Tetrahedron 70 (2014) 3141–3145

Contents lists available at ScienceDirect

Tetrahedron

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

Stereochemical investigation and total synthesis of inuloidin, a biologically active sesquiterpenoid from *Heterotheca inuloides*

Jumpei Kamatani [a], Takehiro Iwadate [b], Reiko Tajima [a], Hideaki Kimoto [a], Yoichi Yamada [c], Noriyoshi Masuoka [d], Isao Kubo [e], Ken-ichi Nihei [a,b,*]

[a] Department of Applied Biochemistry, Faculty of Agriculture, Utsunomiya University, Tochigi 321-0943, Japan
[b] Department of Applied Life Science, United Graduate School of Agricultural Science, Tokyo University of Agriculture and Technology, Tokyo 183-8509, Japan
[c] Department of Chemistry, Faculty of Education, Utsunomiya University, Tochigi 321-0943, Japan
[d] Department of Life Science, Faculty of Science, Okayama University of Science, Okayama 700-0005, Japan
[e] Department of Environmental Science, Policy and Management, University of California, Berkeley, CA 94720-3114, USA

ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form 13 March 2014
Accepted 17 March 2014
Available online 25 March 2014

Keywords:
Heterotheca inuloides
Sesquiterpenoid
Plant growth inhibitory substance
Modified Mosher's method
Burgess dehydration

ABSTRACT

The stereochemistry of inuloidin (**1**), which was a sesquiterpenoid that was characterized as a plant growth inhibitory substance from *Heterotheca inuloides*, was investigated. The modified Mosher's method coupled with a total synthetic study using osmium oxidation and Burgess dehydration as key steps were performed to clarify the stereochemistry of **1**, which was determined to be a 2*S*,4*R* isomer.

1. Introduction

The dried flower of *Heterotheca inuloides* (Asteraceae), which is called 'árnica' in Mexico, is widely used as a folk remedy to treat contusions, sprains, rheumatic disorders, and skin inflammations.[1,2] Several sesquiterpenoids and flavonoids have been identified as biologically active substances in *H. inuloides*.[3–5] A cadalin-type sesquiterpenoid, inuloidin (**1**), was isolated in minute amounts from the methanolic extract of *H. inuloides* (Fig. 1).[6] This compound possessed plant growth inhibitory activity at 500 μg/mL in the lettuce seeding assay, while it did not show any antibacterial activity up to 800 μg/mL. On the other hand, 7-hydroxy-3,4-dihydrocadalin (**2**), a congener of **1**, was isolated as a major cadalin-type sesquiterpenoid from *H. inuloides*,[7] and it proved a potent antibacterial compound without plant growth inhibitory activity.

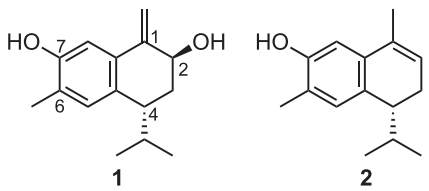


Fig. 1. Structure of **1** and **2** isolated from *H. inuloides*.

The biological activity of **1** and **2** is governed by their slight structural differences, such as the direction of the styryl olefin and the presence of an allylic alcohol moiety. Although the selective activity against plant and bacterial cells was critically interesting,[6] the determination of the stereochemistry and chemical synthesis of **1** have not yet been performed. This study describes the stereochemical investigation of **1** by using the modified Mosher's method, NOE experiments and a synthetic approach using osmium oxidation and Burgess dehydration as key reactions.[8]

2. Results and discussion

Compound **1**, which is a minor constituent of *H. inuloides*, contains a secondary allylic alcohol moiety in its structure. Thus, the modified Mosher's method can be applied to determine the

* Corresponding author. Tel.: +81 28 649 5412; fax: +81 28 649 5401; e-mail address: nihei98@cc.utsunomiya-u.ac.jp (K. Nihei).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.057

stereochemistry of the molecule.[9] To obtain MTPA esters of **1**, the selective protection of the phenolic hydroxy group was needed. However, the reaction failed when using alkylating reagents, such as ethereal diazomethane and iodomethane. Instead, a dialkyl product was obtained when excess amount of alkyl halide was used, suggesting that the phenolic and allylic hydroxy groups in **1** may have a similar reactivity. Hence we envisioned furnishing the MTPA diesters of **1** to determine its stereogenic center.[10]

The method of MTPA diesters was recently applied for the determination of 1,3-diols, for which it has slight limitation.[11,12] It is mainly assumed that two MTPA esterification sites should be apart from each other for avoiding their anisotropic interference. However, by observing the structure of **1**, the phenolic hydroxy group is located far from the allylic hydroxy group. Thus, the modification by MTPA at C-2 would not affect the ^{1}H NMR signals generated by the atoms around the allylic alcohol moiety. As a model experiment, indeed, the comparison of the ^{1}H NMR chemical shifts of (*S*)- and (*R*)-MTPA esters of **2** did not show significant anisotropic effects around C-2 (Fig. 2).

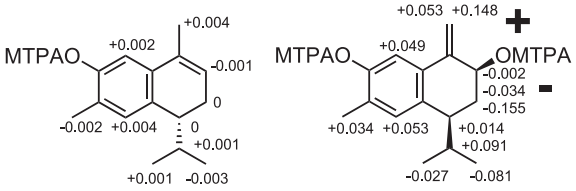


Fig. 2. Δδ values (ppm) obtained from the MTPA ester of **1** and **2**.

The (*S*)- and (*R*)-MTPA diesters of **1** were synthesized in high yield (81% and 95%, respectively) by using the commercially available MTPA chlorides. The ^{1}H NMR chemical shifts of both diastereomers were carefully assigned and the differences ($\Delta\delta=\delta_{S\text{-MTPA ester}}-\delta_{R\text{-MTPA ester}}$) observed for selected protons are summarized in Fig. 2, which according to the rules of the modified Mosher's method clearly shows that the absolute configuration at C-2 is *S*.[9]

This configuration suggests that **1** has an *S*-stereogenic center at C-4 because the relationship between the hydroxy and isopropyl groups was previously established as *cis* by extensive NMR experiments.[6] However, the absolute configuration at C-4 in **2** from *H. inuloides* has been already determined as *R* with the aid of X-ray crystallographic analysis.[13] This contradiction led to preform additional studies to elucidate the relative configuration of **1** by using NMR decoupling and NOE experiments (Fig. 3).

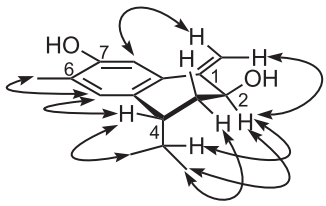


Fig. 3. Significant NOE correlations of **1**.

Significant NOE correlations were observed between the allylic oxymethine and isopropyl protons, indicating that the relative configuration of the allylic hydroxy and isopropyl groups is *trans*. In this case, the bulky isopropyl group is in axial orientation. According to a previous study reporting on the conformational analysis of the similar molecule to **2**,[14] the Boltzmann distribution of the conformer having axial isopropyl group was predominant at room temperature. However, the coupling constants observed between H-2/H-3 and H-2/H-3′ were 3.4 Hz and 7.8 Hz, respectively, indicating that the high-accuracy estimate of the relative configuration of **1** could not be possible only with NMR experiments. Moreover, the total synthesis of **1** has not been reported to date. Thus, we conducted a synthetic study of **1** to confirm its stereostructure as well as to achieve its total synthesis for the first time.

The synthetic plan for **1** is shown in Fig. 4. The reaction started from a methylated cadalin **3**, which is a derivative of **2**.[15] The key reactions were osmium oxidation of the cadalin derivative and selective dehydration of the tertiary hydroxy group. The synthetic route carried out in this experiment to obtain the racemic **1** is summarized in Scheme 1. According to previous reports,[15,16] cadalin **3** was prepared in 16% yield via four steps including Friedel–Crafts and Grignard reactions from 2-methoxytoluene and succinic anhydride as the starting materials. The removal of the methyl group of **3** was conducted in poor yield (<34%) under several acidic conditions, such as BBr_3 in CH_2Cl_2 and pyridinium hydrochloride.[17,18] Fortunately, by using ethanethiolate anion as a nucleophile, this reaction progressed smoothly to give the racemic mixture of phenol **2** in 91% yield.[19]

This phenol was converted into silyl ether **4** using TBSCl in excellent yield (98%). The diastereomeric mixture of diol **5** was furnished in 87% yield from **4** by typical osmium oxidation. The diastereomeric excess (de) of this reaction, which was estimated by the ^{1}H NMR experiment, was 57%, although the diastereomeric mixture of **5** could not be separated by silica gel column chromatography. In the ^{1}H NMR spectra, the coupling constants observed between H-2/H-3 and H-2/H-3′ in **5** were 2.3 Hz and 5.4 Hz, respectively. On the other hand, the minor isomer of **5** possessed 3.7 Hz and 11.8 Hz of the coupling constants at H-2. These values suggested that H-2 of **5** should be equatorial while H-2 of the isomer of **5** projected to the axial direction. Using TBSCl and imidazole, the mixture of **5** was transformed into a diastereomeric mixture of silyl ether **6**. From this reaction mixture, **6** were readily isolated in 53% yields. The coupling constants observed between H-2/H-3 and H-2/H-3′ in **6** were 1.9 Hz and 5.8 Hz, respectively, which were similar to those of **5**. The significant NOE correlations between isopropyl proton and H-5, and methyl proton and H-2 were observed in the NOESY spectra for **6**. These results strongly supported isopropyl and methyl moieties of **6** as well as **5** should be in equatorial positions. Consequently, the 2,4-*trans* orientation of **5** and **6** was determined. Because the bulky osmium reagent was preferentially approached from the opposite site of the isopropyl group in **4**,[14,20] the compound 2,4-*trans* diol **5** was mainly obtained.

The silyl ether **6** can be converted by selective dehydration into olefin **7** as a significant synthetic precursor of **1**. However, the steric hindrance of the tertiary hydroxyl moiety might block the introduction of the leaving group, such as methanesulfonyl or halogen moieties. After several trials, it was found that the Burgess reagent [(methoxycarbonylsulfamoyl) triethylammonium hydroxide] could be used to dehydrate **6**,[8,21] although the reaction yield was slightly poor (33%). The removal of the TBS group of **7** was performed with TBAF to afford racemic **1** in 39% yield. The overall yield of **1** from **3** was 5% via six steps. ^{1}H and ^{13}C NMR data of the racemic mixture of synthesized **1** were fully consistent with those of natural **1**.[6] Consequently, the total synthesis of racemic **1** was achieved and the stereochemistry of natural **1** was determined to be (2*S*,4*R*)-inuloidin.

3. Conclusions

The present study describes the elucidation of the stereochemistry of natural **1** by modified Mosher's method using the di-MTPA esters and reports on its synthesis, which includes two key reactions, osmium oxidation and Burgess dehydration. Accordingly,

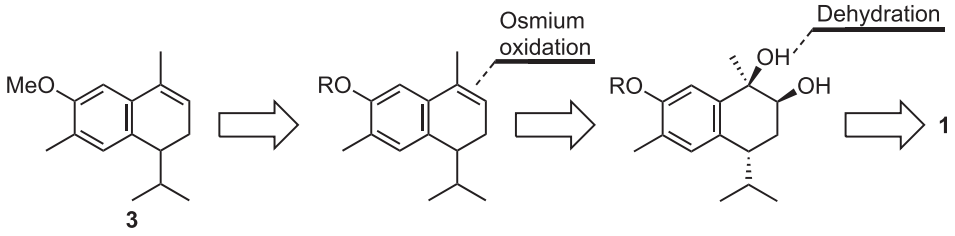
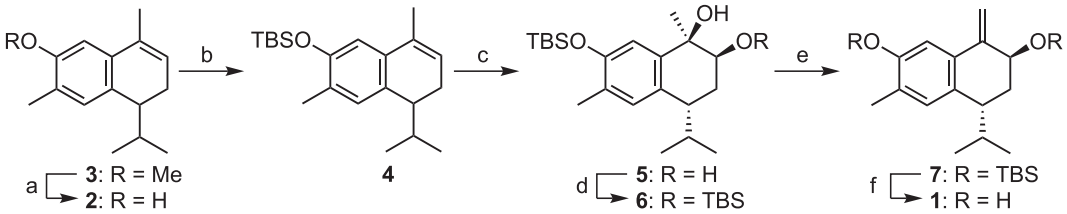


Fig. 4. Synthetic plan for **1**.



Scheme 1. Synthesis of **1**. Reagents and conditions: (a) EtSNa, DMF, reflux, 5 h, 91%; (b) TBSCl, imidazole, DMF, rt, overnight, 98%; (c) OsO_4, NMO, H_2O, *t*-BuOH, acetone, 0 °C to rt, overnight, 87% (57% de); (d) TBSCl, imidazole, DMF, rt, overnight, 53%; (e) Burgess reagent, CH_2Cl_2, reflux, overnight, 33%; (f) TBAF, THF, rt, 2 h, 39%.

it was clarified that natural **1** possessed 2*S* and 4*R* stereogenic centers. The concise synthesis of racemic **1** was additionally demonstrated in short steps starting from cadalin **3**. Although **1** is a minor constituent of *H. inuloides*, an adequate amount of **2** was easily isolated as a single stereoisomer.[3] Thus, our synthetic route is applicable for the semi-synthetic supply of chiral **1** from natural **2** to understand the unique activity of cadalins against plants and microorganisms.

4. Experimental

4.1. General experimental procedures

NMR spectra were recorded in CD_3OD or $CDCl_3$ on a JEOL JNM-ECS400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) or a Varian INOVA-750 (^{1}H at 750 MHz) spectrometer. Chemical shifts were recorded as parts per million relative to the solvent signal for CD_3OD (3.30 ppm for ^{1}H NMR, 49.0 ppm for ^{13}C NMR) or for $CDCl_3$ (7.24 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). HRMS spectra were measured on a JEOL AccuTOF or an AB SCIEX TripleTOF 5600 mass spectrometer fitted with an electrospray ion source in positive ionization mode. IR spectra were measured with a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer. Compound **1** and **2** were isolated along with previous works.[6,7] Spectral data for **2** were consistent with those reported previously.[7]

4.2. Inuloidin (1)

Spectral data for **1** were almost consistent with those reported previously.[6] However, corrected ^{1}H NMR assignments were listed as follows, ^{1}H NMR (400 MHz, CD_3OD): δ 0.773 (3H, d, J=6.8 Hz, *i*-Pr), 0.972 (3H, d, J=6.8 Hz, *i*-Pr), 1.832 (1H, ddd, J=6.3, 7.8, 13.2 Hz, H-3), 1.935 (1H, ddd, J=3.4, 5.8, 13.2 Hz, H-3), 2.153 (3H, s, Me), 2.164 (1H, oct, J=6.8 Hz, *i*-Pr), 2.743 (1H, ddd, J=5.8, 6.3, 6.8 Hz, H-4), 4.534 (1H, dd, J=3.4, 7.8 Hz, H-2), 5.158 (1H, s, CH_2), 5.425 (1H, s, CH_2), 6.913 (1H, s, H-5), 6.971 (1H, s, H-8).

4.3. (*R*)-MTPA diester of 1

A CH_2Cl_2 (0.2 ml) solution of **1** (1.0 mg, 4.3 μmol) was treated with DMAP (3.0 mg, 24.6 μmol) and (*S*)-MTPACl (3.2 mg, 12.6 μmol) at room temperature under a nitrogen atmosphere. After being stirred overnight, the reaction mixture was purified by preparative TLC (10% EtOAc–Hexane) without solvent extraction steps. The corresponding (*R*)-MTPA diester (2.7 mg) was furnished in 95% yield as a colorless solid.

^{1}H NMR (750 MHz, $CDCl_3$): δ 0.795 (3H, d, J=6.8 Hz, *i*-Pr), 0.959 (3H, d, J=6.8 Hz, *i*-Pr), 2.039 (3H, s, Me), 2.073 (2H, m, H-3), 2.172 (1H, m, *i*-Pr), 2.768 (1H, m, H-4), 3.429 (3H, s, OMe), 3.669 (3H, s, OMe), 5.194 (1H, s, CH_2), 5.525 (1H, s, CH_2), 5.928 (1H, br s, H-2), 7.015 (1H, s, H-6), 7.127 (1H, s, H-8), 7.309 (3H, m, Ph), 7.436 (5H, m, Ph), 7.664 (2H, m, Ph).

4.4. (*S*)-MTPA diester of 1

According to the same procedure, (*S*)-MTPA diester (2.3 mg) was furnished by using (*R*)-MTPACl in 81% yield as a colorless solid.

^{1}H NMR (750 MHz, $CDCl_3$): δ 0.714 (3H, d, J=6.8 Hz, *i*-Pr), 0.932 (3H, d, J=6.8 Hz, *i*-Pr), 1.918 (1H, m, H-3), 2.039 (1H, m, H-3), 2.073 (3H, s, Me), 2.263 (1H, m, *i*-Pr), 2.782 (1H, m, H-4), 3.391 (3H, s, OMe), 3.672 (3H, s, OMe), 5.342 (1H, s, CH_2), 5.578 (1H, s, CH_2), 5.926 (1H, br s, H-2), 7.068 (1H, s, H-6), 7.176 (1H, s, H-8), 7.258 (2H, m, Ph), 7.299 (1H, m, Ph), 7.333 (2H, m, Ph), 7.455 (3H, m, Ph), 7.670 (2H, m, Ph).

4.5. (*R*)-MTPA ester of 2

A CH_2Cl_2 (0.2 mL) solution of **2** (1.0 mg, 4.6 μmol) was treated with DMAP (1.5 mg, 12.3 μmol) and (*S*)-MTPACl (1.6 mg, 6.3 μmol) at room temperature under a nitrogen atmosphere. After being stirred overnight, the reaction mixture was purified by preparative TLC (5% EtOAc–Hexane) without solvent extraction steps. The corresponding (*R*)-MTPA diester (2.0 mg) was quantitatively furnished as a colorless solid.

^{1}H NMR (750 MHz, $CDCl_3$): δ 0.784 (3H, d, J=6.8 Hz, *i*-Pr), 0.870 (3H, d, J=6.8 Hz, *i*-Pr), 1.849 (1H, m, *i*-Pr), 1.952 (3H, s, Me), 2.073 (3H, s, Me), 2.344 (3H, m, H-3, H-4), 3.696 (3H, s, OMe), 5.708 (1H, br s, H-2), 6.836 (1H, s, H-5), 6.936 (1H, s, H-8), 7.453 (3H, m, Ph), 7.693 (2H, m, Ph).

4.6. (*S*)-MTPA ester of 2

According to the same procedure, (*S*)-MTPA ester (1.9 mg) was furnished by using (*R*)-MTPACl in 94% yield as a colorless solid.

^{1}H NMR (750 MHz, $CDCl_3$): δ 0.781 (3H, d, J=6.8 Hz, *i*-Pr), 0.871 (3H, d, J=6.8 Hz, *i*-Pr), 1.850 (1H, m, *i*-Pr), 1.956 (3H, s, Me), 2.071

(3H, s, Me), 2.344 (3H, m, H-3, H-4), 3.694 (3H, s, OMe), 5.707 (1H, br s, H-2), 6.840 (1H, s, H-5), 6.938 (1H, s, H-8), 7.453 (3H, m, Ph), 7.695 (2H, m, Ph).

4.7. 7-Hydroxy-3,4-dihydrocadalin (2)

To a solution of ether **3** (0.20 g, 0.87 mmol)[15] and ethanethiol (1.89 ml, 26 mmol) in DMF (20 ml) was slowly added 55% sodium hydride, dispersion in paraffin liquid (1.62 g, 37 mmol), and the resultant solution was heated at reflux for 5 h. The reaction mixture was cooled to room temperature, treated with saturated aqueous NH_4Cl solution (50 ml) and extracted with EtOAc (3×20 ml). The organic layer was washed with brine (3×10 ml) and dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (2–8% EtOAc in hexane) gave 0.17 g (0.79 mmol, 91%) of cadalin **2** as a colorless solid. Spectral data were complete agreement with those previously reported.[7]

4.8. 7-*tert*-Butyldimethylsiloxy-3,4-dihydrocadalin (4)

TBSCl (1.04 g, 6.90 mmol) and imidazole (0.57 g, 8.47 mmol) were added to a solution of cadalin **2** (0.58 g, 2.68 mmol) in DMF (20 ml) at room temperature. After being stirred overnight, the reaction mixture was treated with H_2O (50 ml) and extracted with EtOAc (3×20 ml). The organic layer was washed with brine (3×10 ml) and dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (1–4% EtOAc in hexane) gave 0.87 g (2.63 mmol, 98%) of silyl ether **4** as a colorless oil. IR (film) ν_{max} 2956, 1504, 1254, 1142, 887, 838 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.203 (3H, s, TBS), 0.220 (3H, s, TBS), 0.780 (3H, d, J=6.8 Hz, *i*-Pr), 0.859 (3H, d, J=6.8 Hz, *i*-Pr), 1.013 (9H, s, TBS), 1.833 (1H, oct, J=6.8 Hz, *i*-Pr), 1.956 (3H, s, Me), 2.175 (3H, s, Me), 2.275 (1H, m, H-4), 2.311 (2H, m, H-3), 5.643 (1H, s, H-2), 6.646 (1H, s, H-8), 6.841 (1H, s, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.3 (TBS), −4.1 (TBS), 16.6 (Me), 18.2 (TBS), 19.0 (*i*-Pr), 20.2 (Me), 21.4 (*i*-Pr), 25.77 (C-3), 25.81 (TBS), 30.4 (*i*-Pr), 43.5 (C-4), 113.3 (C-8), 123.2 (C-2), 126.0 (C-6), 130.9 (C-5), 131.3 (C-10), 131.5 (C-9), 133.9 (C-1), 152.0 (C-7). ESIMS m/z 331.2 $[M+H]^+$.

4.9. 7-*tert*-Butyldimethylsiloxy-3,4-dihydro-1,2-dihydroxycadalin (5)

Silyl ether **4** (0.87 g, 2.63 mmol) and 4-methylmorpholine *N*-oxide (0.62 g, 5.29 mmol) were dissolved in acetone (20 ml), *t*-BuOH (10 ml), and H_2O (10 ml). To the cold (0 °C) and stirred solution was added dropwise 4.0% OsO_4 solution (1.00 ml, 0.16 mmol), and resultant mixture was stirred overnight at room temperature. After 10% aqueous Na_2SO_3 solution (30 ml) was added, resultant mixture was stirred for 1 h and extracted with EtOAc (3×20 ml). The organic layer was washed with brine (3×10 ml) and dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (5–20% EtOAc in hexane) gave 0.83 g (2.28 mmol, 87%, 57% de) of the diastereomixture of diol **5** as a colorless oil, which was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 0.201 (3H, s, TBS), 0.222 (3H, s, TBS), 0.643 (3H, d, J=6.8 Hz, *i*-Pr), 0.994 (3H, d, J=6.8 Hz, *i*-Pr), 1.000 (9H, s, TBS), 1.400 (3H, s, Me), 1.788 (1H, ddd, J=2.3, 10.0, 14.4 Hz, H-3), 1.951 (1H, ddd, J=5.4, 6.8, 14.4 Hz, H-3), 2.151 (3H, s, Me), 2.364 (1H, dsept, J=4.6, 6.8 Hz, *i*-Pr), 2.879 (1H, ddd, J=4.6, 6.8, 10.0 Hz, H-4), 3.902 (1H, dd, J=2.3, 5.4 Hz, H-2), 6.965 (1H, s, H-5), 7.010 (1H, s, H-8). ^1H NMR (400 MHz, $CDCl_3$) for the diastereomer: δ 0.201 (3H, s, TBS), 0.222 (3H, s, TBS), 0.635 (3H, d, J=6.8 Hz, *i*-Pr), 1.001 (9H, s, TBS), 1.056 (3H, d, J=6.8 Hz, *i*-Pr), 1.571 (3H, s, Me), 1.864 (1H, ddd, J=3.7, 4.9, 12.5 Hz, H-3), 1.967 (1H, m, H-3), 2.166 (3H, s, Me), 2.492 (1H, m, *i*-Pr), 2.734 (1H, dt, J=11.3, 4.9 Hz, H-4), 3.598 (1H, dd, J=3.7, 11.8 Hz, H-2), 6.976 (1H, s, H-8), 7.047 (1H, s, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.27 (TBS), −4.14 (TBS), 16.2 (Me), 16.7 (*i*-Pr), 18.2 (TBS), 20.7 (*i*-Pr), 25.8 (TBS), 26.0 (C-3), 28.8 (Me), 31.1 (*i*-Pr), 37.6 (C-4), 71.8 (C-1), 73.6 (C-2), 116.0 (C-8), 128.1 (C-6), 129.3 (C-5), 129.8 (C-10), 140.2 (C-9), 152.4 (C-7). ^{13}C NMR (100 MHz, $CDCl_3$) for the diastereomer: δ −4.29 (TBS), −4.05 (TBS), 15.6 (Me), 16.8 (*i*-Pr), 16.72 (Me), 18.2 (TBS), 20.9 (*i*-Pr), 25.8 (TBS), 26.4 (C-3), 29.4 (*i*-Pr), 41.5 (C-4), 71.5 (C-1), 73.9 (C-2), 116.7 (C-8), 128.7 (C-5), 129.0 (C-6), 131.0 (C-10), 139.2 (C-9), 152.3 (C-7).

4.10. 2,7-Bis(*tert*-butyldimethylsiloxy)-3,4-dihydro-1-hydroxy cadalin (6)

TBSCl (1.00 g, 6.64 mmol) and imidazole (0.60 g, 8.81 mmol) were added to a solution of the diastereomixture of **5** (0.80 g, 2.19 mmol) in DMF (20 ml) at room temperature. After being stirred overnight, the reaction mixture was treated with H_2O (50 ml) and extracted with EtOAc (3×20 ml). The organic layer was washed with brine (3×10 ml) and dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (1–4% EtOAc in hexane) gave 0.56 g (1.17 mmol, 53%) of silyl ether **6** as colorless solid. IR (film) ν_{max} 3565, 2956, 1504, 1254, 1087, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.101 (6H, s, TBS), 0.202 (6H, s, TBS), 0.661 (3H, d, J=6.8 Hz, *i*-Pr), 0.815 (9H, s, TBS), 0.988 (3H, d, J=6.8 Hz, *i*-Pr), 0.989 (9H, s, TBS), 1.356 (3H, s, Me), 1.704 (1H, ddd, J=1.9, 10.4, 14.1 Hz, H-3), 1.872 (1H, dt, J=14.1, 5.8 Hz, H-3), 2.149 (3H, s, Me), 2.401 (1H, dsept, J=4.7, 6.8 Hz, *i*-Pr), 2.860 (1H, m, H-4), 3.953 (1H, dd, J=1.9, 5.8 Hz, H-2), 6.926 (1H, s, H-5), 7.004 (1H, s, H-8). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.94 (TBS), −4.25 (TBS), −4.23 (TBS), −4.18 (TBS), 16.4 (Me), 16.7 (*i*-Pr), 18.1 (TBS), 18.2 (TBS), 20.8 (*i*-Pr), 25.8 (TBS), 26.6 (C-3), 28.9 (Me), 30.0 (*i*-Pr), 37.9 (C-4), 71.4 (C-1), 74.8 (C-2), 116.5 (C-8), 127.2 (C-6), 128.5 (C-5), 130.2 (C-10), 141.3 (C-9), 151.8 (C-7). ESIHRMS m/z 501.3144 $[M+Na]^+$ (calcd for $C_{27}H_{50}NaO_3Si_2$, 501.3196).

4.11. 2,7-Bis(*tert*-butyldimethyl)-inuloidin (7)

Under Ar atmosphere, Burgess reagent (0.13 g, 0.55 mmol) was added to a solution of silyl ether **6** (88 mg, 0.18 mmol) in dried CH_2Cl_2 (8 ml) at room temperature. The resultant solution was heated at reflux overnight, treated with H_2O (20 ml) and extracted with EtOAc (3×10 ml). The organic layer was washed with brine (3×10 ml) and dried over Na_2SO_4. Filtration and concentration followed by silica gel chromatography (3–8% Et_2O in hexane) gave 27 mg (59 μmol, 33%) of vinylidene **7** as a colorless oil. IR (film) ν_{max} 2957, 1497, 1254, 1094, 888, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.036 (3H, s, TBS), 0.095 (3H, s, TBS), 0.199 (3H, s, TBS), 0.217 (3H, s, TBS), 0.769 (3H, d, J=6.8 Hz, *i*-Pr), 0.867 (9H, s, TBS), 0.982 (3H, d, J=6.8 Hz, *i*-Pr), 1.005 (9H, s, TBS), 1.835 (1H, ddd, J=5.8, 8.5, 13.2 Hz, H-3), 1.879 (1H, ddd, J=4.2, 5.8, 13.2 Hz, H-3), 2.153 (1H, m, *i*-Pr), 2.164 (3H, s, Me), 2.796 (1H, quart, J=5.8 Hz, H-4), 4.562 (1H, dd, J=4.2, 8.5 Hz, H-2), 5.131 (1H, br s, CH_2), 5.289 (1H, br s, CH_2), 6.929 (2H, m, H-5, H-8). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.57 (TBS), −4.55 (TBS), −4.30 (TBS), −4.10 (TBS), 16.9 (Me), 18.2 (TBS), 18.25 (TBS), 18.32 (*i*-Pr), 21.6 (*i*-Pr), 25.8 (TBS), 25.9 (TBS), 31.8 (*i*-Pr), 33.1 (C-3), 41.2 (C-4), 69.9 (C-2), 106.8 (CH_2), 114.4 (C-8), 128.6 (C-6), 130.4 (C-5), 132.0 (C-10), 132.7 (C-9), 147.7 (C-1), 151.9 (C-7). ESIHRMS m/z 461.3262 $[M+H]^+$ (calcd for $C_{27}H_{49}O_2Si_2$, 461.3271).

4.12. Inuloidin (1)

TBAF trihydrate (0.16 g, 0.51 mmol) was added to a solution of silyl ether **6** (10 mg, 22 μmol) in THF (1 ml) at room temperature. The resultant solution was stirred for 2 h, treated with saturated aqueous NH_4Cl solution (10 ml) and extracted with EtOAc (3×5 ml). The organic layer was washed with brine (3×5 ml) and dried over

Na_2SO_4. Filtration and concentration followed by silica gel chromatography (10–50% EtOAc in hexane) gave 2.0 mg (8.6 μmol, 39%) of inuloidin **1** as a colorless oil. Spectral data were fully consistent with those reported previously.[6]

Acknowledgements

This study is financially supported in part by JSPS KAKENHI Grant Number 23510252. The authors are indebted to Professor K. Tsujimoto, Japan Advanced Institute of Science and Technology, Ishikawa, for invaluable discussion and technical assistance.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.057.

References and notes

1. Heinrich, H.; Robles, M.; West, J. E.; Orliz de Montellano, B. R.; Rodriguez, E. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 539.
2. Gené, R. M.; Segura, L.; Adzet, T.; Marin, E.; Iglesias, J. *J. Ethnopharmacol.* **1998**, *60*, 157.
3. Kubo, I.; Muroi, H.; Kubo, A.; Chaudhuri, S. K.; Sanchez, Y.; Ogura, T. *Planta Med.* **1994**, *60*, 218.
4. Haraguchi, H.; Ishikawa, H.; Sanchez, Y.; Ogura, T.; Kubo, Y.; Kubo, I. *Bioorg. Med. Chem.* **1997**, *5*, 865.
5. Delgado, G.; Olivares, M. S.; Chávez, M. I.; Ramírez-Apan, T.; Linares, E.; Bye, R.; Espinosa-Carcía, F. J. *J. Nat. Prod.* **2001**, *64*, 861.
6. Kubo, I.; Ishiguro, K.; Chaudhuri, S. K.; Kubo, Y.; Sanchez, Y.; Ogura, T. *Phytochemistry* **1995**, *38*, 553.
7. Bohlmann, F.; Zdero, C. *Chem. Ber.* **1976**, *109*, 2021.
8. Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224.
9. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
10. Ichikawa, A.; Takahashi, H.; Ooi, T.; Kusumi, T. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 881.
11. Konno, K.; Fujishima, T.; Liu, Z.; Takayama, H. *Chirality* **2002**, *13*, 72.
12. Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2012**, *112*, 4603.
13. Stipanovic, R. D.; Puckhaber, L. S.; Reibenspies, J. H.; Williams, H. J. *Phytochemistry* **2006**, *67*, 1304.
14. Benincori, T.; Bruno, S.; Celentano, G.; Pilati, T.; Ponti, A.; Rizzo, S.; Sada, M.; Sannicolò, F. *Helv. Chim. Acta* **2005**, *88*, 1776.
15. McCormick, J. P.; Shinmyozu, T.; Pachlatko, J. P.; Schafer, T. R.; Gardner, J. W.; Stipanovic, R. D. *J. Org. Chem.* **1984**, *49*, 34.
16. Cocker, W.; Sainsbury, D. M. *J. Chem. Soc.* **1965**, 3319.
17. Silcoff, E. R.; Sheradsky, T. *New J. Chem.* **1999**, *23*, 1187.
18. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380.
19. Bianco, G. G.; Ferraz, H. M. C.; Costa, A. M.; Costa-Lotufo, L. V.; Pessoa, C.; de Moraes, M. O.; Schrems, M. G.; Pfaltz, A.; Silva, L. F. *J. Org. Chem.* **2009**, *74*, 2561.
20. Nabeta, K.; Katayama, K.; Nakagawara, S.; Katoh, K. *Phytochemistry* **1993**, *32*, 117.
21. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.