Model Study for the Total Synthesis of Antifungal Australifungin: Construction of α-Diketone and β-Ketoaldehyde Moieties

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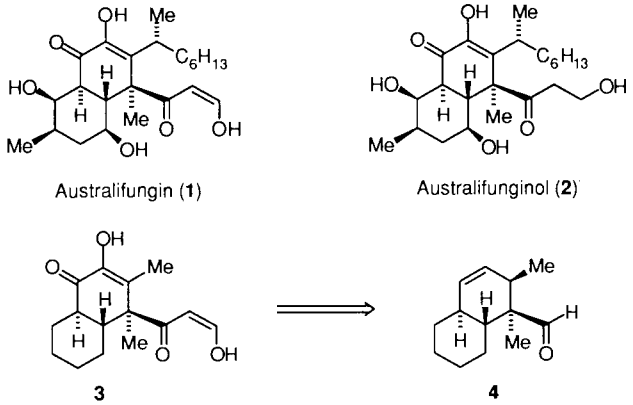
A model study for the total synthesis of australifungin was performed. Olefinic aldehyde was successfully converted to the target molecule having both α-diketone and β-ketoaldehyde moieties.

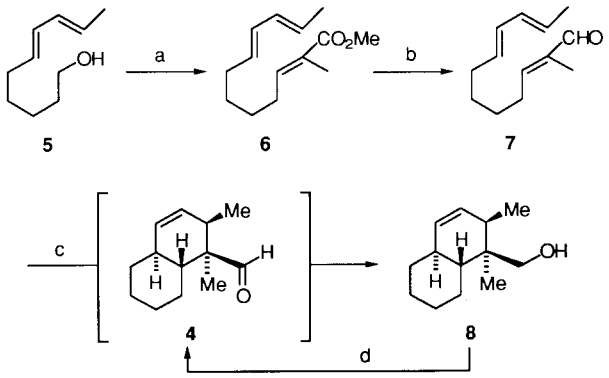
Australifungin (**1**), a potent antifungal agent, inhibits sphingolipid synthesis at the sphinganine *N*-acyltransferase.[1] In contrast to other inhibitors, **1** is structurally unique and is the first nonsphingosine-based inhibitor of sphingolipid biosynthesis. Australifungin contains a unique combination of α-diketone and β-ketoaldehyde moieties. Related australifunginol (**2**), which has a β-ketoalcohol instead of a β-ketoaldehyde moiety at C4, was considerably less active in biological assays. Interested in its intriguing structure and biological activity, we have been investigating the total synthesis of australifungin. We herein describe the synthesis of model compound **3** having both α-diketone and β-ketoaldehyde moieties. The present approach would be applicable to the total synthesis of australifungin.

Olefinic aldehyde **4**, which could be prepared by an intramolecular Diels-Alder reaction, was considered to be a key intermediate for **3**. We expected that the formyl group in **4** might be transformed into the β-ketoaldehyde moiety through an α,β-acetylenic ketone derivative (*vide post*) and that an *endo* double bond could be oxidized to the α-diketone moiety through a 1,2-diol.



Scheme 1.

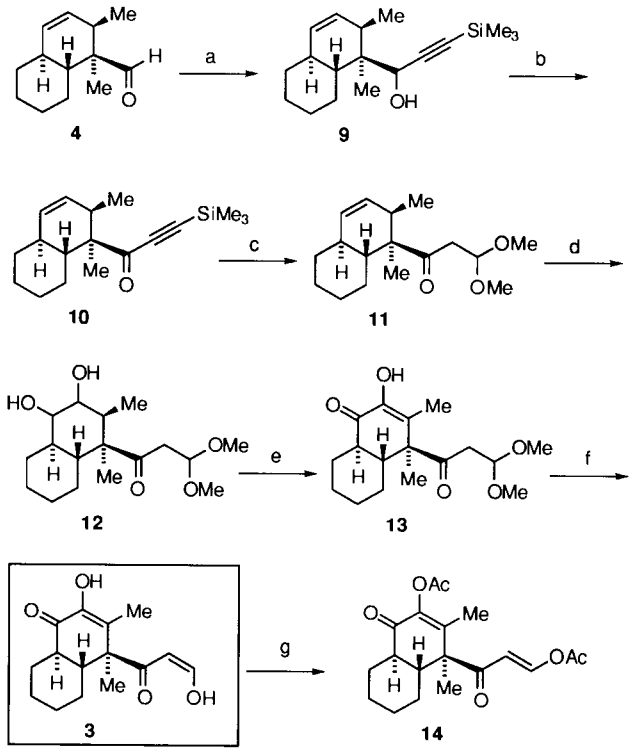
Preparation of the *trans*-decalin **4** is shown in Scheme 2. Thus, dienol **5**[2] was converted to trienoate **6**[3] by PCC oxidation followed by Wittig reaction. Reduction of **6** with Dibal-H and MnO_2 oxidation of the resulting allylic alcohol afforded trienal **7** in good yield. As anticipated, treatment of **7** with Et_2AlCl (1.3 eq) in CH_2Cl_2 effected an intramolecular Diels-Alder reaction with high *endo*-selectivity to give the *trans*-fused derivative.[4] To our surprise, the major product in the present reaction was not aldehyde **4**, but the reduced alcohol **8** (54% yield). The alcohol **8** might probably be formed by Et_2AlCl-mediated Meerwein-Ponndorf-Verley-like reduction of the initially formed aldehyde **4**.[5] Oxidation of **8** with *n*-Pr_4NRuO_4 (TPAP) and NMO provided the aldehyde **4** in 98% yield.[6]



a; (1) PCC, MS-3A, CH_2Cl_2, (2) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, 58%. **b**; (1) Dibal-H, CH_2Cl_2, -50 °C, (2) MnO_2, CH_2Cl_2, 88%. **c**; Et_2AlCl, CH_2Cl_2, 0 °C, 54%. **d**; TPAP, NMO, MS-4A, CH_2Cl_2, 98%.

Scheme 2.

Having established the decalin skeleton, we next examined construction of the α-diketone and β-ketoaldehyde moieties. For this purpose, we employed a conjugate addition of methanol to the activated alkyne.[7] Addition of lithium trimethylsilylacetylide to **4** and oxidation of the resulting **9** (diastereomeric mixture, *ca.* 5:1) gave α,β-acetylenic ketone **10** (Scheme 3). Reaction of **10** with methanol in the presence of K_2CO_3 proceeded smoothly, giving β,β-dimethoxy ketone **11** in 96% yield.[8] Formation of the α-diketone moiety was achieved in two steps. Thus, dihydroxylation of **11** with OsO_4 gave a diol in 91% yield along with 9% of its stereoisomer. These diols **12** were separately subjected to a Swern oxidation[9] to give α-diketone **13** in 81% and 75% yields from the major and minor isomers, respectively. The ^1H NMR spectrum of **13** showed signals attributable to the enolic OH (δ 6.27, s) and the vinylic Me (δ 1.74, s), which indicates that **13** exists as the requisite enolized form. Finally, careful acid hydrolysis of the dimethyl acetal in **13** with 3 M aqueous HCl and THF (1:1) provided the target compound **3** in 84% yield.[10] Synthetic **3**, similarly to **1**, has the enolized β-ketoaldehyde stabilized through internal H-bonding in the *cis* orientation as indicated by the small coupling constant (4.6 Hz).[1b] Formation of the diacetate derivative **14** from **3** unambiguously confirmed the presence of two enolic hydroxyls. In contrast to **3**, the diacetate **14** is enolized in the sterically favored *trans* configuration (J = 12.1 Hz) preferentially.



a; $HCCSiMe_3$, *n*-BuLi, THF, -78 °C, 80%. b; TPAP, NMO, MS-4A, 86%. c; K_2CO_3, MeOH, 96%. d; OsO_4, TMNO, aq. acetone, the major 91%, the minor 9%. e; DMSO, TFAA, Et_3N, -50 °C, 81% from the major, 75% from the minor. f; 3M HCl, THF, 3 h, 84%. g; Ac_2O, pyridine, quant.

Scheme 3.

In conclusion, we were able to develop a method for construction of the α-diketone and β-ketoaldehyde moieties of **1**. Further work on the total synthesis of **1** by the present strategy is now in progress and will be reported in due course.[11]

References and Notes

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3 All new compounds were fully characterized by ^{1}H NMR (270 MHz) and IR spectra, and satisfactory high-resolution MS were obtained for them. Selected data are as follows: **4**: ^{1}H NMR δ 1.02 (3H, s), 1.05 (3H, d, J = 6.9 Hz), 1.08-1.86 (10H, m), 2.01-2.06 (1H, m), 5.41 (1H, d, J = 9.9 Hz), 5.48 (1H, ddd, J = 9.9, 4.3, 2.0 Hz), 9.62 (1H, s), HRMS calcd for $C_{13}H_{20}O$ (M^+) m/z 192.1513, found 192.1520. **11**: ^{1}H NMR δ 0.78 (3H, d, J = 6.9 Hz), 1.18 (3H, s), 0.83-1.81 (10H, m), 2.03-2.07 (1H, m), 2.69 (1H, dd, J = 17.5, 4.3 Hz), 2.80 (1H, dd, J = 17.5, 5.9 Hz), 3.38 (3H, s), 3.41 (3H, s), 4.87 (1H, dd, J = 5.9, 4.3 Hz), 5.34 (1H, d, J = 9.9 Hz), 5.50 (1H, ddd, J = 9.9, 5.0, 2.0 Hz), HRMS calcd for $C_{17}H_{28}O_3$ (M^+) m/z 280.2036, found 280.2030. **13**: mp 92-94 °C; ^{1}H NMR δ 1.19 (3H, s), 1.74 (3H, s), 1.14-2.22 (9H, m), 2.41-2.44 (1H, m), 2.56 (1H, dd, J = 16.0, 5.0 Hz), 2.87 (1H, dd, J = 16.0, 6.3 Hz), 3.35 (3H, s), 3.37 (3H, s), 4.85 (1H, dd, J = 6.3, 5.0 Hz), 6.27 (1H, s), HRMS calcd for $C_{17}H_{26}O_5$ (M^+) m/z 310.1778, found 310.1776. **3**: ^{1}H NMR δ 1.25 (3H, s), 1.77 (3H, s), 1.10-2.24 (9H, m), 2.38-2.40 (1H, m), 5.65 (1H, d, J = 4.6 Hz), 6.25 (1H, s), 7.65 (1H, d, J = 4.6 Hz), 14.13 (1H, br). **14**: ^{1}H NMR δ 1.31 (3H, s), 1.70 (3H, s), 1.12-2.40 (10H, m), 2.22 (3H, s), 2.27 (3H, s), 6.27 (1H, d, J = 12.1 Hz), 8.38 (1H, d, J = 12.1 Hz), HRMS calcd for $C_{19}H_{24}O_6$ (M^+) m/z 348.1573, found 348.1570.

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7 In our early experiment, reaction of the lithium enolate of the methyl ketone derivative prepared from **4** with $HC(OMe)_3$ in the presence of BF_3•OEt_2 was unsuccessful: M. Suzuki, A. Yanagisawa, and R. Noyori, *Tetrahedron Lett.*, **23**, 3595 (1982).

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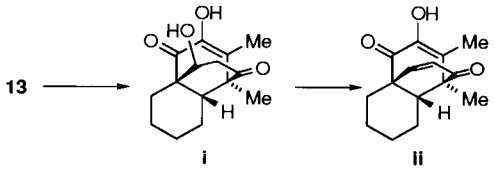
10 The present approach is the first example for the transformation of an α,β-acetylenic ketone into a β-ketoaldehyde. Further, it was also observed that a prolonged reaction time caused the undesired intramolecular aldol condensation giving **ii** (52%) along with **i** (26%). Acetylation of **ii** gave the monoacetate as a sole product.



i **ii**

11 This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.