# 5,11-Epoxymegastigmanes from the Leaves of *Asclepias fruticosa*[1)]

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**Five new megastigmane glucosides and one of their aglycones were isolated, along with (6*S*,9*R*)-roseoside, from the polar fraction of the leaves of *Asclepias fruticosa*, and the structures were determined by spectroscopic methods. Most of them have an epoxy-linkage between C-5 and C-11. The configurations at C-3 and C-9 for each compound were confirmed to be *S* and *R*, respectively, by application of the modified Mosher's method.**

**Key words** 5,11-epoxymegastigmane; ascleposide; *Asclepias fruticosa*; Asclepiadaceae

During investigations of the polar constituents of Asclepiadaceous plants, we isolated an 11-glucosyloxymegastigmane, along with conduritol F and its 3-*O*- and 4-*O*-glucosides from *Cynanchum liukiuense* WARB.[1)] Since the occurrence of 11-hydroxylated megastigmane is rare in Asclepiadaceous plants, we examined other species in this family. This paper deals with the isolation and structure determination of five new glucosides of 5,11-epoxymegastigmanes, named ascleposides A—E (**2**, **4**—**7**), and the aglycone of **2** (**3**), along with (6*S*,9*R*)-roseoside (**1**),[2)] from the leaves of *Asclepias fruticosa* L.

Fresh leaves were soaked in 50% aqueous acetone and the extract was partitioned between *n*-BuOH/$H_2O$. The $H_2O$ layer was chromatographed on a charcoal column and the column was eluted with 5—50% EtOH in $H_2O$. Compounds **2** and **3** were obtained from 10% EtOH, **4** from 20% EtOH, and **1**, **6** and **7** from 50% EtOH effluent. Compound **5** was isolated from the *n*-BuOH soluble fraction, along with **6**, after Diaion HP-20 and silica gel column chromatography. Compound **1** was identified as (6*S*,9*R*)-roseoside, based on a comparison of its optical rotation and the $^1$H- and $^{13}$C-NMR signals reported in the literature.[2)]

Based on high resolution (HR)-FAB-MS, the molecular formula of ascleposide A (**2**) was assigned as $C_{19}H_{32}O_9$ (*m/z*: 427.1943, $[M+Na]^+$). The presence of an anomeric proton signal at $\delta$ 4.35 (d, $J$=8 Hz) and the molecular formula suggested **2** to be a glycoside of megastigmane. In the $^1$H-NMR spectrum of **2**, only two tertiary methyl signals ($\delta$ 0.91, 1.12, each s) and hydroxymethyl signals ($\delta$ 3.72 (d, $J$=8 Hz) and $\delta$ 3.77 (dd, $J$=8, 2 Hz)) were observed instead of three tertiary methyl signals in **1**, and the $^1$H–$^1$H shift correlation spectroscopy (COSY) spectrum suggested a connection from the terminal methyl signal (H-10) to H-7 in the side chain as observed in **1**. A signal at $\delta$ 4.23 (m) seemed to be due to an axial methine proton at C-3. In the $^{13}$C-NMR spectrum, three quaternary carbon signals were assigned to C-1 ($\delta$ 48.8), C-6 ($\delta$ 82.6) and C-5 ($\delta$ 87.3) and the carbon signals due to glucose were also ascribable. Since three bond correlations were observed between protons and carbons (H-12/C-2,6,11; H-13/C-4,6; H-11/C-5,6) as shown in Chart 2 in the heteronuclear multiple bond correlation (HMBC) spectrum, **2** was considered to be a glucoside of 5,11-epoxy-7,8-dehydro-3,6,9-trihydroxymegastigmane.

Upon hydrolysis with cellulase, **2** afforded an aglycone (**2a**, $C_{13}H_{22}O_4$) along with glucose which was confirmed to be in the D-form from its optical rotation ($[\alpha]_D$ +66.0°). The location of D-glucopyranose was assigned to be the 3-hydroxy group based on the glucosylation shifts of C-3 (+7.6 ppm) along with C-2 (−1.8 ppm, pro-*R*) and C-4 (−3.2 ppm, pro-*S*) as well as cross peaks (H-3/C-1′, H-1′/C-3) in the HMBC spectrum. The configuration of C-3 was also suggested to be *S*.[3)]

Since nuclear Overhauser effect (NOE) responses were observed between H-7/H-2$\beta$,4$\beta$ and H-3/H-2$\alpha$,4$\alpha$ in **2a**, a

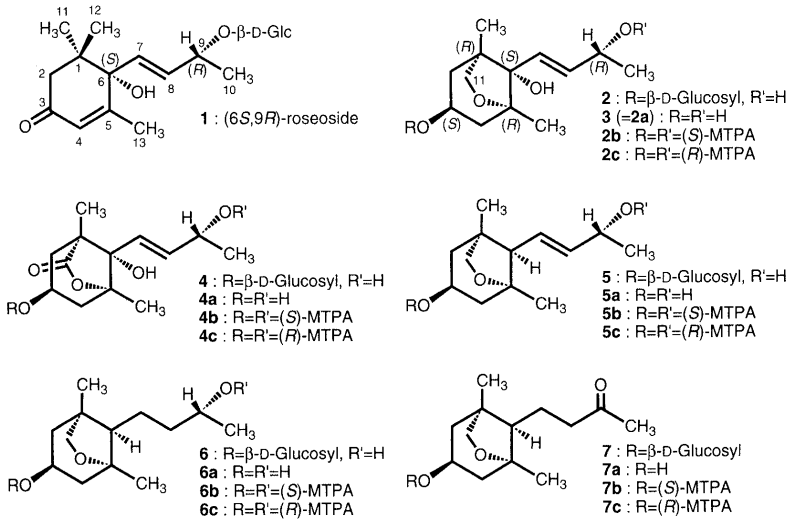


Chart 1

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Table 1. $^{13}C$ Spectral Data for **2**—**7** and **4a**—**7a** in $CD_3OD$ ($\delta$ ppm from tetramethylsilane (TMS))

| C | 2 | 3 (=2a) | 4 | 4a | 5 | 5a | 6 | 6a | 7 | 7a |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 48.8 | 48.8 | 53.1 | 53.1 | 44.7 | 44.7 | 44.0 | 44.0 | 44.0 | 44.0 |
| 2 | 42.7 | 44.5 | 39.4 | 40.9 | 39.1 | 40.8 | 38.8 | 40.6 | 38.7 | 40.5 |
| 3 | 73.6 | 66.0 | 72.8 | 65.2 | 74.5 | 66.9 | 74.4 | 66.7 | 74.3 | 66.6 |
| 4 | 42.7 | 45.9 | 39.3 | 42.2 | 39.5 | 42.7 | 39.1 | 42.3 | 39.0 | 42.3 |
| 5 | 87.3 | 87.4 | 89.7 | 89.9 | 84.7 | 84.9 | 85.3 | 85.4 | 85.1 | 85.3 |
| 6 | 82.6 | 82.6 | 82.2 | 82.3 | 60.0 | 60.0 | 55.6 | 55.5 | 54.8 | 54.7 |
| 7 | 126.9 | 126.9 | 124.5 | 124.6 | 124.4 | 124.3 | 22.1 | 22.1 | 19.6 | 19.6 |
| 8 | 139.5 | 139.6 | 141.3 | 141.4 | 141.8 | 141.9 | 40.0 | 40.0 | 43.6 | 43.6 |
| 9 | 69.1 | 69.1 | 68.8 | 68.8 | 69.1 | 69.0 | 68.8 | 68.8 | 211.0 | 211.0 |
| 10 | 24.0 | 24.0 | 23.9 | 23.8 | 24.0 | 23.9 | 23.5 | 23.5 | 29.8 | 29.8 |
| 11 | 77.0 | 77.2 | 181.2 | 181.4 | 78.7 | 78.8 | 78.1 | 78.2 | 78.0 | 78.2 |
| 12 | 16.2 | 16.2 | 14.3 | 14.4 | 21.4 | 21.4 | 21.8 | 21.8 | 21.7 | 21.7 |
| 13 | 19.5 | 19.4 | 18.3 | 18.3 | 25.0 | 25.0 | 25.8 | 25.7 | 25.7 | 25.6 |
| 1′ | 102.8 | | 103.1 | | 102.7 | | 102.7 | | 102.7 | |
| 2′ | 75.2 | | 75.1 | | 75.2 | | 75.1 | | 75.1 | |
| 3′ | 78.1 | | 78.0 | | 78.1 | | 78.1 | | 78.1 | |
| 4′ | 71.7 | | 71.6 | | 71.7 | | 71.7 | | 71.7 | |
| 5′ | 77.9 | | 77.9 | | 77.9 | | 77.9 | | 77.9 | |
| 6′ | 62.8 | | 62.6 | | 62.8 | | 62.8 | | 62.8 | |

Table 2. $^{1}H$ Spectral Data for **2**—**6** and **7** in $CD_3OD$ ($\delta$ ppm from TMS, $J$ in Hz)

| H | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 2$\alpha$ | 1.93 (ddd, 14, 7, 1) | 1.80 (ddd, 13, 7, 2) | 2.03 (ddd, 14, 7, 1) | 1.82 (dd, 13, 7) | 1.77 (dd, 13, 7) | 1.77 (dd, 13, 7) |
| 2$\beta$ | 1.80 (ddd, 14, 10, 2) | 1.67 (ddd, 13, 11, 2) | 1.90 (dd, 14, 11) | 1.64 (br t, 13) | 1.59 (br t, 13) | 1.57 (br t, 13) |
| 3 | 4.23 (m) | 4.09 (m) | 3.99 (m) | 4.17 (m) | 4.11 (m) | 4.10 (m) |
| 4$\alpha$ | 2.14 (ddd, 14, 7, 1) | 1.99 (ddd, 13, 7, 2) | 2.41 (ddd, 14, 7, 1) | 1.98 (dd, 13, 7) | 1.94 (dd, 13, 7) | 1.95 (dd, 13, 7) |
| 4$\beta$ | 1.79 (dd, 14, 10) | 1.72 (dd, 13, 10) | 1.94 (dd, 14, 10) | 1.56 (dd, 13, 10) | 1.55 (dd, 13, 10) | 1.52 (dd, 13, 10) |
| 6 | | | | 2.04 (br d, 9) | 1.30—1.37 (m) | 1.35 (t, 6) |
| 7 | 6.08 (d, 16) | 6.07 (d, 16) | 6.11 (d, 16) | 5.74 (m) | 1.30—1.37 (m) | 1.60 (m) |
| | | | | | 1.67 (m) | 1.79 (m) |
| 8 | 6.04 (dd, 16, 5) | 6.03 (dd, 16, 5) | 6.07 (dd, 16, 5) | 5.74 (m) | 1.52—1.58 (m) | 2.62 (2H, t, 8) |
| 9 | 4.36 (qd, 7, 5) | 4.35 (qd, 7, 5) | 4.37 (qd, 7, 5) | 4.28 (m) | 3.72 (m) | |
| 10 | 1.27 (d, 7) | 1.27 (d, 7) | 1.28 (d, 7) | 1.25 (d, 6) | 1.18 (d, 6) | 2.15 (s) |
| 11 | 3.72 (d, 8) | 3.68 (d, 7) | | 3.46 (dd, 8, 2) | 3.41 (dd, 8, 2) | 3.41 (dd, 8, 2) |
| | 3.77 (dd, 8, 2) | 3.78 (dd, 7, 2) | | 3.76 (d, 8) | 3.66 (d, 8) | 3.66 (d, 8) |
| 12 | 0.91 (s) | 0.91 (s) | 1.05 (s) | 0.94 (s) | 1.00 (s) | 1.00 (s) |
| 13 | 1.12 (s) | 1.10 (s) | 1.31 (s) | 1.16 (s) | 1.24 (s) | 1.24 (s) |
| 1′ | 4.35 (d, 8) | | 4.33 (d, 8) | 4.37 (d, 8) | 4.35 (d, 8) | 4.34 (d, 8) |
| 2′ | 3.13 (dd, 8, 9) | | 3.13 (dd, 8, 9) | 3.14 (dd, 8, 9) | 3.12 (dd, 8, 9) | 3.12 (dd, 8, 9) |
| 3′ | 3.35 (t, 9) | | 3.34 (t, 9) | 3.35 (t, 9) | 3.34 (t, 9) | 3.34 (t, 9) |
| 4′ | 3.28 (t, 9) | | 3.28 (t, 9) | 3.28 (t, 9) | 3.28 (t, 9) | 3.27 (t, 9) |
| 5′ | 3.27 (m) | | 3.27 (m) | 3.27 (m) | 3.27 (m) | 3.26 (m) |
| 6′ | 3.66 (dd, 11, 5) | | 3.66 (dd, 12, 5) | 3.66 (dd, 12, 5) | 3.66 (dd, 12, 5) | 3.66 (dd, 11, 4) |
| | 3.86 (dd, 11, 1) | | 3.84 (dd, 12, 2) | 3.86 (dd, 12, 2) | 3.86 (dd, 12, 2) | 3.85 (dd, 11, 1) |

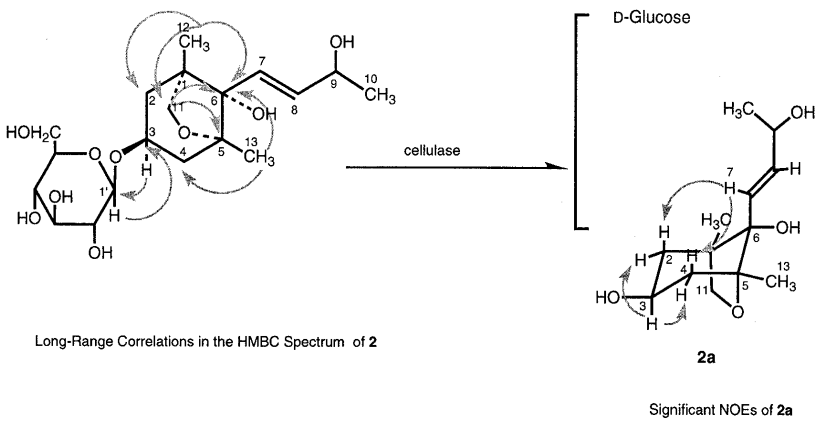
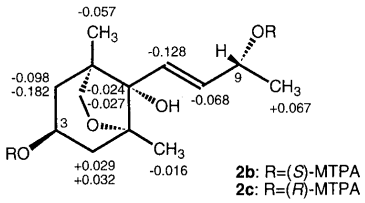



Chart 2




Δδ (δ (**2b**) - δ (**2c**)) values in ppm

Fig. 1

*trans* diaxial relationship between H-3 and the side chain at C-6 was assigned. Comparison of the chemical shifts of (*S*)- and (*R*)-α-methoxy-α-trifluoromethylphenyl acetate (MTPA) derivatives of **2a** (**2b** and **2c**) by the modified Mosher's procedure[4] resulted in the configurations at C-3 and C-9 being assigned as *S* and *R*, respectively (Fig. 1). Therefore, **2** was confirmed to be (1*R*,3*S*,5*R*,6*S*,9*R*)-5,11-epoxy-3,6,9-trihydroxy-7-megastigmene 3-*O*-β-D-glucopyranoside. Compound **3** was identified as **2a**, based on a comparison of the $^1$H- and $^{13}$C-NMR spectra and optical rotations of the two compounds.

Ascleposide B (**4**) afforded a $[M+Na]^+$ peak at *m/z* 441.1737, suggesting the molecular formula, $C_{19}H_{30}O_{10}$. In the $^1$H-NMR spectrum of **4**, signals due to the side chain and the NOE responses were similar to those of **2**. A carbonyl carbon signal, which has a correlation from H-12 in the HMBC spectrum, was observed at δ 181.2 instead of the hydroxymethylene carbon due to C-11 in **2**, suggesting **4** to be an 11-oxo-derivative of **2**, forming a lactone linkage between C-5 and C-11. The aglycone of **4** (**4a**), obtained by enzymatic hydrolysis of **4**, was subjected to the modified Mosher's procedure[4] as in **2a**, to yield (*S*)- and (*R*)-MTPA derivatives (**4b**, **4c**), in which the signals of H-2, 7, 8 were observed at a higher field in **4b** than in **4c**, while H-4 and H-10 were at a lower field. Thus, the configurations at C-3 and C-9 in **4** were confirmed to be *S* and *R*, respectively, as in **2**. The β-glucopyranose at C-3-OH was assigned as being in the D-form since C-2 (pro-*R*) and C-4 (pro-*S*) showed glucosylation shifts of −1.5 ppm and −2.9 ppm, respectively, along with the deshielding of C-3 (+7.6 ppm).[3]

The molecular formula of ascleposide C (**5**) was considered to be $C_{19}H_{32}O_8$, one oxygen less than **2**, based on HR-FAB-MS. A methine proton signal at δ 2.04 (br d, *J*=9 Hz) showed a correlation to the olefinic proton signal at δ 5.74 (H-7) in the $^1$H–$^1$H COSY spectrum and a 3-bond correlation to C-8 (δ 141.8) in the HMBC spectrum, suggesting it to be due to H-6. Since the corresponding carbon signal (C-6) was observed at δ 60.0, showing cross peaks from H-11, 12, 13 in the HMBC spectrum, **5** was assigned to be the 6-deoxy derivative of **2**. The presence of an NOE between H-6 and H-11a strongly suggested the same orientation of the C-6 side chain as that of **2**—**4**. The configurations at C-3 and C-9, and the presence of a β-D-glucosyl residue at C-3-OH were determined as described above.

The molecular formula of ascleposide D (**6**) was shown to be $C_{19}H_{34}O_8$, by HR-FAB-MS, 2H more than **5** and no olefinic proton signals were observed in the $^1$H-NMR spectrum. The presence of two additional methylene carbon signals at δ 22.1 and 40.0, instead of two olefinic carbons observed in **1**—**5**, suggested that **6** is a 7,8-saturated derivative of **5**. NOE correlations were observed at H-6/H-11a (δ 3.41) and H-3/H-11b (δ 3.66). Therefore, **6** was considered to have the same 5,11-epoxymegastigmane structure as **5**, and the configurations at C-3 and C-9 were finally determined based on the modified Mosher's procedure for the aglycone (**6a**)[4] after enzymatic hydrolysis of **6**. Glucose was also confirmed to be in D-form by glucosylation shifts of C-2 and C-4.[3]

HR-FAB-MS of ascleposide E (**7**) showed the same molecular formula as **5**, 2H less than **6**. In the NMR spectra, one carbonyl carbon signal was observed at δ 211.0, and one additional 3H singlet signal was observed at δ 2.15, instead of a 3H doublet signal in **2**—**6**, suggesting **7** to be a 9-oxo-derivative of **6**. The stereochemistry of the megastigmane nucleus in **7** was shown to be the same as **2**—**6** by the NOE correlation and the Δδ value (δ (**7b**)—δ (**7c**)).

Previously, we reported that the 11-*O*-β-D-glucoside of 6,9,11-trihydroxy-4,7-megastigmadien-3-one from *Cynanchum liukiuense* was transformed into an 5,11-epoxy-structure by splitting the glucosyl linkage.[1] The possibility that 5,11-epoxymegastigmanes are biosynthesized in the plant through an 11-glucosyloxy-4-megastigmen-3-one intermediate cannot be excluded.

## Experimental

$^1$H- and $^{13}$C-NMR spectra were recorded on a JEOL JNM-A500 spectrometer in $CD_3OD$. Chemical shifts are given as δ values referred to the internal standard, TMS, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. The *J* value in HMBC experiment was 8 Hz. HR-FAB-MS was recorded on a JEOL HX-110 spectrometer. Optical rotations were measured on a JASCO DIP 360 polarimeter. For silica gel column chromatography and TLC, the following solvent systems were used: $CHCl_3$–MeOH–$H_2O$ (7 : 3 : 1.6—7 : 3 : 1.0, bottom layer, solvent 1), EtOAc–MeOH–$H_2O$ (8 : 1 : 1.2—6 : 1 : 1.2, top layer, solvent 2). For HPLC (Capcell Pak $NH_2$ column, UG 80 type, 10 mm i.d.×250 mm), $CH_3CN$–$H_2O$ was used. Megastigmanes were visualized on TLC plates by spraying with 10% $H_2SO_4$ and heating.

**Plant Materials** *Asclepias fruticosa* L. was cultivated in the medicinal plant garden of Fukuoka University in 1998, and harvested in September.

**Extraction and Isolation of Megastigmanes** Fresh leaves (2.4 kg) were soaked in 50% aqueous acetone for 2 months and filtered. The filtrate was concentrated *in vacuo* and partitioned between *n*-BuOH–$H_2O$. The $H_2O$ layer was concentrated *in vacuo* to dryness (extract 265 g) and chromatographed on a charcoal column. The column was eluted with $H_2O$ (2 l), and then with 5, 10, 20, 50% EtOH in $H_2O$. Each eluate with 10—50% EtOH was further chromatographed on a silica gel column with solvents 1 and 2, and HPLC (80—90% $CH_3CN$). **1**: 44 mg (50% EtOH elution), **2**: 151 mg (10% EtOH), **3**: 17 mg (10% EtOH), **4**: 24 mg (20% EtOH), **6**: 55 mg (50% EtOH), **7**: 9 mg (50% EtOH). The BuOH layer (extract 18.7 g) was chromatographed on a Diaion HP-20 column (Mitsubishi Chem. Ind. Ltd.) with $H_2O$–MeOH and a silica gel column with solvents 1 and 2 to afford **5** (11 mg) and **6** (31 mg).

Ascleposide A (**2**): A solid, $[\alpha]_D^{26}$ −23.2° (*c*=1.37, MeOH), HR-FAB-MS *m/z*: 427.1943 ($[M+Na]^+$) (Calcd for $C_{19}H_{32}O_9$+Na: 427.1944). Compound **2** (50 mg) was subjected to hydrolysis with cellulase (Sigma, grade II) (100 mg) in $H_2O$ (2 ml) for 8 h at 38 °C, and the mixture was extracted with *n*-BuOH. The BuOH layer was purified on a silica gel column with solvent 1 to give **2a** as a solid, $[\alpha]_D^{29}$ +1.0° (*c*=1.05, MeOH), HR-FAB-MS *m/z*: 265.1415 ($[M+Na]^+$) (Calcd for $C_{13}H_{22}O_4$+Na: 265.1416). From $H_2O$ layer D-glucose was obtained, $[\alpha]_D^{29}$ +66.0° (*c*=0.80, $H_2O$, 24 h).

Compound **3** (**2a**): A solid, $[\alpha]_D^{28}$ +3.2° (*c*=0.65, MeOH), HR-FAB-MS *m/z*: 265.1414 (Calcd for $C_{13}H_{22}O_4$+Na: 265.1416).

Ascleposide B (**4**): A solid, $[\alpha]_D^{24}$ −32.4° (*c*=1.30, MeOH), HR-FAB-MS *m/z*: 441.1737 ($[M+Na]^+$) (Calcd for $C_{19}H_{30}O_{10}$+Na: 441.1737). Upon hydrolysis with cellulase under the same conditions as for **2**, an aglycone (**4a**) was obtained as a solid, $[\alpha]_D^{22}$ −22.6° (c=0.35, MeOH), HR-FAB-MS (negative) *m/z*: 255.1234 ($[M-H]^-$) (Calcd for $C_{13}H_{19}O_5$: 255.1232). Glucose in the $H_2O$ layer was confirmed by TLC (solvents 1 and 2).

Ascleposide C (**5**): A solid, $[\alpha]_D^{20}$ −19.3° (*c*=0.55, MeOH), HR-FAB-MS *m/z*: 411.1992 (Calcd for $C_{19}H_{32}O_8$+Na: 411.1994). Upon hydrolysis in the

same manner as **2** and **4**, an aglycone (**5a**) was obtained as a solid, $[\alpha]_D^{22}$ +11.8° ($c$=0.28, MeOH), HR-FAB-MS (negative) $m/z$: 225.1499 (Calcd for $C_{13}H_{22}O_3$−H: 225.1491). Glucose was confirmed by TLC (solvents 1, 2).

Ascleposide D (**6**): A solid, $[\alpha]_D^{26}$ −12.7° ($c$=1.01, MeOH), HR-FAB-MS $m/z$: 413.2161 (Calcd for $C_{19}H_{34}O_8$+Na: 413.2151). Upon hydrolysis, an aglycone (**6a**) was obtained as a solid, $[\alpha]_D^{21}$ +20.4° ($c$=0.28, MeOH), HR-FAB-MS $m/z$: 251.1629 (Calcd for $C_{13}H_{24}O_3$+Na: 251.1623). Glucose was confirmed by TLC (solvents 1 and 2).

Ascleposide E (**7**): Colorless fine prisms, mp 138—139 °C, $[\alpha]_D^{22}$ −7.1° ($c$=0.47, MeOH), HR-FAB-MS $m/z$: 411.1992 (Calcd for $C_{19}H_{32}O_8$+Na: 411.1994). Upon hydrolysis, an aglycone (**7a**) was obtained as a solid, $[\alpha]_D^{22}$ +22.5° ($c$=0.29, MeOH), HR-FAB-MS (negative) $m/z$: 225.1487 (Calcd for $C_{13}H_{22}O_3$−H: 225.1491). Glucose was confirmed by TLC (solvents 1, 2).

MTPA Derivatives of **2a** and **4a**—**7a**: Each solution of **2a**, **4a**—**7a** (1—3 mg) in $CH_2Cl_2$ (0.2—0.3 ml) was treated with (*S*)-MTPA (8—18 mg) in $CH_2Cl_2$ (0.2 ml) in the presence of dicyclohexylcarbodiimide (DCC) (10—15 mg) and 4-dimethylaminopyridine (DMAP) (8—12 mg) and the mixture was allowed to stand for 2 d. The reaction mixture was subjected to a silica gel column chromatography directly and eluted with benzene and benzene–acetone (20 : 1—10 : 1) to give **2b**, **4b**—**7b**. In a similar procedure, **2c**, **4c**—**7c** were obtained with (*R*)-MTPA.

$\Delta\delta$ (**2b**—**2c**) ppm: See Fig. 1.

$\Delta\delta$ (**4b**—**4c**) ppm: H-2 (−0.110, −0.194), H-4 (+0.031, +0.014), H-7 (−0.165), H-8 (−0.056), H-10 (+0.060), H-12 (−0.059), H-13 (−0.019).

$\Delta\delta$ (**5b**—**5c**) ppm: H-2 (−0.092, −0.178), H-4 (+0.030, +0.054), H-6 (−0.058), H-7 (−0.120), H-8 (−0.095), H-10 (+0.063), H-11 (−0.025, −0.005), H-12 (−0.052), H-13 (−0.018).

$\Delta\delta$ (**6b**—**6c**) ppm: H-2 (−0.164, −0.245), H-4 (+0.011, +0.090), H-6 (−0.103), H-8 (−0.19, −0.07), H-10 (+0.074), H-11 (−0.048, −0.052), H-12 (−0.147), H-13 (−0.016).

$\Delta\delta$ (**7b**—**7c**) ppm: H-2 (−0.066, −0.135), H-4 (+0.065, +0.140), H-11 (−0.011, −0.032), H-12 (−0.023), H-13 (+0.022).

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