Expedient Synthetic Transformation of Ptychantins into Forskolin

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Received 22 December 2007

Abstract: Forskolin has been synthesized in 11 steps with a 17% overall yield from ptychantins A and B, which have been isolated from the liverwort *Ptychanthus striatus* in good yield. The 1α-hydroxy group was furnished by stereoselective reduction of the corresponding carbonyl group by sodium cyanoborohydride. The 9α-hydroxy group was introduced stereoselectively by epoxidation of $\Delta^{9,11}$-enol ether.

Key words: terpenoids, total synthesis, forskolin, labdane diterpenoid

The highly oxygenated labdane diterpenoid forskolin (**1**, Figure 1) was isolated from the Indian herb *Coleus forskolii* by a research group from Hoechst India in 1977.[1] Forskolin (**1**) and congeners initially attracted much attention due to characteristic physiological activities of blood pressure lowering and cardioprotective properties,[2] and subsequently due to the property of activating adenylate cyclase.[3]

Owing to interesting physiological activities, numerous synthetic studies appeared in the 1980's. Ziegler et al.[4] reported a formal total synthesis, and the Hashimoto[5] and Corey[6] groups successively completed total syntheses using an intramolecular Diels–Alder strategy. Later, Lett et al.[7] described an alternative total synthesis starting from Corey's intermediate in 1996.[7c] However, all synthetic routes toward forskolin (**1**) provided a racemic material, even though Corey[6b] and Lett[7c] demonstrated the possibility to a nonracemic synthesis by employing an optically active intermediate.

Recently, we have demonstrated successful synthetic transformations of ptychantin A (**3**) to forskolin (**1**) in 12 steps with a 12% overall yield and to 1,9-dideoxyforskolin (**2**) in 8 steps with a 37% overall yield in the naturally enantiomeric form (Scheme 1).[8] Ptychantins A (**3**) and B (**4**) were isolated in sufficient quantity (6.7 g of **3** from 1 kg of dry rhizome) from the common liverwort *Ptychanthus striatus* in western Japan.[9]

Major issues in our previous transformations were introduction of two α-hydroxyl groups at C-1 and C-9 by selective manipulations of four hydroxyl groups considering

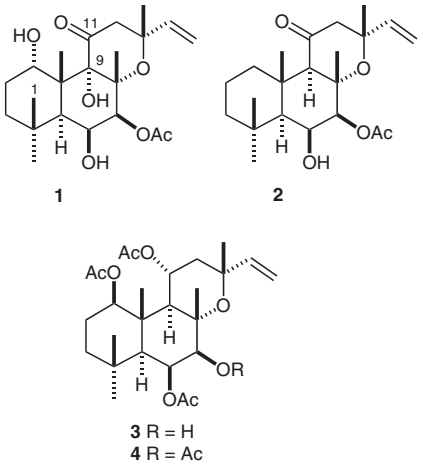
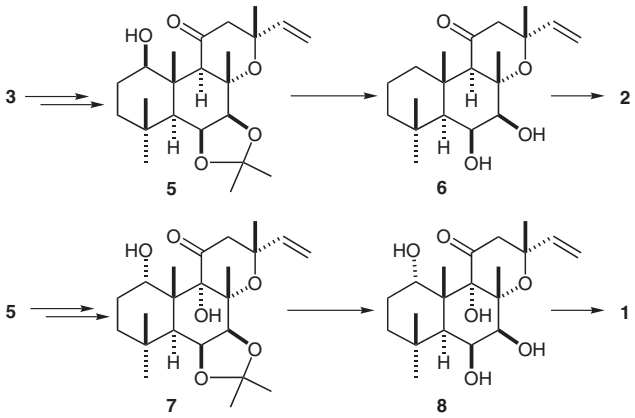


Figure 1



Scheme 1 Previous synthetic transformations of ptychantin A (**3**) to forskolin (**1**) and 1,9-dideoxyforskolin (**2**)

prevention of easy epimerization at C-9 in C-11 keto compounds. Although these issues have been solved successfully in our previous work, one major issue still remained, that is, difficulty in deprotection of acetonide moieties leading to compounds **6** and **8**. Both acetonides at C-6 and C-7 were very stable and deprotections were very sluggish, resulting in moderate yield as already mentioned by Corey[6a] and Lett.[7b]

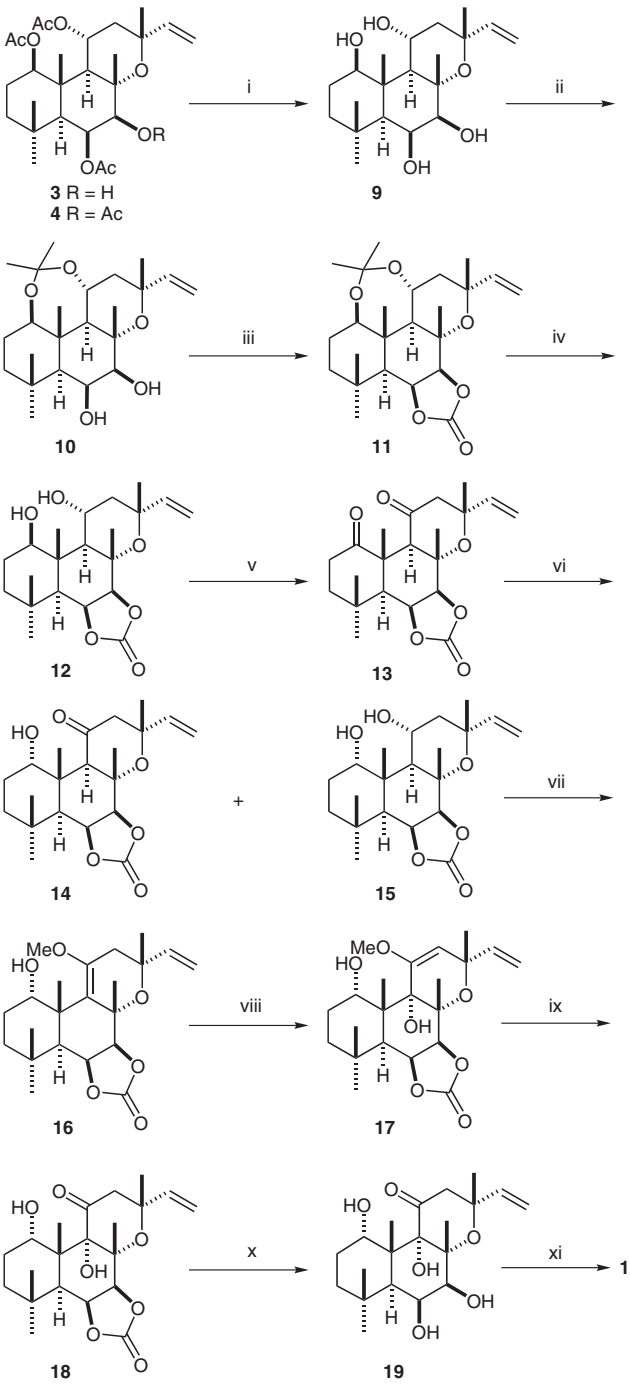
Herein, we present our studies on an alternative and more expedient synthesis of forskolin (**1**) from ptychantins (**3**) and (**4**) to address the long-standing issue on protection at C-6 and C-7.

SYNLETT 2008, No. 6, pp 0929–0931
Advanced online publication: 11.03.2008
DOI: 10.1055/s-2008-1042930; Art ID: U12807ST

Our initial efforts to protect as methylidene, cyclopentylidene, and cyclohexylidene acetals, or bis-MOM or bis-TES ether at C-6 and C-7 gave no satisfactory results in either protection or deprotection. Some protecting groups were fragile for further transformations and others resisted deprotection. Strongly acidic reaction conditions had to be avoided due to side reactions such as opening of the tetrahydropyran ring.

To resolve this issue, we chose carbonate group among other possible protecting groups of 1,2-diols, which was expected to be stable under aprotic basic reaction conditions and could be hydrolyzed easily under protic basic reaction conditions at the end of the synthetic sequence. Towards this end, we had to reinvestigate the whole synthetic sequence.

Ptychantins A (**3**) and B (**4**) were reduced with lithium aluminum hydride to give tetraol **9** in high yield. Sterically less demanding two hydroxyl groups at C-1 and C-11 of tetraol **9** were protected with 2,2-dimethoxypropane regioselectively as an acetonide to afford acetonide **9** (Scheme 2). Treatment of acetonide **10** with triphosgene provided carbonate **11** in quantitative yield, while protection with carbonyldiimidazole gave no satisfactory results. Deprotection of acetonide **11** proceeded smoothly to afford diol **12**, which was oxidized by chromium pyridine complex generated in situ (Sarret reagent) to give diketone **13**, although oxidation with other chromium reagents or Swern oxidation was unsatisfactory. In previous synthetic transformations,[8] reduction of the carbonyl group at C-1 was achieved with sodium in *tert*-butyl alcohol, giving thermodynamically more stable α-alcohol. Since the protecting group at C-6 and C-7 is a carbonate, reduction under nonbasic reaction condition was required to prevent hydrolysis of the carbonate protecting group. In actuality, reduction with sodium borohydride in pyridine according to the known procedure[11] provided 1α-alcohol **14** in only 8% yield along with a large amount of recovered starting material **13** and its deprotected product. Among various reducing agents tested, reduction was carried out with sodium cyanoborohydride in acetic acid and methanol to give stereoselectively the desired 1α-alcohol **14** accompanied by diol **15**, which was oxidized by Sarett reagent back to diketone **13** in 86% yield. The carbonate protecting group was intact under these reaction conditions. Regioselectivity might be ascribed to steric interaction by three axial methyl groups at C-8, C-10, and C-13, which prevented approach of the reducing agent at C-11. Higher stereoselectivity might be explained by attack of hydride from the less-hindered β-face of the carbonyl group at C-1 avoiding steric interference by three 1,3-α-diaxial C–H bonds at C-3, C-5, and C-9. In the absence of acetic acid, only epimerization at C-9 occurred. Treatment of keto alcohol **14** with potassium hydride and dimethyl sulfate proceeded in a thermodynamically controlled manner to afford $\Delta^{9,11}$-enol ether **16**.[10] According to MOPAC AM-1 calculations, $\Delta^{9,11}$-enol ether **16** is 4 kcal/mol more stable than the corresponding $\Delta^{11,12}$-enol ether. Introduction of the C-9 hydroxyl group was accomplished stereoselectively by MCPBA epoxidation of the $\Delta^{9,11}$-enol ether **16** probably via interaction with the α-hydroxyl group at C-1 followed by concomitant in situ epoxide opening to give hydroxyl enol ether **17**. Among other organic and inorganic bases tested, cesium carbonate gave the best result. Hydrolysis of enol ether **17** was carried out in the presence



Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, r.t., 6 h, 97%; ii, 2,2-dimethoxypropane, PPTS, r.t., 17 h, 85%; iii, triphosgene, pyridine, CH_2Cl_2, r.t., 18 h, quant.; iv, 10% $HClO_4$, THF, r.t., 67 h, 86%; v, CrO_3, pyridine, CH_2Cl_2, r.t., 54 h, 81%; vi, $NaBH_3CN$, MeOH, AcOH, r.t., 31 h, 63%, diol **15**, 30%; vii, KH, Me_2SO_4, THF, 0 °C, 2 h, 82%; viii, MCPBA, Cs_2CO_3, DCE, r.t., 13 h, 85%; ix, 10% CSA, dioxane–H_2O, r.t., 14 d, 78%; x, 10% K_2CO_3 aq, MeOH, r.t., 1.5 h, 86%; xi, Ac_2O, pyridine, 0 °C, 18 h, r.t., quant.

of camphorsulfonic acid (CSA) to provide ketone **18** with 2% of **19**. Since hydrolysis of enol ether **17** often resulted in ring opening of the hydropyran ring, mild reaction conditions were employed. Deprotection of the carbonate protecting group proceeded easily as anticipated with methanolic potassium carbonate to give 7-deacetylforskolin (**19**). Final acetylation completed the synthetic transformation to forskolin (**1**), whose spectral data were identical to those of natural **1**.[12]

In summary, we have achieved alternative and more expedient synthetic transformations to forskolin (**1**) from ptychantins A (**3**) and B (**4**) in 11 steps with a 17% overall yield.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas (17035031 for H.H. and T.S.) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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(12) Compounds **9**–**18** have satisfactory ^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data along with optical rotation values.