Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 301–307

TETRAHEDRON: *ASYMMETRY*

Synthesis of a homochiral ketone having a pinguisane skeleton using phenylethylamine as a chiral auxiliary: a formal total synthesis of deoxopinguisone

Motoo Tori,* Chiho Makino, Kenji Hisazumi, Masakazu Sono and Katsuyuki Nakashima

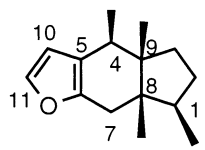
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

Received 20 December 2000; accepted 19 January 2001

Abstract—A homochiral bicyclic ketone having a pinguisane skeleton has been synthesised starting from homochiral methyl 3-[(1′*S*,6′*R*)-1′,6′-dimethyl-2′-oxo-1-yl]propionate prepared from pulegone using phenylethylamine as a chiral auxiliary. The five-membered ring was constructed by the Hosomi–Sakurai reaction of the allylsilane derived from the ketone. This synthesis can be considered a formal synthesis of deoxopinguisone.

1. Introduction

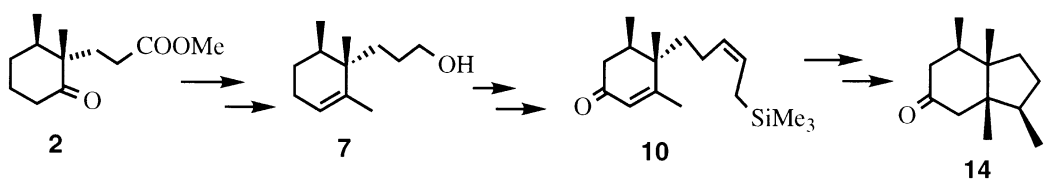
Pinguisanes are unusual sesquiterpenes which most commonly occur in liverworts.[1] Many pinguisane type terpenoids have been characterised so far, among which deoxopinguisone **1** is representative.[2] Interest in this class of terpenoids is high due to their structural novelty.[3] They have four methyl groups, all of which are β-oriented, and all four are attached to contiguous chiral centres. We have reported the total synthesis of trifarienols A and B[4] and striatenic acid[5] starting from the homochiral ketone **2**, which was prepared from (3*R*)-2,3-dimethylcyclohexanone using phenylethylamine as a chiral auxiliary.[4] Key intermediate **2** is easily prepared with a very high e.e. of >99.5%[4] and yields of 60–70%. To further extend the use of **2** in terpene synthesis, we now describe the synthesis of optically active bicyclic ketone **14** which has a basic skeleton of the pinguisane type terpenoid. As conversion of ketone **14** to doeoxopinguisone **1** has literature precedence, the work reported herein can be considered a formal total synthesis of deoxopinguisone **1**.



deoxopinguisone **1**

2. Results and discussion

The *cis*-vicinal dimethyl group at the C-(4) and C-(9) positions of **14** can be derived from the ketone **2**. The other dimethyl groups can be introduced by forming the C–C bond between C-(8) and C-(1) positions, accomplished by the Hosomi–Sakurai reaction. It was thought that *cis*-stereochemistry between the C-(8) and C-(9) positions would be realised when the C-(1)–C-(8) bond is formed because the *cis*-hydrindane system is



Scheme 1. Synthetic plan.

* Corresponding author. Tel.: +81-88-622-9611 (ext. 5631); fax: +81-88-655-3051; e-mail: tori@ph.bunri-u.ac.jp

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00041-6

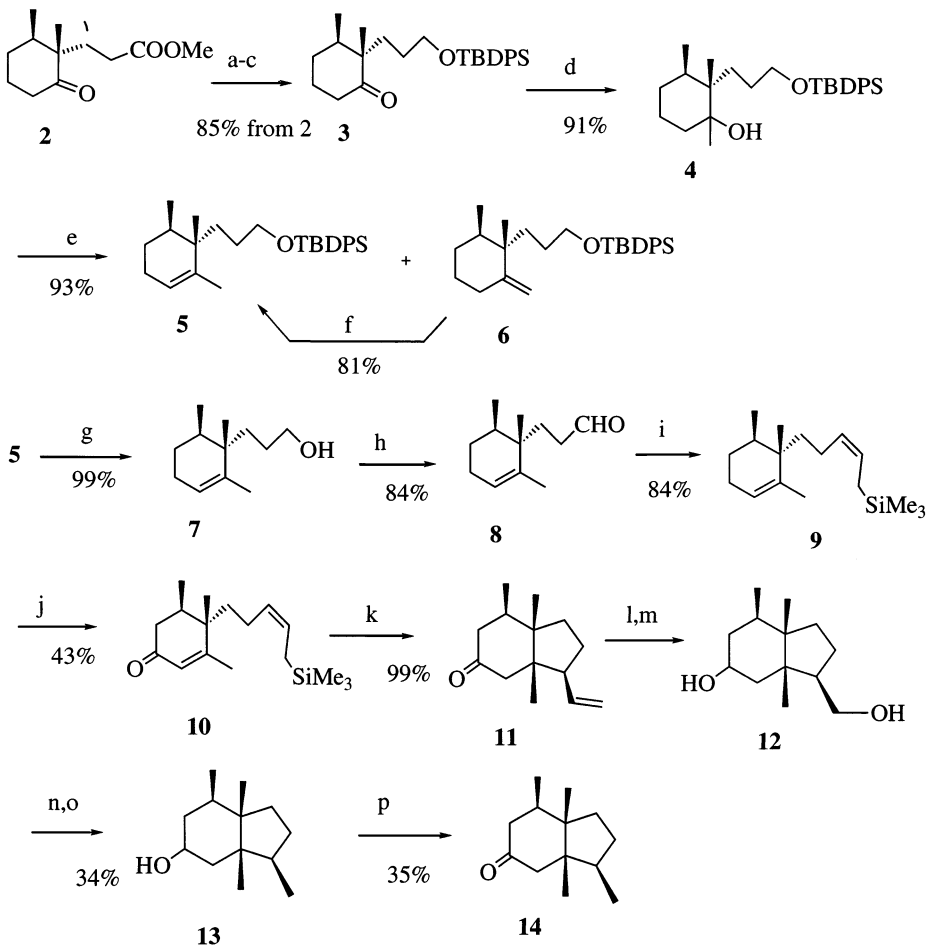
usually much more energetically stable than the *trans*-form (Scheme 1).

The silyl protected ketone **3** was prepared from ketone **2**[4] in three steps, by reduction, chemoselective alcohol protection, and then oxidation (85%). Methylation of ketone **3** was initially difficult because **3** was unreactive to methyl magnesium bromide in ether or THF. However, in the presence of dry $CeCl_3$[6] the methylated product **4** was obtained in 91% yield. These results are presumably explained by the fact that the ketone is easily enolizable and that the steric hindrance of the *cis*-dimethyl groups is large. Dehydration of **4** with $POCl_3$ afforded a mixture of the *endo*- and *exo*-olefins **5** and **6** in a 1:1 ratio (by ^1H NMR, 93%), which were not separated at this stage. However, brief treatment of this mixture with CF_3COOH only produced the *endo*-olefin **5** in 81% yield. Deprotection (TBAF, 99%), Swern oxidation (84%) and olefination using (iodomethyl)trimethylsilane[7] led to silyl ketone **9** in 84% yield; this was assigned from the ^1H and ^{13}C NMR spectra as a 6:1 mixture of *cis*- and *trans*-olefin isomers. This mixture was not separated because both isomers were expected to yield the desired compound in the cyclisation step (Scheme 2).

Allylic oxidation of **9** with PDC and *tert*-butylhydroperoxide afforded the enone **10** in 43% yield. The low yield was attributed to the fact that the allylic position of the side chain was also oxidised to produce the corresponding diketone. After construction of the enone fragment of the six-membered ring, olefination using (iodomethyl)trimethylsilane was unsuccessful. Therefore cyclisation using the Hosomi–Sakurai reaction[8] of **10** was attempted and the results are shown in Table 1.

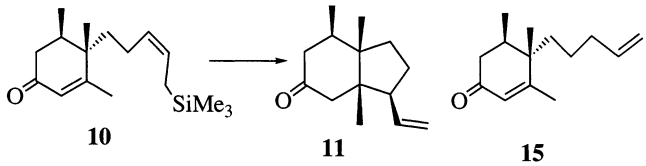
The use of titanium tetrachloride or boron trifluoride etherate in the cyclisation step was unsuccessful owing to the formation of vinyl compound **15** with the double bond at the terminus of the side chain as a result of proton abstraction from trace water present in the reaction mixture. However, the use of anhydrous TBAF dramatically changed the outcome of the reaction and the desired **11** formed in excellent yield.[8] The presence or absence of HMPA did not alter the yield significantly (entries 4 and 5).

The stereochemistry of the product was determined by the NOE experiment, as shown in Fig. 1. This result can be explained by the transition state, as shown in Fig. 2: the *cis*-isomer can approach the β-position of



Scheme 2. (a) $LiAlH_4$; (b) TBDPSCl, NEt_3; (c) Swern oxid.; (d) MeMgBr, $CeCl_3$; (e) $POCl_3$, Py; (f) CF_3COOH, CH_2Cl_2; (g) TBAF, THF; (h) Swern oxid.; (i) Ph_3PMeBr, ICH_2SiMe_3, *n*-BuLi; (j) PDC, *t*BuOOH; (k) TBAF, 4 Å molecular sieves; (l) O_3, CH_2Cl_2; then Me_2S; (m) $NaBH_4$; (n) TsCl, Py; (o) $LiAlH_4$; (p) Jones oxid.

Table 1. Results for the Hosomi–Sakurai reaction of **10**



Entry	Reagents	Solvents	Temp. (°C)	Time (h)	Products (yields, %)
1	$TiCl_4$	CH_2Cl_2	−78 to 12	5	**15** (quant.)
2	$EtAlCl_2$	PhMe	−78 to −70	3	**10**, **15** (1:1)
3	$BF_3{\cdot}Et_2O$	THF	−78 to rt	24	No reaction
4	TBAF	THF, HMPA MS 4Å	−78 to 5	2	**11** (95%)
5	TBAF	THF MS 4Å	−78 to 0	1	**11** (99%)

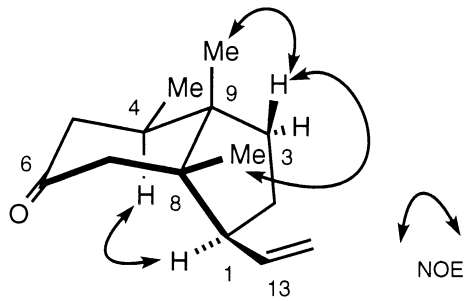


Figure 1. The observed NOEs for **11**.

the enone from the back side of the dimethyl groups as in Fig. 2(A) due to steric hindrance. If approach to the β-position is as shown in Fig. 2(B), steric hindrance between the trimethylsilyl group and the cyclohexenone becomes severe. Thus, the main product **11**, with all substituents *cis*-oriented, is favoured.

Conversion of the vinyl group to a methyl group was then undertaken to complete the synthesis. Ozonolysis of **11** in CH_2Cl_2 at −78°C, followed by treatment with Me_2S afforded the corresponding aldehyde, which was subsequently reduced with $NaBH_4$ to give a mixture of diols **12**. Direct reduction of the ozonide to the diol **12** using $NaBH_4$ in MeOH was unsuccessful as a result of the formation of a considerable amount of unwanted highly polar products. Selective tosylation of the primary alcohol with tosyl chloride in pyridine and reduction with $LiAlH_4$ afforded alcohol **13**, which was oxidised using Jones reagent to complete the synthesis of the desired ketone **14**. Because ketone **14** has previously been converted to deoxopinguisone **1** by Uyehara,[3c,d] the synthetic process developed can be considered a formal total synthesis of deoxopinguisone.

In the CD spectrum of compound **14** the sign of the Cotton effect was negative at 294 nm. If the conformation with a chair form is more stable than non-chair forms, it can be assumed that conformer 2 is the most stable by examination of the model (Fig. 3). However, if it follows the Octant rule, the expected sign of the Cotton effect of conformer 2 is positive. Therefore, conformer 2 must be the energetically least stable. We looked for stable conformers of **14** using CONFLEX.[9] The results are shown in Fig. 3. There are eight conformers within 6 kcal/mol and, surprisingly, conformer 1, the twisted form, is the most stable one. However, the difference in abundance of conformers 1 and 2

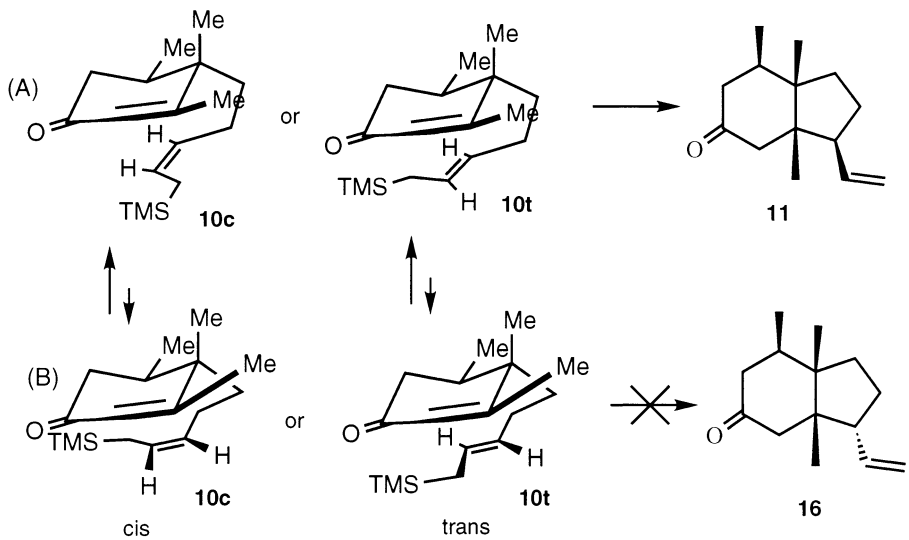


Figure 2. Transition states for cyclisations leading to **14**.

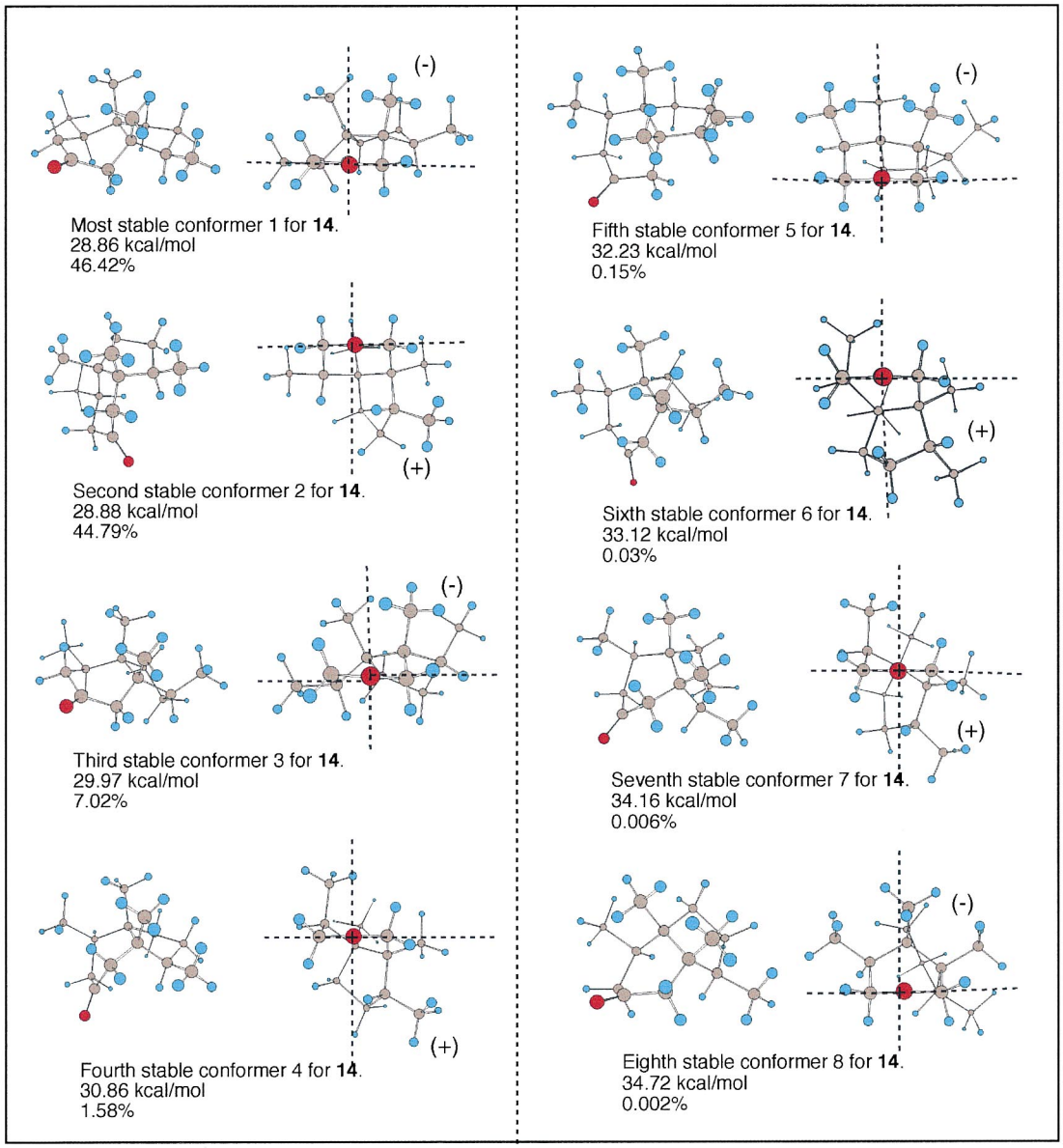


Figure 3. Eight stable conformations for **14** calculated by CONFLEX and the signs of their expected Cotton effects.

differs by less than 2%. Judging from the sign of the CD spectrum, the contribution of conformers 1 and 3 is slightly more than that of conformer 2 and others, providing that the absolute values of CD spectra are almost the same. It is interesting to note that conformers 1 and 2 have almost the same steric energies and each contributes to the opposite sign of Cotton effect. This explains the $[\theta]$ value of the CD spectrum for **14**, which is relatively small compared to those of most carbonyl compounds.[10]

3. Experimental

3.1. General

The IR spectra were measured with a JASCO FT/IR-5300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were taken with a Varian Unity 200 (200 MHz), a Unity 600 (600 MHz) or a JEOL JNM GX400 (400 MHz) spectrometer. The mass spectra including high-resolution mass spectra were taken with a JEOL JMS AX-500 spectrometer. The specific rotation was measured with a JASCO DIP-140 polarimeter and the CD spectra were taken with a JASCO DIP-1000 spectrophotometer. Chemcopak Nucleosil 50-5 (10×250 mm) was used for HPLC (JASCO pump system). Silica gel 60 (70–230 mesh, Merck) was used for column chromatography and silica gel 60 F_{254} plates (Merck) were used for TLC.

3.2. Synthesis of 3

A solution of **2** (9.9 g, 47 mmol) in ether (550 mL) was treated with $LiAlH_4$ (3.3 g, 47 mmol) for 2 h at rt. The reaction was quenched with wet ether, and the organic

materials were extracted with ether. The ethereal solution was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to afford diol (9.5 g) as a colorless oil. TBDPSCl (13.4 mL, 52 mmol) was added to a CH_2Cl_2 (250 mL) solution of the diol (9.5 g) and triethylamine (13 mL, 94 mmol) at rt. After 24 h, the reaction mixture was cooled to 0°C and quenched with water. The products were extracted with CH_2Cl_2, and the organic solution was washed with brine and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated to afford mono-silyl ether (21 g) as a colorless oil. A solution of mono-silyl ether (21 g) in CH_2Cl_2 (300 mL) was oxidised with PDC (20 g, 54 mmol) at rt for 24 h. After filtration and removal of CH_2Cl_2 in vacuo, the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 300 g, 1–5% AcOEt in hexane) to afford **3** (17 g, 85%, three steps).

3: FTIR 1708 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, d, $J=6.6$ Hz), 0.97 (3H, s), 1.05 (9H, s), 1.25–2.0 (9H, m), 2.34 (2H, br t, $J=6.6$ Hz), 3.54–3.76 (2H, m), 7.3–7.45 (6H, m), 7.62–7.7 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.5 (CH_3), 19.0 (CH_3), 19.2 (C), 23.8 (CH_2), 26.9 (CH_3), 27.3 (CH_2), 28.6 (CH_2), 32.7 (CH_2), 38.3 (CH_2), 38.7 (CH), 51.9 (C), 64.3 (CH_2), 127.6 (CH), 129.6 (CH), 134.1 (C), 135.6 (CH), 216.2 (C); MS (CI) m/z 423 $[M+H]^+$, 421, 405, 365, 345, 295, 283, 263, 199, 167 (base), 149; HRMS (CI) found m/z 421.2566 $[M-H]^+$, calcd for $C_{27}H_{37}O_2Si$ 421.2563.

3.3. Synthesis of 4

A THF solution of MeMgBr (0.87 M, 62 mL, 54 mmol) was added to a mixture of ketone **3** (17 g, 40 mmol) and $CeCl_3$ (250 mg, 0.92 mmol) in THF (550 mL) at 0°C. The reaction mixture was stirred for 96 h at rt and quenched with satd NH_4Cl aq. at 0°C. The organic materials were extracted with ether, and the ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 500 g, 1–10% AcOEt in hexane) to afford **4** (16 g, 91%) as a colorless oil. For the determination of the stereochemistry of **4**, the small amount of diastereomixture of **4** was purified by MPLC (SiO_2 50 g, 10% AcOEt in hexane) to afford methyl α-isomer (less polar) and methyl β-isomer (polar), respectively.

4: Methyl α-isomer; FTIR 3500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, d, $J=6.4$ Hz), 0.91 (3H, s), 1.10 (9H, s), 1.26 (3H, s), 1.15–1.95 (11H, m), 3.67 (2H, br t, $J=6.2$ Hz), 7.36–7.5 (6H, m), 7.66–7.77 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.8 (CH_3), 16.9 (CH_3), 19.2 (C), 22.7 (CH_2), 23.6 (CH_3), 26.9 (CH_3), 29.0 (CH_2), 30.5 (CH_2), 33.5 (CH_2), 37.9 (CH), 38.7 (CH_2), 42.7 (C), 65.1 (CH_2), 75.9 (C), 127.6 (CH), 129.5 (CH), 134.2 (C), 135.6 (CH); MS (CI) m/z 421 $[M-H_2O+H]^+$, 381, 363, 343, 199, 181, 165 (base), 123, 109, 95, 83; HRMS (CI) found m/z 421.2917 $[M-H_2O+H]^+$, calcd for $C_{28}H_{41}OSi$ 421.2926.

Methyl β-isomer; FTIR 3500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.74 (3H, s), 0.79 (3H, d, $J=6.8$ Hz), 1.05 (9H, s), 1.15 (3H, s), 1.2–2.1 (11H, m), 3.61 (2H, br t, $J=6.0$ Hz), 7.3–7.45 (6H, m), 7.64–7.73 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.4 (CH_3), 17.4 (CH_3), 19.2 (C), 21.5 (CH_2), 25.9 (CH_3), 26.9 (CH_3), 29.0 (CH_2), 30.3 (CH_2), 32.2 (CH_2), 32.7 (CH), 37.0 (CH_2), 42.1 (C), 65.1 (CH_2), 76.1 (C), 127.6 (CH), 129.5 (CH), 134.1 (C), 135.6 (CH); MS (CI) m/z 421 $[M-H_2O+H]^+$, 405, 381, 363, 343, 303, 199, 181, 165 (base), 137, 123, 109, 95, 83; HRMS (CI) found m/z 421.2938 $[M-H_2O+H]^+$, calcd for $C_{28}H_{41}OSi$ 421.2926.

3.4. Synthesis of 5

To a pyridine (400 mL) solution of **4** (16 g, 36 mmol), $POCl_3$ (13.4 mL, 145 mmol) was added under an Ar atmosphere at 0°C. After heating under reflux for 3 h, the reaction was quenched with wet ether and the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 400 g, 1–10% AcOEt in hexane) to afford a mixture of **5** and **6** (14.1 g, 93%). To a CH_2Cl_2 (200 mL) solution of **5** and **6** (2.05 g, 6.05 mmol), CF_3COOH (4 mL, 52 mmol) was added under an Ar atmosphere at 0°C. After stirring for 18 h at rt, the reaction was quenched with satd $NaHCO_3$ aq. and the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 250 g, 3–10% AcOEt in hexane) to afford **5** (2.05 g, 81%).

5: FTIR 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, $J=5.4$ Hz), 0.87 (3H, s), 1.09 (9H, s), 1.1–1.8 (7H, m), 1.61 (3H, br s), 1.9–2.1 (2H, m), 3.66 (2H, m), 5.44 (1H, br s), 7.35–7.5 (6H, m), 7.7–7.8 (4H, m); MS (CI) m/z 421 $[M+H]^+$, 405, 363, 343, 285, 265, 239, 199, 163 (base), 149, 123, 109, 95, 83, 69; HRMS (CI) found m/z 421.2914 $[M+H]^+$, calcd for $C_{28}H_{41}OSi$ 421.2927.

3.5. Synthesis of 7

To a THF (70 mL) solution of **5** (1.3 g, 310 mmol), TBAF (1.0 M in THF, 8.6 mL) was added under an Ar atmosphere at 0°C. After stirring for 10 h at rt, the reaction was quenched with H_2O and the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 50 g, 5–30% AcOEt in hexane) to afford **7** (558 mg, 99%.).

7: FTIR 3330, 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, $J=7.0$ Hz), 0.87 (3H, s), 1.36–1.5 (2H, m), 1.5–1.8 (5H, m), 1.60 (3H, br s), 1.83–2.1 (2H, m), 3.55–3.7 (3H, m), 5.42 (1H, br s); MS (EI) m/z 182

(M^+), 162, 135, 123 (base), 105, 81, 67, 55; HRMS (EI) found m/z 182.1660, calcd for $C_{12}H_{22}O$ 182.1671.

3.6. Synthesis of 8

A solution of **7** (520 mg, 2.84 mmol) in CH_2Cl_2 (10 mL) was oxidised with oxalyl chloride (0.37 mL, 4.3 mmol) and DMSO (0.6 mL, 8.5 mmol) at −60 to −50°C for 15 min, followed by Et_3N (3.2 mL, 23 mol). The organic materials were extracted with CH_2Cl_2, and the solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 15 g, 1–10% AcOEt in hexane) to afford **8** (430 mg, 84%).

8: FTIR 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (3H, d, $J=6.4$ Hz), 0.91 (3H, s), 1.4–1.8 (2H, m), 1.58 (3H, br s), 1.85–2.05 (3H, m), 2.05–2.6 (4H, m), 5.47 (1H, br s), 9.78 (1H, br t, $J=1.7$ Hz); MS (CI) m/z 180 (M^+), 163, 137, 123 (base), 107, 95, 81, 67; HRMS (CI) found m/z 180.1518, calcd for $C_{12}H_{20}O$ 180.1514.

3.7. Synthesis of 9

A stirred suspension of methyltriphenylphosphonium bromide (3.2 g, 9.1 mmol) in dry THF (30 mL) was cooled to 0°C, treated with *n*-BuLi (1.54 M in hexane, 5.1 mL, 7.8 mmol), warmed to rt, stirred for 1 h and recooled to 0°C. After the addition of (iodomethyl)-trimethylsilane (1.4 mL, 9.1 mmol), the mixture was again allowed to warm to rt, stirred for 1 h, cooled to −78°C and treated again with *n*-BuLi (1.54 M in hexane, 5.1 mL, 7.8 mmol). The dark red solution was stirred for 1.5 h at 20°C, cooled to 0°C and treated for 30 min with a solution of **8** (280 mg, 1.6 mmol) in dry THF (3 mL). The mixture was allowed to warm slowly to rt within 1 h and quenched with satd NH_4Cl aq. (10 mL). The organic materials were extracted with ether, and the ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 40 g, 1–7% AcOEt in hexane) to afford **9** (344 mg, 84%).

9: $[\alpha]_D^{21}$ +43.0 (c 0.86, $CHCl_3$); FTIR 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (9H, s), 0.86 (3H, s), 0.88 (3H, d, $J=6.2$ Hz), 1.35–1.5 (6H, m), 1.62 (3H, br s), 1.85–2.05 (3H, m), 2.02 (2H, br s), 5.2–5.4 (2H, m), 5.42 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.7 (CH_3), 16.0 (CH_3), 18.4 (CH_2), 19.2 (CH_3), 21.0 (CH_3), 21.8 (CH_2), 25.6 (CH_2), 27.1 (CH_2), 33.3 (CH), 36.6 (CH_2), 40.5 (C), 124.0 (CH), 125.0 (CH), 128.1 (CH), 139.7 (C); MS (EI) m/z 264 (M^+), 249, 221, 163, 140 (base), 123, 109, 95, 81, 73; HRMS (EI) found m/z 264.2291, calcd for $C_{17}H_{32}Si$ 264.2273.

3.8. Synthesis of 10

A solution of **9** (38 mg, 0.14 mmol) in benzene (20 mL) was treated with PDC (265 mg, 0.72 mmol) and *t*-BuOOH (5–6 M in decane, 0.14 mL, 0.72 mmol) at 5°C and then stirred at rt for 24 h. After addition of satd $Na_2S_2O_3$ aq. and filtration, the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 15 g, 5–10% AcOEt in hexane) to afford **10** (17 mg, 43%).

10: Major *Z*-isomer; $[\alpha]_D^{21}$ +8.9 (c 0.66, $CHCl_3$); FTIR 1670, 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.00 (9H, s), 0.96 (3H, d, $J=6.6$ Hz), 0.95–1.0 (1H, m), 1.01 (3H, s), 1.43–1.6 (5H, m), 1.92 (3H, d, $J=1.2$ Hz), 2.25–2.35 (3H, m), 5.2 (1H, br dt, $J=9.1$, 6.2 Hz), 5.4 (1H, dtt, $J=9.1$, 9.1, 6.2 Hz), 5.88 (1H, br q, $J=1.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) −1.8 (CH_3), 15.5 (CH_3), 18.6 (CH_2), 19.5 (CH_3), 20.3 (CH_3), 21.9 (CH_2), 33.7 (CH), 36.4 (CH_2), 42.1 (CH_2), 42.3 (C), 126.2 (CH), 126.5 (CH), 128.4 (CH), 168.8 (C), 199.2 (C); MS (EI) m/z 278 (M^+), 263, 250, 223, 209, 195, 182, 138, 73 (base); HRMS (EI) found m/z 278.2072, calcd for $C_{17}H_{30}OSi$ 278.2066.

3.9. Attempted cyclisation reaction of 10 with $TiCl_4$

$TiCl_4$ (4 μL, 0.04 mmol) was added to the CH_2Cl_2 (200 mL) solution of **10** (5.4 mg, 0.019 mmol) at −78°C. The reaction mixture was allowed to stir at rt (12°C) for 5 h and quenched with water. The mixture was extracted with ether, and the ethereal solution washed with brine, dried over anhydrous magnesium sulfate and concentrated to afford **15** (4.1 mg, quant.).

15: FTIR 1670, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (3H, d, $J=1.2$ Hz), 4.93–5.08 (2H, m), 5.67–5.9 (1H, m), 5.86 (1H, d, $J=1.2$ Hz); MS (EI) m/z 206 (M^+), 191, 163, 137, 123, 109 (base), 95, 81, 67, 55; HRMS (EI) found m/z 206.1651, calcd for $C_{14}H_{22}O$ 206.1671.

3.10. Synthesis of 11

To a THF (5 mL) suspension of MS 4Å (350 mg) and **10** (79.3 mg, 0.29 mmol), TBAF (7 mL, 1.0 M in THF), dried previously over MS 4Å (350 mg), was added under an Ar atmosphere at −78°C. The reaction mixture was allowed to reach 0°C over 1 h and the reaction was quenched with water. The organic materials were extracted with ether, and the solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 5 g, 0–10% AcOEt in hexane) to afford **11** (58.4 mg, 99%).

11: $[\alpha]_D^{20}$ −18.0 (c 1.18, $CHCl_3$); CD [θ] 94 nm −1330 ($CHCl_3$); $\Delta\varepsilon=-0.40$; FTIR 1720, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.79 (3H, s), 0.95 (3H, d, $J=6.3$ Hz), 0.98 (3H, s), 1.5–1.65 (2H, m), 1.7–1.9 (2H, m), 2.08 (1H, br t, $J=5.5$ Hz), 2.15 (2H, br s), 2.24 (2H, m), 2.46 (1H, br q, $J=8$ Hz), 4.99 (1H, ddd, $J=17$, 2, 1 Hz), 5.04 (1H, ddd, $J=10.4$, 2, 0.6 Hz), 5.63 (1H, ddd, $J=17$, 10.4, 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8 (CH_3), 17.3 (CH_3), 19.4 (CH_3), 26.2 (CH_2), 33.5 (CH_2), 36.7 (CH), 45.9 (CH_2), 46.7 (C), 47.5 (CH_2), 49.6 (CH), 52.1 (C), 116.7 (CH_2), 138.8 (CH), 211.8 (C); MS (EI) m/z 206 (M^+), 191, 178, 163, 137, 121, 96, 82 (base); HRMS (EI) found m/z 206.1691, calcd for $C_{14}H_{22}O$ 206.1671.

3.11. Synthesis of 12

A solution of **11** (23.9 mg, 0.116 mmol) in CH_2Cl_2 (10 mL) was treated with ozone at −78°C until a blue color persisted. Me_2S (1 mL) was added to the reaction mixture and stirred for 24 h at rt. The reaction mixture was concentrated and purified by silica gel flash chromatography (SiO_2 5 g, AcOEt) to afford aldehyde (125 mg) as a colorless oil. A solution of aldehyde (125 mg) in MeOH (2 mL) was treated with $NaBH_4$ (85 mg, 2.2 mmol) for 2 h at 0°C. The reaction was quenched with water and the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate to afford **12** as a colorless oil (19.5 mg, two steps, 79%).

12: FTIR 3350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.71 (3H, s), 0.73 (3H, s), 0.84 (3H, d, $J=7$ Hz), 1.2–2.0 (11H, m), 3.19 (1H, m), 3.61 (1H, dd, $J=10.1$, 5 Hz), 3.74 (1H, dd, $J=10.1$, 8.4 Hz), 4.08 (1H, quint, $J=2.8$ Hz); MS (EI) m/z 211 $[M-1]^+$, 194, 176, 161 (base), 147, 134, 121, 107, 95; HRMS (CI) found m/z 211.1691 $[M-1]^+$, calcd for $C_{13}H_{23}O_2$ 211.1698.

3.12. Synthesis of 13

To a pyridine (1 mL) solution of **12** (19.5 mg, 0.092 mmol), TsCl (35 mg, 0.18 mmol) was added under an Ar atmosphere at rt. After stirring for 4 h at rt, the reaction was quenched with H_2O and the organic materials were extracted with ether. The ethereal solution was washed with brine and dried over anhydrous magnesium sulfate to afford tosylate (27.5 mg) as a colorless oil. A solution of tosylate (27.5 mg, 0.075 mmol) in THF (3 mL) was treated with $LiAlH_4$ (57 mg, 1.5 mmol) for 4 h at rt. The reaction was quenched with water and the organic materials were extracted with ether. The solution was washed with brine and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography (SiO_2 5 g, 0–100% AcOEt in hexane) to afford **13** (6.2 mg, two steps, 34%).

13: FTIR 3550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (3H, s), 0.75 (3H, s), 0.84 (3H, d, $J=6.6$ Hz), 0.86 (3H, d, $J=6.3$ Hz), 1.0–2.0 (11H, m), 4.04 (1H, quint, $J=3.6$ Hz); MS (EI) m/z 195 $[M-1]^+$, 178, 163, 149, 136, 121, 109 (base), 95, 81; HRMS (CI) found m/z 196.1850 $[M-1]^+$, calcd for $C_{13}H_{24}O$ 196.1828.

3.13. Synthesis of 14

A solution of **13** (6.2 mg, 0.032 mmol) in acetone (3 mL) was oxidised with Jones' reagent (0.3 mL) at 0°C for 1.25 h. After removal of acetone in vacuo, the organic materials were extracted with ether, and the solution was washed with brine and dried over anhydrous magnesium sulfate. The product was purified by silica gel flash chromatography (SiO_2 5 g, 0–10% AcOEt in hexane) to afford **14** (2.2 mg, 35%).

14: $[\alpha]_D^{25}$ −22.6 (c 0.15, $CHCl_3$); CD $[\theta]$ 94 nm −1130 ($CHCl_3$); $\Delta\varepsilon=-0.34$; FTIR 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, s), 0.84 (3H, d, $J=6.6$ Hz), 0.94 (3H, d, $J=6.3$ Hz), 0.97 (3H, s), 1.4–2.2 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 14.5, 17.3, 18.7, 29.7, 33.4, 36.8, 38.9, 45.8, 46.9, 47.7, 50.7, 212.2; MS (EI) m/z 194 $(M)^+$ 179, 161, 151, 137, 123, 109 (base), 95, 82; HRMS (CI) found m/z 195.1746 $[M+H]^+$, calcd for $C_{13}H_{23}O$ 195.1749.

Acknowledgements

We thank Dr. M. Tanaka and Miss Y. Okamoto, this university, for measurement of 600 MHz NMR and MS spectra, respectively.

References

1. (a) Asakawa, Y. In *Chemical Constituents of the Bryophytes*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds. Progress in the Chemistry of Organic Natural Products. Springer-Verlag: Wien, 1982; Vol. 42, pp. 1–285; (b) Asakawa, Y. In *Chemical Constituents of the Hepaticae*; Herz, W.; Moore, R. E.; Steglich, W.; Tamm, Ch., Eds. Progress in the Chemistry of Organic Natural Products. Springer-Verlag: Wien, 1995; Vol. 65, pp. 1–562.
2. Asakawa, Y.; Toyota, M.; Aratani, T. *Tetrahedron Lett.* **1976**, *40*, 3619–3622.
3. (a) Bernasconi, S.; Ferrari, M.; Gariboldi, P.; Jommi, S.; Sisti, M.; Destro, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1981–1994; (b) Bernasconi, S.; Gariboldi, P.; Jommi, G.; Montanari, S.; Sisti, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2394–2397; (c) Uyehara, T.; Kabasawa, Y.; Kato, T.; Furuta, T. *Tetrahedron Lett.* **1985**, *26*, 2343–2346; (d) Uyehara, T.; Kabasawa, Y.; Kato, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2521–2528; (e) Solaja, B.; Huguet, J.; Karpf, M.; Dreiding, A. S. *Tetrahedron* **1987**, *43*, 4875–4886; (f) Gambacorta, A.; Botta, M.; Turchetta, S. *Tetrahedron* **1988**, *44*, 4837–4846; (g) Baker, R.; Selwood, D. L.; Swain, C. J.; Webster, N. M. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 471–480; (h) Mateos, A. F.; Barrueco, O. F.; González, R. R. *Tetrahedron Lett.* **1990**, *31*, 4343–4346; (i) Schinzer, D.; Ringe, K. *Tetrahedron* **1996**, *52*, 7475–7485; (j) Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3295–3296; (k) Srikrishna, A.; Vijaykumar, D. *Tetrahedron Lett.* **1998**, *39*, 4901–4904.
4. Tori, M.; Hisazumi, K.; Wada, T.; Sono, M.; Nakashima, K. *Tetrahedron: Asymmetry* **1999**, *10*, 961–971.
5. Tori, M.; Aiba, A.; Koyama, H.; Hashimoto, T.; Nakashima, K.; Sono, M.; Asakawa, Y. *Tetrahedron* **2000**, *56*, 1655–1659.
6. Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787–6790.
7. Fleming, I.; Paterson, I. *Synthesis* **1979**, 446–448.
8. Majetich, G.; Hull, K.; Defauw, J.; Shawe, T. *Tetrahedron Lett.* **1985**, *26*, 2755–2758.
9. Materia Ver. 3.2, CONFLEX module was used; cf. (a) Goto, H.; Ôsawa, E. *Tetrahedron Lett.* **1992**, *33*, 1343–4346; (b) Goto, H.; Ôsawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187–198; (c) Tori, M.; Ikawa, M.; Sagawa, T.; Furuta, H.; Sono, M.; Asakawa, Y. *Tetrahedron* **1996**, *52*, 9999–10010.
10. Toyota, M.; Nagashima, F.; Asakawa, Y. *Phytochemistry* **1989**, *28*, 1661–1665.