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

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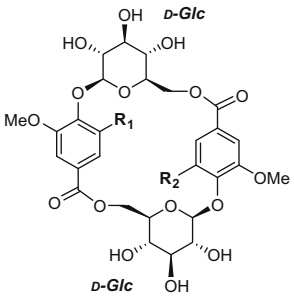
ABSTRACT

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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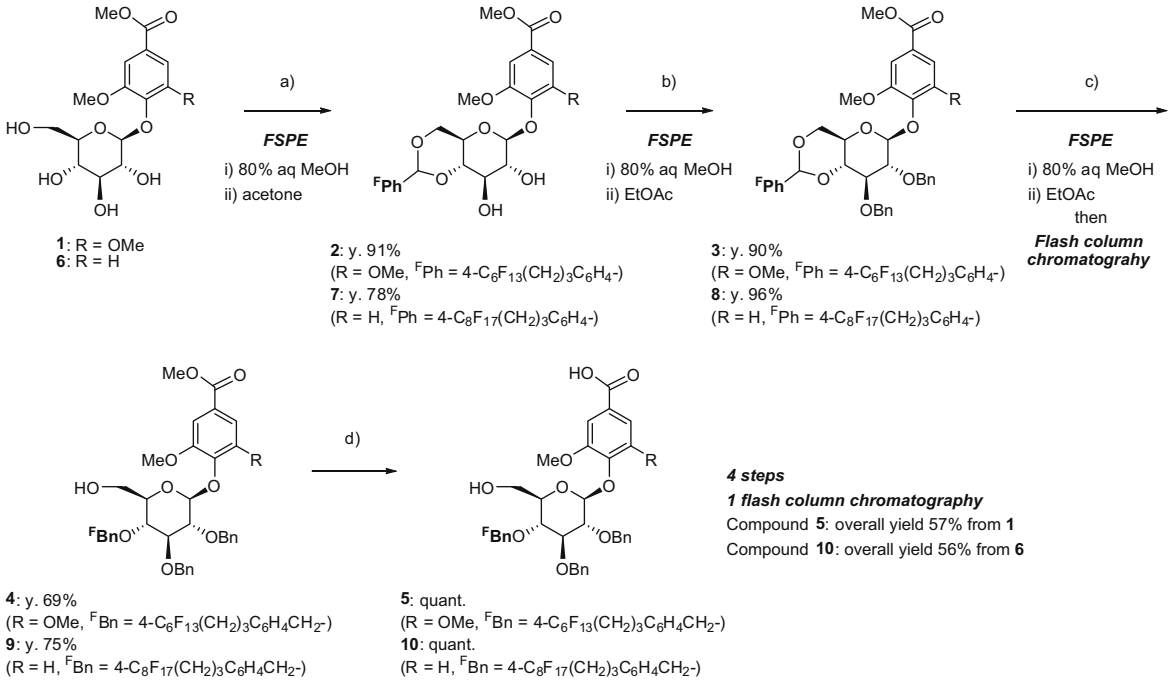


1: R = OMe
6: R = H

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-$C_8F_{17}(CH_2)_3C_6H_4$-)

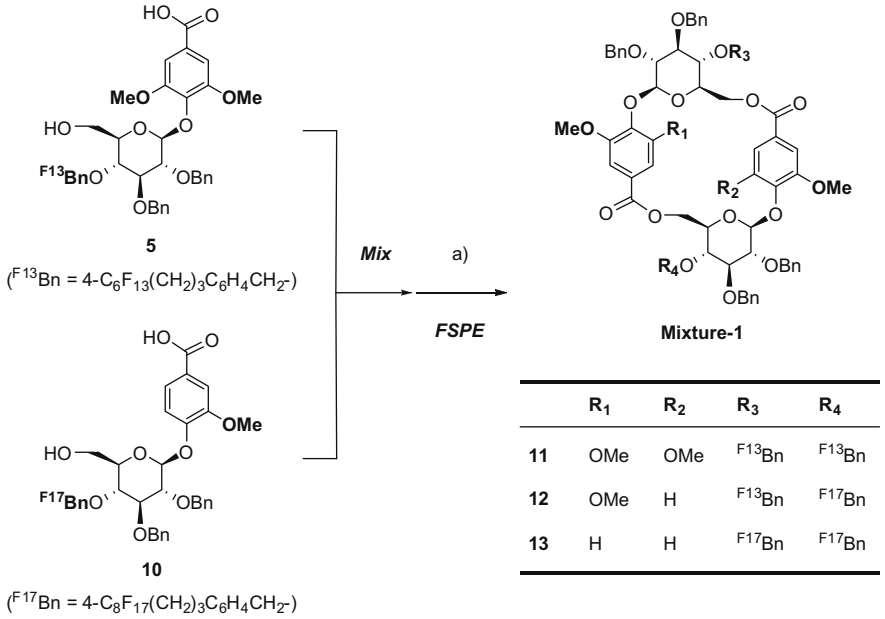
4: y. 69%
(R = OMe, ^{F}Bn = 4-$C_6F_{13}(CH_2)_3C_6H_4CH_2$-)
9: y. 75%
(R = H, ^{F}Bn = 4-$C_8F_{17}(CH_2)_3C_6H_4CH_2$-)

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.