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Total synthesis of macrocyclic glycosides, clemochinenosides A and B, and berchemolide, by fluorous mixture synthesis

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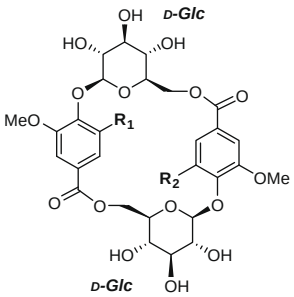
ABSTRACT

The total synthesis of clemochinenoside A and the first total syntheses of clemochinenoside B and berchemolide were achieved simultaneously via macrocyclization of 4-*O*-(4-*O*-^{F13}benzyl-β-D-glucopyranosyl)syringic acid with 4-*O*-(4-*O*-^{F17}benzyl-β-D-glucopyranosyl)vanillic acid by a fluorous mixture synthetic method. The spectroscopic data of the synthetic products were identical with those of the natural products, although the optical rotation of clemochinenoside A differed from the published values in sign and magnitude.

Berchemolide (Fig. 1) was isolated from the stems of *Berchemia racemosa*[1] and *Clematis armandii*.[2] Clemochinenosides A and B (Fig. 1) were isolated from the roots and rhizomes of *C. chinensis*,[3] *C. armandii*,[2] *C. mandshurica*,[4] *C. hexapetala*,[4] and *Capparis tenera*.[5] The stems of *B. racemosa* have been used as a folk medicine to treat gall stones and stomachache in Japan. The roots and rhizomes of *Clematis* species have been used as anti-inflammatory, anti-tumor, and analgesic agents in the Chinese Pharmacopoeia. Despite these plants possessing beneficial health effects, only a few macrocyclic glycosides have been scientifically evaluated for biological activity. The structures of macrocyclic glycosides were initially characterized by Sakurai's[1] and Song's group,[3] with the assignment of ^{1}H and ^{13}C NMR data of clemochinenoside B recently revised by Su's group.[5] Additionally, Wang and co-workers were the first to report the total synthesis of clemochinenoside A from levoglucosan in an eight-step reaction.[6] However, the identity of clemochinenoside A could not be established unambiguously, because the only physical property of the synthetic product to be reported was the melting point. Therefore, we decided to undertake the total syntheses of clemochinenosides A and B and berchemolide for the purpose of confirming their reported spectroscopic data and for further investigation of their biological activity.

Curran and co-workers have recently proposed fluorous mixture synthesis as a new combinatorial technique for simple and fast synthesis of natural products.[7] Fluorous mixture synthesis has shown power in preparing small molecule libraries and studying structure/activity relationships and structure assignments for natural products. The high efficiency and practicality of the methodology have attracted many researchers' interest. We thought that fluorous mixture synthesis was suited for the expeditious synthesis of macrocyclic glycosides, because these natural products have a high degree of structural similarity and are comparatively small molecules.

Recently, we reported the synthesis of fluorous benzylidene groups as a new fluorous-protecting group.[8] This protecting group is regioselectively introduced into hydroxyl groups of hexopyranosides and is transformed into the corresponding 4-*O*-benzyl group by ring-opening reduction. Hence, the fluorous benzylidene group is considered to be a valuable tool in fluorous mixture synthesis of macrocyclic glycosides, because solid-phase extraction with a fluorous reverse-phase silica gel column (fluorous solid-phase extraction; FSPE)[9] and the unique chemical properties of the benzylidene group can be utilized for the synthesis.



	R_1	R_2
Berchemolide	H	H
Clemochinenoside A	OMe	OMe
Clemochinenoside B	OMe	H

Figure 1. The structures of macrocyclic glycosides.

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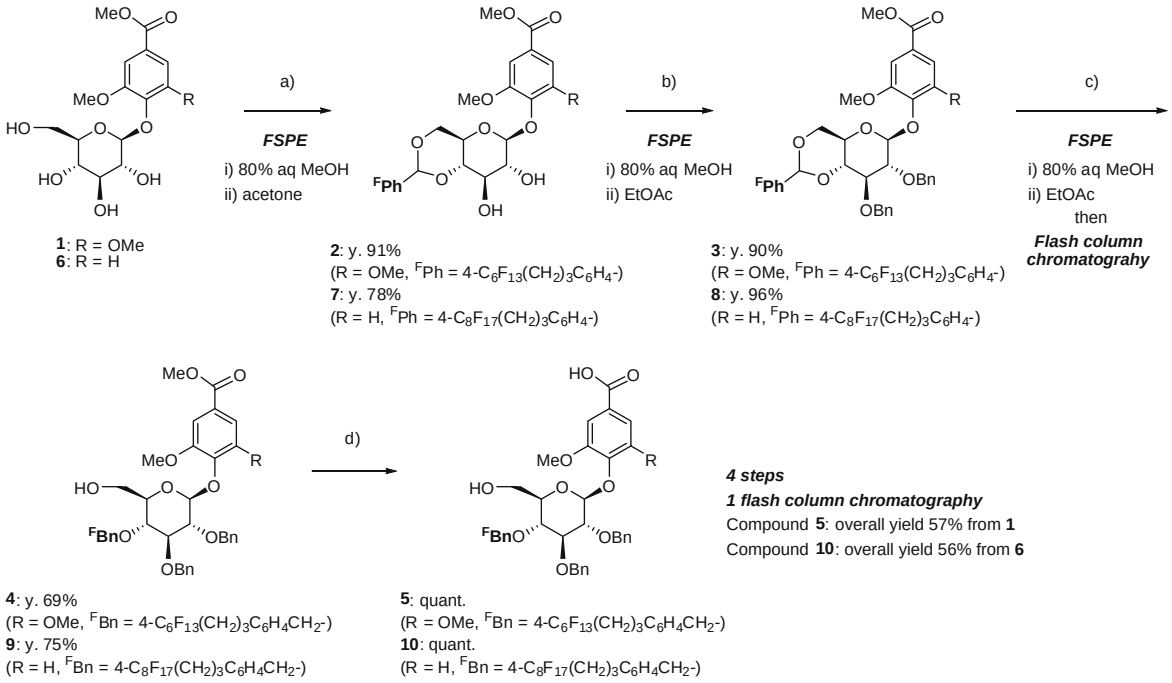


1: R = OMe
6: R = H

2: y. 91%
(R = OMe, ^{F}Ph = 4-$C_6F_{13}(CH_2)_3C_6H_4$-)
7: y. 78%
(R = H, ^{F}Ph = 4-$C_8F_{17}(CH_2)_3C_6H_4$-)

3: y. 90%
(R = OMe, ^{F}Ph = 4-$C_6F_{13}(CH_2)_3C_6H_4$-)
8: y. 96%
(R = H, ^{F}Ph = 4-$C_8F_{17}(CH_2)_3C_6H_4$-)

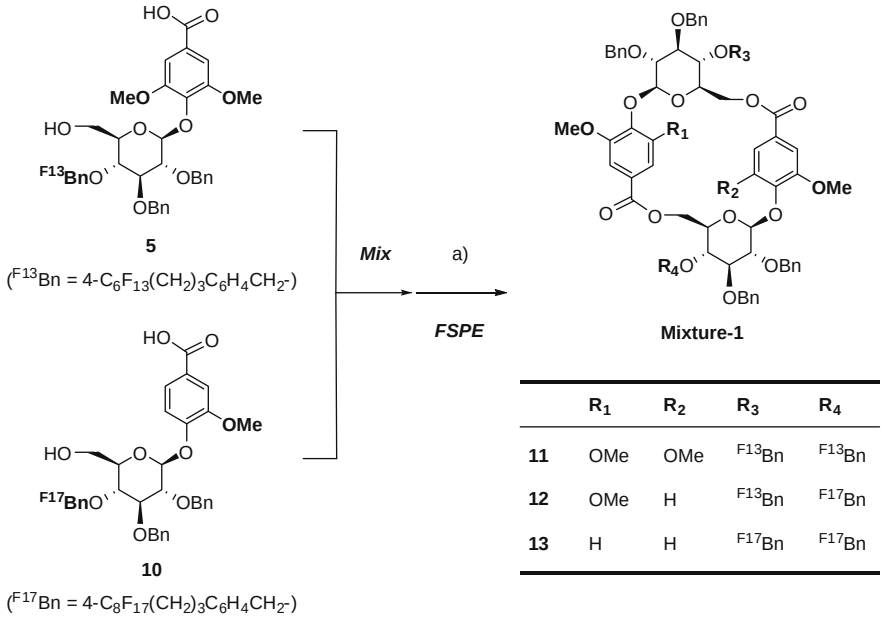
4: y. 69%
(R = OMe, ^{F}Bn = 4-$C_6F_{13}(CH_2)_3C_6H_4CH_2$-)
9: y. 75%
(R = H, ^{F}Bn = 4-$C_8F_{17}(CH_2)_3C_6H_4CH_2$-)

5: quant.
(R = OMe, ^{F}Bn = 4-$C_6F_{13}(CH_2)_3C_6H_4CH_2$-)
10: quant.
(R = H, ^{F}Bn = 4-$C_8F_{17}(CH_2)_3C_6H_4CH_2$-)

Scheme 1. Reagents and conditions: (a) 4-C_nF_{n+1} $(CH_2)_3C_6H_4$–CHO (n = 6 or 8), $CH(OMe)_3$, p-TsOH·H_20, Na_2S0_4/CH_3CN, rt; (b) BnBr, NaH/DMF, 0 °C; (c) $PhBCl_2$, Et_3SiH, MS-4 Å/CH_2C1_2, −78 °C; (d) KOH/EtOH–H_20 (10:1), reflux.

We describe herein the fluorous mixture synthesis of clemochinenosides A and B and berchemolide using fluorous benzylidene groups from phenyl β-D-glucopyranosides and compare their analytical properties with the previous reports.

As shown in Scheme 1, ^{F13}Bn-protected carboxylic acid **5** was prepared from 4-*O*-β-D-glucopyranosylsyringic acid methyl ester (**1**)[10] in a four-step reaction. ^{F13}Benzaldehyde (1.0 equiv) was reacted with **1** (2.5 equiv) in CH_3CN to give the 4,6-*O*-^{F13}benzylidene derivative **2** in 91% yield. Benzylation of **2** with NaH (3.0 equiv) and BnBr (3.0 equiv) in DMF gave the 2,3-di-O-benzylated derivative **3** in 90% yield. In order to convert the 4,6-*O*-^{F13}benzylidene group into a 4-*O*-^{F13}benzyl group, compound **3** was treated with Et_3-SiH–$PhBCl_2$. The crude product was purified by standard silica gel column chromatography to provide the 4-*O*-^{F13}benzyl derivative **4** in 69% yield. Saponification of **4** using KOH (2.0 equiv) in 90% aq EtOH gave 4-*O*-(4-*O*-^{F13}benzyl-β-D-glucopyranosyl)syringic acid **5** in quantitative yield [^{1}H NMR, $J_{1,2}$ = 6.6 Hz, H-1 (β-linkage)]. In these reaction steps, FSPE was utilized for the speedy purification



5
(^{F13}Bn = 4-$C_6F_{13}(CH_2)_3C_6H_4CH_2$-)

10
(^{F17}Bn = 4-$C_8F_{17}(CH_2)_3C_6H_4CH_2$-)

	R_1	R_2	R_3	R_4
11	OMe	OMe	^{F13}Bn	^{F13}Bn
12	OMe	H	^{F13}Bn	^{F17}Bn
13	H	H	^{F17}Bn	^{F17}Bn

Scheme 2. Reagents and conditions: (a) 2-chloro-1-methylpyridinium iodide, pyridine, DMAP/CH_2C1_2 (1.5 mM), 0 °C.

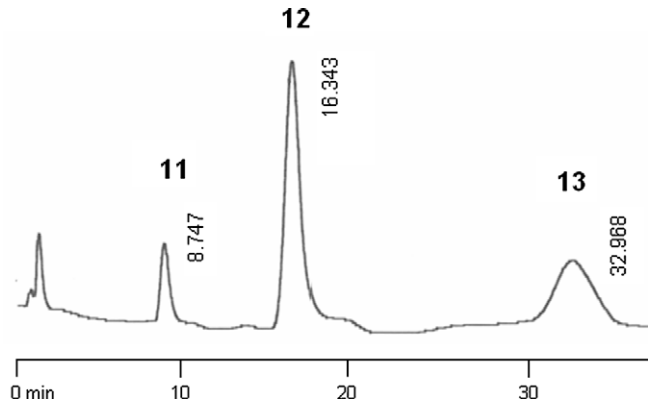
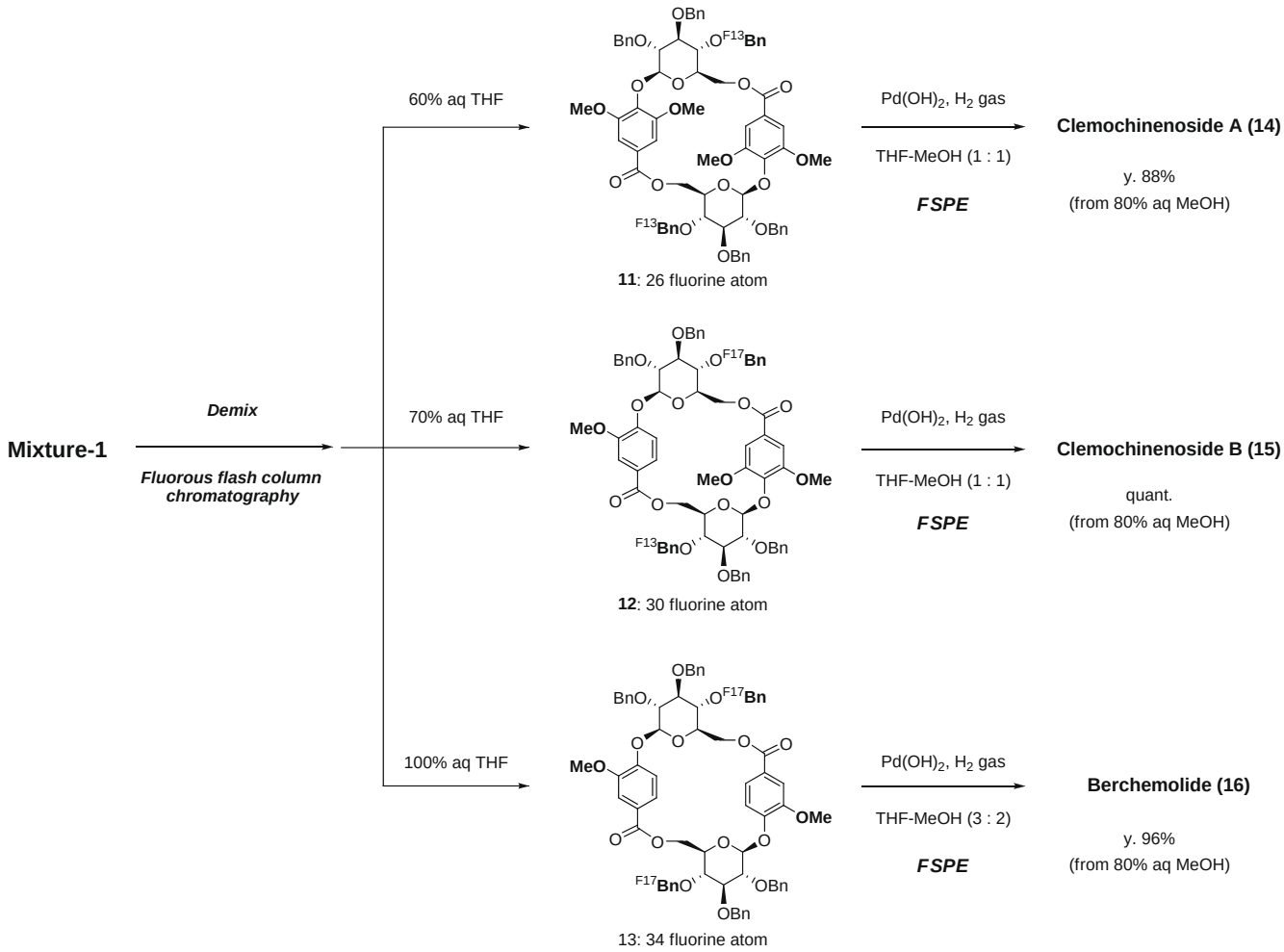


Figure 2. HPLC analysis of **Mixture-1**. Fluoro*Flash*® column (4.6 mm i.d. × 50 mm length, 5 μm), solvent THF–H_2O (70:30), flow rate 1.0 ml/min, UV detection at 254 nm.

of the fluorous intermediates **2**–**4**. Standard flash column chromatography was carried out only once, but compound **5** was successfully prepared in 57% overall yield from **1** with sufficient purity for subsequent use. In FSPE, the reaction mixture was loaded onto a Fluoro*Flash*® column and the column was eluted with 80% aq MeOH to remove the non-fluorous compounds. Then the desired fluorous compound was eluted with a fluorophilic solvent.[11] Next, a component of berchemolide, 4-*O*-(4-*O*-^{F17}benzyl-β-D-glucopyranosyl)vanillic acid **10**, was prepared using a ^{F17}benzylidene group via a similar synthetic route. As a result, the desired compound **10** [^{1}H NMR, $J_{1,2}$ = 7.3 Hz, H-1 (β-linkage)] was synthesized in 56% overall yield from 4-*O*-β-D-glucopyranosylvanillic acid methyl ester (**6**).[10,12]

Using compounds **5** and **10**, successfully prepared thus far, we attempted a fluorous mixture synthesis of macrocyclic glycosides. We expected that the three precursors of berchemolide, clemochinenosides A and B would be obtained simultaneously by a single macrocyclization of C_6F_{13}-Bn-syringic acid **5** and C_8F_{17}-Bn-vanillic acid **10**. In addition, the three components of the mixture could be separated easily by column chromatography with a Fluoro *Flash*® silica gel, because the total number of fluorine atoms in the products **11**, **12,** and **13** was 26, 30, and 34, respectively. At first, cyclodimerization of carboxylic acids **5** and **10**, using 2-chloro-1-methylpyridinium iodide,[13] was carried out while maintaining high dilution conditions (Scheme 2).[14] After purification of the crude product by FSPE, **Mixture-1**, including the three structural isomers, was analyzed by HPLC with a Fluoro*Flash*® column to determine the optimal separation conditions (Fig. 2). When a THF–H_2O (70:30) solvent system was used as a mobile phase, the three components of the product were cleanly separated with large differences in the retention times for them.[15] Therefore, these three compounds were separated by flash chromatography



Scheme 3.

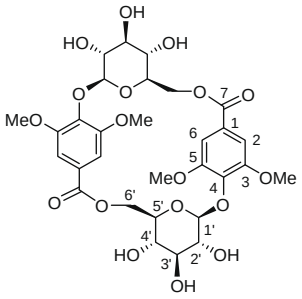
with a Fluoro*Flash*® silica gel column (Scheme 3).[16] As expected, the structural isomers were eluted in order of increasing fluorine content. The homodimer **11** and the heterodimer **12** were obtained from the 60% and 70% aq THF fractions, respectively. The pure homodimer **13** was obtained from 100% THF fraction.[17] The MS analysis, ^{1}H, and ^{13}C NMR data of the products demonstrated that compounds **11**–**13** were the desired dimers.[18] In addition, noticeable formation of high molecular weight congeners such as trimers was not observed in **Mixture-1** using fluorous HPLC and TLC analyses. Both the standard and fluorous benzyl groups of dimers **11**–**13** were removed by hydrogenolysis (Scheme 3). After the crude products were purified by FSPE, clemochinenosides A and B and berchemolide were obtained in 88%,[19a] quantitative,[19b] and 96% yield,[19c] respectively.

Synthetic clemochinenoside A (**14**) was isolated as colorless needles by recrystallization from DMSO–MeOH. The melting point of synthetic **14** (275.5–278.6 °C) was in good agreement with the reported values (276–278 °C). The ^{1}H and ^{13}C NMR data of synthetic **14** agreed well with a previous report. Careful analysis of the ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectra of **14** resulted in all the protons and carbons being assigned, as shown in Table 1. Additionally, the ^{1}H and ^{13}C NMR spectra of synthetic **14** were identical to those of natural clemochinenoside A, kindly supplied by Professor P.-F. Tu and Dr. S.-P. Shi. However, when the optical rotation of synthetic **14** was measured just after the preparation of the sample solution, the values of $[\alpha]_D^{26}$ dramatically decreased from +415.6 to +2.2 (*c* 0.50, pyridine) within 30 min. After 4 h, the optical rotation reached $[\alpha]_D^{26}$ −2.0 (*c* 0.50, pyridine) and differed from the published value ($[\alpha]_D$ +73.3 (*c* 0.53, pyridine)) in both magnitude and sign.[20] Considering this result, it seems that the conformation of clemochinenoside A gradually changed from a stable conformation in its crystalline state into its most stable conformation in pyridine.

Synthetic clemochinenoside B (**15**) was isolated as a colorless solid by recrystallization from MeOH. The ^{1}H and ^{13}C NMR data of synthetic **15** agreed well with the previous reports, except for the assignment of H-4″, 5″, 4‴, and 5‴ in the pyranosidic ring (Table 2). All signal assignments of synthetic **15** were confirmed by the ^{1}H–^{1}H and ^{13}C–^{1}H COSY experiments. The ^{1}H and ^{13}C NMR spectra of synthetic **15** were also identical to those of natural clemochinenoside B, kindly supplied by Professor P.-F. Tu and Dr. S.-P. Shi. However, its optical rotation ($[\alpha]_D^{25}$ +66.9 (*c* 0.49, pyridine)) and melting point (264.1–265.3 °C) differed from the published value ($[\alpha]_D$ +40.6 (pyridine, the concentration was not shown in the literature) and mp 290–293 °C) in magnitude.[21]

Synthetic berchemolide (**16**) was isolated as colorless needles by recrystallization from DMSO–MeOH. Synthetic **16** ($[\alpha]_D^{24}$ +119.1

Table 1
^{1}H and ^{13}C NMR data of clemochinenoside A[3] (400 MHz, 25 MHz) and synthetic **14**[a] (600 MHz, 151 MHz) in pyridine-d_5



Clemochinenoside A (**14**)

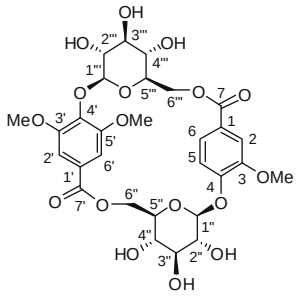
$[\alpha]_D$ -2.0 (*c* 0.50, pyridine, 26 °C)[d]

lit.[3a] $[\alpha]_D$ +77.3 (*c* 0.53, pyridine)

Position	Clemochinenoside A[3] Carbon δ (ppm)	Synthetic **14** Carbon δ (ppm)	Clemochinenoside A[3] Proton [δ (multiplicity, J(Hz))]	Synthetic **14** Proton [δ (multiplicity, J (Hz))]
1	125.85	126.00		
2	107.60	107.55	7.23 (d, J = 1.3)	7.27 (d, J = 1.7)
3	152.58	152.61		
4	138.93	138.86		
5	154.52	154.62		
6	107.86	107.74	7.50 (d, J = 1.3)	7.51 (d, J = 1.7)
7	165.68	165.76		
3-OMe		56.18[b]	3.44 (s)	3.55 (s)
5-OMe		56.25[b]	3.83 (s)	3.82 (s)
1′	102.99	103.15	5.92 (d, J = 7.3)	5.94 (d, $J_{1,2}$ = 7.4)
2′	75.21	75.38	3.97 (m)	4.42 (dd, $J_{2,1}$ = 7.4, $J_{2,3}$ = 9.1)[c]
3′	78.35	78.48	4.39 (m)	4.38 (dd, $J_{3,2}$ = 9.1, $J_{3,4}$ = 8.4)
4′	72.78	72.87	4.39 (m)	3.98 (dd, $J_{4,3}$ = 8.8, $J_{4,5}$ = 9.1)[c]
5′	75.41	75.54	4.39 (m)	4.35 (ddd, $J_{5,4}$ = 10.0, $J_{5,6'}$ = 2.2, $J_{5,6}$ = 10.3)
6′	65.28	65.38	5.17 (dd, J = 9.6, 9.6)	5.17 (dd, $J_{6,5}$ = 10.8, $J_{6,6'}$ = 10.8)
			5.00 (dd, J = 9.6, 1.5)	5.00 (dd, $J_{6',6}$ = 11.5, $J_{6',5}$ = 2.2)

[a] Signal assignments were made based on the ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra.
[b] These signals were supplements.
[c] Signal assignments differed from the literature.
[d] In the case of low concentration, the optical rotation was $[\alpha]_D$ −2.9 (*c* 0.103, pyridine, 22 °C).

Table 2
^{1}H and ^{13}C NMR data of clemochinenoside B[5] (500 MHz, 125 MHz) and synthetic **15**[a] (600 MHz, 151 MHz) in pyridine-d_5



Clemochinenoside B (**15**)

$[\alpha]_D$ +66.9 (*c* 0.49, pyridine, 25 °C)[d]

lit.[3b] $[\alpha]_D$ +40.6 (pyridine)

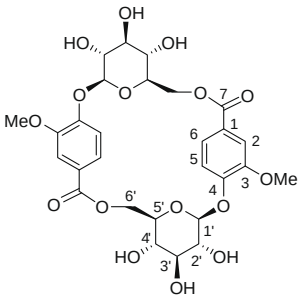
Position	Clemochinenoside B[5] Carbon δ (ppm)	Synthetic **15** Carbon δ (ppm)	Clemochinenoside B[5] Proton [δ (multiplicity, *J* (Hz))]	Synthetic **15** Proton [δ (multiplicity, *J* (Hz))]
1	123.3	123.1		
2	115.3	113.0[b]	7.67 (d, *J* = 1.5)	7.70 (d, *J* = 1.9)
3	149.7	149.7		
4	151.4	151.3		
5	113.0	115.2[b]	7.53 (d, *J* = 9.0)	7.55 (d, *J* = 8.6)
6	124.3	123.8	7.42 (dd, *J* = 9.0, 2.0)	7.45 (dd, *J* = 8.6, 1.9)
7	166.2	166.1		
1′	126.1	126.0		
2′	107.7	107.7	7.87 (d, *J* = 1.5)	7.90 (d, *J* = 1.9)
3′	153.3	153.2		
4′	139.5	139.4		
5′	154.7	154.6		
6′	108.5	108.4	7.52 (d, *J* = 2.0)	7.54 (d, *J* = 1.9)
7′	166.0	165.9		
3-OMe	56.2	55.5	3.57 (s)	3.60 (s)
3′-OMe	55.5	56.6	3.91 (s)	3.94 (s)
5′-OMe	56.6	56.1	3.49 (s)	3.51 (s)
1″	101.5	101.4	5.61 (d, *J* = 7.5)	5.66 (d, $J_{1,2}$ = 7.6)
2″	74.6	74.6	4.32–4.42 (m)	4.46–4.36 (m)
3″	78.7	78.6	4.51–4.56 (m)	4.46–4.36 (m)
4″	72.5	72.4	4.32–4.42 (m)	4.08 (dd, $J_{4,3}$ = 8.6, $J_{4,5}$ = 9.6)[c]
5″	75.4	75.4	3.98 (t, *J* = 9.0)	4.57 (m)[c]
6″	65.5	65.5	5.29 (dd, *J* = 11.5, 2.0)	5.30 (dd, $J_{6,6'}$ = 11.3, $J_{6,5}$ = 2.1)
			5.03 (dd, *J* = 11.5, 2.0)	5.09 (dd, $J_{6',6}$ = 11.2, $J_{6',5}$ = 10.1)
1‴	103.2	103.2	6.13 (d, *J* = 7.0)	6.17 (d, $J_{1,2}$ = 7.4)
2‴	75.2	75.6[b]	4.32–4.42 (m)	4.46–4.36 (m)
3‴	78.9	78.8	4.21 (t, *J* = 9.0)	4.46–4.36 (m)
4‴	72.8	72.8	4.32–4.42 (m)	4.01 (dd, $J_{4,3}$ = 8.6, $J_{4,5}$ = 9.4)[c]
5‴	75.7	75.1[b]	4.05 (t, *J* = 9.0)	4.23 (ddd, $J_{5,4}$ = 10.0, $J_{5,6}$ = 2.4, $J_{5,6'}$ = 10.3)[c]
6‴	66.2	66.2	5.18 (dd, *J* = 11.5,2.0)	5.20 (dd, $J_{6,6'}$ = 11.2, $J_{6,5}$ = 2.4)
			4.55 (dd, *J* = 11.5, 2.0)	4.57 (dd, $J_{6',6}$ = 11.2, $J_{6',5}$ = 10.5)

[a] Signal assignments were made based on the ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra.
[b] Signals may be exchanged.
[c] Signal assignments differed from the literature.
[d] In the case of low concentration, the optical rotation was $[\alpha]_D$ +66.7 (*c* 0.063, pyridine, 22 °C).

(*c* 0.11, pyridine)) showed almost identical optical rotation with that reported for natural berchemolide ($[\alpha]_D^{32}$ +116 (*c* 0.1, pyridine)).[22] In addition, the ^{1}H and ^{13}C NMR data for synthetic **16** agreed well with the previously reported values (Table 3).

In conclusion, we have simultaneously synthesized three macrocyclic glycosides, berchemolide, clemochinenoside A, and clemochinenoside B, using the fluorous mixture synthesis technique. The isolation of fluorous intermediates by FSPE was very easy and quick, and the desired carboxylic acids were obtained during the synthesis by a single silica gel column chromatographic purification step. It was also demonstrated that the three fluorous precursors of the natural products were cleanly separated by fluorous flash column chromatography, depending upon the total number of fluorine atoms. The complete synthesis of the proposed chemical structure for clemochinenoside A was achieved; although there is a discrepancy in the magnitude and sign of the optical rotation for synthetic **14** and an authentic sample.[23] The investigation of the interesting physical properties and the conformation of clemochinenoside A is now in progress.

Table 3
^{1}H and ^{13}C NMR data of berchemolide[1] (400 MHz, 100 MHz) and synthetic **16**[a] (600 MHz, 151 MHz) in DMSO-d_6



Berchemolide (**16**)

$[\alpha]_D$ +119.1 (*c* 0.11, pyridine, 24 °C)[b]

lit.[1] $[\alpha]_D$ +116 (*c* 0.1, pyridine, 32 °C)

Position	Berchemolide[1] Carbon δ (ppm)	Synthetic **16** Carbon δ (ppm)	Berchemolide[1] Proton [δ (multiplicity, *J* (Hz))]	Synthetic **16** Proton [δ (multiplicity, *J* (Hz))]
1	122.50	122.46		
2	112.19	112.09	7.42 (d, *J* = 2.0)	7.40 (d, *J* = 2.1)
3	148.43	148.40		
4	149.85	149.81		
5	114.42	114.44	7.37 (d, *J* = 8.6)	7.37 (d, *J* = 8.8)
6	122.91	122.93	7.75 (dd, *J* = 8.6, 2.0)	7.74 (d, *J* = 8.6, 2.1)
7	165.06	165.12		
3-OMe	55.50	55.49	3.80 (s)	3.79 (s)
1′	98.33	98.28	5.24 (d, *J* = 7.1)	5.24 (d, $J_{1,2}$ = 7.4)
2′	72.80	72.83	3.39 (dd, *J* = 7.1, 9.0)	3.37 (m)
3′	76.92	76.94	3.39 (t, *J* = 9.0)	3.37 (m)
4′	70.59	70.59	3.18 (t, *J* = 9.0)	3.17 (dd, $J_{4',3}$ = 8.6, $J_{4',5}$ = 9.8)
5′	73.46	73.48	3.97 (ddd, *J* = 9.6, 9.0, 2.0)	3.97 (ddd, $J_{5,4}$ = 10.0, $J_{5,6'}$ = 1.9, $J_{5,6}$ = 10.1)
6′	64.99	65.08	4.09 (dd, *J* = 11.2, 9.6)	4.07 (dd, $J_{6,6'}$ = 11.3, $J_{6',5}$ = 10.5)
			4.41 (dd, *J* = 11.2, 2.0)	4.40 (dd, $J_{6',6}$ = 11.3, $J_{6',5}$ = 1.7)

[a] Signal assignments were made based on the ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra.
[b] In the case of low concentration, the optical rotation was $[\alpha]_D$ +110 (*c* 0.03, pyridine, 23 °C).

Acknowledgments

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References and notes

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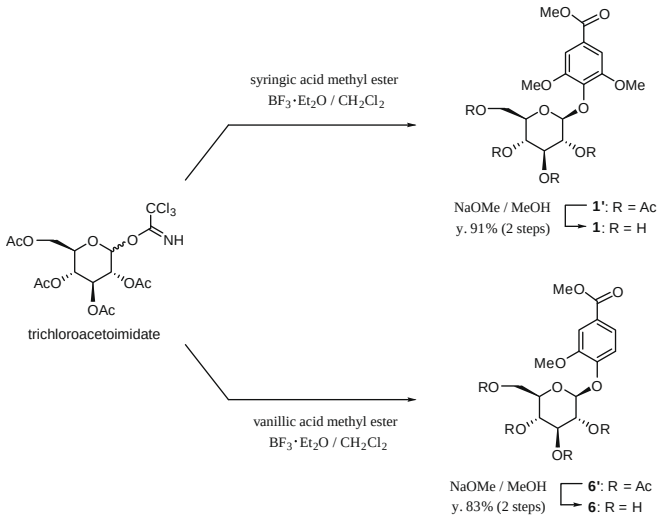
10. *Synthetic method for starting materials* (**1**) *and* (**6**): 2,3,4,6-Tetra-*O*-acetyl D-glucopyranosyl trichloroacetoimidate was prepared from D-glucose according to the traditional procedure. The glycosylation of the trichloroacetoimidate derivative with syringic acid methyl ester (1.1 equiv) in the presence of $BF_3{\cdot}Et_2O$ (1.7 equiv) in anhydrous CH_2Cl_2 gave the phenyl β-D-glucopyranoside **1′**, which was then treated with NaOMe (0.5 equiv) in MeOH to afford 4-*O*-β-D-glucopyranosylsyringic acid methyl ester (**1**) in 91% overall yield. According to a similar procedure, **6** was synthesized from trichloroacetoimidate derivative in 83% overall yield. The physical data for **1′**, **1**, **6′**, and **6** were almost identical to the reported values. The ^{1}H and ^{13}C NMR spectra for synthetic **1** were identical to those of natural **1**, kindly supplied by Professor J. Kitajima. (a) Klick, S.; Herrmann, K. *Z. Lebensm. Unters. Forsch.* **1988**, *187*, 444. (b) Fujimatu, E.; Ishikawa, T.; Kitajima, J. *Phytochemistry* **2003**, *63*, 609. (c) Durkee, A. B.; Siddiqui, I. R. *Carbohydr. Res.* **1979**, *77*, 252. Compound **1′**: $[\alpha]_D^{24}$ −9.3 (*c* 0.3, MeOH); mp 109.2–111.5 °C (EtOAc–Hexane) [*lit.* mp 105 °C (MeOH)[10a]]. Compound **1**: $[\alpha]_D^{24}$ −17.1 (*c* 0.48, MeOH); mp 186.1–188.7 °C (MeOH) [*lit.* $[\alpha]_D^{24}$ −20 (*c* 0.9, MeOH); mp 91–93 °C (MeOH)[10b]]. Compound **6′**: $[\alpha]_D^{24}$ −33.0 (*c* 0.5, $CHCl_3$); mp 145.2–147.3 °C (EtOAc–hexane) [*lit.* $[\alpha]_D^{25}$ −34 (*c* 1.0, $CHCl_3$); mp 143–144 °C (EtOH)[10c]]. Compound **6:** $[\alpha]_D^{18}$ −69.9 (*c* 0.7, MeOH); mp 196.2–198.2 °C (MeOH) [*lit.* $[\alpha]_D^{25}$ −71 (*c* 0.7, MeOH); mp 170–171 °C (H_2O)[10c]].



11. Usually MeOH is used to elute fluorous compounds from a Fluoro*Flash*® column. When the fluorous compounds were sparingly soluble in MeOH, EtOAc or acetone was used to quickly elute the fluorous compounds from the column.
12. C_6F_{13}– and C_8F_{17}-benzaldehydes were dissolved completely in the same amount of CH_3CN. Therefore, a lower yield of product **7** than that of **2** is considered to be due to lower solubility of 4-*O*-β-D-glucopyranosylvanillic acid methyl ester (**6**) in CH_3CN compared to that of **1**.
13. To identify the optimal reaction conditions for cyclodimerization, we initially examined the conversion of monomer **5** into the corresponding dimer **11** under various conditions. (a) DCC, DMAP/CH_2Cl_2, rt, (y. 11%): Wang, Y.; Mao, J.; Cai, M. *Synth. Commun.* **1999**, *29*, 2093. (b) 2-Methyl-6-nitrobenzoic anhydride, DMAP/CH_2Cl_2, rt, (y. 52%): Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822. (c) 2-Chloro-1,3-dimethylimidazolinium chloride, DMAP/CH_2Cl_2, 0 °C then rt, (y. 47%): Isobe, T. *J. Org. Chem.* **1999**, *64*, 6984. (d) (i) 2,4,6-Trichlorobenzoyl chloride, Et_3N/THF, rt. (ii) DMAP/toluene, rt then reflux, (y. 47%): Inanaga, J.; Hirata, K. Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (e) DEAD, PPh_3/THF, −20 °C then rt, (y. 50%): Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (f) 2-Chloro-1-methylpyridinium iodide, pyridine, DMAP/CH_2Cl_2, 0 °C, (y. 59%): Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, *5*, 49.
14. *Cyclodimerization procedure*: To a stirred mixture of the carboxylic acids **5** (46.7 mg, 0.047 mmol), **10** (50 mg, 0.047 mmol), and 2-chloro-1-methylpyridinium iodide (120 mg, 0.47 mmol) in CH_2Cl_2 (63 ml), pyridine (114 μl, 1.41 mmol) was slowly added at 0 °C. The reaction mixture was stirred for 24 h, and then DMAP (69 mg, 0.57 mmol) was added to the reaction mixture. After monitoring the disappearance of the starting materials on TLC, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with 3% HCl, dried over Na_2SO_4, and concentrated. The residue was loaded onto a Fluoro*Flash*® silica gel (3 g) column and eluted with 80% aq MeOH (100 ml); the column was subsequently eluted with EtOAc (200 ml) to give a fraction containing **Mixture-1** (94.5 mg).
15. Using a Fluoro*Flash*® column, **Mixture-1** was analyzed with the following gradient solvent system. The column was initially eluted with CH_3CN–H_2O (80:20), then with increasing CH_3CN–H_2O to 100:0 over a 10-min period. Compounds **11**, **12**, and **13** were eluted individually at 10.2, 13.3, and 16.7 min.
16. The three components of **Mixture-1** were separated clearly by fluorous TLC and the differences in R_f values were large enough to separate the components by fluorous silica gel column chromatography depending upon their fluorine atom content. Comparatively, on a standard silica gel TLC, the top two spots were very close and the second spot overlapped with the tail of the top spot. Therefore, it was predicted that the three components would be difficult to separate by standard silica gel column chromatography without the fluorous tags. In addition, it is impossible to predict the structures of the components, even if separation was successful.
17. From 94.5 mg **Mixture-1**, homodimer **11** (18.5 mg), heterodimer **12** (47.8 mg), and homodimer **13** (14.4 mg) were obtained from 60%, 70%, and 100% aq THF fractions, respectively.
18. ^1H, ^{13}C NMR data and other physical data of compounds **11**–**13**.*Compound* **11**: $[\alpha]_D^{17}$ +1.7 (*c* 0.94, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.67–7.05 (32H, m, aromatic protons), 5.21 (2H, d, $J_{1,2}$ = 7.4 Hz, glc H-1), 5.17, 4.80 (4H, each d, *J* = 11.0 Hz, –CH_2Ph), 5.03, 4.81 (4H, each d, *J* = 11.1 Hz, –CH_2Ph), 4.86, 4.57 (4H, each d, *J* = 11.1 Hz, –CH_2Ph), 4.43 (2H, dd, $J_{6,5}$ = 3.1 Hz, $J_{6,6'}$ = 11.3 Hz, glc H-6), 4.36 (2H, dd, $J_{6',5}$ = 10.0 Hz, $J_{6',6}$ = 11.2 Hz, glc H-6′), 3.85–3.78 (4H, m, glc H-2, 3), 3.75, 3.62 (12H, each s, –OCH_3 × 2), 3.67 (2H, ddd, $J_{5,4}$ = 9.5 Hz, $J_{5,6}$ = 3.2 Hz, $J_{5,6'}$ = 9.6 Hz, glc H-5), 3.45 (2H, dd, $J_{4,5}$ = 9.5 Hz, $J_{4,3}$ = 8.5 Hz, glc H-4), 2.70 (4H, t, *J* = 7.4 Hz, –$CH_2CH_2CH_2C_6F_{13}$), 2.18–1.86 (8H, m, –$CH_2CH_2CH_2C_6F_{13}$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.25, 153.41, 151.59, 140.44, 138.57, 137.80, 135.75, 128.48, 128.39, 128.30, 128.29, 127.81, 127.61, 125.23, 106.92, 106.28, 102.96, 84.81, 82.14, 78.62, 77.20, 75.69, 74.55, 74.41, 72.82, 63.97, 56.34, 56.04, 34.71, 30.25 (t), 21.76. MS (ESI-pos.) calcd for $C_{90}H_{82}F_{26}O_{18}Na$ (M+Na)$^+$ 1967.4984, found: 1967.4990.
Compound **12**: $[\alpha]_D^{17}$ −13.2 (*c* 0.98, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–6.84 (33H, m, aromatic protons), 5.27, 4.80 (2H, each d, *J* = 10.9 Hz, –CH_2Ph), 5.21 (1H, d, *J* = 10.8 Hz, –CH_2Ph), 5.08–4.98 (4H, m, –CH_2Ph × 3, glc H-1, 6), 4.92–4.78 (7H, m, –CH_2Ph × 6, glc′ H-1), 4.62 (1H, *J* = 11.4 Hz, –CH_2Ph), 4.58 (1H, *J* = 11.1 Hz, –CH_2Ph), 4.45 (1H, dd, $J_{6,5}$ = 1.6 Hz, $J_{6,6'}$ = 11.0 Hz, glc′ H-6), 4.05 (1H, dd, $J_{6',5}$ = 10.3 Hz, $J_{6',6}$ = 10.7 Hz, glc H-6′), 4.00 (1H, dd, $J_{6',5}$ = 10.1 Hz, $J_{6',6}$ = 10.7 Hz, glc′ H-6′), 3.94–3.76 (5H, m, glc H-2, 3, 5, glc′ H-2, 3), 3.88, 3.87, 3.55 (9H, each s, –OCH_3 × 3), 3.62–3.43 (3H, m, glc H-4, glc′ H-4, 5), 2.73, 2.70 (4H, each d, *J* = 7.5, 7.3 Hz, –$CH_2CH_2CH_2C_8F_{17}$, –$CH_2CH_2CH_2C_6F_{13}$), 2.16–1.91 (8H, m, –$CH_2CH_2CH_2C_8F_{17}$, –$CH_2CH_2CH_2C_6F_{13}$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.73, 165.30, 154.25, 152.84, 150.55, 149.12, 140.56, 140.51, 138.75, 138.67, 138.64, 138.24, 138.07, 135.61, 135.59, 128.55, 128.51, 128.51, 128.45, 128.40, 128.37, 128.28, 128.20, 127.93, 127.85, 127.80, 127.76, 127.60, 127.57, 125.94, 124.18, 123.32, 118.42, 114.61, 112.35, 107.01, 106.59, 104.60, 101.62, 84.98, 84.47, 82.24, 81.06, 78.53, 78.38, 77.20, 75.94, 75.75, 74.76, 74.70, 74.67, 74,47, 73.30, 72.83, 64.71, 63.81, 56.21, 56.11, 55.83, 34.73, 30.28 (t), 21.80. MS (ESI-pos.) calcd for $C_{91}H_{80}F_{30}O_{17}Na$ (M+Na)$^+$ 2037.4814, found: 2037.4788.
Compound **13**: $[\alpha]_D^{17}$ +12.0 (*c* 0.75, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.72–7.15 (34H, m, aromatic protons), 5.21, 4.87 (4H, each d, *J* = 10.8 Hz, –CH_2Ph), 5.11 (2H, d, $J_{1,2}$ = 7.4 Hz, glc H-1), 5.05, 4.85 (4H, each d, *J* = 11.0 Hz, –CH_2Ph), 4.89, 4.59 (4H, each d, *J* = 10.9 Hz, –CH_2Ph), 4.59 (2H, dd, glc H-6), 4.10 (2H, dd, $J_{6',5}$ = 10.5 Hz, $J_{6',6}$ = 10.9 Hz, glc H-6′), 3.90 (2H, ddd, $J_{5,4}$ = 9.8 Hz, $J_{5,6}$ = 1.5 Hz, $J_{5,6'}$ = 10.1 Hz, glc H-5), 3.87 (6H, s, –OCH_3), 3.87–3.78 (4H, m, glc H-2, 3), 3.49 (2H, dd, $J_{4,5}$ = 9.4 Hz, $J_{4,3}$ = 8.7 Hz, glc H-4), 2.70 (4H, t, *J* = 7.4 Hz, –$CH_2CH_2CH_2C_6F_{13}$), 2.19–1.88 (8H, m, –$CH_2CH_2CH_2C_6F_{13}$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.62, 150.25, 149.49, 140.65, 138.28, 138.11, 135.44, 128.57, 128.51, 128.48, 128.45, 128.42, 127.86, 127.78, 124.19, 123.26, 115.44, 112.70, 101.09, 84.68, 81.21, 78.43, 77.21, 75.92, 75.02, 74.74, 73.31, 64.56, 55.92, 34.75, 30.30 (t), 21.80. MS (ESI-pos.) calcd for $C_{92}H_{78}F_{34}O_{16}Na$ (M+Na)$^+$ 2107.4645, found: 2107.4657.
19. After purification of the crude products by FSPE, 4-(3-perfluoroalkyl)propyl toluenes were recovered from the MeOH fraction. (a) 4-(3-Perfluorohexyl)propyl toluene was obtained in 49% yield. (b) A mixture of 4-(3-perfluorohexyl)propyl toluene and 4-(3-perfluorooctyl)propyl toluene was obtained in 64% yield. (c) 4-(3-Perfluorooctyl)propyl toluene was obtained in 65% yield. Conversion of 4-(3-perfluoroalkyl)propyl toluenes into the corresponding 4-(3-perfluoroalkyl)propyl benzaldehydes for reuse is now in progress.
20. Physical data of clemochinenoside A (**14**): colorless needles (DMSO–MeOH), mp 275.5–278.6 °C; $[\alpha]_D^{26}$ −2.0 (*c* 0.5, pyridine) [*lit*. mp 276–278 °C, $[\alpha]_D$ +73.3 (*c* 0.53, pyridine)[3a]]; ^1H and ^{13}C NMR (Table 1). MS (ESI-pos.) calcd for $C_{30}H_{36}O_{18}Na$ (M+Na)$^+$ 707.1799, found: 707.1793.
21. Physical data of clemochinenoside B (**15**): colorless solid (MeOH), mp 264.1–265.3 °C; $[\alpha]_D^{25}$ +66.9 (*c* 0.49, pyridine) [*lit*. mp 290–293 °C, $[\alpha]_D$ +40.6 (pyridine)[3b]]; ^1H and ^{13}C NMR (Table 2). MS (ESI-pos.) calcd for $C_{29}H_{34}O_{17}Na$ (M+Na)$^+$ 677.1694, found: 677.1695.
22. *Physical data of berchemolide* (**16**): colorless needles (DMSO–MeOH); $[\alpha]_D^{24}$ +119.1 (*c* 0.11, pyridine) [*lit*. $[\alpha]_D^{32}$ +116 (*c* 0.1, pyridine)[1]]; ^1H and ^{13}C NMR (Table 3). MS (ESI-pos.) calcd for $C_{28}H_{32}O_{16}Na$ (M+Na)$^+$ 647.1588, found: 647.1612.
23. It was not possible to measure the optical rotation of the natural products. No samples of natural clemochinenosides A and B were available (Personal communication by Professor P.-F. Tu and Dr. S.-P. Shi).