Highly Oxygenated Diterpenoids Associated to the Central Nervous System: Syntheses of Salvinorin and Forskolin

Hisahiro Hagiwara* and Masato Nozawa

Graduate School of Science and Technology, Niigata University
8050 2-Nocho, Ikarashi, Nishi-ku, Niigata 950-2181, Japan

(Received June 9, 2009; E-mail: hagiwara@gs.niigata-u.ac.jp)

Abstract: Total synthesis of salvinorin A (1), a densely functionalized neoclerodane diterpenoid, having the most potent hallucinogenic activity and a selective κ-opioid agonist, has been completed in 20 steps starting from enantiothermically–pure Wieland–Miescher ketone derivative 23. Subsequently, alternative total synthesis of salvinorin A (1) has been developed via palladium-catalyzed double carbonylation to bis-enol triflate followed by samarium diiodide–mediated double conjugate reduction in 13 steps. Forskolin (2), a highly oxygenated labdane diterpenoid and an activator of adenylate cyclase, has been synthesized in 12 steps and 12% overall yield from ptychantin A (62), which has been isolated from liverwort Ptychanthus striatus in sufficient yield. Tuning of the synthetic pathway enabled more expedient synthesis of forskolin (2) in 11 steps with 17% overall yield from ptychantins A (62) and B (63). In addition, synthesis of 1,9-dideoxyforskolin (3), an inhibitor of glucose transporter, has been accomplished in 8 steps and 37% overall yield from ptychantin A (62).

1. Introduction

Diterpenoids are widely distributed in terrestrial as well as marine organisms, which exhibit diversities in chemical structures as well as biological activities such as anti–mutagenic,1 anti–bacterial and anti–fungal,2 cytotoxic,3 anti–inflammatory, analgesic activities,4 and so on.

In view of such intriguing aspects of diterpenoids, many synthetic studies have been carried out so far and still greater efforts are required to develop more efficient, stereo–controlled and general synthetic approaches. At the same time, some diterpenoids are expected to be candidates for new drugs as exemplified by the successful example of taxoids.5 Some diterpenoids are expected to be candidates for new drugs as exemplified by the successful example of taxoids.5

Pharmacological treatments of diseases and disorders of the central nervous system (CNS) are less developed among a variety of geriatric diseases, which should be improved due to the increase of senior citizens. In addition, psychotropic therapeutic needs by the increase of strain of society will prompt development of new effective reagents.

In this account, we describe syntheses of highly oxygenated diterpenoids, salvinorin A (1), forskolin (2) and 1,9-dideoxyforskolin (3) (Figure 1), in which derivatives of these compounds have physiological activities associated to CNS.

Salvinorin A (1), forskolin (2) and 1,9-dideoxyforskolin (3).

Figure 1. Salvinorin A (1), forskolin (2) and 1,9-dideoxyforskolin (3).

2. Total Synthesis of Salvinorin A (1)

Salvinorin A (1), a trans–neoclerodane diterpenoid, isolated from the Mexican hallucinogenic plant Salvia divinorum,6 is a selective κ-opioid receptor (KOR) agonist.7 Its hallucinogenic activity is the most potent among any other known non–nitrogenous and nitrogenous compounds such as tetrahydrocannabinol (THC) or lysergic acid diethylamide (LSD), respectively.6b 8 Since a different mechanism from LSD and mescaline is anticipated for its activity, salvinorin A (1) and its congeners are expected to be lead compounds for drug development for the treatment of many diseases associated with disorder of CNS such as pain, obesity, pruritus and so on.

Due to their fascinating physiological properties, investigation of salvinorins from natural sources have been extensively carried out and eight congeners, salvinorins B (4)–I (11)6b 9 have been isolated to date (Figure 2). In addition, chemical transformations of salvinorins have been achieved extensively to pursue and evaluate more active ingredients for binding affinity to cloned KOR.8

On the other hand, synthetic studies have been quite limited10 probably due to difficulties associated with issues regarding the construction of chemical architectures having seven asymmetric centers and five oxygenated functionalities, until the recent first total synthesis by Evans et al. in 29 steps in 0.8% overall yield based on the transannular sequential Michael strategy of 14–membered macrocyclic lactone (Scheme 1).11 Another issue is the facile epimerization at C–8 under either acidic or basic reaction conditions.6c 10a 10c 10d Evans et al. utilized this isomerization at the penultimate step in their total synthesis, in which salvinorin A (1) was furnished via partial isomerization of the corresponding 8–epi–precursor 15.

2.1 Total Synthesis of Salvinorin A (1): First Generation

Intrigued by its very characteristic biological activity and highly oxygenated chemical architecture, along with our recent results on the first total synthesis of a neoclerodane diterpenoid, methyl barbascoate (21) starting from Wieland–Miescher ketone (17) (Scheme 2),11 we indepen-
dently investigated an alternative total synthesis of salvino-
rin A (1). 14

Wieland–Miescher ketone (17) and its analogues are still
useful precursors for the syntheses of terpenoids having
decal frameworks as core structures. 15 Easy availability of
both the enriched enantiomers 16 facilitates their use for enan-
tiocontrolled syntheses. A rigid bicyclic core enables stereose-
lective introduction of various requisite functional groups.

Initial attempts to synthesize salvino- rin A (1) were car-
ried out starting from methyl 12–epi–barbascoate (22) (Equa-
tion 1). However, we encountered difficulties in allylic oxida-
tions at C–2 and subsequent transformations, which prompt-
ed us to introduce oxygen functionalities at C–1 at the very
beginning of the synthetic sequence.

To this end, hydroxy–enone 23 was chosen as the starting
material, which was readily obtained from enantiomeri-
cally–pure (R)–(−)–Wieland–Miescher ketone (17) accord-
ing to a known procedure (Scheme 4). 17 We anticipated that
reductive alkylation of hydroxy–enone 23 with 2–alkoxy–2–
(3–furyl)methyliodide 24 and its derivatives with lithium in liq-
uid ammonia will be feasible for the convergent connection
of the C–9–C–11 bond. However, only reduction of the enone
23 proceeded, probably due to steric congestion of the furyl
unit (Equation 2).

These attempts prompted us to take the linear synthetic
approach and our retro–synthetic plan is outlined in Scheme
3. 14 Salvino- rin A (1) could be derived from ester 26 by oxida-
tion, which in turn could be obtained by furyllithium addi-
tion to aldehyde 27. Stereochemistry at C–4 and C–8 of 27
could be controlled by isomerization into a thermodynam-
ically more stable configuration. Reductive alkylation of
hydroxy Wieland–Miescher ketone (29) was envisaged to pro-
duce stereochemistry at C–9 and C–10.

Reductive alkylation with lithium in liquid ammonia with
less sterically demanding ethyl iodoacetate provided alkyla-
tion product 31 bearing three requisite contiguous asymmet-
ric centers and four requisite functionalities for further trans-
formations (Scheme 4). Formation of dehydration product 32
could be suppressed by keeping the reaction temperature low,
while protection of the hydroxyl group at C–1 of enone 23 as
a silyl ether increased the amount of 32.

After hydrolysis of acetal 31, two carbon units at C–4 and
C–8 were introduced by double Wittig methylation to
provide bis-exo-methylene 34. Steric congestion at
C–4 and C–8 as neopentyl positions was so severe that the
reaction with methoxymethylene triphenylphosphorane
resulted in complete recovery of 33. The lactonic portion was
reduced with lithium aluminium hydride (LAH) and the
resulting diol 35 was selectively protected as t–butyldime-
thylsilylether at first and then as p–methoxyphenyl-
methylether to provide 36 for future selective transformations
of the two alcohols.

Hydroboration of bis-olefin 36, oxidation of the resulting
diol with pyridinium dichromate (PDC) and subsequent
treatment with base afforded thermodynamically more stable
bis-α-aldehyde 37 preferentially (Scheme 5).

Prior to arranging the oxidation state of functional
groups at C–1, C–4 and C–8, the furyl unit was installed,
because in the presence of a carboxy moiety at C–8, undesir-
able lactonization between C–12 and C–17 was anticipated
during deprotection of r-butyldimethylsilyl ether at C–12.
Thus, formyl groups were protected as acetals to give
bis-acetal 38. Deprotection of r-butyldimethylsilyl ether and
subsequent PDC oxidation provided aldehyde 39, which was
reacted with 3-furyllithium to give the desired 12S-furylalco-
hol 40 and its 12R-epimer 41 in 2:3 ratio. The absolute stereo-
chemistry at C–12 of less polar 40 was determined to be S
after transformation into deacetoxysalvinorin A (43) as
judged from 10% nOe enhancement between a proton at
C–12 and a methyl group at C–9.

The resulting 12S-furylalcohol 40 was treated with acid
to give hemiacetal 42. Deprotection of the p-methoxyphenyl-
methylether was followed by three fold oxidation at C–1, C–17 and C–18 with PDC, and subsequent esterification with
dicyclohexylcarbodiimide and methanol afforded 2-deace-

toxysalvinorin A (43). In a similar manner, 12R-deace-

toxysalvinorin A was obtained.

The major issue in the introductio of α-acetoxy group at
C–2 was the facile epimerization at C–8 of salvinorin A (1)
as well as 2-deacetoxysalvinorin (43) as 8S-isomers, which
was not solved by the total synthesis of Evans et al.12 As
anticipated, various preliminary studies to introduce the
2-acetoxy group directly into 2-deacetoxysalvinorin (43)
were troublesome. After screening a wide variety of reagents
and reaction conditions, this crucial problem was solved by the
Rubottom method,19 in which brief treatment of deace-
toxysalvinorin A (43) with sodium bis(trimethylsilyl)amide at
−78°C and subsequently with triethylsilyl chloride success-
fully led to triethylsilyl enol ether 44 without C–8 epimerization
(Scheme 6). Prolonged treatment with the base resulted in
partial epimerization at C–8 even under −78°C. Trimethylsi-
lyl enol ether was not suitable due to its instability for subse-
quent epoxidation. Oxidation of triethylsilyl enol ether 44
with m-chloroperbenzoic acid (MCPBA) in the two-phase
system19 proceeded sterically from the less hindered β-face of
selectively, and subsequent hydrolysis of the resulting triethylsilyl ether provided 2-\textit{epi}-salvinorin B (45). Finally, inversion at C-2 was carried out by the Mitsunobu reaction\textsuperscript{10d,10h} to furnish salvinorin A (1). Thus, total synthesis of salvinorin A (1) was accomplished in 0.95% overall yield in 20 steps.

2.2 Synthesis of Salvinorin A (1): Second Generation

Our first generation synthesis was successful in controlling six stereogenic centers except C-12, and especially successful in arranging stereocenter at C-8 properly. However, its rather lengthy and conventional synthetic sequence prompted us to re-investigate more expeditious synthetic protocol.\textsuperscript{20}

Our second synthetic approach is outlined in Scheme 7. In our initial total synthesis cited above, requisite functional groups were introduced step by step, especially in arranging the oxidation state of two carboxy groups at C-4 and C-8 separately. One way to save steps is to install similar functionalities at the same time. To this end, we focused on double introduction of the ester at C-4 and the lactone at C-8 to the decaline framework. We envisaged that palladium-catalyzed double carbonylation\textsuperscript{21} to bis-enol triflate 47 followed by double 1,4-conjugate reduction of two unsaturated carbonyl moieties of 46 would satisfy our intention.

Our alternative total synthesis started from known diketo-ester 33 (Scheme 8).\textsuperscript{20} Although protection of the hydroxy group at C-1 as triethylsilyl ether was very sluggish, it was successfully protected employing more reactive triethylsilyl trifluoromethanesulfonate. Formation of triethylsilyl enol ether as a by-product was suppressed by carrying out the reaction in a shorter period of time at 100 °C. Prior to the introduction of the furyl unit at C-12, carbonyl groups at C-4 and C-8 were transformed into bis-enol triflate 50 as scaffolds to introduce two ester groups at C-4 and C-8 by palladium-catalyzed carbonylation and at the same time to protect carbonyl groups at C-4 and C-8 in the next furyllithium addition. Prior to such synthetic sequences, the ester group at C-11 was transformed into Weinreb amide\textsuperscript{51} quantitatively,\textsuperscript{22} in which furyl unit was introduced by addition of 3-furyllithium to give furyl ketone 52.

Double carbonylation of bis-enol triflate 52 was successful in affording bis-ester 55 along with a small amount of mono-ester 54 employing palladium tetraakis(triphenylphosphine) with 1,1-bis(diphenylphosphino)ferrocene (dppf) in methanol and N,N-dimethylformamide (DMF) (Scheme 9). The mono-ester 54 was transformed into bis-ester 55 under the same reaction conditions. Addition of dppf in DMF was essential for an efficient double carbonylation.

Attempts of triple-reduction of the bis-ester 55 by
L-Selectride\textsuperscript{8}, that is, 1,4–reduction of the double bonds at C–3, C–7 and 1,2–reduction of ketone at C–12, provided a complex diastereomeric mixture. Though the reduction proceeded to give saturated lactone, no stereoselectivity was observed. To this end, reduction of carbonyl group at C–12 and two double bonds at C–3 and C–7 were independently carried out. By testing various reducing agents, reduction of the furyl–ketone 52 with K–Selectride furnished, after concomitant ring closure, desired 12\textit{S}–lactone 56 as a sole diastereomer, in which relative stereochemistry was confirmed by nOe between methyl group at C–9 and the proton at C–12 along with its coupling constant (dd, \(J = 12.0\) and \(4.0\) Hz). This high diastereoselection was anticipated by Re face attack of a hydride to C–12 carbonyl group, in which more stable conformer 53\textit{A} might be fixed by chelation of two carbonyl groups with potassium cation (Equation 3. triethylsilyloxy group at C–1 is omitted for clarity).

Subsequently, double reduction of two unsaturated moieties at C–3 and C–7 of 56 proceeded successfully by samarium diiodide.\textsuperscript{23} Careful tuning of reaction conditions revealed that freshly prepared samarium diiodide furnished lactonic ester 57 in the presence of triethylamine\textsuperscript{24} as a ligand and acetic acid as a proton source in toluene as a single diastereomer. When the reaction was quenched by oxygen bubbling, recovery of the product was improved by minimizing side reactions with excess samarium diiodide.\textsuperscript{25} Inspection of thin layer chromatography during the reaction showed that the double bond at C–7 was reduced initially probably due to \(s\text{-}cis\) configuration of the unsaturated moiety. The relative stereochemistry at C–8 of 57 was determined to be \(S\) by nOe between the proton at C–12 and methyl group at C–9. The stereochemistry at C–4 was established to be \(R\) judging from coupling constants of the proton at C–4 (\(\delta_{21}, J = 12.7, 3.2\) Hz) of alcohol 59. Formation of 4\textit{R} and 8\textit{S} configurations is explained by kinetically–controlled axial protonation toward samarium ester– and lactone–enolates. Attempts to change the course of axial protonation at C–8 by the addition of a bulky proton source such as pivalic acid or 1–adamantanol were not successful.

Triethylsilyl ether \(57\) was deprotected by treatment with tetrabutyrammonium fluoride, in which isomerization at C–8 proceeded during the reaction to give 8\textit{R}–60 and 8\textit{S}–isomers 59 in 3:7 ratio. Stereochemistry at C–8 of 60 was determined by a coupling pattern of C–8 proton. Epimerization of the 8\textit{S}–isomer 59 was carried out with potassium carbonate to give 8\textit{R}–isomer 60 and 8\textit{S}–isomer 59 also in 3:7 ratio. Oxidation of 8\textit{R}–isomer 60 by Dess–Martin periodinane gave 2–deacetoxysalvinorin A (43) without any problem. Transformations of 2–deacetoxysalvinorin A (43) into salvinorin A (1)
had already been accomplished (vide supra). Thus, more expedient total synthesis of salvinorin A (1) was accomplished in 13 steps in 2.8% overall yield.

3. Synthesis of Forskolins

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

Forskolin (2) is a highly oxygenated labdane diterpenoid with four alkoxy substituents and a tetrahydropyran ring (Figure 3). Seven out of eight asymmetric centers are located in the decalin portion. The right ring of the decalin portion of forskolin (2) has a structural similarity with α-D-galactose (61). As a result, forskolin (2) binds to the glucose transporter to activate adenylate cyclase (AC), an enzyme regulating the level of cAMP, and subsequently activates protein kinase. Due to its activity, forskolin (2) has been an important tool for studying the physiological role of AC and related phenomena. Recently, the physiological role of forskolin (2) has been re-evaluated extensively to investigate the function of CNS receptors and clinically Alzheimer's disease.

![Figure 3. Structure similarity between forskolins (2) and (3), and galactose (61).](image3.png)

The interesting physiological activities along with an attractive chemical structure led organic chemists toward synthetic studies of forskolin (2). In 1987, Ziegler et al. reported a formal total synthesis, and in 1988, the Hashimoto groups independently completed total syntheses using an intramolecular Diels–Alder strategy. Subsequently, in 1996, Lett et al. described an alternative total synthesis starting from Corey's intermediate. However, all synthetic routes toward forskolin (2) provided racemic material, even though Corey and Lett demonstrated the possibility of a non-racemic synthesis by employing an optically active intermediate.

Recently, the new labdane diterpenoids ptychantin A (62), B (63) and related compounds have been isolated from the common liverwort Ptychanthus striatus in western Japan (Figure 4). 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).

3.1 Synthesis of Forskolin (2): First Generation

There were several issues prior to starting synthetic transformations into forskolins from ptychantin A (62) and B (63). Four alkoxy groups are found in similar structural environments, which make the selective manipulations 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 group. The tetrahydropyran ring of the 11-keto derivative is not stable and is opened easily under either acidic or basic reaction conditions. In addition, the C-9 of the 11-keto derivative of ptychantin A (62) is prone to epimerize under weakly basic reaction conditions to relieve 1,3-steric repulsions of methyl groups. Thus, mild and selective reaction conditions were required for satisfactory transformations to forskolins.

At the initial stage, the selective transformation of four hydroxy groups was investigated, leading to a common intermediate for forskolin (2) and 1,9-dideoxyforskolin (3) syntheses (Scheme 10). Treatment of ptychantin A (62) with potassium hydroxide in methanol led to the selective hydrolysis of the 6-acetoxyl group to give 6,7-diol 64 quantitatively. This selectivity is probably due to severe 1,3-diaxial repulsion by the three methyl groups at C-4, 8 and 10 to shift the acetyl group at C-6 to the neighboring 7-OH group in intramolecular fashion and subsequent hydrolysis. Hydrolysis of ptychantin B (63) proceeded in a similar manner to provide the diol 64. Before manipulation of the acetoxy groups at C-1 and C-11 of diol 64, it was required to install appropriate protecting groups at C-6 and C-7. After some unfruitful attempts to protect C-6 and C-7 hydroxyls separately, both hydroxy groups were protected as an acetal to give acetomide 65.

The acetoxy groups at C-1 and C-11 of acetomide 65 were reduced with LAH to provide diol 66. The less hindered hydroxy group at C-11 was selectively oxidized by pyridinium chlorochromate (PCC) to give hydroxy-ketone 67, which is a common precursor to the synthesis of forskolin (2) and 1,9-dideoxyforskolin (3). The steric congestion at the neopentyl C-1 position of 66 might allow the selective oxidation of the α-equatorial hydroxy group at C-11.

The initial task for the forskolin (2) synthesis was the epimerization of the β-hydroxy group at C-1 of the 11-keto derivative 67, since the hydroxy group at C-1 should be in the α-axial orientation for a selective introduction of the 9α-hydroxy group (Scheme 11). However, Mitsunobu inversion led to complete recovery of the starting material 67 due to neopentyl steric congestion. The mesylate could not be formed. Although protection of the carbonyl group at C-11 was difficult, treatment of 67 with potassium hydride and dimethyl sulfate in THF provided selectively the Δ1,12- enol ether 68. No Δ9- enol ether was formed even under thermodynamic conditions, which was anticipated to be favorable for introduction of hydroxy group at C-9. Mitsunobu inversion of the enol ether 68 again resulted in recovery of the starting material.
Due to the very sensitive nature of the enol ether 68, PCC or PDC oxidation provided the 1,11-diketo compound. Fortunately, a Sarret oxidation was successful, probably due to the basic reaction conditions necessary to give the desired 1-keto derivative 69. Among various reduction conditions tested, reduction of 69 by sodium in t-butyl alcohol\(^{57}\) at 30 °C provided the desired 1α-hydroxy derivative quantitatively. Steric repulsion by the α-equatorial methoxy group at C-11 (peri-repulsion) positioned the intermediary ketyl radical at C-1 in the thermodynamically more stable α-axial configuration. Hydrolysis of Δ\(^{9,11}\)-enol ether 70 was carried out by 1% HCl to give the 11-keto derivative 71 quantitatively. More acidic reaction conditions resulted in the exclusive opening of the tetrahydropyran ring.

The requisite 9α-hydroxy group was introduced according to the modified procedure by Hrib.\(^{38}\) Treatment of potassium hydride and dimethyl sulfate afforded the Δ\(^{9,11}\)-enol ether 72 selectively in this case (vide supra). A higher regioselectivity might originate from the abstraction of the 9α-proton by the 1α-alkoxide to give the Δ\(^{9,11}\)-enolate. Epoxydation of the enol ether 72 with MCPBA in the presence of potassium carbonate furnished the 9α-hydroxy-11,12-enol ether 74. The epoxidation proceeded from the less hindered α-face of the molecule to give the α-epoxide 73 probably via interaction of MCPBA with the 1α-hydroxy group of 72, which was followed by hydrolysis. Hydrolysis of the methyl enol ether 74 proceeded smoothly without the tetrahydropyran ring opening. However, the acetone at C-6 and C-7 resisted hydrolysis.\(^{34b}\) After prolonged exposure to weakly acidic conditions for 11 days, deprotection of the acetone was successful and gave the naturally occurring 7-desacetylforskolin (75). Extensive investigations of a variety of acidic reaction conditions in the presence or absence of semicarbazide\(^{38b}\) did not succeed in facilitating the hydrolysis. Catalysis by stronger acid resulted in opening of the pyran ring. Finally, conventional acetylation of 7-desacetylforskolin (75) quantitatively completed the synthesis of forskolin (2) in natural form and in 12 steps from ptychantin A (62) in 12% overall yield.

### 3.2 Synthesis of Forskolin (2) : Second Generation

The major issue in our previous transformations was the introduction of two α-hydroxy groups at C-1 and C-9 by selective manipulations of four hydroxy groups avoiding easy epimerization at C-9 of C-11 keto-compound such as 71. Although this issue was solved in our previous work, another major issue still remained, namely, acetonide at C-6 and C-7 was too stable resulting in very sluggish deprotection as already mentioned by Corey\(^{33a}\) and Lett.\(^{33b}\)

We investigated an alternative and more expedient synthesis of forskolin (2) from ptychantins A (62) and B (63) to address the long-standing issue of protection at C-6 and C-7.\(^{38}\) Our initial efforts to protect alcohols at C-6 and C-7 as various acetics or ethers gave no satisfactory results in either protection or deprotection. Some protecting groups were too fragile for further transformations and others were tough to accept deprotection. Strongly acidic reaction conditions had to be avoided due to side reactions such as opening of the tetrahydropyran ring.

To solve this issue, we chose a carbonate group among other possible protecting groups of 1,2-diols, which was expected to be stable under an aprotic basic reaction condition and could be hydrolyzed easily under protic basic reaction conditions at the end of the synthetic sequence. Owing to the change of protecting groups at C-6 and C-7, we had to re-investigate a new synthetic protocol.

Reduction of ptychantins A (62) and B (63) with LAH provided tetaol 76 (Scheme 12). Two sterically less demanding hydroxyl groups at C-1 and C-11 of tetaol 76 were pro-

---

### Scheme 10. Synthesis of common intermediate 67 for forskolin (2) and 1,9-dideoxyforskolin (3).

### Scheme 11. Synthesis of forskolin (2) from common precursor 67.
tected at first with 2,2-dimethoxypropane regioselectively as an acetonide to afford acetonide 77. Treatment of acetonide 77 with triphosgene provided carbonate 78. Deprotection of acetonide 78 proceeded smoothly to afford diol 82, which was oxidized by a Sarret reagent generated in situ to give diketone 80. Since the protecting group at C-6 and C-7 is a carbonate, reduction under a non-basic reaction condition was required to prevent hydrolysis of the carbonate protecting group. Among various reducing reagents tested, reduction completed with sodium cyanoborohydride in acetic acid and methanol to give regioselectively the desired 1a-alcohol 81 accompanied by diol 82, which was oxidized by Sarrett reagent back to diketone 80. The carbonate protecting group was intact under the reaction condition. Regioselctivity 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 an 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. Introduction of the hydroxy at C-9 was achieved in the same manner as our first generation synthesis via MCPBA oxidation of Δ9,11-enol ether 83. Among other organic and inorganic bases tested, cesium carbonate gave the best result in this transformation (vide supra). Hydrolysis of enol ether 84 was carried out in the presence of camphorsulfonic acid to provide ketone 85 with a small amount of 86. Deprotection of the carbonate protecting group proceeded easily as anticipated with methanolic potassium carbonate to give 7-deacetylforskolin (86). Final acetylation completed the synthetic transformation to forskolin (2), which realized more expedient synthetic transformations to forskolin (2) from pychamtns A (62) and B (63) in 11 steps with a 17% overall yield.

3.3 Synthesis of 1,9-Dideoxyforskolin (3)

1,9-Dideoxyforskolin (3), a second major constituent of C. forskolii, does not have antihypertensive activity but exhibits strong inhibitory activity towards glucose transport in rat adipocytes in the micromolar range without stimulating adenylate cyclase, which is expected to treat diseases caused by abnormal glucose uptake such as Alzheimer’s, diabetes or cancer. Due to this interesting activity, a synthetic approach by Morin et al. from the natural diterpenoid larixol appeared in 2001.

The synthesis of 1,9-dideoxyforskolin (3) was carried out starting from the common intermediate 67, which was prepared in the previous first generation synthesis of forskolin (2) (Scheme 13). Removal of the hydroxy group at C-1 of hydroxy-ketone 67 was investigated by radical deoxygenation, since the hydroxy group was located at a highly hindered neopentyl position. The radical precursor was prepared by a solid state reaction with thiocarbonyldiimidazole in the presence of N,N-dimethylaminopyridine at 50 °C, originally developed by us, to afford thiocarbonylimidazolide 87 in 82% yield. The reaction in THF did not go to completion even in 23 h. A neutral reaction condition was essential to prevent epimerization at C-9.

The radical cleavage of the imidazolide 87 with tri-n-butyltin hydride and azobisobutyronitrile in toluene at 120 °C provided ketone 88. Deprotection of the acetonide moiety of ketone 88 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 (89). A selective acetylation of the hydroxy group at C-7 with acetic anhydride and N,N-dimethylaminopyridine
furnished 1,9-dideoxyforskolin (3). Thus, the synthesis of 1,9-dideoxyforskolin (3) was accomplished in 8 steps and 37% overall yield from ptychyanin A (62) or B (63).

4. Conclusion

In summary, we have completed total synthesis of salvinorin A (1) in 20 steps starting from enantiomerically-pure Wieland–Miescher ketone derivative 23. Subsequently, more expeditious total synthesis of salvinorin A (1) was developed via palladium-catalyzed double carbylation to bis-enol triurate in 13 steps in 2.8% overall yield. Forskolin (2) was synthesized in 12 steps and 12% overall yield from ptychyanin A (62). The synthetic pathway was revised to enable more expeditious synthesis of forskolin (2) in 11 steps with 17% overall yield from ptychyanins A (62) and B (63). Moreover, synthesis of 1,9-dideoxyforskolin (3) was accomplished in 8 steps and 37% overall yield from ptychyanins A (62).

Acknowledgements

We thank our colleagues for their dedication toward these synthetic works, whose names are listed in the literature cited in references. H.H. thanks Grant-in-Aid for Scientific Research on Priority Areas (17035031) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT). M.N. thanks JSPS for their promotion of young Researchers on Priority Areas (17035031) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT). M.N. thanks JSPS for their promotion of young chemists.

References and notes


---

**PROFILE**

Hisahiro Hagiwara is a professor of the Graduate School of Science and Technology, Niigata University. He received his B.Sc. (professor K. Nakamish) (1969) and M.Sc (professor A. Yoshikoshi) (1971) from Tohoku University, and joined as an assistant professor in the Chemical Research Institute of Non-aqueous Solutions, Tohoku University. After receiving his Ph.D. degree (professor H. Uda) from Tohoku University, he stayed two years as a post-doctoral fellow in a group of professor B. M. Trost’s in University of Wisconsin, USA. After coming back to Tohoku University, he was promoted to his present position in 1996. His research interests involve total synthesis of physiologically interesting terpenoids and development of environmentally benign synthetic protocols employing ionic liquids.

Masato Nozawa was born in 1980 and received his B.Sc. (2002), M.Sc. (2004) and Ph.D. (2007) from Niigata University. During his Ph.D. course, he was awarded a scholarship as a JSPS young chemist. He is now a research chemist in Denka Seiken Ltd. His research interests involve synthesis of physiologically active natural products.