The First Total Synthesis of (±)-Saudin

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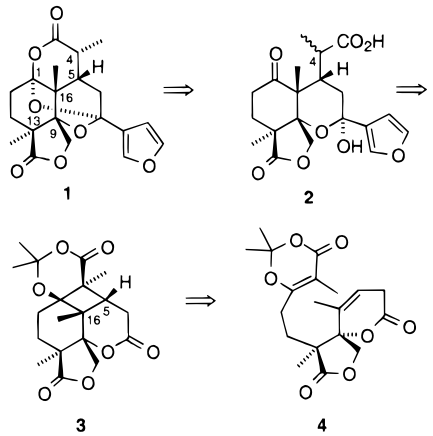
Saudin **1**, which was isolated from the leaves of the toxic plant *Cluytia richardiana* in Saudi Arabia,[1] is notable both for its unique rearranged labdane carbon skeleton as well as for its potent hypoglycemic activity.[2] The structural complexity of saudin, which contains seven stereogenic centers and six oxygenated carbons in its 13-carbon core, has stimulated interest in its total synthesis.[3] Its potential as a lead for therapeutic development makes the availability of analogues for structure−activity relationship studies an important goal.

We identified the establishment of the two quaternary carbons (C-13 and C-16) in the sterically congested hexacyclic ring system of saudin **1** as the central stereochemical challenge for total synthesis. Preliminary results from our laboratory have demonstrated that the intramolecular dioxenone photocycloaddition reaction[4] leads to the establishment of that relative stereochemical relationship in a model system lacking the C-9 oxygen functionality.[5] We report herein the extension of those findings to the synthesis of a more highly functionalized photosubstrate **4** that leads to the first total synthesis of saudin in 15 steps from readily available precursors.

Our retrosynthetic analysis is outlined in Scheme 1. Disconnection of the C-1 ketal of **1** leads to the hemiketal keto-acid **2**. In the synthetic sense, it is important to note that the more stable equatorial orientation of the epimerizable C-4 methyl group in **1** would be established in the conversion of **2** to **1**, making the C-4 stereochemistry of **2** of little consequence. The furyl hemiketal **2** could in turn be derived from the addition of a furyl anion or its equivalent to lactone **3**, which would result from the intramolecular photocycloaddition of dioxenone **4**. The δ-lactone ring in **4** serves to constrain the trisubstituted alkene, thereby ensuring the establishment of the desired C-5, C-16 relative stereochemistry as shown in photoadduct **3**.

The synthesis of **4** is outlined in Scheme 2. Reaction of **5**[6] with **6**[7] led to the exclusive formation of the cis-fused Michael-aldol product **7**.[8] Reaction of ketone **7** with trimethylsilyliodide and hexamethyldisilazide as described by Boeckman and Fang[9,10] gave the thermodynamic enol silyl ether **8**. Ozonolysis of **8** gave an aldehydo carboxylic acid, which was not isolated but treated in situ with methanolic HCl to effect esterification, dimethyl acetal formation, and desilylation of the tertiary alcohol in a single pot to give **9** in 70% yield. Cyclization of **9** in the presence of benzyl alcohol and PPTS led to the formation of benzyl acetal **10** in 70% yield.

Scheme 1



Introduction of the C-16 methyl group at the sterically congested neopentyl ketone in **10** proved to be problematic. Reaction of the enol triflate **11**[11] with lithium dimethylcuprate led to reduction to the disubstituted alkene without incorporation of the requisite methyl group.[12] The desired alkene **12** was ultimately obtained by reaction of **11** with trimethylaluminum under Pd catalysis.[13] Successful alkenylation at this sterically hindered position using palladium-mediated coupling with trimethylaluminum underscores the advantage of this methodology over the more commonly employed cuprate chemistry.

Hydrolysis of ester **12** gave the acid **13**, which was homologated to **14** by the method of van der Baan.[14] The reaction conditions for the formation of the dioxenone chromophore typically involve the condensation of a β-keto acid (or acid-labile ester) with acetone under harshly acidic reaction conditions.[15] However, the presence of the acid-labile benzyl acetal precluded the use of such conditions for the formation of **15**. After considerable experimentation, we found that addition of the acid chloride derived from **14** to a solution of 5 equiv of triethylamine in 1:2 acetone−benzene (70 °C internal temperature) led to the formation of the desired heterocycle **15** in 70% yield. This reaction, which presumably occurs via acetone trapping of the ketoketene intermediate,[16] proceeds with complete retention of the labile benzyl acetal moiety. The photosubstrate **4** was then obtained by hydrogenolysis of the benzyl acetal and Dess−Martin oxidation of the intermediate hemiketal **16**.

The constraint of the trisubstituted alkene into the δ-lactone in **4** serves to establish the requisite stereochemical relationships at both C-5 and C-16. Photocycloaddition of **4** can only occur with approach of the dioxenone chromophore to the δ-lactone to give **3**, since approach of the dioxenone from the other face of the lactone ring of **4** is not energetically feasible. In addition, the presence of the lactone ring ensures that the triplet diradical intermediate in the photocycloaddition reaction (A in Scheme 2)[5,17]

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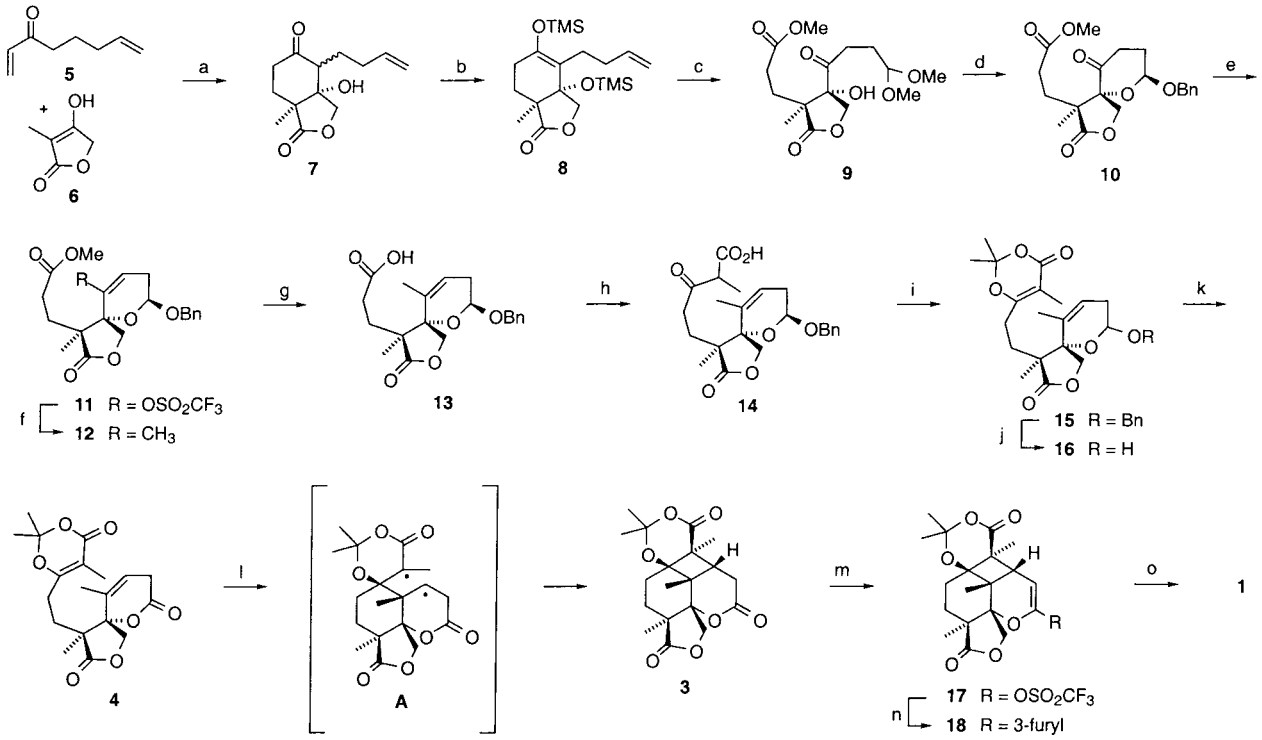
Scheme 2



(a) pyrrolidine, AcOH, THF (76%); (b) TMSI, HMDS, CH_2Cl_2, -20 °C (99%); (c) O_3, MeOH, -78 °C; Me_2S; H^+ (70%); (d) BnOH, PPTS, benzene, reflux (70%); (e) KHMDS; 2-[N,N-Bis(trifluoromethylsulfonyl)amino]-pyridine, THF, -78 - 0 °C (91%); (f) $AlMe_3$, LiCl, $Pd(PPh_3)_4$, THF (81%); (g) 1 N LiOH, MeOH (94%); (h) $(COCl)_2$, CH_2Cl_2; $LiC(CH_3)(CO_2TMS)_2$, THF, 0 °C; aq. $NaHCO_3$; citric acid (97%); (i) $(COCl)_2$, benzene; NEt_3, Me_2CO, benzene 95 °C (70%); (j) H_2, Pd/C, EtOAc (97%); (k) Dess-Martin (93%); (l) 9:1 CH_3CN:Me_2CO, hυ, 0 °C (80%); (m) *n*-BuLi, TMEDA; Tf_2O, THF, -95 °C (81%); (n) (3-furyl)$SnBu_3$, LiCl, $Pd(AsPh_3)_4$, THF, reflux (95%); (o) 1 N LiOH, MeOH, 65 °C; H_3O^+; PPTS, benzene, reflux (52%).

will close to give **3** with the desired C-5 stereochemistry. In the event, irradition of a 3.8 mM solution of **4** in 9:1 acetonitrile−acetone (medium-pressure Hg Hanovia lamp, Pyrex filter) led to the formation of **3** as a single diastereomer in 80% yield. The structure and stereochemistry of **3** were confirmed by X-ray crystallographic analysis.

The introduction of the furan ring proved challenging. Direct addition of 3-furyllithium to lactone **3** led to a mixture of recovered starting material and the product of retro-Michael fragmentation of the cyclobutane ring with none of the desired lactol product. A Stille strategy for the incorporation of the furan was next examined. However, attempted formation of the enol triflate of **3** under Comins' conditions led only to retro-Michael fragmentation. We found that reaction of **3** with *n*-BuLi and Tf_2O in the presence of TMEDA at −95 °C led to the formation of the elusive enol triflate **17** in 81% yield. Stille coupling of **17** with 3-furyltributylstannane gave the furyl enol ether **18** in 95% yield. Exposure of **18** to LiOH and cyclization of the crude product with pyridinium tosylate led to the formation of (±)-saudin **1** in 52% yield, which was identical in all respects with an authentic sample with the exception of optical rotation and melting point.

The preparation of saudin in 15 steps from **5** and **6** (5% overall yield with an average 83% yield/step) illustrates the utility of the intramolecular dioxenone photocycloaddition for the assembly of structurally complex carbocyclic ring systems with high levels of stereochemical control. The synthesis of analogues of saudin to probe the basis of its hypoglycemic activity is currently underway and our progress with be reported in due course.

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Supporting Information Available: Synthetic procedures and spectroscopic data for the preparation of **1**, **3**, **4**, and **7**−**18** as well as crystallographic data for **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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