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Synthetic Transformation of Ptychantin into Forskolin and 1,9-Dideoxyforskolin

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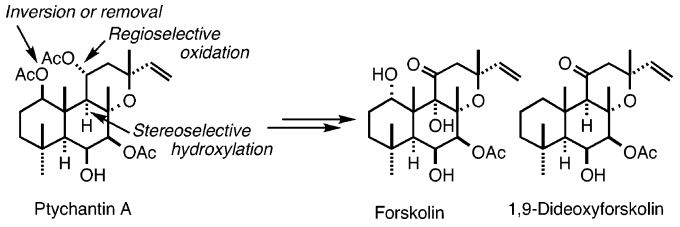

Forskolin (**1**), a highly oxygenated labdane diterpenoid and an activator of adenylate cyclase, has been synthesized in 12 steps and 12% overall yield from ptychantin A (**4**), which has been isolated from liverwort *Ptychanthus striatus* in good yield. The 1α-hydroxy group was furnished by stereoselective reduction of the corresponding carbonyl group by sodium in *t*-BuOH. The 9α-hydroxy group was introduced stereoselectively by epoxidation of $\Delta^{9.11}$-enolether. 1,9-Dideoxyforskolin (**2**), an inhibitor of glucose transporter, has been synthesized in 8 steps and 37% overall yield. The hydroxy group at C-1 was removed by solid-state thicarbonylimidazolation and subsequent radical cleavage.

Introduction

The Indian herb *Coleus forskolii* has been utilized as a traditional folk medicine to treat disorders of the digestive organs.[1] In 1977, a research group from Hoechst, India isolated the labdane diterpenoids forskolin (**1**), 1,9-dideoxyforkolin (**2**), and their congeners from the roots of *C. forskolii*.[2] Since forskolin (**1**) and some congeners display blood pressure lowering and cardio protective properties,[1] the physiological activities of forskolins have been extensively investigated and shown to have therapeutic potential in glaucoma, congestive heart failure, bronchial asthmas, etc.[3]

The right ring of the Decalin portion of forskolin (**1**) has a structural similarity with α-D-galactose (**3**). As a result, forskolin (**1**) binds to the glucose transporter to activate adenylate cyclase, an enzyme regulating the level of cAMP, and subsequently activates protein kinase.[4] Due to its activity, forskolin (**1**) has been an important tool for studying the physiological role of adenylate cyclase and related phenomena.[5]

Forskolin (**1**) is a highly oxygenated labdane diterpenoid with four alkoxy substituents and a tetrahydropyran ring. Seven out of eight asymmetric centers are located in the Decalin portion.

The interesting physiological activities along with an attractive chemical structure stimulated organic chemists toward synthetic studies of forskolin (**1**).[6] In 1987 Ziegler et al.[7] reported a formal total synthesis, and in 1988, the Hashimoto[8] and Corey[9] groups

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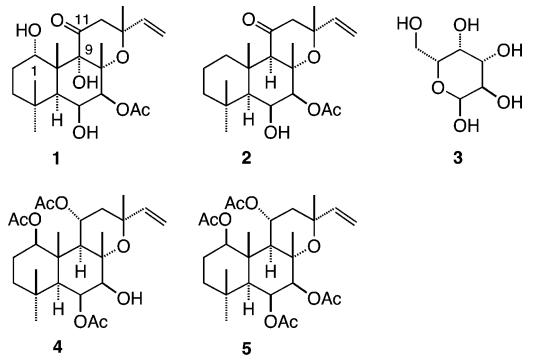
independently completed total syntheses using an intramolecular Diels−Alder strategy. Subsequently, in 1996 Lett et al.[10] described an alternative total synthesis starting from Corey's intermediate.[9a] However, all synthetic routes toward forskolin (**1**) provided racemic material, even though Corey[9b] and Lett[10c] demonstrated the possibility of a nonracemic synthesis by employing an optically active intermediate.

1,9-Dideoxyforskolin (**2**), a second major constituent of *C. forskolii*, does not have antihypertensive activity but exhibits strong inhibitory activity toward glucose transport in rat's adipocytes in the micromolar range without stimulating adenylate cyclase,[11] which is expected to treat diseases caused by abnormal glucose uptake such as Alzheimers, diabetes, or cancer.[4] Due to this interesting activity, a synthetic approach by Morin et al. from the natural diterpenoid larixol appeared in 2001.[12]



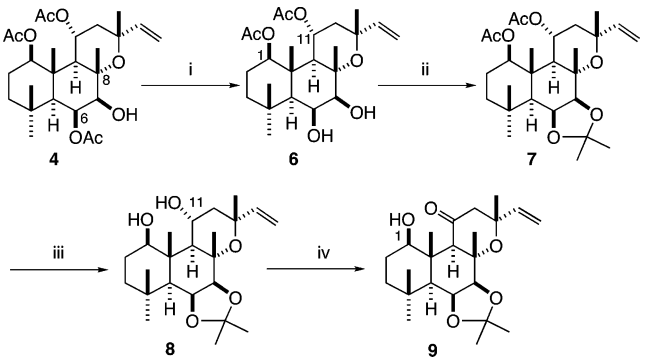
Recently, the new labdane diterpenoids ptychantin A (**4**) and B (**5**) and related compounds have been isolated from the common liverwort *Ptychanthus striatus* in western Japan.[13] These compounds, although not antihypertensive, have the same ring framework with the same absolute stereostructure and similar oxygenated functionalities, and are expected to be starting materials for the forskolin synthesis since they were found in higher contents in the liverwort (6.7 g from 1 kg of dry *P. striatus*).

In the present study, syntheses of forskolin (**1**) and 1,9-dideoxyforskolin (**2**) were investigated starting from ptychantins A (**4**) and B (**5**).

Results and Discussions

Several issues must be taken into consideration prior to embarking on a synthetic study of ptychantin A (**4**) and B (**5**). Four hydroxy groups are found in similar structural environments, which makes the selective manipulation of each hydroxy group difficult. The β-face of the molecule is highly congested due to the presence of four axial methyl groups and a hydroxy function. The tetrahydropyran ring of the 11-keto derivative is not stable and is opened easily under acidic reaction conditions. In addition, the C-9 of the 11-keto derivative of **4** is prone to epimerize under weakly basic reaction conditions. Thus, mild and selective reaction conditions are required for satisfactory transformations to the desired compounds **1** and **2**.

SCHEME 1[a]



[a] Reagents and conditions: (i) KOH, MeOH, rt, 13 h, 100%; (ii) 2,2-dimethoxypropane, PTSA, rt, 93%; (iii) LAH, Et_2O, rt, 2.5 h, 96%; (iv) PCC, AcONa, CH_2Cl_2, rt, 3 h, 89%.

Transformation of Ptychantin A (4) and B (5) to a Common Intermediate, Hydroxy Ketone 9. At an initial stage, the selective transformation of four hydroxy groups was investigated, leading to a common intermediate **9** for forskolin (**1**) and 1,9-dideoxyforskolin (**2**) syntheses (Scheme 1). Treatment of ptychantin A (**4**) with potassium hydroxide in methanol led to the selective hydrolysis of the 6-acetoxy group to give 6,7-diol **6** quantitatively. This selectivity is probably due to severe 1,3-diaxial repulsion by the three methyl groups at C-4, -8, and -10 to transfer acetyl group to the neighboring 7-OH group in intramolecular fashion and subsequent hydrolysis, though any other intermediate was not observed by TLC monitoring. Hydrolysis of ptychantin B (**5**) proceeded in a similar manner to provide the diol **6** in 89% yield.

Before manipulation of the acetoxy groups at C-1 and C-11 of diol **6**, it was required to install appropriate protecting groups at C-6 and C-7. Since the hydroxy group at C-6 is highly hindered and thus less reactive, it was anticipated initially that protection at this position was not required. Selective protection of the C-7 hydroxy group as a TES or an MOM ether was successful. However, for subsequent transformations, the C-1 and C-11 acetoxy groups were not satisfactory due to their instability. Thus, both C-6 and C-7 hydroxy groups were protected to give acetal **7** in 93% yield. Among other acetal protecting groups, the methylene, anisylidene, or cyclopentylidene acetals were not satisfactory either due to their lability or too stable nature during protection or deprotection.

The acetoxy groups at C-1 and C-11 of acetonide **7** were reduced with lithium aluminumhydride to provide diol **8** in 96% yield. After several attempts, the less hindered hydroxy group at C-11 was selectively oxidized by pyridinium chlorochromate to give a 89% yield of hydroxy-ketone **9** in 89% yield, which is a common precursor for the synthesis of forskolin (**1**) and 1,9-dideoxyforskolin (**2**). The steric congestion at the neopentyl C-1 of **8** might allow the selective oxidation of the α-equatorial hydroxy group at C-11.

Synthesis of 1,9-Dideoxyforskolin (2). With the common intermediate **9** in hand, the synthesis of 1,9-dideoxyforskolin (**2**) was investigated first (Scheme 2). Removal of the hydroxy group at C-1 of hydroxy-ketone **9** was investigated by radical

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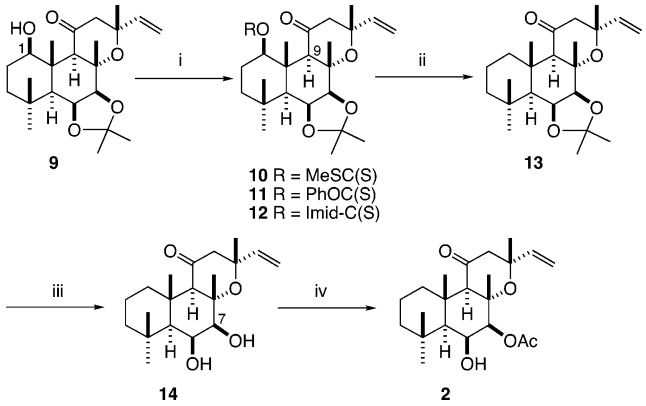
SCHEME 2 [a]



[a] Reagents and conditions: (i) *n*-BuLi, CS_2, MeI, THF, 0 °C, 4 h, 33% for **10**; phenyl chlorothionoformate, DMAP, $CHCl_3$, reflux, 23 h, 54% for **11**; thiocarbonyldiimidazole, DMAP, 2 h, 82% for **12**; (ii) AIBN, *n*-Bu_3SnH, toluene,100−120 °C, 30−45 min, 72% from **10**, 41% from **11**, 86% from **12**; (iii) 10% $HClO_4$, THF (1:2), rt, 7 days, 100%; (iv) Ac_2O, Pyr, DMAP, 0 °C, 1 h, 86%.

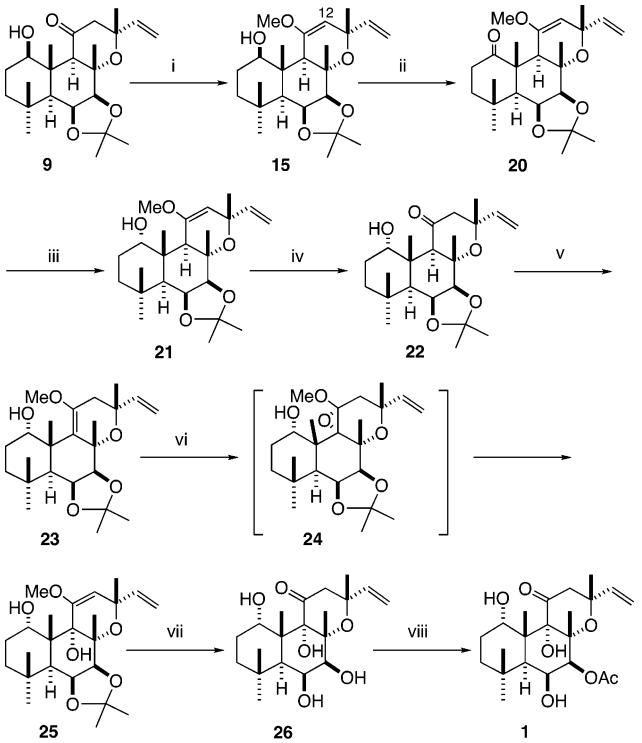
deoxygenation, since the hydroxy group was located at a highly hindered neopentyl position. An initial attempt to prepare xanthate ester **10** provided the desired product in 33% yield. The low yield is due to the formation of a byproduct, an epimer at C-9. To prevent the epimerization, the procedure was investigated under nonbasic condition. Phenylthionocarbonylformate (**11**)[14] was obtained in 54% yield. The yield of radical precursor was further improved by employing a solid state reaction with thiocarbonyldiimidazole in the presence of DMAP at 50 °C, originally developed by us,[15] to afford thiocarbonylimidazolide (**12**) in 82% yield. The reaction in THF did not go to completion even in 23 h.

The radical cleavage of the xanthate **10** and the imidazolide **12** with tri-*n*-butyltin hydride and azobisisobutyronitrile in toluene at 120 °C provided ketone **13** in 72% and 86% yield, respectively. On the other hand, the reaction of phenylthionocarbonylformate (**11**) resulted in a 41% yield of the desired product in addition to several unidentified products.

Deprotection of the acetonide moiety of ketone **13** proceeded with 10% perchloric acid in THF at room temperature sluggishly in 7 days but in quantitative yield to the naturally occurring 7-desacetyl-1,9-dideoxyforskolin (**14**).[2] A selective acetylation of the hydroxy group at C-7 with acetic anhydride and DMAP furnished 1,9-dideoxyfroskolin (**2**) in 86% yield. The spectral data including the optical rotation were identical with those reported. Thus, the total synthesis of 1,9-dideoxyforskolin (**2**) was accomplished for the first time in 8 steps and 37% overall yield from ptychantin A (**4**) or B (**5**).[16]

Synthesis of Forskolin (1). The initial task for the forskolin (**1**) synthesis is the epimerization of the *β*-hydroxy group at C-1 of the 11-keto derivative **9**, since the hydroxy group at C-1 should be in the α-axial configuration for a selective introduction of the 9α-hydroxy group (Scheme 3). However, Mitsunobu inversion[17] led to complete recovery of starting material **9** due

SCHEME 3 [a]



[a] Reagents and conditions: (i) KH, Me_2SO_4, THF, 0 °C, 30 min, 54%; (ii) CrO_3, pyridine, CH_2Cl_2, rt, 24 h, 80%; (iii) Na, *t*-BuOH, 30 °C, 29 h, 100%; (iv) 1% HCl, THF, rt, 15 min, 100%; (v) KH, Me_2SO_4, THF, rt, 8 min, 96%; (vi) MCPBA, CH_2Cl_2, K_2CO_3, 0 °C, 30 min, 61%; (vii) 10% $HClO_4$, THF, rt, 11 days, 59%; (viii) Ac_2O, pyridine, 0 °C, 18 h, 100%.

to neopentyl steric congestion. The mesylate could not be formed. The inversion at C-1 was investigated by an oxidation−reduction protocol, which required the protection of the 11-keto group. However, attempts to protect the 11-keto group as an acetal also led to recovered **9** even with TMSOTf and TMSOMe. Then, treatment of **9** with potassium hydride and dimethyl sulfate in THF provided selectively the $\Delta^{11,12}$-enolether **15** in 54% yield. In contrast, trapping the enolate with *tert*-butyldimethylsilyl chloride gave the corresponding $\Delta^{11,12}$-enolether in much lower yield. Since the $\Delta^{9,11}$-enolether **16** is 3.5 kcal/mol more stable than the $\Delta^{11,12}$-enolether **15** according to a PM3 calculation, the reaction might proceed via kinetic control. With an aim to prepare the tetrasubstituted $\Delta^{9,11}$-enolether **16**, which is a precursor for the introduction of a hydroxy group at C-9 (vide infra), the 11-keto derivative **9** was treated under thermodynamically controlled reaction conditions with potassium *tert*-butoxide and dimethyl sulfate in *t*-BuOH. However, a reaction either at room temperature or at 50 °C resulted in the exclusive formation of the $\Delta^{11,12}$-enolether **17**, an epimer of **15** at C-9. Facile epimerization at C-9 is rationalized by the relief of severe 1,3-diaxial interactions of the methyl group at C-8 by the C-10 and C-13 methyl groups that drive the C-8 methyl group into an equatorial orientation. Actually, in the absence of dimethyl sulfate, the C-9 of the 11-keto derivative **9** was epimerized quantitatively by potassium *tert*-butoxide in *t*-BuOH at room temperature. Mitsunobu inversion of the enolether **15** also resulted in recovery of the starting material.

Attempts to oxidize enolether **15** by TPAP, Swern, or Ag_2CO_3 led to recovery of starting material. PCC or PDC oxidation

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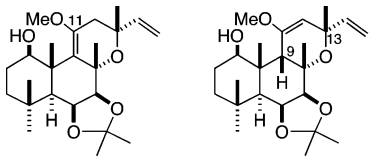
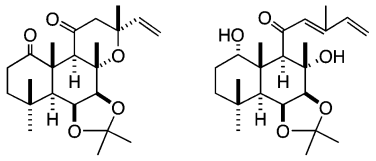
provided the 1,11-diketo compound **18** due to the very sensitive nature of the enolether **15** to hydrolysis even under weakly acidic reaction conditions. Fortunately, a Sarret oxidation was successful probably due to the basic reaction conditions to give the desired 1-keto derivative **20** in 80% yield. Among various reduction conditions tested, reduction of **20** by sodium in *t*-BuOH[18] at 30 °C provided the desired 1α-hydroxy derivative **21** in 100% yield. Steric repulsion by the α-equatorial methoxy group at C-11 (peri-repulsion) might position the intermediary ketyl radical at C-1 in the thermodynamically more stable α-axial configuration. However, attempts to reduce the 1,11-diketo compound **18** by various reducing agents resulted in epimerization at C-9 and provided mainly 1*β*-hydroxy derivative. Hydrolysis of 11,12-enolether **21** was carried out by 1% HCl to give the 11-keto derivative **22** quantitatively. More acidic reaction conditions resulted in the exclusive opening of the tetrahydropyran ring to give **19**.





The requisite 9α-hydroxy group was introduced according to the modified procedure by Hrib[19] as follows. Treatment of potassium hydride and dimethyl sulfate afforded the $\Delta^{9,11}$-enolether **23** selectively in 96% yield. A higher regioselectivity might originate from the abstraction of the 9α-proton by the 1α-alkoxide to give the $\Delta^{9,11}$-enolate. Epoxidation of the enolether **23** with MCPBA in the presence of potassium carbonate furnished the 9α-hydroxy-11,12-enolether **25** in 61% yield. The epoxidation proceeded from the less hindered α-face of the molecule to give the α-epoxide **24** probably via interaction of MCPBA with the 1α-hydoxy group of **23**, followed by hydrolysis. Hydrolysis of the methyl enolether **25** proceeded smoothly without tetrahydropyran ring opening. However, the acetonide at C-6,7 resisted hydrolysis.[10b] After prolonged exposure to weakly acidic conditions for 11 days, deprotection of the acetonide was successful and gave the naturally occurring 7-desacetylforskolin (**26**)[2] in 59% yield. Extensive investigations of a variety of acidic reaction conditions in the presence or absence of semicarbazide[9a] did not facilitate the hydrolysis. Catalysis by stronger acid resulted in opening of the pyran ring. Finally, conventional acetylation of **26** completed quantitatively the synthesis of forskolin (**1**) in natural form and in 12 steps from ptychantin A (**4**) in 12% overall yield. The spectroscopic data of our sample were identical with those reported, including the optical rotation (Scheme 3).

In summary, we have completed the syntheses of forskolin (**1**) and 1,9-dideoxyforskolin (**2**) from ptychantin A (**4**) and B (**5**). Since ptychantins are available in large quantity from the liverwort, the present protocol is expected to offer an improved practical supply of the physiologically potent compounds **1** and **2**.

Experimental Section

(2*S*,7*S*,13*S*,6*R*,9*R*,14*R*)-14-(Imidazolylthioxomethoxy)-4,4,7,9,-13,17,17-heptamethyl-3,5,8-trioxa-9-vinyltetracyclo[11.4.0.0^{2,6}0^{7,12}]-heptadecan-11-one (12). A solution of hydroxy-ketone **9** (21 mg, 0.054 mmol), thiocarbonyldiimidazolide (29 mg, 0.16 mmol), and (dimethylamino)pyridine (2 mg, 0.16 mmol) in a minimum amount of ether was evaporated to dryness. Resulting solid was heated at 50 °C for 2.5 h under nitrogen atmosphere. Purification of residue by column chromatography and subsequent medium-pressure LC (eluent: ethyl acetate:*n*-hexane 2:1) afforded thiocarbonylimiazolide **12** (21 mg, 82%) as an oil: $[\alpha]^{25}_{D}$ +40.6 (*c* 1.18); ν_{max}/cm^{-1} 1721, 1460, 1392, 1289, and 1163; ^{1}H NMR (200 MHz) δ 1.07 (s, 3H), 1.23 (s, 3H), 1.26 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.57 (s, 3H), 1.67 (s, 3H), 1.00−1.80 (m, 5H), 2.21 (d, 1H, J = 12.8 Hz), 2.72 (d, 1H, J = 12.8 Hz), 2.91 (s, 1H), 4.31 (d, 1H, J = 6.6 Hz), 4.63 (dd, 1H, J = 6.6, 4.0 Hz), 4.98 (d, 1H, J = 10.6 Hz), 5.15 (d, 1H, J = 17.2 Hz), 5.47 (dd, 1H, J = 11.3, 4.8 Hz), 5.89 (dd, 1H, J = 17.2, 10.6 Hz), 7.06 (s, 1H), 7.69 (s, 1H), and 8.40 (s, 1H); ^{13}C NMR (50 MHz) δ 14.6 (q), 23.1 (q), 24.3 (q), 24.9 (q), 25.0 (q), 26.1 (t), 28.4 (q), 32.0 (q), 34.0 (s), 40.6 (t), 41.3 (s), 51.9 (d), 54.3 (t), 65.4 (d), 74.1 (d), 79.4 (s), 83.2 (s), 84.4 (d), 90.3 (d), 109.4 (d), 111.0 (t), 118.1 (d), 130.4 (d), 137.7 (d), 145.8 (d), 184.4 (s), and 207.1 (s); *m*/*z* (EI) 502.2511 (7%, M^+, $C_{27}H_{38}N_2O_5S$ requires 502.2501), 231 (71), 153 (100), 123 (93), 95 (86), 69 (86).

(2*S*,7*S*,13*S*,6*R*,9*R*)-4,4,7,9,13,17,17-Heptamethyl-3,5,8-trioxa-9-vinyltetracyclo[11.4.0.0^{2,6}0^{7,12}]heptadecan-11-one (13). A solution of thiocarbonylimidazolide **12** (11 mg, 0.024 mmol), tributyltinhydride (8 μL, 0.029 mmol), and azobisisobutyronitrile (0.4 mg, 0.0024 mmol) in toluene (1 mL) was heated at 100 °C for 15 min under nitrogen atmosphere. After addition of extra tributyltinhydride (8 μL, 0.029 mmol) and azobisisobutyronitrile (0.4 mg, 0.0024 mmol), the solution was heated at 100 °C for 15 min. Column chromatography (eluent: ethyl acetate:*n*-hexane = 1:1) followed by medium-pressure LC purification (eluent: ethyl acetate: *n*-hexane = 1:5) provided acetonide **13** (7.8 mg, 86%) as a solid: mp 143 °C; $[\alpha]^{20}_{D}$ −17.3 (*c* 0.78); ν_{max}/cm^{-1} 1718, 1381, 1367, 1250, 1203, and 1182; ^{1}H NMR (200 MHz) δ 1.00 (s, 3H), 1.14 (s, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.54 (s, 3H), 0.75−1.95 (m, 6H), 2.42 (m, 1H), 2.52 (d, 1H, J = 17.2 Hz), 2.61 (s, 1H), 2.67 (d, 1H, J = 17.2 Hz), 4.30 (d, 1H, J = 6.6 Hz), 4.59 (dd, 1H, J = 6.6, 3.7 Hz), 5.03 (dd, 1H, J = 10.6, 0.9 Hz), 5.19 (dd, 1H, J = 17.5, 0.9 Hz), and 5.98 (dd, 1H, J = 17.5, 10.6 Hz); ^{13}C NMR (50 MHz) δ 17.5 (q), 18.3 (t), 23.3 (q), 25.0 (q), 26.2 (q), 26.6 (q), 31.0 (q), 32.7 (q), 34.3 (s), 36.0 (s), 39.9 (t), 43.3 (t), 50.6 (t), 53.9 (d), 65.0 (d), 74.3 (d), 75.8 (s), 80.1 (s), 84.9 (d), 109.0 (s), 111.7 (t), 146.8 (d), and 206.9 (s); *m*/*z* (EI) 376.2611 (9%, M^+, $C_{23}H_{36}O_4$ requires 376.2613), 361 (94), 291 (29), 233 (100), 95 (29), 43 (68).

(1*S*,7*S*,9*S*,5*R*,8*R*)-8,9-Dihydroxy-1,5,7,11,11-pentamethyl-6-oxa-vinyltricyclo[8.4.0.0$^{-2,7}$]tetradecan-3-one (14). A solution of acetonide **13** (16 mg, 0.042 mmol) in THF (2 mL) and 10% perchloric acid (1 mL) was stirred at ambient temperature for 109 h. Reaction was quenched by addition of aq sodium hydrogencarbonate. Product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Residue was purified by column chromatography (eluent: ethyl acetate:*n*-hexane 1:1) to give dihydroxy-ketone **14** (16 mg, quantitative) as a solid: mp 152 °C; $[\alpha]^{25}_{D}$ −96.0 (*c* 1.80); ν_{max}/cm^{-1} 1721, 1365, 1221, and 1182; ^{1}H NMR (200 MHz) δ 0.97 (s, 3H), 1.21 (s, 3H), 1.28 (s, 3H), 1.38 (s, 3H), 1.50 (s, 3H), 0.70−1.90 (m, 6H), 2.11 (br s, 1H), 2.46 (m, 1H), 2.58 (d, 1H, J = 18.3 Hz), 2.60 (s, 1H), 2.68 (d, 1H, J = 18.3 Hz), 2.88 (br s, 1H), 3.71 (d, 1H, J = 3.8 Hz), 4.39 (br s, 1H), 5.05 (d, 1H, J = 10.4 Hz), 5.16 (d, 1H, J =

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17.5 Hz), and 5.95 (dd, 1H, J = 17.5, 10.4 Hz); ^{13}C NMR (50 MHz) δ 17.0 (q), 18.4 (t), 23.5 (q), 23.8 (q), 31.4 (q), 33.3 (q), 34.2 (s), 37.8 (s), 41.2 (t), 43.6 (t), 49.8 (t), 55.1 (d), 65.2 (d), 70.2 (d), 75.1 (s), 79.7 (s), 80.8 (d), 112.2 (t), 146.4 (d), and 206.1 (s),; *m*/*z* (EI) 336.2299 (25%, M^+, $C_{20}H_{32}O_4$ requires 336.2300), 321 (61), 251 (100), 207 (65), 69 (48), 43 (58).

1,9-Dideoxyforskolin (2). To a solution of dihydroxy-ketone **14** (16 mg, 0.042 mmol) in pyridine (0.5 mL) was added DMAP (1.5 mg, 0.012 mmol) and acetic anhydride (6 μL, 0.061 mmol) at 0 °C under nitrogen atmosphere. After the solution was stirred at 0 °C for 1 h, the reaction was quenched by addition of water. Product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Residue was purified by column chromatography (eluent: ethyl acetate:*n*-hexane 1:1) followed by medium-pressure LC (eluent: ethyl acetate:*n*-hexane 1:2) affording 1,9-dideoxyforskolin (**2**) (14 mg, 86%) as a solid: mp 158 °C (lit.[2] mp 162−165 °C); $[\alpha]_D$ −89.2 (*c* 0.81, $CHCl_3$) {lit.[2] $[\alpha]_D$ −89.4 (*c* 2.45, $CHCl_3$)}; ν_{max}/cm^{-1} 3605, 1746, 1721, 1370, 1237, and 1213; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.75 (1H, td, J = 13, 3.3 Hz), 0.86 (1H, br s), 0.88 (s, 3H), 1.10 (1H, m), 1.13 (s, 3H), 1.14 (s, 3H), 1.24 (1H, d, J = 12.7 Hz), 1.30 (1H, m), 1.31 (s, 3H), 1.48 (s, 3H), 1.63 (1H, qt, J = 13.5, 3 Hz), 2.08 (s, 3H), 2.27 (1H, d, J = 12.8 Hz), 2.48 (1H, br s), 2.56 (1H, d, J = 18 Hz), 2.66 (1H, td, J = 13, 3.3 Hz), 2.68 (1H, d, J = 18 Hz), 4.20 (1H, br s), 4.80 (1H, d, J = 5.3 Hz), 5.01 (1H, dd, J = 10.7, 1.2 Hz), 5.21 (1H, dd, J = 17.4, 1.2 Hz), and 5.96 (1H, dd, J = 17.4, 10.7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.6, 18.2, 23.7, 24.0, 31.3, 33.0, 34.0, 37.4, 40.8, 43.3, 49.8, 54.1, 65.4, 67.3, 74.8, 78.0, 81.4, 112.5, 147.0, 170.3, and 206.3; *m*/*z* (EI) 379.2491 (6%, $M^+ + 1$, $C_{21}H_{35}O_5$ requires 379.2484), 311 (40), 309 (47), 303 (99), 251 (56), 249 (100).

(1*S*,6*S*,12*S*,16*S*,2*R*,11*R*)-14-Methoxy-1,4,4,8,8,12,16-heptamethyl-3,5, 17-trioxa-16-vinyltetracyclo[11.4.0.0.^{2,6}0^{7,12}]heptadec-14-en-11-ol (15). To a stirred mixture of potassium hydride (31 mg, 0.27 mmol) and dimethyl sulfate (15 μL, 0.163 mmol) in THF (0.5 mL) was added a solution of hydroxy-ketone **9** (21 mg, 0.0543 mmol) in THF (0.9 mL) at 0 °C under nitrogen atmosphere. After the solution was stirred for 30 min, the reaction was quenched by addition of aq ammonium chloride. Product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and evaporated to dryness. Residue was purified by medium-pressure LC (eluent: ethyl acetate:*n*-hexane = 1:2) to give enolether **15** (12 mg, 54%) as a colorless oil that decomposed soon after NMR measurement: ^{1}H NMR (200 MHz) δ 1.02 (s, 3H), 1.15 (s, 3H), 1.29 (s, 3H), 1.30 (s × 2, 6H), 1.37 (s, 3H), 1.54 (s, 3H), 0.81−2.20 (m, 5H), 2.25 (s, 1H), 3.29 (t like, 1H), 3.70 (s, 3H), 4.16 (d, 1H, J = 6.8 Hz), 0.4.62 (dd, 1H, J = 6.8, 3.7 Hz), 4.77 (d, 1H, J = 1.8 Hz), 4.86 (dd, 1H, J = 10.3, 1.7 Hz), 5.12 (dd, 1H, J = 17.1, 1.7 Hz), 5.63 (s, 1H, OH), and 5.82 (dd, 1H, J = 17.1, 10.3 Hz); ^{13}C NMR (50 MHz) δ 14.5 (q), 23.3 (q), 24.1 (q), 25.1 (q), 26.1 (q), 28.0 (t), 30.3 (q), 32.6 (q), 34.4 (s), 40.3 (t), 43.9 (s), 51.2 (d), 54.8 (q), 55.8 (d), 74.2 (d), 74.4 (s), 78.5 (d), 80.7 (s), 83.6 (d), 101.2 (d), 108.9 (s), 110.2 (t), 144.3 (d), and 154.8 (s).

(1*S*,6*S*,12*S*,16*S*,2*R*)-14-Hydroxy-4,4,7,9,13,17,17-heptamethyl-3,5,8-trioxa-9-vinyltetracyclo[11.4.0.0.^{2,6}0^{7,12}]heptadecan-11-on (20). To a stirred solution of pyridine (0.38 mL, 4.7 mmol) in dichloromethane (5 mL) was added chromium oxide (235 mg, 2.35 mmol) at 0 °C. After the solution was stirred for 1 h at ambient temperature, enolether **15** (95 mg, 0.235 mmol) in dichloromethane (11 mL) was added. The resulting slurry was stirred for 24 h at ambient temperature under nitrogen atmosphere and subsequently diluted with ethyl acetate. The organic layer was passed through a short silica gel column and evaporated to dryness. Residue was purified by medium-pressure LC (eluent: ethyl acetate:*n*-hexane 2:1) to afford keto−enolether **20** (76 mg, 80%) as a solid: mp 133 °C; $[\alpha]^{20}_D$ +87.7 (*c* 1.31); ν_{max}/cm^{-1} 3542, 1703, 1460, 1369, 1251, 1205, and 1159; ^{1}H NMR (200 MHz) δ 1.04 (s, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.56 (s, 3H), 1.60 (s, 3H), 1.10−1.90 (m, 3H), 2.14 (ddd, 1H, J = 11.8, 4.4, 2.8 Hz), 2.65 (s, 1H), 3.29 (ddd, 1H, J = 14.0, 11.8, 6.6 Hz), 3.47 (s, 3H), 4.08 (d, 1H, J = 6.5 Hz), 4.47−4.52 (m, 2H), 4.82 (dd, 1H, J = 10.3, 1.7 Hz), 5.15 (dd, 1H, J = 17.5, 1.7 Hz) and 5.83 (dd, 1H, J = 17.5, 10.3 Hz); ^{13}C NMR (50 MHz) δ 19.6 (q), 23.8 (q), 23.9 (q), 25.1 (q), 26.0 (q), 29.6 (q), 31.1 (q), 34.9 (s), 35.1 (t), 46.2 (t), 47.5 (d), 50.7 (s), 54.3 (q), 56.3 (d), 74.7 (d), 75.3 (s), 78.7 (s), 83.7 (d), 97.8 (d), 109.1 (t), 109.5 (s), 144.7 (d), 154.3 (s), and 214.2 (s); *m*/*z* (EI) 404.2561 (12%, M^+, $C_{24}H_{36}O_5$ requires 404.2563), 389 (100), 361 (76), 203 (30), 123 (33), 43 (61).

(1*S*,6*S*,11*S*,12*S*,2*R*)-14-Methoxy-1,4,4,8,8,12,16-heptamethyl-3,5,17-trioxa-16-vinyltetracyclo[11.4.0.0.^{2,6}0^{7,12}]heptadec-14-en-11-ol (21). A mixture of keto−enolether **20** (25 mg, 0.0618 mmol) and sodium (40 mg, 1.61 mmol) in *tert*-butyl alcohol (3 mL) was stirred at 30 °C for 3 h under nitrogen atmosphere. Extra sodium (142 mg, 6.18 mmol) and *tert*-butyl alcohol (4 mL) were added. After the solution was stirred for 26 h, the reaction was quenched by addition of two drops of aq ammonium chloride from a Pasteur pipet. The organic layer was passed through a short silica gel column and evaporated to dryness. The residue was purified by column chromatography (eluent: ethyl acetate:*n*-hexane 1:2) to provide hydroxy-ketone **21** (25 mg, 100%) as a solid: mp 98 °C; $[\alpha]^{20}_D$ 95.2 (*c* 0.876); ν_{max}/cm^{-1} 3632, 1651, 1462, 1381, 1251, 1208, and 1157; ^{1}H NMR (200 MHz) δ 1.04 (s, 3H), 1.15 (s, 3H), 1.21 (s, 3H), 1.31 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.54 (s, 3H), 0.81−2.20 (m, 6H), 2.54 (s, 1H), 3.55 (s, 3H), 4.09 (d, 1H, J = 6.7 Hz), 0.4.36 (m, 1H), 4.53 (d, 1H, J = 2.3 Hz), 4.65 (dd, 1H, J = 6.7, 3.0 Hz), 4.81 (dd, 1H, J = 10.4, 1.7 Hz), 5.11 (dd, 1H, J = 17.1, 1.7 Hz) and 5.79 (dd, 1H, J = 17.1, 10.4 Hz); ^{13}C NMR (50 MHz) δ 19.8 (q), 22.9 (q), 24.0 (q), 25.1 (q), 25.2 (t), 26.2 (q), 29.1 (q), 32.5 (q), 34.5 (s), 36.5 (t), 41.3 (s), 46.4 (d), 47.8 (d), 54.1 (q), 72.4 (d), 74.0 (s), 74.8 (d), 79.7 (s), 83.8 (d), 98.9 (d), 108.6 (s), 109.3 (t), 145.2 (d), and 155.4 (s); *m*/*z* (EI) 406.2719 (17%, M^+, $C_{24}H_{38}O_5$ requires 406.2717) 391 (100), 375 (82), 374 (81), 333 (65), 123 (69).

(1*S*,6*S*,11*S*,12*S*,2*R*,16R)-14-Methoxy-1,4,4,8,8,12,16-heptamethyl-3,5,17-trioxa-16-vinyltetracyclo[11.4.0.0^{2,6}0^{7,12}]heptadec-13-en-11-ol (23). To stirred slurry of potassium hydride (21 mg, 0.187 mmol) and dimethyl sulfate (7 μL, 0.079 mmol) in THF (0.26 mL) was added a solution of hydroxy-ketone **22** (10 mg, 0.026 mmol) in THF (1 mL) at ambient temperature under nitrogen atmosphere. After the solution was stirred for 8 min, the reaction was quenched by addition of aq ammonium sulfate. The product was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Purification by column chromatography (eluent: ethyl acetate:*n*-hexane 2:1) afforded methyl enolether **23** (10 mg, 96%) as an oil: ν_{max}/cm^{-1} 3590, 1632, 1462, 1379, 1340, 1250, 1208, 1159, and 1072; ^{1}H NMR (200 MHz) δ 1.05 (s, 3H), 1.17 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.54 (s, 3H), 1.55 (s, 3H), 0.80−2.10 (m, 4H), 1.99 (d, 1H, J = 3.7 Hz), 2.29 (d, 1H, J = 15.7 Hz), 0.2.48 (d, 1H, J = 15.7 Hz), 3.06 (dd, 1H, J = 4.5, 1.9 Hz, OH), 3.55 (s, 3H), 4.20 (d, 1H, J = 6.6 Hz), 4.32 (m, 1H), 4.64 (dd, 1H, J = 6.6, 3.7 Hz), 4.99 (d, 1H, J = 10.8 Hz), 5.01 (d, 1H, J = 17.5 Hz) and 5.81 (dd, 1H, J = 17.5, 10.8 Hz); ^{13}C NMR (50 MHz) δ 23.9 (q), 24.9 (t), 25.3 (q), 25.5 (q), 26.2 (q), 32.1 (q), 33.0 (q), 35.0 (s), 36.2 (t), 37.1 (t), 42.2 (d), 45.8 (s), 55.8 (q), 54.1 (q), 72.1 (d), 73.8 (s), 73.9 (d), 78.8 (s), 83.0 (d), 108.7 (s), 113.0 (t), 128.3 (s), 143.9 (d), and 144.7 (s). This methyl enolether **23** was subjected to the next reaction without measuring optical rotation and exact mass due to instability.

(6*S*,11*S*,16*S*,1*R*,2*R*,12*R*,13*R*)-14-Methoxy-1,4,4,8,8,12,16-heptamethyl-3,5,1-7-trioxa-16-vinyltetracyclo[11.4.0.0.^{2,6}0^{7,12}]heptadec-14-en-11,13-diol (25). To a solution of methyl enolether **23** (6.7 mg, 0.017 mmol) in dichloromethane (0.2 mL) was added potassium carbonate (10 mg, 0.074 mmol) and *m*-chloroperbenzoic acid (53 mg, 0.025 mmol) at 0 °C. After the solution was stirred for 0.5 h, the reaction was quenched by addition of sodium hydrogensulfate

(7.7 mg, 0.074 mmol) and aq sodium hydrogencarbonate. The product was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Purification of residue by column chromatography (eluent: ethyl acetate:*n*-hexane = 2:1) provided 9-hydroxy methyl enolether **25** (4.3 mg, 61%) as a solid: mp 202 °C; $[\alpha]^{25}_{D}$ −22.3 (*c* 0.69); ν_{max}/cm^{-1} 3521, 1653, 1462, 1383, 1260, 1215, and 1157; ^{1}H NMR (200 MHz) δ 1.08 (s, 3H), 1.18 (s, 3H), 1.19 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.54 (s, 6H), 0.80−2.10 (m, 4H), 2.52 (d, 1H, J = 5.0 Hz), 3.24 (s, 1H, OH), 3.58 (s, 3H), 4.23 (d, 1H, J = 6.6 Hz), 4.59 (s, 1H), 4.61 (br s, 1H, OH), 4.69 (dd, 1H, J = 6.6, 5.0 Hz), 4.98 (dd, 1H, J = 10.4, 1.3 Hz), 5.08 (m, 1H), 5.29 (dd, 1H, J = 17.0, 1.3 Hz), and 5.86 (dd, 1H, J = 17.0, 10.4 Hz); ^{13}C NMR (67.5 MHz) δ 21.4 (q) 23.8 (q), 25.1 (q), 26.0 (q), 26.1 (t), 26.2 (q), 28.8 (q), 32.7 (q), 35.2 (s), 36.3 (t), 40.6 (d), 43.7 (s), 54.3 (q), 74.1 (s), 74.5 (d), 74.6 (d), 81.0 (s), 81.2 (d), 81.8 (s), 100.3 (d), 108.1 (s), 110.4 (t), 145.7 (d), and 158.3 (s); *m*/*z* (EI) 422.2660 (4%, M^+, $C_{24}H_{38}O_6$ requires 422.2668), 407 (100), 321 (95), 191 (60), 139 (44), 95 (41).

6-Deacetylforskolin (26). A solution of 9-hydroxy-methyl enolether **25** (3.9 mg, 0.0092 mmol) in 10% perchloric acid (0.3 mL) and THF (0.6 mL) was stirred at room temperature for 11 days. The reaction was quenched by addition of aq sodium hydrogencarbonate. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Residue was purified by column chromatography (eluent: ethyl acetate:*n*-hexane 1:2) followed by medium-pressure LC (eluent: ethyl acetate:*n*-hexane 1:2) to give 7-deacetylforskolin (**26**) (2.0 mg, 59%) as a solid: mp 177 °C (lit.[2] mp 177−180 °C); $[\alpha]^{25}_{D}$ −17.9 (*c* 0.34); ν_{max}/cm^{-1} 3344, 1711, 1643, 1460, 1377, 1264, and 1175; ^{1}H NMR (270 MHz) δ 1.07 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.41 (s, 3H), 1.66 (s, 3H), 0.80−2.60 (m, 4H), 2.11 (d, 1H, J = 2.7 Hz), 2.45 (br s, 1H OH), 2.51 (d, 1H, J = 17.3 Hz), 2.57 (br s, 1H, OH), 3.18 (d, 1H, J = 17.3 Hz), 4.15 (m, 1H), 4.50 (t like, 1H), 4.64 (m, 1H), 4.99 (dd, 1H, J = 10.7, 0.9 Hz), 0.5.20 (d, 1H, J = 17.3, 0.9 Hz), 6.13 (dd, 1H, J = 17.3, 10.7 Hz), and 6.45 (br s, 1H OH); ^{13}C NMR (67.5 MHz) δ 20.1 (q), 23.1 (q), 24.2 (q), 27.0 (t), 30.9 (q), 33.1 (q), 34.4 (s), 36.1 (t), 42.8 (d), 43.1 (s), 48.8 (t), 70.5 (d), 74.7 (d), 74.8 (d), 75.1 (d), 82.2 (s), 82.3 (s), 110.4 (t), 146.4 (d), and 205.4 (s); *m*/*z* (EI) 368.2190 (6%, M^+, $C_{20}H_{32}O_6$ requires 368.2199), 350 (75), 123 (82), 95 (98), 81 (100), 67 (82).

Forskolin (1). A solution of 7-deacetylforskolin (**26**) (5.6 mg, 0.015 mmol) and acetic anhydride (25 μL, 0.135 mmol) in pyridine (0.3 mL) was stirred at 0 °C for 18 h under nitrogen atmosphere. The reaction was quenched by addition of water. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and evaporated to dryness. The residue was purified by column chromatography (eluent: ethyl acetate:*n*-hexane 1:1) and subsequently by medium-pressure LC (eluent: ethyl acetate:*n*-hexane 1:2) to furnish forskolin (**1**) (6.5 mg, 100%) as a solid: mp 232 °C (lit.[2] mp 230−232 °C); $[\alpha]^{25}_{D}$ −26.4 (*c* 0.37) {lit.[2] $[\alpha]^{25}_{D}$ −26.2 (*c* 1.68, $CHCl_3$)}; ν_{max}/cm^{-1} 3603, 3460, 1743, 1712, 1644, 1462, 1371, 1273, and 1172; ^{1}H NMR (270 MHz) δ 1.04 (s, 3H), 1.26 (s, 3H), 1.35 (s, 3H), 1.44 (s, 3H), 1.71 (s, 3H), 2.17 (s, 3H), 1.10−2.26 (m, 5H), 2.49 (d, 1H, J = 17.0 Hz), 2.94 (br s, 1H, OH), 3.20 (d, 1H, J = 17.0 Hz), 4.46 (m, 1H), 4.58 (m, 1H), 4.99 (dd, 1H, J = 10.6, 1.0 Hz), 5.30 (d, 1H, J = 17.2, 1.0 Hz), 5.48 (d, 1H, J = 4.3 Hz), 5.93 (dd, 1H, J = 17.2, 10.6 Hz), and 6.01 (br s, 1H, OH); ^{13}C NMR (125 MHz) δ 19.8 (q), 21.2 (q), 23.6 (q), 24.3 (q), 26.6 (t), 31.5 (q), 33.0 (q), 34.4 (s), 36.0 (t), 42.8 (d), 43.0 (s), 48.7 (t), 70.0 (d), 74.4 (d), 75.0 (s), 76.4 (d), 81.4 (s), 82.6 (s), 110.8 (t), 146.2 (d), 169.6 (s), and 205.3 (s); *m*/*z* (EI) 410.2304 (6%, M^+, $C_{22}H_{34}O_7$ requires 410.2305), 392 (100), 123 (85), 95 (85), 81 (85).

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Supporting Information Available: Experimental details for compounds **6**, **7**, and **22**, and ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **6**−**9**, **12**−**15**, **21**−**23**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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