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Convenient synthesis of mono(6^A-*N*-allylamino-6^A-deoxy)-permethylated β-cyclodextrin: a promising chiral selector for an HPLC chiral stationary phase

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Abstract—Mono(6-(*p*-toluenesulfonyl))permethylated β-cyclodextrin, a versatile precursor for a wide variety of mono-functionalized permethyl β-cyclodextrins, has been generated successfully by the direct methylation of monotosylated cyclodextrin. This afforded a convenient synthesis of mono(6^A-*N*-allylamino-6^A-deoxy)permethylated β-cyclodextrin. Hydrosilylation of the chiral selector with $(EtO)_3SiH$ and reaction of the resultant reactive siloxane with pristine silica gel afforded a facile entry into a structurally well-defined chiral HPLC stationary phase.

Cyclodextrins (CDs) are cyclic oligomers of α-D-glucose bonded through α-(1,4) linkages; the shape of a CD molecule is similar to a truncated cone with a cavity.[1,2] In order to obtain cyclodextrins with the desired properties, many modified CDs have been prepared.[3,4] Native and derivatized CDs are used as chiral selectors in many enantioselective separations.

Over the past decade, permethylated CDs have been widely used as the stereoselective selector in chiral stationary phases (CSP) for chromatographic methodologies affording good enantioseparation performances. Schurig and co-workers studied permethylated cyclodextrins and successfully applied their derivatives as chiral stationary phases in capillary supercritical fluid chromatography (CSFC),[5,6] open capillary electrochromatography (o-CEC),[7] pressure-assisted micro-packed capillary electrochromatography (CEC),[8] gas–liquid chromatography (GLC),[9] and gas chromatography (GC).[10–12] Konig and co-workers[13] and Ciucanu[14] reported the application of permethylated β-cyclodextrin in enantioselective high performance liquid chromatography (HPLC). However, the preparation of the chiral stationary phases involved the protection/deprotection of hydroxyl groups on the cyclodextrin, which made the syntheses tedious with diminished yields of products.

As a part of an ongoing program aimed at exploiting the applicability of CD derivatives as chiral selectors for enantioseparation by HPLC, we have studied the utility of mono-substituted CDs, in which a single primary hydroxyl group is first converted to a reactive moiety, which may be used subsequently for further immobilization of the derivatives onto the surface of silica gel.[15] In our previous work, the CSP afforded using mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated β-CD as the chiral selector was shown to have outstanding enantioseparation capabilities toward a wide range of chiral compounds.[16] We decided to develop a convenient synthetic approach to mono(6^A-allylamino-6^A-deoxy)permethylated β-CD for subsequent immobilization onto the surface of silica gel via hydrosilylation.

To our knowledge, the synthesis of the key intermediate, mono(6^A-allylamino-6^A-deoxy)permethylated β-CD, was unknown although permethylation of pristine CDs has been extensively studied.[17] From the readily available starting material, mono(6-(*p*-tolylsulfonyl)) β-cyclodextrin (**1**),[18] we investigated two possible

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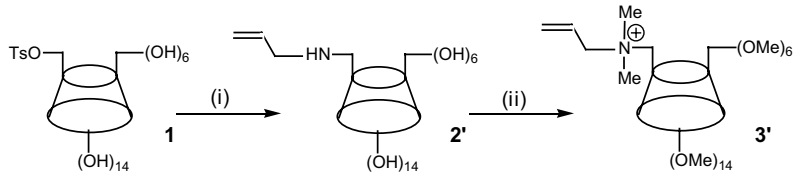
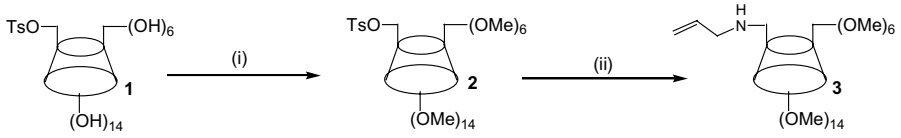


Scheme 1. Methylation of mono(6^A-*N*-allylamino-6^A-deoxy) β-CD. Reagents and conditions: (i) $CH_2{=}CHCH_2NH_2/\Delta$; (ii) MeI/DMF/NaH.



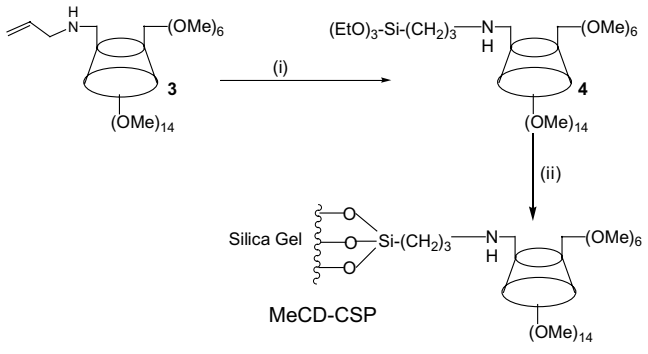
Scheme 2. Direct permethylation of mono(6-(*p*-tolylsulfonyl)) β-CD. Reagents and conditions: (i) MeI/DMF/NaH; (ii) $CH_2{=}CHCH_2NH_2/\Delta$.

syntheses. Of these, one proved to be easier affording a convenient approach toward our goal.

The synthesis previously reported[16,19] was first attempted but the desired compound was not obtained (see Scheme 1). The amino group in compound **2′** was fully methylated and a charged CD derivative **3′**[20] was isolated.

With a view to avoid methylation of the amino group, an alternative synthesis was investigated as depicted in Scheme 2. This involved the direct-permethylation of mono(6-(*p*-tolylsulfonyl)) β-CD (**1**).[21] Compound **2** (see Scheme 2) is a versatile precursor for a wide variety of mono-functionalized permethyl β-CDs, and the reactive *p*-tolylsulfonyl group was reacted with allylamine to afford the desired compound **3**[22] under mild conditions and with good yields.

Thereafter, hydrosilylation of **3** with $(EtO)_3SiH$ in the presence of a catalytic amount of tetrakis(triphenylphosphine)platinum(0) gave the reactive siloxane **4**, which was directly immobilized onto the surface of silica gel to afford the desired **MeCD-CSP** (see Scheme 3). The carbon content in the elemental analysis (C, 8.01%; H, 1.91%) of the CSP showed that the cyclodextrin moieties had been successfully immobilized onto the surface of the silica gel. According to the microanalytical data, the surface concentration[23] of the cyclodextrin derivative on the silica gel was determined to be 0.4×10^{-6} mol/m^2.



Scheme 3. Immobilization of the CD derivative via hydrosilylation. Reagents and conditions: (i) $(EtO)_3SiH$/cat. $Pt(PPh_3)_4$/THF/Δ; (ii) silica gel/$CH_3C_6H_5/\Delta$.

After the resultant CSP had been packed into a stainless HPLC column (Ø4.6×250 mm), its chromatographic properties were evaluated using a wide range of structurally diverse racemic compounds, with representative chromatograms depicted in Figure 1. It should be noted that **MeCD-CSP** exhibits excellent enantioseparation abilities toward a series of flavanones; representative examples are listed in Table 1. Further details of these analytical results will be reported elsewhere.

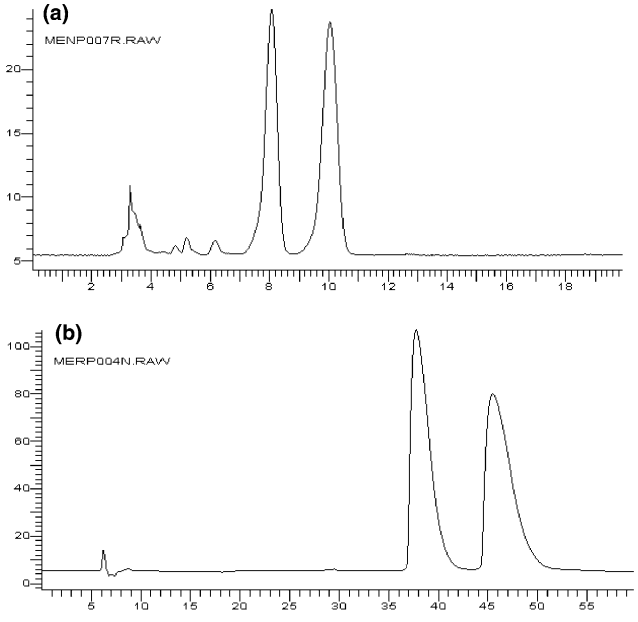
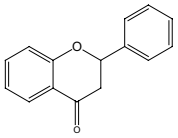
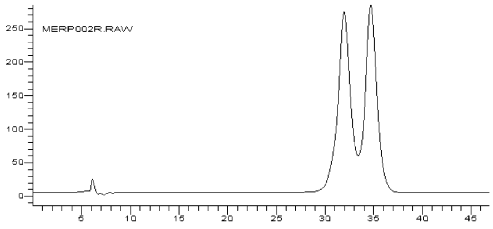
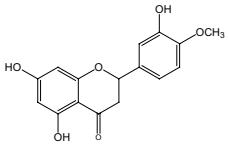
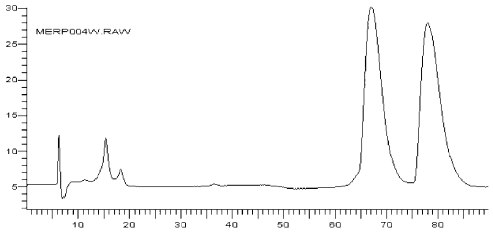
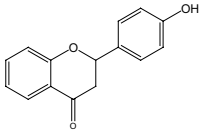
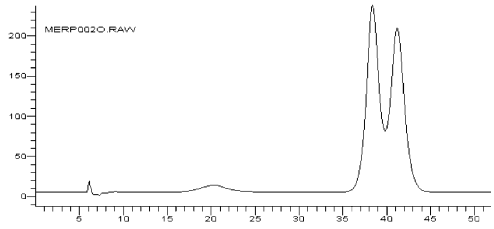
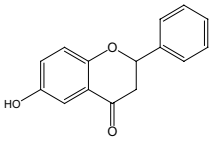
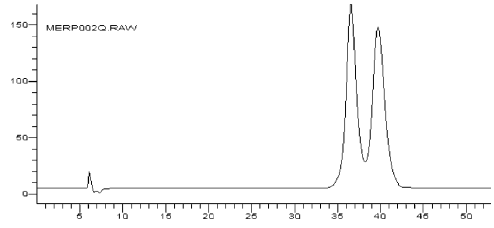
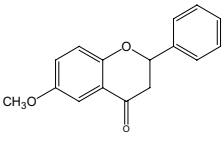
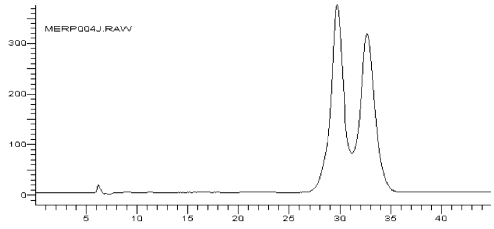
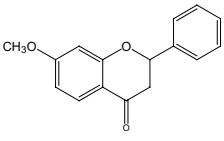
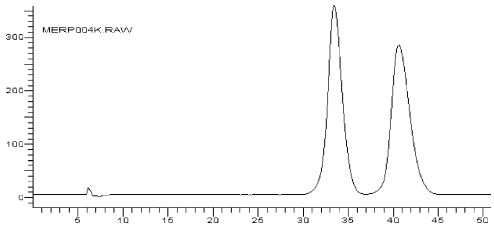


Figure 1. Representative chromatograms on the column packed with **MeCD-CSP** (a) 1-(4-bromophenyl)-ethanol; Separation conditions: hexane/IPA = 97/3 (v/v), 1.0 mL/min, UV detector, 254 nm. (b) Suprofen; Separation conditions: buffer (1% TEA aqueous adjusted with HOAc, pH = 5.5)/MeOH = 65/35 (v/v), 0.5 mL/min, UV detector, 254 nm.

Table 1. Enantioseparation of some flavanones on **MeCD-CSP** under reversed phase conditions

S/N	Compound	Enantioseparation data	
		Separation results	Chromatograms
1	flavanone 	$k_1 = 4.21$ $k_2 = 4.66$ $\alpha = 1.11$ $R_s = 0.95$	
2	hersperatine 	$k_1 = 9.98$ $k_2 = 11.79$ $\alpha = 1.18$ $R_s = 1.63$	
3	4′-hydroxyflavanone 	$k_1 = 5.25$ $k_2 = 5.72$ $\alpha = 1.09$ $R_s = 0.93$	
4	6-hydroxyflavanone 	$k_1 = 4.97$ $k_2 = 5.48$ $\alpha = 1.10$ $R_s = 1.20$	
5	6-methxoyflavanone 	$k_1 = 3.84$ $k_2 = 4.33$ $\alpha = 1.13$ $R_s = 1.15$	
6	7-methoxyflavanone 	$k_1 = 4.48$ $k_2 = 5.66$ $\alpha = 1.26$ $R_s = 2.06$	

Separation conditions: buffer (1% TEA aqueous adjusted with HOAc, pH = 5.5)/MeOH = 65/35 (v/v), 0.5 mL/min, UV detector, 254 nm.

In summary, mono(6-(*p*-tolylsulfonyl))permethylated β-CD (**2**), a key precursor for a wide variety of mono-functionalized permethyl β-CDs, has been successfully generated by the direct methylation of tosylated CD. Accordingly, this afforded a convenient synthesis of mono(6^A-*N*-allylamino-6^A-deoxy)permethylated

β-cyclodextrin (**3**). Thereafter, hydrosilylation of the chiral selector with $(EtO)_3SiH$ and reaction of the resultant reactive siloxane with pristine silica gel afforded a facile entry into a structurally well-defined chiral stationary phase **MeCD-CSP** for HPLC.

Acknowledgements

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20. Deliquescent white crystal. Melting point: 85–90 °C; ESI MS for $C_{67}H_{120}O_{34}N$ (1483), m/z: $[M + Na]^+$ 1506.
21. Preparation of mono(6-(*p*-tolylsulfonyl))permethylated β-CD (**2**): A solution of **1** (5.0 g, 3.9 mmol) in DMF (ca. 80 mL) was added dropwise to sodium hydride (8.0 g, 180.0 mmol) (55–60% in paraffin, washed with hexane) with stirring; iodomethane (10.0 mL, 160.0 mmol) was then added slowly to the reaction mixture and allowed to stir for 12 h. Water (100 mL) was then added cautiously to stop the reaction. The crude product was extracted with ethyl acetate and then purified by chromatography over silica gel using ethyl acetate–acetone (1:1, v/v) as eluent to afford **2** as very light yellow crystal **2**: (3.4 g, 56%): mp 84–86 °C; IR (cm^{-1}): 29 28 (sp^3C–H, s), 28 36 (–CH_2–, m), 1039 (C–O, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.55 (*C*H_3-ϕ), 58.40–58.96 (*C*H_3–O–) 61.43 (C-6), 70.82 (C-2), 71.00–71.15 (C-5), 71.31 (C-3), 80.16–81.95 (C-4), 98.82 (C-1), 127.79 (*C*H–C–S), 129.77 (*C*H–C–CH_3), 133.25 (*C*–S), 144.71 (*C*–CH_3); ESI MS for $C_{69}H_{116}O_{37}S$ (1569), m/z: $[M + Na]^+$ 1592.
22. Preparation of mono(6^A-*N*-allylamino-6^A-deoxy)permethylated β-CD (**3**): A solution of compound **2** (3.0 g, 1.9 mmol) in allylamine (23 g, 400 mmol) was refluxed for 5 h; the resultant solution was cooled to rt and the excess allylamine was removed under vacuum. Water was then added to the residue and the crude product was extracted using ethyl acetate and then purified by chromatography over silica gel using ethyl acetate–acetone (1:1, v/v) as eluent to afford **3** as white crystals: (2.0 g, 74%): mp 81–82 °C; IR (cm^{-1}, KBr): 2928 (sp^3C–H, s), 2831 (–CH_2–, m), 1142 (C–N, m), 1038 (C–O–C, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.64 (*C*H_2NH), 57.75–58.05 (*C*H_3O), 60.60 (C-6), 70.32 (C-2), 71.08 (C-5), 79.53 (C-3), 81.19–81.52 (C-4), 97.70 (C-1), 114.77 (CH=*C*H_2), 137.69 (*C*H=CH_2); ESI MS for $C_{65}H_{115}O_{34}N$ (1454), m/z: $[M + H]^+$ 1455.
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