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COMMUNICATION TO THE EDITOR

The first total synthesis of nidulalin A, a dihydroxanthone possessing multiple bioactivities

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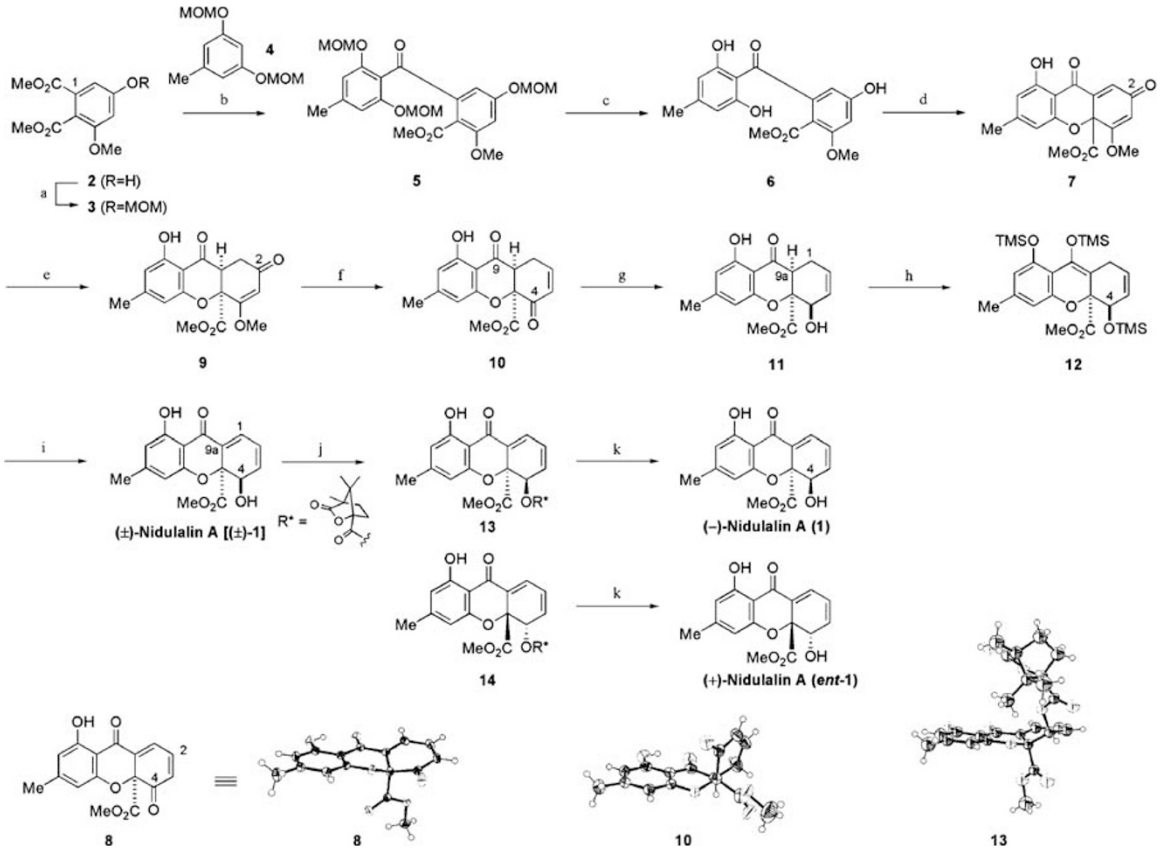
Nidulalin A (**1**) was isolated by Kawahara's group from the rice culture of an ascomycetous fungus, *Emericella nidulans* (Eidam) Vuill. var. lata (Thom and Raper) Subram. (anamorph: *Aspergillus nidulellus*, Samon and W Gams), strain IN-68.[1] The structure of nidulalin A (**1**) was determined by X-ray crystallography and Mosher's method as well as by comparison of CD spectra with known xanthone derivatives.[1] In the later studies, nidulalin A (**1**) was found to possess potent inhibitory activity against DNA topoisomerase II and immunomodulatory activity.[2,3] Although natural products having the dihydroxanthone skeleton have been seen to be widespread,[4–8] only a few total syntheses have been achieved.[9,10] Interested in the structure and bioactivities of nidulalin A, we embarked on the synthetic studies of the natural product.

An overview of our total synthesis of nidulalin A (**1**) including the ORTEP drawing of X-ray crystallography of the key intermediates is disclosed in Scheme 1. (The spectrum



Scheme 1 *Reagents and conditions*: (**a**) MOMCl, NaH, DMF, 0 °C to rt, 40 min, quant.; (**b**) *t*-BuLi, TMEDA, Et_2O-THF, −78 to −20 °C, 2 h, 90%; (**c**) TsOH•H_2O, MeOH, reflux, 5 h, quant.; (**d**) $Pb(OAc)_4$, AcONa, $MeNO_2$, rt, 10 min, 39%; (**e**) $NaBH(OAc)_3$, $B(OAc)_3$, THF, rt, 30 min, 79%; (**f**) DIBAL, THF, −78 °C, 10 min then, 6 N HCl, rt, 14 h, quant.; (**g**) $LiAlH_4$, THF, −60 °C, 2 h, 60% (recovery of SM, 30%); (**h**) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h; (**i**) SeO_2, 1,4-dioxane, 50 °C, 20 h (60% from **11**); (**j**) (−)-camphanic acid, WSCI-HCl, 4-DMAP, CH_2Cl_2, rt, 30 min, 75% (1:1); (**k**) K_2CO_3, MeOH, 0 °C, 5 h, 80% for (−)-nidulalin A (**1**), 76% for (+)-nidulalin A (*ent*-**1**).

data of compounds in Scheme 1 as well as ^{1}H and ^{13}C NMR spectra of synthetic (−)-nidulalin A (**1**) are provided as supplementary information.) The total synthesis started with dimethyl 5-hydroxy-3-methoxyphthalate (**2**).[11] The hydroxy group of **2** was protected as methoxymethyl ether to provide **3**, which was submitted to regioselective coupling to give ketone **5**. Treatment of bis(methoxymethyl ether) **4** with *t*-BuLi in the presence of *N,N′*-tetramethylethylene diamine (TMEDA) at −78 °C produced regioselectively lithiated **4**, which reacted with diester **3** regioselectively at the C-1 carbonyl group at −20 °C to provide ketone **5** in 90% yield. Acid hydrolysis of **5** gave trihydroxyketone **6** in quantitative yield. Oxidative cyclization of **6** was performed with lead (IV) tetraacetate (2 eq) in the presence of sodium acetate (23 eq) to afford tricyclic **7**, the structure of which was confirmed by X-ray crystallography. (Crystallographic data (excluding structure factors) for the structures of **7**, **8**, **10**, **13**, **14**, and **1** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 728664 for **7**, 728665 for **8**, 728666 for **10**, 728667 for **13**, 728668 for **14**, and 728669 for **1**.)

1,2-Reduction of **7** at the C-2 position with DIBAL (in CH_2Cl_2, −78 °C, 30 min) followed by hydrolysis of methyl vinyl ether (addition of THF, 6 N HCl, rt, 2 h) gave enone **8** (the ORTEP drawing is shown in Scheme 1). The hydride reduction of **8** gave 4-*epi*-nidulalin A exclusively.[12] As the methoxycarbonyl group of **8** covered the α-face of C-4 carbon, hydride attacked the C-4 carbonyl group from the β-face to give the α alcohol (4-*epi*-nidulalin A). To invert the face selectivity, we set up *cis*-fused intermediate **10**, which would be submitted to hydride addition from the α-face (the convex face) to give β-alcohol **11**.

The *cis*-fused **9** was derived by 1,4-reduction of the oxidative cyclization product **7**. The subsequent regio-selective reduction of C-2 ketone and hydrolysis gave enone **10** whose structure was determined by X-ray crystallography (the ORTEP drawing is shown in Scheme 1). The α-face of **10** was situated as the convex face as expected. Enone **10** was submitted to regio- and stereoselective reduction to afford β-alcohol **11**. To avoid reduction at the C-9 position of ketone **10**, the reaction mixture was quenched after stirring at −60 °C for 2 h. Dehydrogenation to construct Δ1,9a double bond of nidulalin A was performed in two steps. Treatment of ketone **11** with TMSOTf in the presence of Et_3N provided silyl enol ether **12** concomitant with protection of alcohol. Allylic oxidation of **12** proceeded with SeO_2 at 50 °C, accompanied by de-*O*-silylation at position C-4, to give (±)-nidulalin A [(±)−**1**]. Spectral properties of synthetic (±)−**1** were identical with those of natural products including ^{1}H NMR, ^{13}C NMR, IR and MS.[1]

(±)-Nidulalin A in hand, we next examined resolving the enantiomers with a chiral auxiliary. Esterification of (±)-nidulalin A [(±)−**1**] with (−)-camphanic acid gave diastereomers separable by silica gel column chromatography. The absolute structures of both isomers were determined by X-ray crystallography (the ORTEP drawing of (4*R*, 4a*S*)-nidulalin A ester **13** is shown in Scheme 1). Saponification of camphanic ester of (4*R*, 4a*S*)-nidulalin A (**13**) gave orange crystals of **1**, the solution of which showed the optical rotation $[\alpha]_D^{24}$ –570° (*c* 0.28, $CHCl_3$), levorotatory as the natural nidulalin A[12] (orange needles, $[\alpha]_D^{25}$ −463° (*c* 0.28, $CHCl_3$)). (4*S*, 4a*R*)-nidulalin A (*ent*-**1**) was also obtained from the other diastereomer **14** by the same procedure as above. (4*S*, 4a*R*)-nidulalin A shows the optical rotation $[\alpha]_D^{25}$ +569° (*c* 0.28, $CHCl_3$), being (+)-nidulalin A. Therefore, (−)-nidulalin A was synthesized to confirm the structure of the natural product.

In conclusion, the first total synthesis of nidulalin A has been achieved. Construction of the stereogenic center at the C-4 position was accomplished through *cis*-fused tricyclic intermediate **10** to submit the stereospecific reduction. (−)- and (+)-nidulalin A was obtained from (±)-nidulalin A by derivation to (−)-camphanic esters.

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Supplementary Information accompanies the paper on the Journal of Antibiotics website (http://www.nature.com/ja)