by the fusion of many contiguous sp²-hybridized carbons within a polycyclic ring system confers to the furanosteroids an enhanced reactivity towards nucleophiles that accounts for their varied and often potent biological activities. For instance, wortmannin, which has attracted the most interest based on its antiproliferative activity,² inhibits the PI-3 kinase, an enzyme responsible in part for cell growth and differentiation. The timing of the installation of this sensitive functional group has been referred to as the “greatest strategic conundrum” in the synthesis of furanosteroids.²

As part of a program to investigate the mechanism of action of various furanosteroids and their analogs, we report herein our discovery of a new strategy for the synthesis of diacylated furans executed on hibiscone C, one of the structurally less complex members of this family of natural products. In addition we report related reactivity of some synthetic intermediates that provide additional insights into furanosteroid construction.

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Supplementary data

¹H NMR, ¹³C NMR, IR, and HRMS spectra are provided for hibiscone C, for compounds **5**, **7**, **8**, and **13**, and for all intermediates between compounds **3** and **5** (Scheme 2).^{3b}

To date two total syntheses of hibiscone C have been reported.³ In planning our approach we were attracted in particular to the elegant synthesis of Kraus and Wan,^{3b} which utilizes many classical organic transformations to rapidly construct the fused polycyclic skeleton. The only drawback we saw to their approach was the expense of the starting material, 1,3-cyclohexanedione (**3**).⁴ We developed a scalable five-step sequence of reactions that prepares **3** from isobutyraldehyde in high yield without requiring purification of any intermediates (Scheme 1). An aldol dehydration of acetone and isobutyraldehyde yields enone **1**,⁵ which undergoes a Michael addition with diethylmalonate to yield ketone **2**.⁶ An annulation followed by ester hydrolysis and decarboxylation yields dione **3** in 62% isolated overall yield following column chromatography. As would be expected from a 1,3-dione, NMR analysis of **3** indicates it exists primarily as its enol tautomer **4**. Of note, this modular approach to **3** would allow preparation of hibiscone C analogs that bear different side chains on the cyclohexane ring, depending on the identity of the starting aldehyde.

With an efficient route to **3** in hand, we utilized the strategy of Kraus and Wan to prepare dienone **5**; however, in our hands standard dihydroxylation reaction conditions did not yield desired triol **6**. Instead, we obtained only pentaol **7** in 71% yield (Scheme 2). This result occurred regardless of whether or not the stock solution of OsO₄ used in the reaction was freshly prepared.

As there is literature evidence that some conjugated dienes undergo exhaustive dihydroxylation with OsO₄/NMO,⁷ we felt it would be advantageous to employ a different set of reagents (K₂OsO₄/K₃Fe(CN)₆) that has been found to mediate regioselective dihydroxylations on a range of conjugated dienes.⁸ Under these conditions we were surprised to isolate cyclized diol **8** in 86% yield instead of desired triol **6** (Scheme 3).⁹ Our hypothesis is that following initial regioselective dihydroxylation to yield **9** an elimination takes place to generate dienone **10**, which undergoes a second regioselective dihydroxylation to yield **11**, which then cyclizes to produce stable hemiketal **8**.

We designed a mechanistic probe of this unusual oxidation cascade reaction. Primary alcohol **5** was acetylated with the intent of precluding cyclization, and resulting acetate **12** was then exposed to the same reagents that generate **8** from **5** (Scheme 5, conditions f). No reaction was observed even after extended reaction times, indicating that the primary hydroxyl likely has a strong rate-accelerating effect on the dihydroxylation reaction.

Molecule **8** requires only an oxidation and aromatizing elimination to generate hibiscone C, which occur simultaneously and in quantitative yield upon its exposure to Swern oxidation conditions (Scheme 5). Proton and carbon NMRs of the isolated product matched recently published revised assignment data.¹⁰

Interestingly, we found that heating **8** in refluxing toluene open to the atmosphere induced both an elimination to yield alcohol **13** (41% yield) and a subsequent heteroarylic oxidation to generate hibiscone C (16% yield) directly from **8** without the use of any manufactured oxidizing agents (Scheme 5, path h). Heating **8** in an oxygen-free sealed tube generates primarily **13** with only trace amounts of hibiscone C detectable by crude ¹H NMR. Both

routes to hibiscone C illustrated in Scheme 5 represent new pathways for furanosteroid construction.

In summary, we have accomplished a total synthesis of furanosteroid hibiscone C from inexpensive starting materials. Key features of this synthesis include an unusual oxidation/cyclization cascade to yield **8** and a tandem elimination/oxidation of **8** to yield the natural product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. Procedure: A biphasic mixture of **5** (1 equiv.), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $CH_3SO_2NH_2$ (3 equiv.), K_2OsO_4 (0.12 equiv.), and 3:5 $tBuOH:H_2O$ (0.14 M) was stirred vigorously at room temperature for two days. Following extractive work-up between EtOAc and H_2O , **8** was obtained as a clear oil after purification through a SiO_2 column (1:1 EtOAc:hexanes). 1H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 7.6 Hz, 3H), 1.58 (dt, J = 12.8, 4.8 Hz, 1H), 1.82–1.92 (m, 2H), 1.96–2.08 (m, 1H), 2.22–2.32 (m, 2H), 2.37 (dd, J = 19.2, 4.0 Hz, 1H), 2.45 (bs, 1H), 2.64–2.74 (m, 1H), 3.00 (bs, 1H), 3.72 (d, J = 2.4 Hz, 1H), 4.71 (dd, J = 13.2, 2.8 Hz, 1H), 4.88 (dd, J = 9.2, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 17.1, 21.3, 27.1, 31.1, 32.0, 33.4, 37.5, 47.8, 71.0, 75.4, 108.1, 134.2, 158.9, 196.2. IR (neat, cm^{-1}) 3372, 2959, 2934, 2876, 1669. HRMS (EI^+) Calcd. 266.1519 (M^+), found 266.1518. Relative stereochemistry was not determined.
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Figure 1.

Four members of the furanosteroid family of natural products.

(a) acetone, NaOH, H₂O, 5 → 23 °C; (b) *p*-TsOH, Na₂SO₄ benzene, 80 °C; (c) CH₂(CO₂Et)₂, NaOEt, EtOH, 80 °C; (d) KOH, H₂O, 90 °C; (e) H₂SO₄, H₂O, 90 °C, 62% (five steps)

Scheme 1.

Preparation of 1,3-cyclohexane dione (**3**) from inexpensive starting materials.

Scheme 2.

Double dihydroxylation of dienone 5.

Scheme 3.

Proposed pathway for the conversion of **5** to **8** mediated by $K_2OsO_4/K_3Fe(CN)_6$.

Scheme 4. Mechanistic probe of the conversion of **5** to **8**.

(f) $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , NaHCO_3 , $\text{CH}_3\text{SO}_2\text{NH}_2$, K_2OsO_4 (12 mol%), $t\text{BuOH}$, H_2O , 86%; (g) COCl_2 , DMSO , Et_3N , CH_2Cl_2 , -78°C , quant.; (h) toluene, 110°C , 57% combined (41% **13** + 16% hibiscone C)

Scheme 5.

Two routes for the preparation of hibiscone C from **5**.