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# Syntheses of macrocyclic bisbibenzyls on solid support

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**Abstract**—We describe a route for the polymer supported total synthesis of the cyclic bisbibenzyls of the isoplagiochin type found in liverworts. TentaGel® resins were used as solid support for a sequence involving Suzuki, Wittig and hydrogenation protocols. The polymer linked intermediates could be characterized by HR-MAS NMR. This route is to be extended to the synthesis of small libraries of differently halogenated derivatives.


## 1. Introduction

The cyclic bisbibenzyls isoplagiochin C (**1**) and D (**2**) were isolated from the liverworts *Plagiochila fruticosa*,[1] *Plagiochila deflexa*[2] and *Herbertus sakuraii* (Fig. 1).[3] Altogether, 21 chlorinated derivatives of the type **3** were detected in the liverworts *Bazzania trilobata*,[4] *Lepidozia incurvata*,[5] *Mastigophora diclados*, *H. sakuraii*,[6] *Plagiochila peculiaris*[7] and *P. deflexa*.[8] Phenolic compounds of the bibenzyl and bisbenzyl type exhibit remarkable antitumoural, antibacterial and antimycotic activities.[9,10] The isoplagiochin framework proved to be of substantial structural interest because of the chirality of the entire molecule.[11]

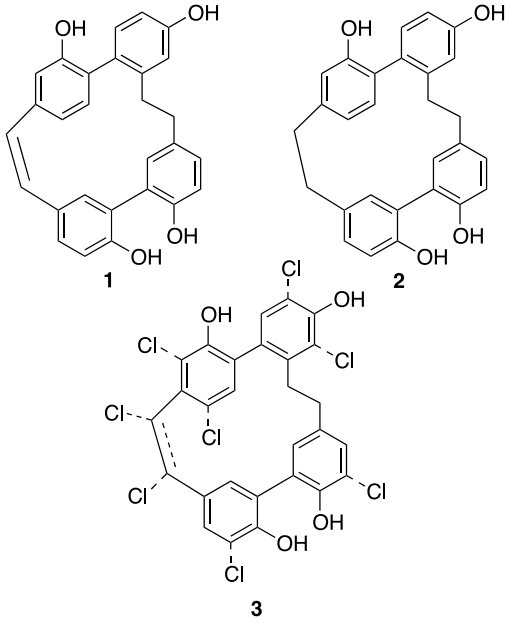


**Figure 1.** Structures of isoplagiochins **1**, **2** and halogenated derivatives **3**.

Conventional total syntheses ('in solution') for **1** and **2**[12] and for three examples of **3**[13] were described applying an efficient and flexible unit construction system and making extensive use of Suzuki and Wittig protocols.

Syntheses of **1** and **2** on solid support[14] especially using TentaGel® resins[15] should give valuable contributions to Suzuki and Wittig reactions on this carrier[16,17] as well as to the characterization of polymer bound intermediates by HR-MAS NMR.[18]

TentaGel resins are poly(ethylene glycol) polystyrene graft copolymers consisting of ~30% polystyrene matrix (cross-linked with ~1% divinylbenzene) and of ~70% poly(ethylene glycol). They are available in different types of functional anchor groups (Fig. 2) chargeable up to 0.40–0.60 mmol/g and are well capable of swelling in

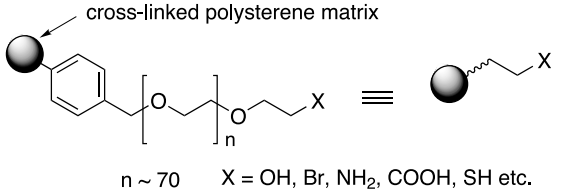


**Figure 2.** Chemical constitution of TentaGel resins.

*Keywords*: Macrocycles; Bisbibenzyls; Solid phase synthesis; TentaGel; HR-MAS NMR.
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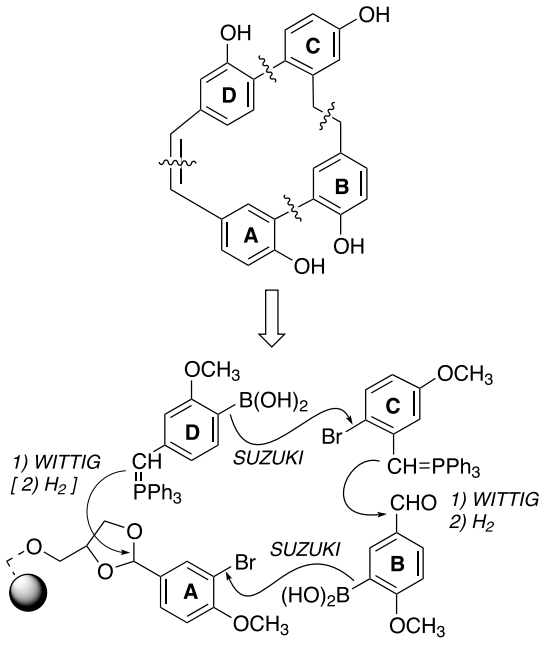



**Scheme 1.** Fragments and strategy for the synthesis of isoplagiochins on solid support.

dichloromethane, chloroform, dioxane, DMF, THF, water, methanol and pyridine (bad, however, in ethanol and diethylether).[15,19]

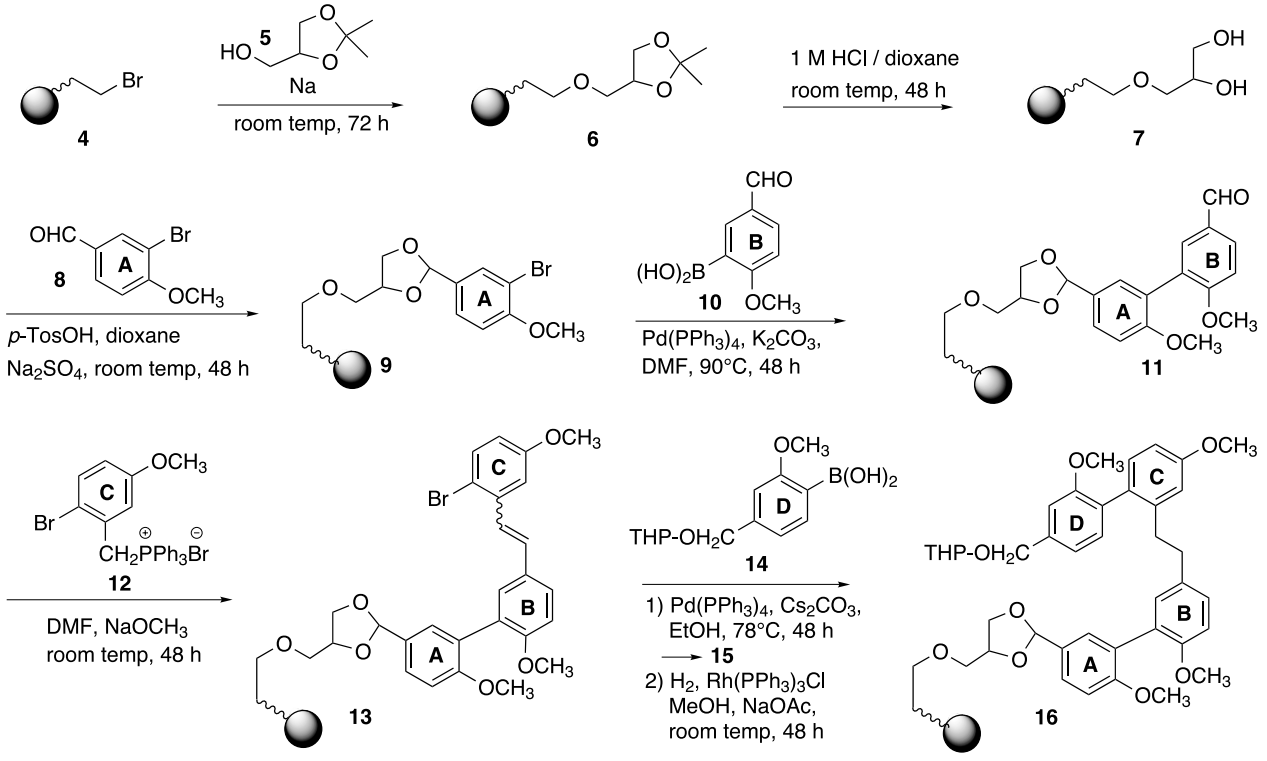
## 2. Results and discussion

Our strategy of synthesis (Scheme 1) was to start with a polymer bound aldehyde fragment **A**. Subsequently, Suzuki, Wittig and hydrogenation protocols should lead to an acyclic polymer bound **A–B–C–D** precursor, which has to be ring-closed after cleavage from the solid support.

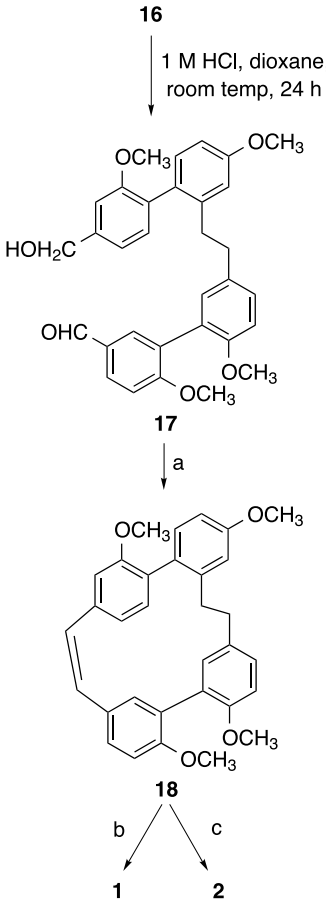
Thus, starting from TentaGel–Br (**4**) with a coverage density of 0.41 mmol/g resin a glycerol linker was introduced according to the procedure of Leznoff (formerly applied for Merrifield type resins)[20] by Williamson-coupling with the 1,3-dioxolane protected glycerol **5** (to **6**) and subsequent acidic hydrolysis to the polymer-bound 1,2-diol **7**. Coupling with the aldehyde **8** by acetal formation yielded the TentaGel linked starting subunit **9** (fragment **A**). Suzuki reaction of the polymer-bound bromoarene **9** with the boronic acid **10**[12] yielded the biaryl dialdehyde **11** (**A–B** fragment) on solid support, which was then reacted with the phosphonium salt **12**[21] (**C** fragment) to the stilbene **13** according to a Wittig protocol. After coupling with the boronic acid **14** (**D** fragment), the double bond in **15** (*E*/*Z*-mixture of isomers) was hydrogenated in presence of a homogeneous Wilkinson catalyst[22] resulting in the TentaGel linked acyclic **A–B–C–D** precursor **16** (Scheme 2).

On acidic hydrolysis of **16** the hydroxyaldehyde **17** was liberated from the solid support (Scheme 3). According to the spectroscopical data the acyclic **A–B–C–D** fragment **17** could be clearly identified as the known precursor for the ring-closing to **18** and completion of the syntheses of isoplagiochins C/D **1** and **2**.[12]

The TentaGel coupled intermediates could be unambiguously characterized by HR-MAS NMR spectroscopy as can be demonstrated for the final polymer bound compound **16** (see Fig. 3, for all intermediates see Supporting information).




**Scheme 2.** Formation of the TentaGel linked acyclic **A–B–C–D** precursor **16**.




**Scheme 3.** Cleavage from the solid support and completion of the synthesis for **1** and **2**. Reagents and conditions:[12,13] (a) (i) $Ph_3PH^+Br^-$, $CH_3CN$, reflux 24 h, 95%;[13] (ii) $NaOCH_3$, $CH_2Cl_2$, rt, 24 h, 82%; (b) $BBr_3$, $CH_2Cl_2$, −70 °C→rt, 48 h, 86%; (c) (i) $H_2$ 3 bar, 5% Pd/C, EtOAc, 88%; (ii) $BBr_3$, $CH_2Cl_2$, −70 °C→rt, 48 h, 82%.

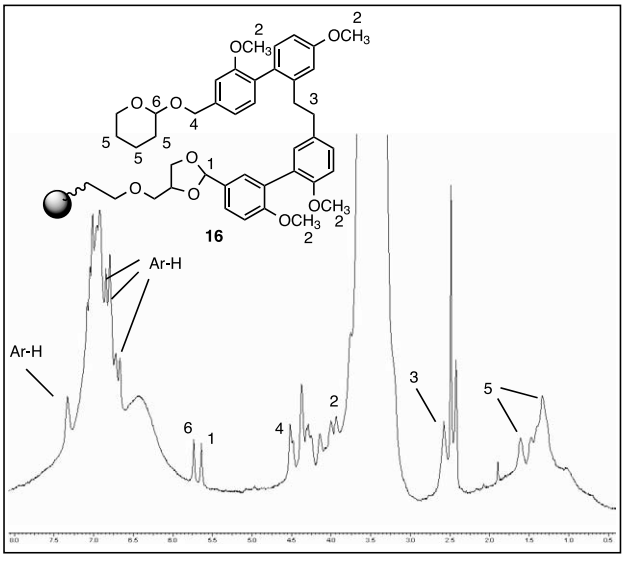
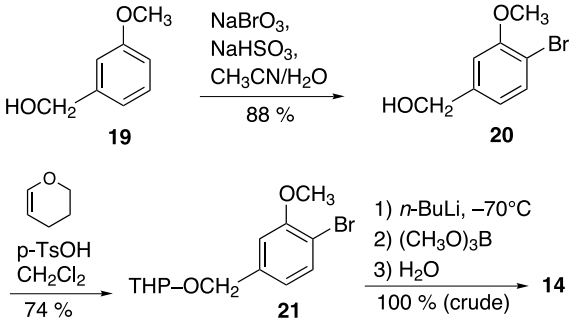



**Figure 3.** HR-MAS $^1H$ NMR spectrum of **16**.

The **D**-fragment **14** was prepared from 4-bromo-3-methoxybenzylalcohol **19** by regioselective bromination, (to **20**), formation of the THP ether **21** and transformation to the corresponding boronic acid (see Scheme 4).




**Scheme 4.** Preparation of the **D**-fragment **14**.

## 3. Conclusion

The multi-step synthesis of the target molecule could be realized with a final charging of about 0.10 mmol/g resin and a 25% overall-yield for **17** after cleavage from the solid support. The intermediates could be directly characterized by HR-MAS NMR spectroscopy. The procedure can be extended to the synthesis of small libraries of differently halogenated derivatives **3**.

## 4. Experimental

### 4.1. General

TentaGel® S–Br (0.41 mmol/g) was purchased from Rapp Polymere, Tübingen, Germany. All reactions with shaking at room temperature (rt) were performed on an IKA® Vibrax VXR basic at 500 rpm. Reactions requiring heating were performed in a Labnet® VorTemp 1550 at 600 rpm. NMR spectra in solution ($CDCl_3$, DMSO-$d_6$) were obtained with a Bruker DRX 500. Chemical shifts ($\delta$) are given in ppm relative to TMS. HR-MAS NMR spectra were obtained with a Bruker DRX 500 using a 4 mm HR-MAS probe. Rotational frequency: $^1H$: 8 kHz, $^{13}C$: 8 kHz. Pulse repetition time: $^1H$: 4 s, $^{13}C$: 2 s. Solvents were commonly dried and purified by conventional methods prior to use. All air- or moisture-sensitive reactions were carried out under an argon atmosphere.

### 4.2. Preparation of the boronic acid 14

**4.2.1. 4-Bromo-3-methoxybenzylalcohol (20).** To a stirred solution of the 3-methoxybenzylalcohol (**19**) (10.0 g, 72.4 mmol, 8.98 mL) in $CH_3CN/H_2O$ 1:1 (500 mL) were added $NaBrO_3$ (19.1 g, 127 mmol) and $NaHSO_3$ (13.2 g, 127 mmol). The reaction was stirred for 1.5 h at rt and continuously monitored by TLC. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ and extracted with $Et_2O$ (3×200 mL). The combined organic layers were washed with aqueous $Na_2CO_3$, $H_2O$, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel/$CHCl_3$ to give a colourless oil; 13.9 g (88%).

$^1$H NMR ($CDCl_3$) $\delta$ (ppm) 7.40 (d, $J=8.8$ Hz, 1H, Ar-H), 7.05 (d, $J=3.1$ Hz, 1H, Ar-H), 6.70 (dd, $J_1=8.8$ Hz, $J_2=3.1$ Hz, 1H, Ar-H), 4.69 (s, 2H, Ar-$CH_2O$), 3.80 (s, 3H, $OCH_3$), 2.14 (br s, 1H, OH).

$^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 159.25, 140.74, 133.14, 144.77, 144.22, 112.50, 64.99, 55.52.

**4.2.2. THP ether 21 of 4-bromo-3-methoxybenzylalcohol.** The benzyl alcohol **20** (13.9 g, 63.9 mmol) was dissolved in anhydrous $CH_2Cl_2$ (250 mL). 3,4-Dihydro-2*H*-pyrane (13.4 g, 160 mmol, 14.6 mL) and toluene-4-sulfonic acid monohydrate (243 mg, 1.28 mmol) were added and the mixture was stirred at rt for 16 h. The solvent was evaporated and the residue was chromatographed on silica gel/$CH_2Cl_2$ to give a yellowish liquid; 14.2 g (74%).

$^1$H NMR ($CDCl_3$) $\delta$ (ppm) 7.41 (d, $J=8.5$ Hz, 1H, Ar-H), 7.09 (d, $J=3.2$ Hz, 1H, Ar-H), 6.70 (dd, $J_1=8.5$ Hz, $J_2=3.2$ Hz, 1H, Ar-H), 4.78 (t, $J=3.5$ Hz, 1H, O–CH–O), 4.78, 4.54 (2d, $J=13.6$ Hz, 2H, Ar-$CH_2O$), 3.96–3.89 (m, 1H, –$CH_2O$), 3.80 (s, 3H, $OCH_3$), 3.60–3.55 (m, 1H, $CH_2O$), 1.95–1.50 (m, 6H, –$(CH_2)_3$–).

$^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 159.06, 138.91, 133.00, 114.65, 114.23, 112.81, 98.43, 68.46, 62.22, 55.46, 30.54, 25.45, 19.36.

**4.2.3. Boronic acid 14.** The aryl bromide **21** (10.0 g, 33.2 mmol) was dissolved in THF (200 mL). *n*-Butyllithium (16.1 mL, 40.2 mmol, 2.5 M in *n*-hexane) was added at −70 °C and the reaction mixture was stirred for 30 min at −70 °C. After addition of trimethyl borate (10.4 g, 99.6 mmol, 11.1 mL) stirring was continued for 1 h while the reaction mixture was allowed to warm up to rt. $H_2O$ (150 mL) was added, the aqueous layer was extracted with $Et_2O$ (3×50 mL) and the combined organic layers were washed with satd aqueous NaCl, dried ($MgSO_4$) and evaporated. For purification, the product was dissolved in $Et_2O$, extracted with 2 M NaOH and neutralized to pH 6–7. The product was extracted with $Et_2O$, dried ($MgSO_4$) and the solvent was evaporated to give the crude boronic acid as a colourless solid; 8.84 g (100%).

$^1$H NMR ($d_6$-DMSO) $\delta$ (ppm) 7.49 (d, $J=8.2$ Hz, 1H, Ar-H), 6.92 (d, $J=2.5$ Hz, 1H, Ar-H), 6.79 (dd, $J_1=8.2$ Hz, $J_2=2.5$ Hz, 1H, Ar-H), 4.80, 4.61 (2d, $J=12.6$ Hz, 2H, Ar-$CH_2O$) 4.65 (t, $J=3.5$ Hz, 1H, O–CH–O), 3.83–3.77 (m, 1H, –$CH_2O$), 3.74 (s, 3H, $OCH_3$), 3.48–3.43 (m, 1H, –$CH_2O$), 1.80–1.40 (comb m, 6H, –$(CH_2)_3$–).

$^{13}$C NMR ($d_6$-DMSO) $\delta$ (ppm) 160.00, 144.55, 135.49, 112.83, 111.10, 97.59, 68.51, 61.21, 54.81, 30.11, 25.03, 19.02.

### 4.3. Preparations on solid support

For the HR-MAS NMR spectra of all polymer-bound intermediates see Supporting information.

**4.3.1. Coupling of TentaGel–S–Br 4 with the hydroxy dioxolane 5.** Sodium (236 mg, 10.3 mmol) was added to 4-hyroxymethyl-2,2-dimethyl-1,3-dioxolane **5** (20 mL) and the mixture was stirred and heated to 60 °C until the sodium had completely dissolved. The solution was cooled to rt and TentaGel–S–Br resin **4** (2.50 g) was added. The mixture was shaken at rt for 3 days and for additional 4 h at 80 °C. The resin was collected by filtration and washed with 1,4-dioxane (3×10 mL), $H_2O$ (6×10 mL), EtOH/$H_2O$ (1:1; 3×10 mL), EtOH (3×10 mL) and dry $Et_2O$ (3×10 mL) to give the pale yellow polymer-bound dioxolane **6** (2.73 g).

**4.3.2. Hydrolysis of the polymer-bound dioxolane 6.** The polymer-bound dioxolane **6** (2.30 g) was suspended in a mixture of 1,4-dioxane/1 M HCl (1:1, 30 mL) and the slurry was shaken for 48 h at rt. The resin was filtered off and washed with $H_2O$ (6×10 mL), acetone (10 mL), EtOH (3×10 mL) and dry $Et_2O$ (3×10 mL) to give the yellow polymer-bound diol **7** (2.30 g).

**4.3.3. Acetalization of the aldehyde 8 with the polymer-bound diol 7.** The diol-modified TentaGel **7** (2.13 g) was suspended in anhydrous 1,4-dioxane (30 mL). 3-Bromo-4-methoxybenzaldehyde **8** (1.61 g, 7.52 mmol), toluene-4-sulfonic acid monohydrate (16.6 mg, 0.09 mmol) and anhydrous $Na_2SO_4$ (2.00 g) were added and the mixture was shaken at rt for 48 h with exclusion of moisture and then shaken for additional 4 h at 80 °C. The resin was filtered off and washed with anhydrous pyridine (2×10 mL), pyridine/$H_2O$ (1:1; 2×10 mL), $H_2O$ (10×10 mL), EtOH (3×10 mL) and dry $Et_2O$ (3×10 mL) to give the pale yellow polymer-bound bromoarene **9** (2.00 g).

**4.3.4. Suzuki-coupling of the boronic acid 10 with the polymer-bound bromo arene 9.** The TentaGel-bound bromo arene **9** (1.80 g) was swelled in DMF (40 mL) for 10 min. To this slurry were added the boronic acid **10** (439 mg, 2.45 mmol), $Pd(PPh_3)_4$ (36.7 mg, 24.5 μmol) and $K_2CO_3$ (169 mg, 1.22 mmol). The mixture was shaken for 48 h at 90 °C under an argon atmosphere. The resin was filtered and washed alternately with DMF/$H_2O$ (4:1, 3×10 mL), followed by MeOH (3×10 mL) and $CH_2Cl_2$ (3×10 mL). The solid was dried in vacuo at rt to give a yellowish brown polymer-bound biarylaldehyde **11** (1.78 g).

**4.3.5. Wittig-reaction between the polymer-bound aldehyde 11 and the phosphonium salt 12.** To a solution of the phosphonium salt **12** (3.55 g, 6.55 mmol) in anhydrous DMF (40 mL) was added $NaOCH_3$ (1.06 g, 19.6 mmol) under argon atmosphere. After shaking for 5 min, the polymer-bound aldehyde (1.77 g) was added to the orange solution. The mixture was shaken at rt for 48 h. Then the resin was filtered and washed alternately with DMF (3×10 mL), DMF/$H_2O$ (1:1, 3×10 mL), $H_2O$ (3×10 mL), followed by MeOH (3×10 mL) and $CH_2Cl_2$ (3×10 mL). The solid was dried in vacuo at rt to give a beige polymer-bound stilbene **13** (1.77 g).

**4.3.6. Suzuki coupling of the boronic acid 14 with the polymer-bound bromide 13.** The polymer-bound bromide **13** (1.18 g) was swelled in EtOH (20 mL). To the mixture was added the boronic acid **14** (606 mg, 2.10 mmol), $Pd(PPh_3)_4$ (24.4 mg, 21.1 μmol) and $Cs_2CO_3$ (339 mg, 1.05 mmol). The mixture was shaken for 48 h at 90 °C under an argon atmosphere. Then the resin was filtered and

washed alternately with EtOH (3×10 mL), DMF/$H_2O$ (1:1, 3×10 mL), $H_2O$ (3×10 mL), followed by MeOH (3×10 mL) and $CH_2Cl_2$ (3×10 mL). The solid was dried in vacuo at rt to give a brown polymer-bound stilbene **15** (1.20 g).

**4.3.7. Catalytic hydrogenation of the stilbene 15.** A two-necked round bottom flask containing the polymer-bound stilbene **15** (713 mg) was evacuated a few times and flushed with argon. After the last evacuation, a hydrogen-atmosphere was adjusted by a balloon. Wilkinson-catalyst $Rh(PPh_3)_3Cl$ (43.5 mg, 47 μmol) and NaOAc (40 mg) were dissolved in MeOH (20 mL) and added by a syringe. The mixture was shaken at rt for 24 h. The resin was filtered and washed alternately with MeOH (3×10 mL) and $CH_2Cl_2$ (3×10 mL). The solid was dried in vacuo at rt to give a brown polymer-bound bibenzyl **16** (700 mg).

**4.3.8. Hydrolytic cleavage from the solid support.** The polymer-bound bibenzyl **16** (633 mg) was swelled in dioxane/3 M HCl (1:1, 20 mL) and shaken at rt for 48 h. The resin was filtered and washed alternately with $H_2O$ (6×5 mL), acetone (1×10 mL), EtOH (3×5 mL) and $Et_2O$ (3×10 mL). The aqueous layer was extracted with $Et_2O$ (3×40 mL), the combined organic layers were washed with $H_2O$ (6×40 mL) and dried ($MgSO_4$). The solvent was evaporated to give the crude bibenzyl (81 mg). Purification by column chromatography ($SiO_2$/$CHCl_3$–EtOAc 3:1) yielded pure **17** as a colourless oil (32 mg, 25% overall for eight steps).

The NMR-spectroscopic data were identical with those reported in the literature:[12]

$^1$H NMR ($CDCl_3$) $\delta$ (ppm) 9.92 (s, 1H, –CHO), 7.86 (dd, $J_1$=8.4 Hz, $J_2$=2.0 Hz, 1H, Ar-H), 7.68 (d, $J$=2.2 Hz, 1H, Ar-H), 7.08 (d, $J$=8.4 Hz, 1H, Ar-H), 7.05 (d, $J$=8.3 Hz, 1H, Ar-H), 7.02 (d, $J$=7.6 Hz, 1H, Ar-H), 6.98 (d, not resolved, 1H, Ar-H), 6.93–6.91 (not resolved, 2H, Ar-H), 6.83 (d, $J$=2.7 Hz, 1H, Ar-H), 6.80 (d, $J$=8.4 Hz, 1H, Ar-H), 6.80 (dd, not resolved, 1H, Ar-H), 6.74 (d, $J$=2.2 Hz, 1H, Ar-H), 4.67 (s, 2H, Ar-$CH_2O$), 3.84 (s, 3H, –$OCH_3$), 3.82 (s, 3H, –$OCH_3$), 3.75 (s, 3H, –$OCH_3$), 3.72 (s, 3H, –$OCH_3$), 2.69 (br s, 4H, –$CH_2CH_2$–), 1.69 (br s, 1H, –OH).

$^{13}$C NMR ($CDCl_3$) $\delta$ (ppm) 191.2, 162.3, 158.9, 157.1, 155.2, 141.8, 141.7, 134.1, 132.6, 131.9, 131.6, 131.3, 131.2, 130.6, 129.6, 129.1, 128.9, 126.2, 118.6, 114.4, 111.1, 110.9, 110.7, 109.1, 65.3, 56.0, 55.8, 55.5, 55.2, 36.3, 36.1.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.048. HR-MAS NMR spectra of all polymer-bound intermediates.

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