Camptothecins and Two New Monoterpene Glucosides from *Ophiorrhiza liukiuensis*

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Two new monoterpene glucosides, demethylsecologanol and 3‴-*O*-glucosylsenburiside II, were isolated from *Ophiorrhiza liukiuensis* (Rubiaceae) together with 23 known compounds, including camptothecins and β-carboline-type alkaloids. Their structures were determined by spectroscopic analysis.

Key words *Ophiorrhiza liukiuensis*; alkaloid; iridoid; secoiridoid; camptothecin; β-carboline

Camptothecin (**1**),[1—6] a well-known monoterpenoid indole alkaloid possessing remarkable anti-tumor activity, was isolated for the first time from *Camptotheca acuminata*[7] (Nyssaceae). At present, two semi-synthetic camptothecins, topotecan and irinotecan, are used clinically as anti-tumor agents. To date, several camptothecin-producing plants have been reported: *Nothapodytes foetida*,[8] *Merrilliodendron megacarpum*,[9] *Pyrenacantha klaineana*[10] (Icacinaceae), *Ervatamia heyneana*[11] (Apocynaceae), *Mostuea brunonis*[12] (Loganiaceae), *Ophiorrhiza mungos*,[13] and *O. filistipula*[14] (Rubiaceae). In our previous study of the chemical constituents of *Ophiorrhiza* plants distributed in Japan, we found that *O. pumila*[15—18] produced camptothecin (**1**) and its related alkaloids (**4**, **6**—**8**), whereas *O. kuroiwai*,[5,19] which was recently shown to be an interspecies hybrid of *O. pumila* and *O. liukiuensis* by us, produced not only camptothecins (**1**, **4**, **5**) but also β-carboline-type alkaloids (**9**—**12**). On the basis of these findings, we obtained callus[20] and tissue cultures[21—23] of *O. pumila* and examined their constituents to obtain camptothecin. As a continuation of our studies, we investigated the secondary metabolites of *O. liukiuensis*, which is distributed in Okinawa, Japan, Taiwan, and the Philippines, and isolated two new monoterpenoid glucosides (**2**, **3**) together with 23 known compounds, including camptothecins and β-carboline-type alkaloids, which will be described herein.

Whole plants of *O. liukiuensis* (145.0 g) were extracted with hot MeOH to give the extract (16.0 g). Partitioning the MeOH extract between H_2O and $CHCl_3$ and extracting the aqueous layer with *n*-BuOH gave the $CHCl_3$ extract (2.7 g), the *n*-BuOH extract (2.9 g) and the water-soluble portion (10.3 g). Each extract was purified by repeated chromatography to afford two new monoterpene glucosides (**2**, 6.5 mg, **3**, 282.7 mg) as well as camptothecin (**1**, 18.4 mg) and its related alkaloids, such as 9-methoxycamptothecin (**4**, 18.3 mg), 10-methoxycamptothecin (**5**, 4.3 mg), pumiloside (**6**, 21.0 mg), (3*R*)-deoxypumiloside (**7**, 26.3 mg) and strictosamide (**8**, 3.7 mg); β-carboline-type alkaloids, such as lyalosidic acid (**9**, 339.4 mg), ophiorine A (**10**, 5.6 mg), ophiorine B (**11**, 6.4 mg) and harman (**12**, 25.2 mg); and 13 known compounds (**13**—**25**). The structures of the known compounds were deduced from spectroscopic data and confirmed by comparison with those of authentic samples or reported data. From the results, it was proved that *O. liukiuensis* produced both camptothecins and β-carboline-type alkaloids.

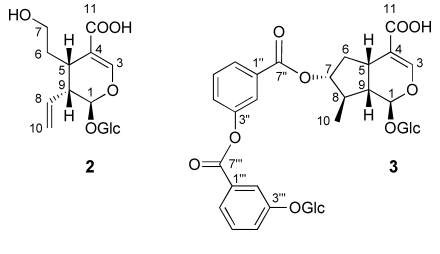

Fig. 1. Structures of New Compounds

The HR-FAB-MS spectrum of new secoiridoid **2** gave a protonated molecular ion peak at *m/z* 377.1426 ($[M+H]^+$) that corresponded to the molecular formula $C_{16}H_{25}O_{10}$ (*m/z* 377.1447). The UV spectrum showed the characteristic absorption of β-alkoxyacrylic acid or its ester at 233.0 nm. The ^{1}H-NMR spectrum showed signals that indicated the presence of the olefinic proton of β-alkoxyacrylic acid at δ 7.35 (s, H-3), a set of three protons on the vinyl group at δ 5.73 (ddd, J=17.4, 9.7, 9.7 Hz, H-8), 5.28 (d, J=17.4 Hz, H-10), and 5.24 (d, J=9.7 Hz, H-10), an acetal proton at δ 5.45 (d, J=6.3 Hz, H-1), and one sugar unit containing a β-linked anomeric proton at δ 4.76 (d, J=8.0 Hz, H-1′), which were characteristic of secoiridoid-type monoterpene glycosides. Furthermore, signals assigned to the protons of methylene bearing a hydroxy group were observed at δ 3.57—3.48 (2H, overlapped, H_2-7). The ^{13}C-NMR spectrum revealed 16 carbons, including one carboxyl carbon (δ 172.3, C-11), four alkenyl carbons [δ 151.4 (C-3) and δ 112.0 (C-4) due to the β-alkoxyacrylic acid group, δ 134.0 (C-8) and δ 119.6 (C-10) due to the vinyl group], one anomeric carbon (δ 98.9, C-1′), one acetal carbon (δ 97.5, C-1), and two hydroxymethyl carbons (δ 59.8, C-7 and δ 60.8, C-6′). The above data and 2D-NMR analysis indicated that **2** was a lactone open form of sweroside (**13**). To confirm the structure and the relative and absolute configurations, chemical correlations of **2** with known compounds were performed. Sweroside (**13**) was treated with 1 N LiOH–THF (1 : 2) to give a mixture of **2** and the starting material that was regenerated from **2** during workup with Amberlite IR-120B. Then, we attempted to convert **2** into its methyl ester derivative known as secologanol,[24] by treatment with CH_2N_2. This, however, gave sweroside (**13**). All the spectroscopic data of semi-synthetic **13** (^{1}H- and ^{13}C-NMR, MS, $[\alpha]_D$) were identical with those of natural **13**. Therefore, the structure of **2** was deduced

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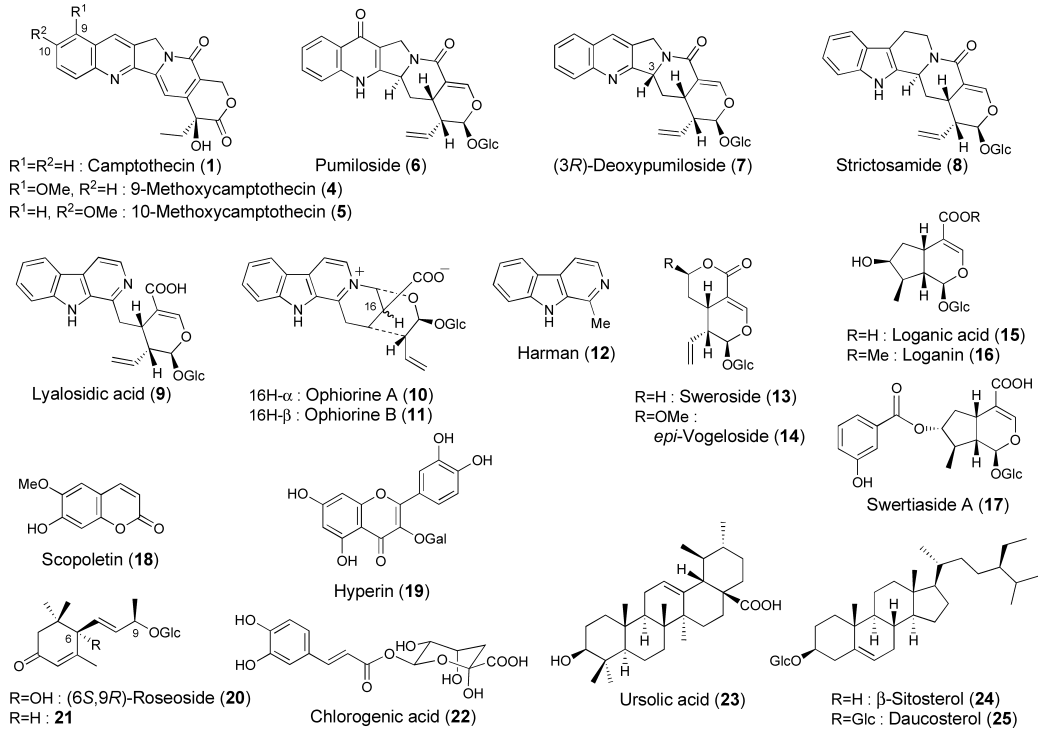

Fig. 2. Structures of Known Compounds Isolated from *Ophiorrhiza liukiuensis*

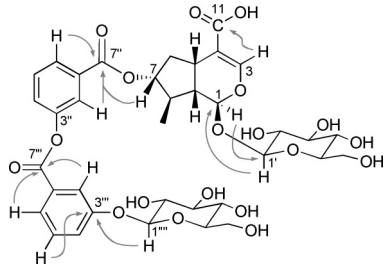

Fig. 3. Selected HMBC Correlations of **3**

to be demethylsecologanol.

The HR-FAB-MS spectrum of new iridoid glucoside **3** gave a protonated molecular ion peak at *m/z* 779.2371 ($[M+H]^+$, Δ −2.7 mmu) and established the molecular formula as $C_{36}H_{43}O_{19}$. Acid hydrolysis of **3** was performed to give D-glucose. The ^{1}H-NMR spectrum was very similar to that of swertiaside A (**17**)[25] except for the aromatic and sugar regions. It showed signals indicative of an olefinic proton at δ 7.46 (d, J=1.5 Hz, H-3), an acetal proton at δ 5.51 (d, J=3.7 Hz, H-1), and a β-linked anomeric proton at δ 4.66 (d, J=7.8 Hz, H-1′), as well as a doublet assignable to the methyl group at δ 1.24 (d, J=7.0 Hz, H_3-10), all of which were characteristic of iridoid glycosides. Furthermore, signals assignable to two sets of aromatic protons due to 1,3-disubstituted benzenes and one extra glucose unit were observed. The ^{13}C-NMR spectrum revealed one carboxyl carbon (δ 170.7), two ester carbons [δ 166.8 (C-7″), δ 166.1 (C-7‴)] and two anomeric carbons [δ 100.2 (C-1′), δ 102.4 (C-1⁗)]. The above data suggested that **3** was a glucosyl derivative of senburiside II.[26] The HMBC spectrum of **3** showed correlation between the anomeric proton at δ 5.00 (H-1⁗) and an aromatic carbon at δ 159.3, indicating that one extra glucose was attached to C-3‴ of the terminal benzene ring through an ether linkage. The HMBC correlations between the oxymethine proton at δ 4.97 (H-7) and the carbonyl carbon at δ 166.8 and between the proton at δ 7.86 (H-6‴) and the carbonyl carbon at δ 166.1 were observed. Therefore, the structure of **3** was deduced to be 3‴-*O*-glucosylsenburiside II.

Experimental

General Experimental Procedures Optical rotation: JASCO P-1020. UV: JASCO V-560. IR: JASCO FT/IR-230. ^{1}H- and ^{13}C-NMR spectra: JEOL JNM-ECP600 at 600 (^{1}H) and 150 (^{13}C) MHz, JEOL JNM A-500 at 500 (^{1}H) and 125.65 (^{13}C) MHz, or JEOL JNM-ECP400 at 400 (^{1}H) and 100 (^{13}C) MHz, respectively. FAB-MS and HR-FAB-MS: JEOL JMS-HX110. CD: JASCO J-720WI. TLC: Precoated silica gel 60 F_{254} plates (Merck, 0.25 mm thick), RP-18 F_{254S} plates (Merck, 0.25 mm thick). Column chromatography: Silica gel 60 (Merck, 230—400 mesh for flash column chromatography), Cosmosil 75 C_{18}-OPN (ODS, Nacalai Tesque), DIAION HP20 (Mitsubishi Chemical). MPLC: C. I. G. prepacked column CPS-HS-221-05 (SiO_2) and CPO-HS-221-20 (ODS) (Kusano Kagakukikai). HPLC: CAPCELL PAK NH_2 UG80 (Shiseido Fine Chemicals).

Plant Material *Ophiorrhiza liukiuensis* Hayata was collected from Ishigaki Island, Okinawa, Japan, in July 2002. Taxonomic identification of the collected plant was based on the specimen kept in Koishikawa Botanical Gardens, Graduate School of Science, The University of Tokyo. A voucher specimen was deposited at the Graduate School of Pharmaceutical Sciences, Chiba University.

Extraction and Isolation Whole plants of *O. liukiuensis* (145.0 g, wet weight) were extracted with hot MeOH five times to give the extract (16.0 g). The MeOH extract was then partitioned between H_2O and $CHCl_3$. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated to give the $CHCl_3$ extract (2.7 g). The aqueous layer was extracted with *n*-BuOH and the organic layer was evaporated to give the *n*-BuOH extract (2.9 g). The aqueous layer was freeze-dried to give the water-soluble portion (10.3 g). The water-soluble portion was subjected to column chromatography on DIAION HP20 to give six fractions: fr. A, H_2O (500 ml) 8.58 g; fr. B, H_2O (500 ml) 365 mg; fr. C, 30% MeOH/H_2O (500 ml) 363 mg; fr. D, 50% MeOH/H_2O (500 ml) 389 mg; fr. E, MeOH (1000 ml) 572 mg; and fr. F, acetone (500 ml) 10 mg. Fr. B was purified by using a combination of MPLC (SiO_2, $CHCl_3$/MeOH/H_2O=7 : 4 : 1), silica gel flash column chromatography ($CHCl_3$/MeOH/H_2O=7 : 4 : 1), and MPLC (SiO_2, $CHCl_3$/MeOH/H_2O=

10 : 5 : 1) to give new secoiridoid **2** (6.5 mg). Fr. E was separated by silica gel flash column chromatography ($CHCl_3$/MeOH/H_2O=10 : 5 : 1—7 : 4 : 1—7 : 5 : 1.5). The $CHCl_3$/MeOH/H_2O=7 : 4 : 1 eluate was purified by a combination of silica gel flash column chromatography ($CHCl_3$/MeOH/H_2O gradient), ODS open column chromatography (5% CH_3CN/H_2O), and MPLC (SiO_2, 15% MeOH/$CHCl_3$ or ODS, 20% CH_3CN/H_2O) to give new iridoid glucoside **3** (282.7 mg). From the water-soluble portion, lyalosidic acid (**9**, 145.0 mg), ophiorine A (**10**, 5.6 mg), ophiorine B (**11**, 6.4 mg), sweroside (**13**, 20.8 mg),[27,28] loganic acid (**15**, 5.6 mg),[29] swertiaside A (**17**, 45.0 mg),[25] and chlorogenic acid (**22**, 111.8 mg)[30,31] were isolated. From the $CHCl_3$ extract, camptothecin (**1**, 18.4 mg), 9-methoxycamptothecin (**4**, 18.3 mg), 10-methoxycamptothecin (**5**, 4.3 mg), harman (**12**, 12.5 mg), scopoletin (**18**, 4.0 mg),[32] ursolic acid (**23**, 38.4 mg),[33,34] and daucosterol (**25**, 4.2 mg)[35] were isolated. From the *n*-BuOH extract, pumiloside (**6**, 21.0 mg), (3*R*)-deoxypumiloside (**7**, 26.3 mg), strictosamide (**8**, 3.7 mg), lyalosidic acid (**9**, 194.4 mg), harman (**12**, 12.7 mg), sweroside (**13**, 15.4 mg), *epi*-vogeloside (**14**, 1.7 mg),[36,37] loganin (**16**, 3.0 mg),[36,38] hyperin (**19**, 94.1 mg),[39,40] (6*S*,9*R*)-roseoside (**20**, 2.2 mg),[41,42] (6*R*,7*E*,9*R*)-9-hydroxymegastigma-4,7-dien-3-one-9-*O*-β-D-glucoside (**21**, 2.9 mg),[43] and β-sitosterol (**24**, 24.2 mg)[44] were obtained. The detailed NMR data of 10-methoxycamptothecin (**5**) have not been reported elsewhere. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.55 (1H, s, H-7), 8.07 (1H, d, J=9.2 Hz, H-12), 7.52 (1H, s, H-9), 7.50 (1H, overlapped, H-11), 7.28 (1H, s, H-14), 6.51 (1H, br-s, OH), 5.41 (2H, s, H_2-17), 5.26 (2H, s, H_2-5), 3.93 (3H, s, 10-OMe), 1.85 (2H, m, H_2-19), 0.87 (3H, dd, J=7.2, 7.2 Hz, H_3-18). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 172.7 (C-21), 158.4 (C-10), 157.1 (C-16a), 150.4 and 150.3 (C-2, 15), 146.0 (C-3), 144.2 (C-13), 130.7 (C-12), 130.5 (C-6), 130.2 (C-7), 129.7 (C-8), 123.2 (C-11), 118.6 (C-16), 106.5 (C-9), 96.3 (C-14), 72.6 (C-20), 65.4 (C-17), 56.0 (OMe), 50.4 (C-5), 30.4 (C-19), 8.0 (C-18).

Demethylsecologanol (2) Amorphous. $[\alpha]_D^{23}$ −108.3° (c=0.06, MeOH). UV λ_{max} (MeOH) nm: 233.0. FAB-MS (Glycerol, positive) m/z: 377 $[M+H]^+$. HR-FAB-MS (Glycerol+H_2O/PEG) m/z: 377.1426 $[M+H]^+$ (Calcd for $C_{16}H_{25}O_{10}$: 377.1447). ^{1}H-NMR (600 MHz, D_2O) δ: 7.35 (1H, s, H-3), 5.73 (1H, ddd, J=17.4, 9.7, 9.7 Hz, H-8), 5.45 (1H, d, J=6.3 Hz, H-1), 5.28 (1H, d, J=17.4 Hz, H-10), 5.24 (1H, d, J=9.7 Hz, H-10), 4.76 (1H, d, J=8.0 Hz, H-1′), 3.85 (1H, d, J=12.3 Hz, H-6′), 3.65 (1H, dd, J=12.3, 5.8 Hz, H-6′), 3.57—3.48 (2H, overlapped, H_2-7), 3.41 (1H, overlapped, H-5′), 3.43 (1H, dd, J=9.3, 9.3 Hz, H-3′), 3.33 (1H, dd, J=9.3, 9.3 Hz, H-4′), 3.23 (1H, dd, J=9.3, 8.0 Hz, H-2′), 2.72 (1H, m, H-5), 2.62 (1H, m, H-9), 1.73 (1H, dddd, J=13.9, 13.9, 6.9, 6.9 Hz, H-6), 1.66 (1H, dddd, J=13.9, 13.9, 6.9, 6.9 Hz, H-6). ^{13}C-NMR (150 MHz, D_2O) δ: 172.3 (C-11), 151.4 (C-3), 134.0 (C-8), 119.6 (C-10), 112.0 (C-4), 98.9 (C-1′), 97.5 (C-1), 76.4 (C-5′), 75.7 (C-3′), 72.7 (C-2′), 69.6 (C-4′), 60.8 (C-6′), 59.8 (C-7), 43.6 (C-9), 31.8 (C-6), 29.4 (C-5). CD (c=1.67 mmol/l, MeOH, 24 °C) $\Delta\varepsilon$ (λ nm): 0 (273), +0.84 (249), 0 (240), −4.25 (222), −2.35 (203).

3‴-*O*-Glucosylsenburiside II (3) Amorphous. $[\alpha]_D^{26}$ −83.4° (c=0.69, MeOH). UV λ_{max} (MeOH) nm: 232.5, 286.0. IR ν_{max} (KBr) cm^{-1}: 3447, 1716, 1261, 1075. FAB-MS (Glycerol, positive) m/z: 779 $[M+H]^+$. HR-FAB-MS (Glycerol+H_2O/PEG) m/z: 779.2371 $[M+H]^+$ (Calcd for $C_{36}H_{43}O_{19}$: 779.2398). ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.91 (1H, ddd, J=7.9, 1.3, 1.3 Hz, H-6″), 7.90 (1H, overlapped, H-1‴), 7.86 (1H, ddd, J=7.9, 1.3, 1.3 Hz, H-6‴), 7.82 (1H, br-dd, J=1.8, 1.8 Hz, H-2″), 7.55 (1H, dd, J=7.9, 7.9 Hz, H-5″), 7.49 (1H, dd, J=7.9, 7.9 Hz, H-5‴), 7.47 (1H, ddd, J=7.9, 2.3, 1.3 Hz, H-4″), 7.46 (1H, d, J=1.5 Hz, H-3), 7.43 (1H, ddd, J=7.9, 2.6, 1.3 Hz, H-4‴), 5.51 (1H, d, J=3.7 Hz, H-1), 5.00 (1H, br-d, J=7.6 Hz, H-1⁗), 4.97 (1H, ddd, J=7.1, 4.4, 4.4 Hz, H-7), 4.66 (1H, d, J=7.8 Hz, H-1′), 3.90 (1H, dd, J=12.2, 2.1 Hz, H-6⁗), 3.83 (1H, br-dd, J=11.9, 1.5 Hz, H-6′), 3.71 (1H, dd, J=12.2, 5.6 Hz, H-6⁗), 3.64 (1H, br-dd, J=11.9, 5.2 Hz, H-6′), 3.51—3.47 (1H, overlapped, H-2⁗, 3⁗, 5⁗), 3.41 (1H, m, H-3′), 3.36 (1H, br-dd, J=9.0, 9.0 Hz, H-4⁗), 3.31—3.27 (2H, overlapped, H-4′, 5′), 3.18 (1H, dd, J=9.2, 7.8 Hz, H-2′), 3.05 (1H, m, H-5), 2.53 (1H, ddd, J=14.3, 7.1, 7.1 Hz, H-6), 2.12 (1H, m, H-8), 2.03 (1H, ddd, J=14.3, 4.4, 4.4 Hz, H-6), 2.00 (1H, ddd, J=8.2, 8.2, 3.7 Hz, H-9), 1.24 (3H, d, J=7.0 Hz, H_3-10). ^{13}C-NMR (125 MHz, CD_3OD) δ: 170.7 (C-11), 166.8 (C-7″), 166.1 (C-7‴), 159.3 (C-3‴), 152.4 (C-3, C-3″), 133.2 (C-1″), 131.8 (C-1‴), 131.0 (C-5‴), 130.8 (C-5″), 128.1 (C-6″), 127.7 (C-4″), 125.1 (C-6‴), 124.0 (C-2″), 123.5 (C-4‴), 119.3 (C-2‴), 112.6 (C-4), 102.4 (C-1⁗), 100.2 (C-1′), 96.2 (C-1), 83.8 (C-7), 78.3 (C-5′, 5⁗), 77.9 (C-3′, 3⁗), 74.9 (C-2⁗), 74.7 (C-2′), 71.5 (C-4′), 71.3 (C-4⁗), 62.7 (C-6′), 62.4 (C-6⁗), 48.7 (C-9), 43.1 (C-8), 37.9 (C-6), 32.6 (C-5), 18.4 (C-10).

Reaction of Natural 2 with CH_2N_2 An ether solution of freshly prepared CH_2N_2 was added to a solution of **2** (3.6 mg) in MeOH (1.0 ml). After 5 min, the solvent was removed under reduced pressure. The residue was purified by silica gel open column chromatography (20% MeOH/$CHCl_3$) to give sweroside {4.2 mg yield quant., $[\alpha]_D^{22}$ −137.0° (c=0.07, MeOH)}, as identified from ^{1}H- and ^{13}C-NMR spectra.

Acid Hydrolysis of 3 A solution of **3** (14.8 mg) in 1 N HCl aq. (2.0 ml) and 1,4-dioxane (0.25 ml) was heated at 130 °C for 2 h under Ar. The reaction mixture was extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The aqueous layer was neutralized by passage through Amberlite IRA-93 and elution with H_2O. This was followed by evaporation *in vacuo* to give a sugar fraction. The identity and configuration of the sugars were determined by comparison with authentic D-(+)-glucose (t_R, 20.0 min) on HPLC. HPLC conditions: column, Shiseido Fine Chemicals CAPCELL PAK NH_2 UG80 (4.6×250 mm i.d.); solvent, 85% CH_3CN–H_2O; flow rate, 0.5 ml/min; temperature, 40 °C; RI detection, Shodex RI-72 and chiral detection, JASCO OR-1590. The sugar fraction gave peak that corresponded to D-(+)-glucose (t_R, 20.2 min).

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