Tetrahedron 65 (2009) 4820–4825

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Second-generation synthesis of salvinorin A

Hisahiro Hagiwara[a,*], Yuhki Suka[a], Takashi Nojima[a], Takashi Hoshi[b], Toshio Suzuki[b]

[a] *Graduate School of Science and Technology, Niigata University, 8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata 950-2181, Japan*
[b] *Faculty of Engineering, Niigata University, 8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata 950-2181, Japan*

## ARTICLE INFO

*Article history:*
Received 31 March 2009
Received in revised form 14 April 2009
Accepted 14 April 2009
Available online 21 April 2009

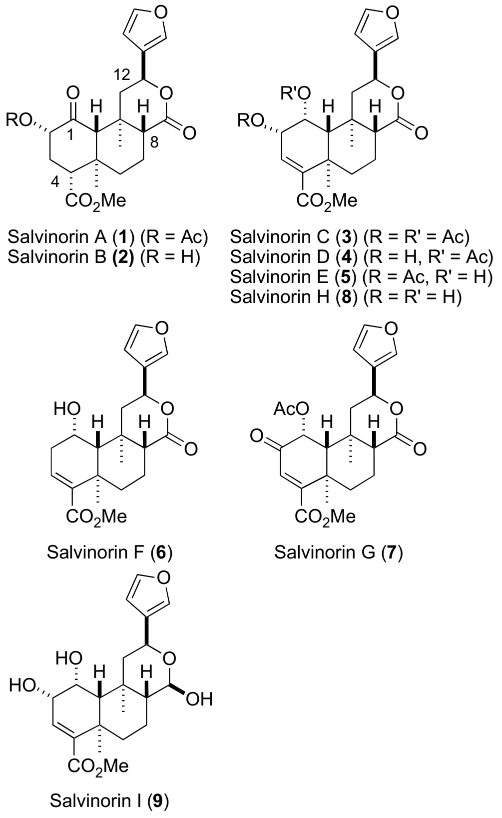
## ABSTRACT

Functionalization toward total synthesis of the hallucinogenic neoclerodane diterpenoid salvinorin A was accomplished via three double sequences: bis-enol triflate synthesis, palladium-catalyzed double carbonylation to the bis-enol triflate, and samarium diiodide-mediated double conjugate reduction. The configuration at C-12 was controlled by chelation-controlled diastereoselective reduction.

## 1. Introduction

Salvinorin A (**1**), isolated from the Mexican sage *Salvia divinorum*,[1] is a unique and densely functionalized furolactone neoclerodane diterpenoid with seven asymmetric centers and five different oxygen functionalities. Eight congeners, salvinorins B (**2**) to I (**9**), have been isolated so far (Fig. 1).[2] Salvinorin A (**1**) has the strongest hallucinogenic activities among known compounds and was identified as a selective non-nitrogeneous agonist of a κ-opioid receptor.[3] Because a different mechanism from LSD or other nitrogeneous hallucinogenic compounds is anticipated for its physiological activities, salvinorin A (**1**) attracts much attention as a lead compound for diseases associated with disorder of central nervous system.

Because of its very characteristic physiological activities, much effort has been devoted to chemical transformations of salvinorin A (**1**) and its congeners to more potent forms by investigating structure–activity relationships.[4] At the same time, its highly oxygenated chemical structure has attracted much attention among synthetic organic chemists.[5] Evans et al. reported the first total synthesis in 29 steps,[6] in which a transannular Michael reaction cascade was the key step in construction of the decalin framework, to introduce requisite functionalities and to control requisite stereochemistries. Subsequently, we reported its total synthesis[7] as part of our efforts in synthetic study of clerodane diterpenoids,[8] in which the Wieland–Miescher ketone derivative was transformed linearly into salvinorin A (**1**) in 20 steps. However, a rather lengthy synthetic sequence prompted us to re-investigate the synthetic protocol and we delineate herein an alternative and more expeditious total synthesis of salvinorin A (**1**).



Salvinorin A (**1**) (R = Ac)
Salvinorin B (**2**) (R = H)

Salvinorin C (**3**) (R = R' = Ac)
Salvinorin D (**4**) (R = H, R' = Ac)
Salvinorin E (**5**) (R = Ac, R' = H)
Salvinorin H (**8**) (R = R' = H)

Salvinorin F (**6**)

Salvinorin G (**7**)

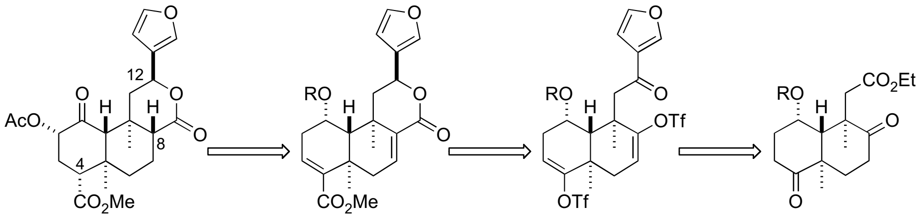
Salvinorin I (**9**)

**Figure 1.** Salvinorin A (**1**) and its congeners **2**–**9**.

---

* Corresponding author.
*E-mail address:* hagiwara@gs.niigata-u.ac.jp (H. Hagiwara).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.04.053



Salvinorin A (**1**) **10** **11** **12**

**Scheme 1.** Synthetic plan of salvinorin A (**1**).

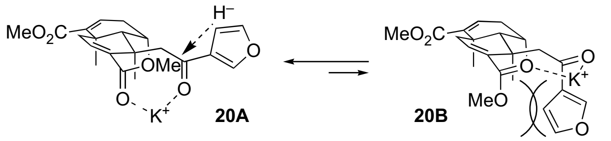
## 2. Results and discussions

Our synthetic plan is outlined in Scheme 1. In our previous total synthesis, the stereochemical issues were controlled by constraints characteristic to a decaline framework and requisite functional groups were introduced step by step. In particular, owing to neopentyl steric hindrance, functionalizations at C-4 and C-8 were difficult, in which the lactone group at C-8 and the ester group at C-4 were installed by double Wittig methylenation followed by hydroboration, oxidation, and protection. To reduce the number of synthetic steps, we focused on a concomitant introduction of the ester at C-4 and the lactone at C-8 into the decaline framework. We envisaged that palladium-catalyzed double carbonylation to bis-enol triflate **11** followed by double 1,4-conjugate reduction of two unsaturated carbonyl moieties of **10** would fulfill our intention.

The second-generation total synthesis started from known diketo-ester **14**,[7] which was obtained by lithium/ammonia reductive alkylation of optically active 1-hydroxy-Wieland–Miescher ketone **13** and subsequent quantitative hydrolysis of the ketal (Scheme 2). The hydroxy group at C-1 was protected as triethylsilyl ether in 93% yield. Formation of triethylsilyl enol ethers as by-products was suppressed by carrying out the reaction in a shorter period of time with more reactive triethylsilyl trifluoromethanesulfonate at 100 °C. The carbonyl groups at C-4 and C-8 were converted into bis-enol triflate **16** in 66% yield to protect the C-4 and C-8 carbonyls during the addition of furyllithium and to provide a scaffold for the introduction of the two ester groups by palladium-catalyzed carbonylation. Addition of excess base gave unknown complex by-products. The ester group at C-11 was transformed into Weinreb amide **17** quantitatively,[9] in which the furyl unit was introduced by the addition of 3-furyllithium in 70% yield to afford furyl-ketone **18**.

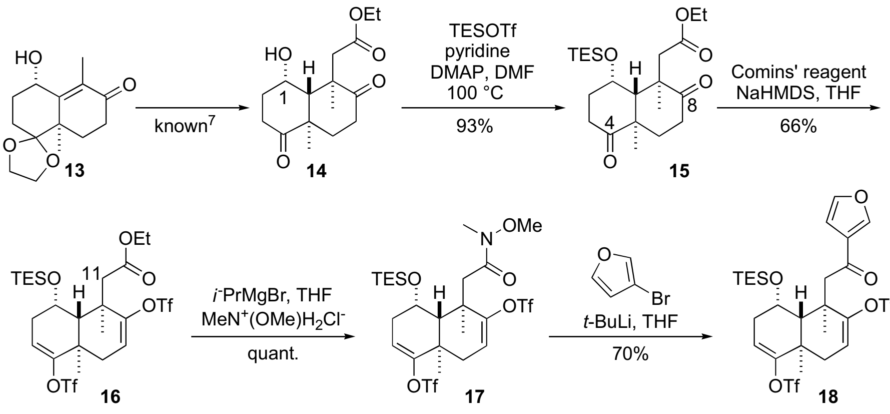
After extensive investigations, we found that the use of palladium tetrakis(triphenylphosphine) with 1,1-bis(diphenylphosphino)ferrocene (dppf) in methanol and *N*,*N*-dimethylformamide led to double carbonylation of bis-enol triflate **18** to afford bis-ester **20** in 69% yield along with 7% of mono-ester **19** (Scheme 3).[10] The mono-ester **19** was transformed into bis-ester **20** in 84% yield under the same reaction conditions. Addition of dppf in DMF was crucial for the efficient double carbonylation.

With the bis-unsaturated ester **20** in hand, triple reductions, that is, 1,4-reduction of the double bonds at C-3, C-7, and 1,2-reduction of ketone at C-12, was attempted by L-Selectride to give a complex mixture of diastereomeric saturated lactones. Although triple reduction did occur, no stereoselectivity was observed. To this end, reductions of carbonyl group at C-12 and two double bonds at C-3 and C-7 were independently investigated. After trying the reaction with other reducing agents such as sodium or lithium borohydride, we found that the reduction of the furyl-ketone **20** with K-Selectride furnished, after concomitant ring closure, the desired 12*S*-lactone **21** in 95% yield as the sole diastereomer (Fig. 2. triethylsilyloxy group at C-1 is omitted for clarity), whose relative stereochemistry was confirmed by 11% NOE enhancement 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 is understood by attack of hydride to *Re* face of C-12 carbonyl group of the more stable conformer **20A**, in which two carbonyl groups were fixed by chelation with potassium cation (Eq. 1 the triethylsilyloxy group at C-1 is omitted for clarity).

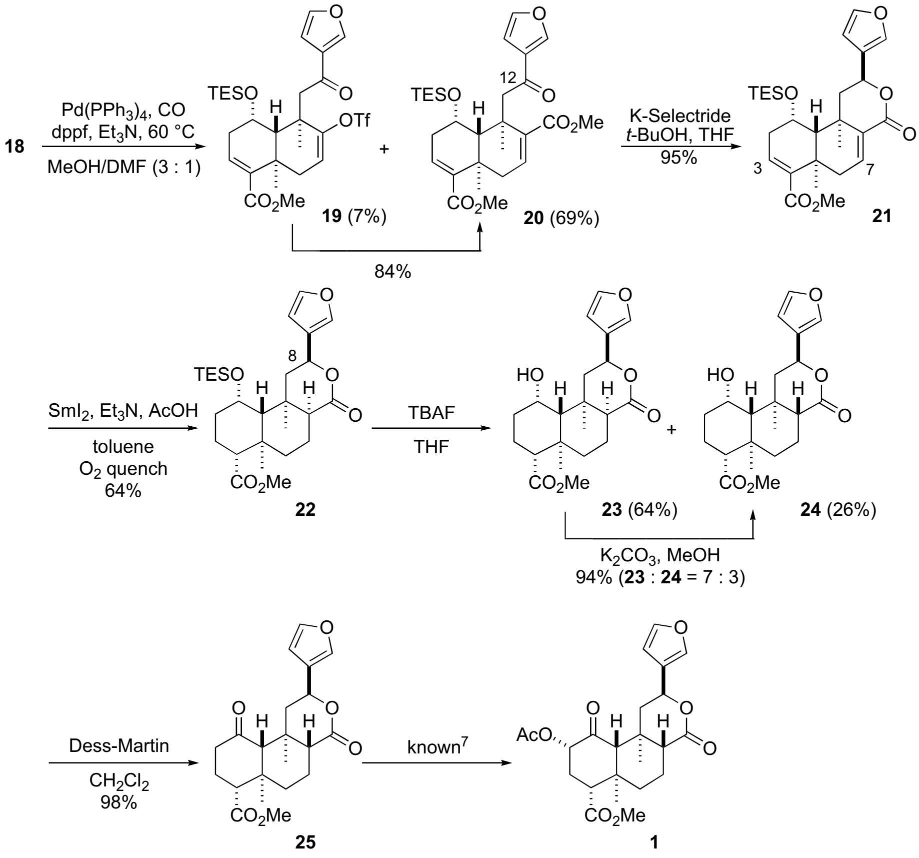


**20A** **20B** (**1**)

With the unsaturated lactonic ester **21** in hand, the double reduction of two unsaturated moieties at C-3 and C-7 was investigated. After numerous attempts employing magnesium in methanol, lithium naphthalenide, and catalytic hydrogenation, we



**Scheme 2.** Synthesis of bis-enol triflate **18**.



**Scheme 3.** Double carbonylation and 1,4-reduction: synthesis of 2-deacetoxysalvinorin (**25**).

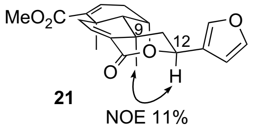


**Figure 2.** Relative stereochemistry of **21**.

finally found that the double reduction proceeded successfully with samarium diiodide.[11] Careful tuning of reaction conditions revealed that the freshly prepared samarium diiodide furnished lactonic ester **22** in the presence of triethylamine[12] as a ligand and acetic acid as a proton source in toluene in 64% yield as a single diastereomer. No other steroisomers were obtained. Quenching the reaction by oxygen bubbling was effective to get better recovery of the product as a result of minimizing side reactions by excess samarium diiodide.[13] Monitoring the reaction by thin-layer chromatography revealed that the double bond at C-7 was reduced first, probably because of *s-cis* configuration of the unsaturated lactonic moiety. The relative stereochemistry of the new chiral center at C-8 of **22** was determined by NOE measurement to be *S*, as shown in Figure 3. While, the new chiral center at C-4 was established to be *R* by coupling constants of the proton at C-4 ($\delta$ 2.21, dd, $J$=12.7, 3.2 Hz) of alcohol **23**. The formations of these stereoisomers are 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 at 0 °C did not afford any 8*R*-isomer.

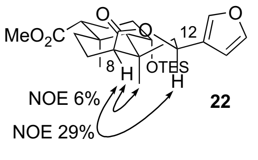


**Figure 3.** Relative stereochemistry of **22**.

Triethylsilyl ether **22** was deprotected by treatment with tetrabutylammonium fluoride in THF in 90% yield, in which isomerization at C-8 proceeded during the reaction to give 8*R*-**24** and 8*S*-isomers **23** in 3:7 ratio. Relative stereochemistry at C-8 of **24** was determined by the coupling pattern of the C-8 proton. Isomerization at C-8 has been a long-standing issue in salvinorin chemistry,[14] as the C-8 center is configurationally unstable under either weakly basic or acidic reaction conditions even if there is no carbonyl group at C-1.[1b] The penultimate step of Evans' total synthesis was base-catalyzed isomerization of 8*S*-epimer into 8*R*-epimer, although starting 8*S*-epimer predominated.[6] While, deacetoxysalvinorin A (**25**) partly equilibrated to 8*S*-epimer of **25** during work up after treatment with potassium carbonate in methanol. Alternatively, equilibration of the 8*S*-isomer **23** was carried out under the same reaction conditions to give **24** and **23** also in 3:7 ratio. The reasons for this easy epimerization of **23** despite the low acidity of the proton at C-8, are yet to be clarified.[14] Oxidation of 8*R*-isomer **24** by Dess–Martin periodinane gave 2-deacetoxysalvinorin A (**25**) in 98% yield. Transformations of 2-deacetoxysalvinorin A (**25**) into salvinorin A (**1**) were already accomplished in our previous total synthesis.[7]

## 3. Conclusion

In summary, we have completed total synthesis of salvinorin A (**1**) from the known keto-ester **14** in 13 steps in 2.8% overall yield, while our previous synthesis required 20 steps in 0.95% overall yield and Evans et al. finished in 29 steps in 0.8% overall yield. Ester and lactone moieties required for salvinorin synthesis were introduced concisely by three double transformations, namely double enol triflate synthesis, double carbonylation, and double conjugate reduction. Two issues in the control of stereochemistry at C-4 and C-12 were solved by axial protonation to the ester enolate and by chelation-controlled reduction by K-Selectride, respectively. Although stereochemical outcome in the isomerization at C-8 in manipulation of salvinorins remains a long-standing issue and is yet to be solved,[6,14] we have succeeded in the second-generation synthesis of salvinorin A (**1**) to present more expeditious synthetic route.

## 4. Experimental

### 4.1. General

All reactions were performed under nitrogen atmosphere unless otherwise noted. All commercially available reagents were used without further purification unless otherwise noted. Dichloromethane was distilled from $CaH_2$ under nitrogen. Diethyl ether and tetrahydrofuran were freshly distilled from benzophenone ketyl radical under nitrogen prior to use. Mp's were determined with a Yanaco MP hot-stage apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR-4200 spectrophotometer in chloroform unless otherwise indicated. $^1$H NMR spectra were obtained for solutions in deuteriochloroform with a JEOL EX-270 (270 MHz) and a Varian Unity 500 plus (500 MHz) instruments with tetramethylsilane as internal standard. $^{13}$C NMR spectra were obtained for solutions in deuteriochloroform with a JEOL DATUM 270 (67.5 MHz) instrument. Mass spectral data were obtained with a JEOL GC-Mate spectrometer. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for solutions in chloroform at 20 °C. Medium pressure LC (MPLC) was carried out on Hitachi LC system.

### 4.2. Ethyl 2-[(2*R*,6*R*,10*S*)-10-(1,1-diethyl-1-silapropoxy)-2,6-dimethyl-3,7-dioxobicyclo[4.4.0]dec-2-yl]acetate (15)

A stirred solution of alcohol **14** (20 mg, 0.069 mmol), dimethylaminopyridine (0.8 mg, 0.0066 mmol), triethylsilyl trifluoromethanesulfonate (46 μL, 0.20 mmol) in dry DMF (45 μL) and pyridine (5 μL, 0.062 mmol) was heated at 100 °C for 45 min. The reaction was quenched by aqueous ammonium chloride. Product was extracted with ethyl acetate twice. The extract was washed with water, brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by medium pressure chromatography of the residue (eluent: ethyl acetate/*n*-hexane=1:3) provided silyl ether **15** (26 mg, 93%) as pale yellow oil; $[\alpha]_D^{20}$ +96.9 (*c* 9.9); IR ($CHCl_3$) $\nu_{max}$/cm$^{-1}$ 1729, 1706, 1374, 1248, 1191; $^1$H NMR (270 MHz, TMS, $CDCl_3$) δ (ppm) 0.70 (q, *J*=7.7 Hz, 6H), 1.04 (t, *J*=7.8 Hz, 9H), 1.24 (t, *J*=7.2 Hz, 3H), 1.40 (s, 3H), 1.65 (s, 3H), 1.78 (m, 1H), 1.95–2.30 (m, 5H), 2.50–2.70 (m, 2H), 2.50 (A of AB-type, *J*=17.2 Hz, 1H), 3.05 (B of AB-type, *J*=17.2 Hz, 1H), 3.05–3.18 (m, 1H), 4.00–4.18 (m, 2H), 4.35 (br s, 1H); $^{13}$C NMR (67.5 MHz, TMS, $CDCl_3$) δ (ppm) 5.32, 7.07, 14.08, 20.91, 24.32, 31.86, 32.85, 34.50, 35.22, 42.28, 48.21, 49.50, 50.51, 60.39, 67.68, 171.08, 212.84, 213.18; *m*/*z* 410 (M$^+$, 10%), 381 (100), 322 (9), 278 (27), 103 (80), 75 (100). (Found: M$^+$, 410.2485. $C_{22}H_{38}O_5Si$ requires, 410.2488.)

### 4.3. Ethyl 2-{(1*R*,4a*R*,8*S*)-8-(1,1-diethyl-1-silapropoxy)-2,5-bis[(trifluoromethyl)sulfonyl]-1,4a-dimethyl-1,4,4a,7,8,8a-hexahydronaphthyl}acetate (16)

To a solution of diketone **15** (821 mg, 2.00 mmol) in THF (5 mL) was added sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 4.4 mL, 4.4 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 1 h, a solution of Comins' reagent (2.356 g, 6.00 mmol) in THF (11.5 mL) was added. The solution was allowed to stir for 2 h at −78 °C and 1.5 h until −40 °C. The reaction was quenched by aqueous ammonium chloride. Product was extracted with ethyl acetate twice. The organic layer was washed with water, brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:20) gave bis-enol triflate **16** (896 mg, 66%) as pale yellow oil; $[\alpha]_D^{20}$ −36.9 (*c* 1.0); IR ($CHCl_3$) $\nu_{max}$/cm$^{-1}$ 1731, 1415, 1246, 1142; $^1$H NMR (270 MHz, TMS, $CDCl_3$) δ (ppm) 0.62 (q, *J*=8 Hz, 6H), 0.95 (t, *J*=8 Hz, 8H), 1.20 (t, *J*=7 Hz, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 1.55 (s, 1H), 2.20 (m, 2H), 2.37 (m, 1H), 2.43–2.43 (m, 2H), 2.45 (A of AB-type, *J*=14 Hz, 1H), 2.65 (B of AB-type, *J*=14 Hz, 1H), 4.0–4.2 (m, 2H), 4.40 (br s, 1H), 5.60 (m, 1H), 5.78 (t, *J*=5 Hz, 1H); $^{13}$C NMR (67.5 MHz, TMS, $CDCl_3$) δ (ppm) 5.42, 7.01, 14.13, 18.58, 21.14, 34.78, 36.27, 38.01, 41.88, 42.97, 47.72, 60.67, 64.24, 115.92, 120.61, 151.06, 153.65, 169.75; *m*/*z* 674 (M$^+$, 0.2%), 645 (53), 305 (17), 103 (51), 69 (100). (Found: M$^+$−Et, 645.1078. $C_{22}H_{31}O_9F_6SiS_2$ requires, 645.1082.)

### 4.4. 2-{(1*R*,4a*R*,8*S*)-8-(1,1-Diethyl-1-silapropoxy)-2,5-bis[(trifluoromethyl)sulfonyl]-1,4a-dimethyl-1,4,4a,7,8,8a-hexahydronaphthyl}-*N*-methoxy-*N*-methyl acetamide (17)

To a stirred solution of methylmethoxyamine hydrochloride (68 mg, 0.70 mmol) in THF (1.3 mL) was added at −20 °C isopropylmagnesium bromide (0.78 M in THF, 1.8 mL, 1.40 mmol) under nitrogen atmosphere. After being stirred for 15 min, the solution was cannulated into the solution of ester **16** (189 mg, 0.281 mmol) in THF (1.5 mL). After being stirred for 2 h 20 min, a solution prepared from methylmethoxyamine hydrochloride (72 mg, 0.73 mmol) in THF (1.0 mL) and isopropylmagnesium chloride (0.78 M in THF, 1.9 mL, 1.48 mmol) was cannulated. After being stirred for 40 min, the reaction was quenched by addition of aqueous ammonium chloride. Product was extracted with ethyl acetate twice and the organic layer was washed with water and brine. The organic layer was evaporated to dryness to give residue, which was purified by column chromatography (eluent: ethyl acetate/*n*-hexane=1:3) to afford Weinreb amide **17** (195 mg, quant.) as colorless oil; $[\alpha]_D^{20}$ −38.4 (*c* 1.0); IR ($CHCl_3$) $\nu_{max}$/cm$^{-1}$ 1656, 1413, 1217, 1142; $^1$H NMR (270 MHz, TMS, $CDCl_3$) δ (ppm) 0.63 (q, *J*=7.9 Hz, 6H), 0.97 (t, *J*=7.7 Hz, 9H), 1.39 (s, 3H), 1.50 (s, 3H), 2.16–2.40 (m, 4H), 2.46–2.52 (m, 1H), 2.63 (A of AB-type, *J*=15.5 Hz, 1H), 2.75 (B of AB-type, *J*=15.5 Hz, 1H), 3.12 (s, 3H), 3.68 (s, 3H), 4.4 (br s, 1H), 5.61 (dd, *J*=2.4, 3.0 Hz, 1H), 5.79 (dd, *J*=2.2, 4.6 Hz, 1H); $^{13}$C NMR (67.5 MHz, TMS, $CDCl_3$) δ (ppm) 5.43, 7.01, 18.96, 21.66, 31.87, 34.80, 36.13, 38.15, 41.86, 47.46, 61.17, 64.53, 111.45, 115.31, 115.91, 120.61, 151.58, 153.85, 170.20; *m*/*z* 689 (M$^+$, 0.2%), 556 (28), 540 (16), 394 (9), 115 (56), 69 (100). (Found: M$^+$, 689.1598. $C_{24}H_{37}O_9F_6NSiS_2$ requires, 689.1583.)

### 4.5. 2-{(1*R*,4a*R*,8*S*)-8-(1,1-Diethyl-1-silapropoxy)-2,5-bis[(trifluoromethyl)sulfonyl]-1,4a-dimethyl-1,4,4a,7,8,8a-hexahydronaphthyl}-1-(3-furyl)ethan-1-one (18)

To a stirred solution of 3-bromofuran (45 μL, 0.50 mmol) in THF (400 μL) at −70 °C under nitrogen atmosphere was added *t*-BuLi (1.58 M in THF, 570 μL, 0.90 mmol) dropwise. After being stirred for 1 h, a solution of Weinreb amide **17** (138 mg, 0.20 mmol) in THF (7.7 mL) was added dropwise. After being stirred for 40 min, the reaction was quenched by aqueous ammonium chloride. Product was extracted with ethyl acetate twice and the organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:6) gave furyl-ketone **18** (97 mg, 70%) as colorless oil; $[\alpha]_D^{20}$ −27.3 (*c* 1.0); IR ($CHCl_3$) $\nu_{max}$/cm$^{-1}$ 1682, 1414, 1245, 1143; $^1$H NMR (270 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 0.6 (q, $J$=7.7 Hz, 6H), 1.0 (t, $J$=7.7 Hz, 9H), 1.4 (s, 3H), 1.50 (s, 3H), 2.15–2.30 (m, 2H), 2.33–2.41 (m, 2H), 2.6 (s, 1H), 2.8 (A of AB-type, $J$=15.5 Hz, 1H), 3.1 (B of AB-type, $J$=15.5 Hz, 1H), 4.4 (br s, 1H), 5.6 (dd, $J$=2.6, 2.8 Hz, 1H), 5.7 (dd, $J$=2.3, 4.3 Hz, 1H), 6.7 (m, 1H), 7.4 (t, $J$=1.6 Hz, 1H), 8.0 (s, 1H); $^{13}$C NMR (67.5 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 5.43, 7.02, 18.83, 21.50, 34.73, 36.19, 38.11, 42.41, 46.78, 47.20, 64.48, 108.36, 111.46, 115.91, 115.98, 120.58, 128.36, 144.38, 147.42, 150.98, 153.68, 192.22; *m*/*z* 696 (M$^+$, 0.1%), 573 (28), 267 (12), 105 (32), 95 (100). (Found: M$^+$−Et, 667.0925. $C_{24}H_{29}O_9F_6SiS_2$ requires, 667.0926.)

### 4.6. Methyl (1*R*,4a*R*,8*S*)-8-(1,1-diethyl-1-silapropoxy)-1-(2-(3-furyl)-2-oxoethyl)-5-(methoxycarbonyl)-1,4a-dimethyl-1,4,4a,7,8,8a-hexahydronaphthalene-2-carboxylate (20) and methyl (4*S*,5*R*,8a*R*)-4-(1,1-diethyl-1-silapropoxy)-5-(2-(3-furyl)-2-oxoethyl)-5,8a-dimethyl-6-[(trifluoromethyl)-sulfonyloxy]-3,4,4a,5,8,8a-hexahydronaphthalene-carboxylate (19)

After evacuation of a mixture of furyl-ketone **18** (233 mg, 0.334 mmol), palladium tetrakis(triphenylphosphine) (78 mg, 0.067 mmol), dppf (112 mg, 0.20 mmol), carbon monoxide was introduced to the flask. To the mixture were added methanol (5.0 mL), DMF (1.65 mL) and triethylamine (140 μL, 1.0 mmol). Resulting solution was heated at 60 °C for 20 h under carbon monoxide atmosphere. After addition of ethyl acetate, the solution was passed through short silicagel column and evaporated to dryness. The residue was purified by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:6) to afford di-ester **20** (120 mg, 69%) and mono-ester **19** (15 mg, 7%).

**20**: colorless oil; $[\alpha]_D^{20}$ −53.9 (*c* 1.0); IR (CHCl$_3$) $\nu_{max}$/cm$^{-1}$ 1705, 1436, 1362, 1160, 1103; $^1$H NMR (270 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 0.62 (q, $J$=8.2 Hz, 6H), 0.95 (t, $J$=8.2 Hz, 9H), 1.52 (s, 3H), 1.54 (s, 3H), 2.06 (m, 1H), 2.29 (s, 1H), 2.36 (m, 2H), 2.88 (A of AB-type, $J$=15.7 Hz, 1H), 2.98 (m, 1H), 3.64 (s, 3H), 3.71 (s, 3H), 3.84 (B of AB-type, $J$=15.7 Hz, 1H), 4.56 (br s, 1H), 6.65 (m, 1H), 6.87 (m, 1H), 7.06 (dd, $J$=6.9, 2.0 Hz, 1H), 7.37 (t, $J$=1.7 Hz, 1H), 7.98 (m, 1H); $^{13}$C NMR (67.5 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 5.57, 7.14, 20.32, 23.05, 36.45, 37.24, 39.75, 40.85, 47.74, 48.14, 51.30, 64.57, 108.51, 128.84, 133.50, 135.84, 137.97, 141.26, 143.83, 147.41, 166.55, 166.85, 194.49; *m*/*z* 516 (M$^+$, 0.6%), 391 (20), 215 (36), 95 (100), 75 (88). (Found: M$^+$, 516.2539. $C_{28}H_{40}O_7Si$ requires, 516.2543.)

**19**: colorless oil; $[\alpha]_D^{20}$ −54.6 (*c* 0.30); IR (CHCl$_3$) $\nu_{max}$/cm$^{-1}$ 1709, 1663, 1561, 1512, 1413; $^1$H NMR (270 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 0.61 (q, $J$=7.6 Hz, 6H), 0.95 (t, $J$=8.0 Hz, 9H), 1.44 (s, 3H), 1.58 (s, 3H), 2.0 (m, 1H), 2.36 (m, 3H), 2.79 (A of AB-type, $J$=15.0 Hz, 1H), 2.92 (dd, $J$=17.3, 7.2 Hz, 1H), 3.04 (B of AB-type, $J$=15.0 Hz, 1H), 3.71 (s, 3H), 4.47 (br s, 1H), 5.70 (d, $J$=5.5 Hz, 1H), 6.68 (s, 1H), 6.89 (m, 1H), 7.41 (s, 1H), 8.00 (s, 1H); $^{13}$C NMR (67.5 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 5.47, 7.07, 19.54, 21.71, 36.78, 37.33, 42.71, 47.13, 47.45, 51.32, 64.76, 108.37, 115.87, 117.19, 120.57, 128.53, 135.89, 137.18, 144.21, 147.33, 150.76, 166.21, 192.52; *m*/*z* 606 (M$^+$, 0.2%), 545 (0.4), 483 (13), 473 (5), 199 (23), 95 (100). (Found: M$^+$, 606.1926. $C_{27}H_{37}O_8SiF_3S$ requires, 606.1930.)

### 4.7. Methyl (4*S*,4b*R*,6*S*,10a*R*)-4-(1,1-diethyl-1-silapropoxy)-6-(3-furyl)-4b,10a-dimethyl-8-oxo-3,4,4a,4b,5,6,7,10,10a-nonahydro-7-oxaphenanthrenecarboxylate (21)

To a solution of di-ester **20** (214 mg, 0.415 mmol) in THF (8.2 mL) and *t*-butyl alcohol (115 μL, 1.24 mmol) was added K-Selectride (620 μL, 0.62 mmol) at −78 °C under nitrogen atmosphere. The solution was allowed to warm to −30 °C for 30 min. The reaction was quenched by addition of methanol followed by addition of aqueous sodium hydroxide (3 N solution, 420 μL) and hydrogen peroxide (140 μL). After being stirred for 30 min, product was extracted with ether twice. The organic layer was washed with water, brine and, dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate/*n*-hexane=1:3) provided lactone **21** (192 mg, 95%) as white solid: mp 123 °C; $[\alpha]_D^{20}$ −16.2 (*c* 1.0); IR (CHCl$_3$) $\nu_{max}$/cm$^{-1}$ 1709, 1649, 1459, 1436, 1363, 1107; $^1$H NMR (500 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 0.63 (q, $J$=8.0 Hz, 6H), 0.96 (t, $J$=8.0 Hz, 9H), 1.39 (s, 1H), 1.54 (s, 3H), 1.59 (m, 1H), 1.62 (s, 3H), 2.09 (d, $J$=19.5 Hz, 1H), 2.33 (dd, $J$=13.5, 4.5 Hz, 1H), 2.38–2.50 (m, 2H), 3.10 (dd, $J$=19.5, 5.5 Hz, 1H), 3.74 (s, 3H), 4.48 (s, 1H), 5.64 (dd, $J$=12.0, 4.0 Hz, 1H), 6.42 (s, 1H), 6.92 (m, 2H), 7.41 (s, 1H), 7.48 (s, 1H); $^{13}$C NMR (67.5 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 5.38, 6.99, 19.79, 20.99, 35.64, 35.89, 36.90, 40.53, 44.86, 51.28, 51.93, 64.06, 70.71, 108.34, 125.15, 132.84, 135.34, 137.48, 138.39, 139.38, 144.35, 165.76, 166.17; *m*/*z* 486 (M$^+$, 5%), 429 (6), 260 (73), 103 (62), 75 (100). (Found: M$^+$, 486.2443. $C_{27}H_{38}O_6Si$ requires, 486.2437.)

### 4.8. Methyl (1*R*,3*S*,6*R*,7*R*,8*S*,10*R*,13*S*)-3-(1,1-diethyl-1-silapropoxy)-13-(3-furyl)-1,7-dimethyl-11-oxo-12-oxatricyclo[8.4.0.0$^{2,7}$]tetradecane-6-carboxylate (22)

To a solution of unsaturated lactone **21** (9.4 mg, 0.019 mmol) and acetic acid (35 μL, 0.62 mmol) in toluene (390 μL) were added a solution of samarium diiodide (1.55 mL, 0.1 M in THF, 0.155 mmol) prepared separately and triethylamine (43 μL, 0.31 mmol) at −78 °C under nitrogen atmosphere. The solution was allowed to warm to −40 °C in 15 min. The reaction was quenched by bubbling oxygen and ethyl acetate was added. The solution was passed through short silicagel column and evaporated to dryness. Purification of the residue by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:3 to 1:6) provided saturated lactone **22** (6.1 mg, 64%) as white solid: mp 140 °C; $[\alpha]_D^{20}$ +15.7 (*c* 0.52); IR (CHCl$_3$) $\nu_{max}$/cm$^{-1}$ 1794, 1730, 1465, 1380, 1093; $^1$H NMR (270 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 0.62 (q, $J$=7.8 Hz, 6H), 0.90 (s, 1H), 0.97 (t, $J$=7.8 Hz, 9H), 1.32 (s, 3H), 1.34–1.54 (m, 1H), 1.56 (s, 3H), 1.58–1.65 (m, 1H), 1.71 (t, $J$=12.9 Hz, 2H), 1.80–1.93 (m, 2H), 2.03 (d, $J$=13.7 Hz, 1H), 2.06–2.15 (m, 3H), 2.20 (dd, $J$=13.7, 3.4 Hz, 1H), 2.39 (d, $J$=3.9 Hz, 1H), 3.62 (s, 3H), 4.23 (br s, 1H), 5.25 (d, $J$=11.3 Hz, 1H), 6.42 (m, 1H), 7.42 (m, 1H), 7.47 (br s, 1H); $^{13}$C NMR (67.5 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 5.44, 7.15, 17.03, 17.98, 20.23, 25.83, 35.34, 36.56, 37.33, 37.67, 46.93, 49.02, 51.04, 56.84, 67.24, 69.74, 108.40, 124.00, 139.47, 143.48, 174.17; *m*/*z* 490 (M$^+$, 29%), 461 (100), 309 (11), 103 (54), 75 (62). (Found: M$^+$, 490.2742. $C_{27}H_{42}O_6Si$ requires, 490.2750.)

### 4.9. Methyl (1*R*,3*S*,6*R*,7*R*,8*R*,10*R*,13*S*)-13-(3-furyl)-3-hydroxy-1,7-dimethyl-11-oxo-12-oxatricyclo[8.4.0.0$^{2,7}$]tetradecane-6-carboxylate (24)

To a stirred solution of TES-ether **22** (11 mg, 0.023 mmol) in THF (240 μL) was added TBAF in THF (115 μL, 0.116 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 4 h, the reaction was quenched by aqueous ammonium chloride. Resulting solution was passed through short silicagel column with the aid of ethyl acetate and evaporated to dryness. Medium pressure LC of the residue (eluent: ethyl acetate/*n*-hexane=1:1) provided 8*R*-alcohol **24** (2.3 mg, 26%) and 8*S*-alcohol **23** (5.6 mg, 64%).

**24**: white solid: mp 185 °C; $[\alpha]_D^{20}$ −6.1 (*c* 0.43); IR (CHCl$_3$) $\nu_{max}$/cm$^{-1}$ 1793, 1730, 1465, 1378, 1094; $^1$H NMR (270 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 1.00 (s, 1H), 1.12 (d, $J$=3.2 Hz, 1H), 1.15–1.35 (m, 1H), 1.41 (s, 3H), 1.44 (s, 3H), 1.50–1.75 (m, 4H), 1.75–1.95 (m, 1H), 2.08–2.20 (m, 3H), 2.22 (dd, $J$=13.3, 3.5 Hz, 1H), 2.46 (dd, $J$=13.1, 5.3 Hz, 1H), 3.66 (s, 3H), 4.37 (br s, 1H), 5.55 (dd, $J$=11.9, 5.7 Hz, 1H), 6.42 (m, 1H), 7.42 (m, 1H), 7.44 (m, 1H); $^{13}$C NMR (67.5 MHz, TMS, CDCl$_3$) $\delta$ (ppm) 16.81, 17.82, 18.67, 19.93, 35.71, 37.25, 37.68, 40.95, 44.37, 51.29, 52.76, 57.12, 57.65, 66.00, 71.85, 108.36, 125.74, 139.20, 143.60, 172.02, 173.83; *m*/*z* 376 ($M^+$, 16%), 235 (38), 188 (24), 154 (7), 94 (100). (Found: $M^+$, 376.1889. $C_{21}H_{28}O_6$ requires, 376.1886.)

**23**: white solid: mp 193 °C; $[\alpha]_D^{20}$ −7.0 (*c* 0.65); IR ($CHCl_3$) $\nu_{max}$/cm$^{-1}$ 1793, 1727, 1466, 1381, 1095; $^1H$ NMR (270 MHz, TMS, $CDCl_3$) $\delta$ (ppm) 0.97 (s, 1H), 1.07 (d, *J*=3.4 Hz, 1H), 1.33 (s, 3H), 1.35–1.60 (m, 4H), 1.61 (s, 3H), 1.65–1.82 (m, 2H), 1.89 (dd, *J*=14.0, 3.7 Hz, 1H), 2.14 (d, *J*=13.1 Hz, 2H), 2.21 (dd, *J*=12.7, 3.2 Hz, 1H), 2.41 (d, *J*=3.5 Hz, 1H), 3.62 (s, 3H), 4.20 (br s, 1H), 5.25 (d, *J*=11.4 Hz, 1H), 6.40 (m, 1H), 7.40 (m, 1H), 7.46 (m, 1H); $^{13}C$ NMR (67.5 MHz, TMS, $CDCl_3$) $\delta$ (ppm) 17.16, 18.02, 19.91, 26.28, 35.79, 36.62, 37.33, 37.43, 46.77, 49.20, 51.10, 56.21, 56.53, 66.49, 69.82, 108.36, 123.96, 139.46, 143.45, 174.02, 174.19; *m*/*z* 376 ($M^+$, 7%), 308 (94), 235 (34), 175 (53), 95 (100). (Found: $M^+$, 376.1889. $C_{21}H_{28}O_6$ requires, 376.1886.)

### 4.10. Isomerization of 23

A solution of **23** (19 mg, 0.051 mmol) and potassium carbonate (31 mg, 0.22 mmol) in methanol (1.0 mL) was stirred at room temperature for 1.5 h under nitrogen atmosphere. The reaction was quenched by aqueous ammonium chloride. Resulting solution was passed through short silicagel column with the aid of ethyl acetate and evaporated to dryness. Purification by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) gave 8*R*-alcohol **24** (5.3 mg, 28%) and starting 8*S*-alcohol **23** (12.6 mg, 66%).

### 4.11. Methyl (1*R*,6*R*,7*R*,8*R*,10*R*,13*S*)-13-(3-furyl)-1,7-dimethyl-3,11-dioxo-12-oxatricyclo-[8.4.0.0$^{2,7}$]tetradecane-6-carboxylate=Deacetoxysalvinorin A (25)

To a mixture of alcohol **24** (22.5 mg, 0.06 mmol) and Dess–Martin periodinane (125 mg, 0.29 mmol) was added methylenedichloride (600 μL) under nitrogen atmosphere. After being stirred for 2 h, the solution was passed through short silicagel column with the aid of ethyl acetate. Evaporation of solvents followed by column chromatography of the residue (eluent: ethyl acetate/*n*-hexane=1:1) gave 2-deacetoxysalvinorin A **25** (22 mg, 98%) as white solid: mp 149 °C; $[\alpha]_D$ −25.9 (*c* 0.45), lit.[1] $[\alpha]_D^{20}$ −22 (*c* 0.39); IR ($CHCl_3$) $\nu_{max}$/cm$^{-1}$ 1793, 1728, 1466, 1378, 1162; $^1H$ NMR (270 MHz, TMS, $CDCl_3$) $\delta$ (ppm) 1.12 (s, 3H), 1.25 (m, 1H), 1.41 (s, 3H), 1.45–1.75 (m, 5H), 1.95–2.20 (m, 2H), 2.20–2.30 (m, 1H), 2.35 (dd, *J*=12.7, 7.1 Hz, 1H), 2.40–2.50 (m, 1H), 2.58–2.72 (m, 2H), 3.70 (s, 3H), 5.54 (dd, *J*=11.7, 5.2 Hz, 1H), 6.37 (m, 1H), 7.37–7.41 (m, 2H); $^{13}C$ NMR (67.5 MHz, TMS, $CDCl_3$) $\delta$ (ppm) 15.08, 16.49, 18.18, 25.18, 35.38, 38.19, 41.44, 41.63, 43.80, 51.54, 51.70, 55.71, 66.06, 72.04, 108.29, 125.46, 139.14, 143.52, 171.32, 172.81, 208.14; *m*/*z* 374 ($M^+$, 11%), 263 (4), 236 (19), 121 (14), 108 (100), 94 (78) (Found: $M^+$, 374.1737. $C_{21}H_{26}O_6$ requires, 374.1729).

## Acknowledgements

We gratefully acknowledge 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).

## References and notes

1. (a) Koreeda, M.; Brown, L.; Valdés, L. J., III. *Chem. Lett.* **1990**, 2015–2018; (b) Valdés, L. J., III; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716–4720; (c) Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2505–2508.
2. (a) Ma, Z.; Lee, D. Y. W. *Tetrahedron Lett.* **2007**, *48*, 5461–5464; (b) Shirota, O.; Nagamatsu, K.; Sekita, S. *J. Nat. Prod.* **2006**, *69*, 1782–1786; (c) Bigham, A. K.; Munro, T. A.; Rizzacasa, M. A.; Browne, R. M. B. *J. Nat. Prod.* **2003**, *66*, 1242–1244; (d) Munro, T. A.; Rizzacasa, M. A. *J. Nat. Prod.* **2003**, *66*, 703–705; (e) Valdés, L. J., III; Chang, H.-M.; Visger, D. C.; Koreeda, M. *Org. Lett.* **2001**, *3*, 3935–3937.
3. (a) Yan, F.; Mosier, P. D.; Westkaemper, R. B.; Stewart, J.; Zjawiony, J. K.; Vortherms, T. A.; Sheffler, D. J.; Roth, B. L. *Biochemistry* **2005**, *44*, 8643–8651; (b) Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11934–11939; (c) Siebert, D. *J. Ethnopharmacol.* **1994**, *43*, 53–56.
4. (a) Prisinzano, T. E. *J. Nat. Prod.* **2009**, *72*, 581–587; (b) Prisinzano, T. E.; Rothman, R. B. *Chem. Rev.* **2008**, *108*, 1732–1743; (c) Tidgewell, K.; Byrd, N.; Cobb, H.; Dersch, C. M.; Butelman, E. R.; Rothman, R. B.; Prisinzano, T. E. *J. Med. Chem.* **2005**, *48*, 4765–4771.
5. (a) Bergman, Y. E.; Mulder, R.; Perlmutter, P. *J. Org. Chem.* **2009**, *74*, 2589–2591; (b) Burns, A. C.; Forsyth, C. J. *Org. Lett.* **2008**, *10*, 97–100; (c) Lingham, A. R.; Hugel, H. M.; Rook, T. J. *Aust. J. Chem.* **2006**, *59*, 340–348; (d) Vangapandu, S.; Phillip, A.; Stewart, J. D.; Zjawiony, J.; Avery, M. A.; McCurdy, C. R. *Abstracts of Papers*, 225th ACS National Meeting, New Orleans, LA, United States, March 23–27, 2003; 2003, ORGN-421. CODEN: 69DSA4 AN 2003:184914.
6. Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969.
7. Nozawa, M.; Suka, Y.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 1365–1368.
8. Hagiwara, H.; Hamano, K.; Nozawa, M.; Hoshi, T.; Suzuki, T.; Kido, F. *J. Org. Chem.* **2005**, *70*, 2250–2255.
9. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
10. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1097–1100.
11. Jan, N.-W.; Liu, H.-J. *Org. Lett.* **2006**, *8*, 151–153.
12. Dahlen, A.; Hilmersson, G. *Chem. Eur. J.* **2003**, *9*, 1123–1128.
13. Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008–5010.
14. Munro, T. A.; Duncan, K. K.; Staples, R. J.; Xu, W.; Liu-Chen, L.-Y.; Béguin, C.; Carlezon, W. A., Jr.; Cohen, B. M. *Beilstein J. Org. Chem.* **2007**, *3*, 1 and references cited therein.