Solid-phase combinatorial synthesis of ester-type banana-shaped molecules by sequential palladium-catalyzed carbonylation[†]

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Received (in Cambridge, UK) 27th January 2009, Accepted 26th February 2009 First published as an Advance Article on the web 23rd March 2009 DOI: 10.1039/b901788g

16 five-ring ester-type Br-substituted banana-shaped molecules were synthesized in a combinatorial manner using palladiumcatalyzed carbonylative esterification on a polymer-support and their mesophase behavior was investigated.

Combinatorial chemistry has been exploited in broad area of research fields. Since a split & pool method using a solid-support enables a high speed synthesis of a variety of compounds, such libraries of compounds have been applied to exploration for drugs, catalysts, materials, and so on.^{1,2} We have reported that palladium-catalyzed carbonylation is efficiently performed on solid-phases³ and is utilized for combinatorial syntheses of liquid crystals⁴ as well as natural products, such as macrosphelide.⁵ In this study, Br-substituted banana-shaped molecules **1** that possess four phenol ester linkages were synthesized by way of palladium-catalyzed carbonylative esterification on a polymer-support.

Banana-shaped molecules P-n-O-PIMB (2a) possessing two phenol ester and two imine linkages exhibits ferroelectric and antiferroelectric properties even though it is achiral (Fig. 1).⁶ We have already reported a combinatorial synthesis of banana-shaped molecules 4Br-P-n-O-PIMB (2b), 4Cl-P-n-O-PIMB (2c) and 5Cl-P-n-O-PIMB (2d) having halogen atoms on the phenyl ring in the central core⁷ and unsymmetrical P(m,n)-O-PIMB (3) having flexible alkyl chains with different lengths on both side wings.⁸ Interestingly, the mesomorphic behavior and mesophase structures of the 4Br-P-n-O-PIMB (2b) homologous series differ from those of the parent P-n-O-PIMB (2a) homologues.^{7,9} Recently, it was found that the analogues in which all five benzene rings are connected by ester linkages also exhibit mesophase behavior similarly as 2^{10-12} We became interested in the development of a facile synthetic method for a variety of banana-shaped molecules 1 that have a halogen substituent at the central core, four phenol ester linkages, and alkyl chains with the different lengths at the side wings.13,14

We divided 1 into five fragments A-E as illustrated in Scheme 1. All phenol ester linkages in 1 can be constructed

by palladium-catalyzed carbonylative esterification of aryl iodides B-E with polymer-supported phenols. Aryl iodides can be used as masked activated esters in the presence of a palladium catalyst under a carbon monoxide atmosphere as we previously reported.³ We planned that the fragment A can be added onto a polymer-support via a silvl linker that could be displaced with a halogen atom in the final stage of the synthesis of 1. After acylation of polymer-supported phenol 5 with alkoxyphenyl iodide B by palladium-catalyzed carbonylation, selective deprotection of phenol and carbonylation can be sequentially performed using arvl iodides C, D and E to afford 4. Displacement of the silyl linker in 4 with Br₂ would lead to the desired 1 by electrophilic substitution. According to this strategy, four alkyl chains (C2, C4, C6 and C8) will be independently introduced in the side wings toward the combinatorial synthesis of a 16-member library of 1.

Attachment of resorcinol **A** onto a polymer-support using a silyl linker was investigated (Scheme 2). Direct attachment of **A** to the polymer-support was unsuccessful either by addition of the corresponding lithiated derivative to the polymer-supported chlorosilane¹⁵ or by palladium-catalyzed coupling of aryl bromide with the polymer-supported trialkylsilane.¹⁶ Therefore, the rearrangement of trialkyl(2-bromophenoxy)-silane **7** was carried out. Commercially available PS-DES resin (**6**) was converted to the corresponding silyl triflate, which was treated with phenol **A** to afford **7**.¹⁷ The loading amount of **7** was determined to be 0.5 mmol/g-resin by gravimetric analysis



Fig. 1 Five-ring banana-shaped liquid crystals.

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[†] Electronic supplementary information (ESI) available: Experimental details and ¹H NMR spectra. See DOI: 10.1039/b901788g



Scheme 1 Synthetic strategy for the solid-phase synthesis of a 16-member combinatorial library of banana-shaped molecules 1(m,n) repeatedly utilizing palladium-catalyzed carbonylation of aryl iodides **B**, **C**, **D1–D4** and **E1–E4**.



Scheme 2 Reagents and conditions: (i) (a) TMSCl (0.3 M), CH_2Cl_2 , rt, 1 h (b) TfOH (0.2 M), CH_2Cl_2 , rt, 30 min, (c) A (0.2 M), 2,6-lutidine (0.4 M), CH_2Cl_2 , rt, 12 h; (ii) BuLi (0.3 M), THF, -78 °C, 1.5 h; (iii) (a) CSA (0.1 M), THF–MeOH (2 : 1), rt, 4 h, (b) BzCl (0.2 M), DMAP (0.3 M), CH_2Cl_2 , rt, 4 h, (c) Br₂– CH_2Cl_2 , rt, 30 min.

after acid cleavage. Lithiation of 7 with BuLi at -78 °C induced 1,3-silyl rearrangement to provide the desired polymer-supported trialkylsilylphenol 5.¹⁸ Removal of the THP group, dibenzoylation of the resulting resorcinol with BzCl, and displacement of the silyl group using Br₂ afforded **8** in 96% yield from 7.^{19,20}

The first acylation of polymer-supported phenol **5** by the palladium-catalyzed carbonylation of the fragment **B** was performed using Et₃N/DMAP in the presence of Pd(PPh₃)₄ at 80 °C for 48 h under 30 atm of CO (Scheme 3).³ The THP group in the central core of **9** was selectively removed under mild acidic conditions (PPTS/MeOH/THF, 24 h). The second acylation of **10** by the carbonylation of the fragment **C** was carried out under the same reaction conditions described above. After selective removal of the THP group in **11**, the third acylation of **12** was performed using the fragment **D4** (n = 8) in the same manner to provide four-ring bent core compound **13**. The MEM group in **13** was removed by treatment with 20% TFA–CH₂Cl₂. Benzoylation of **14** with BzCl–DMAP, followed by treatment with Br₂ provided **15** in 84% overall yield.



Scheme 3 Reagents and conditions: (i) **B** (0.3 M), Pd(PPh₃)₄ (0.01 M), NEt₃ (0.4 M), DMAP (0.1 M), CO (30 atm), DMF, 80 °C, 48 h; (ii) CSA (0.1 M), THF–MeOH (2 : 1), rt, 4 h; (iii) C (0.2 M), Pd(PPh₃)₄ (0.01 M), NEt₃ (0.3 M), DMAP (0.1 M), DMF, 48 h; (iv) **D1** (n = 8) (0.2 M), Pd(PPh₃)₄ (0.01 M), NEt₃ (0.3 M), DMAP (0.1 M), DMF, 80 °C, 48 h; (v) 20% TFA–CH₂Cl₂, rt, 3 h; (vi) (a) BzCl (0.2 M), DMAP (0.3 M), CH₂Cl₂, rt, 4 h, (b) Br₂–CH₂Cl₂, rt, 30 min.

Toward the completion of the solid-phase synthesis of 1, acylation of the left wing in 14 by the carbonylative esterification using fragment E1 (m = 2) was investigated (Scheme 4). The reaction was initially attempted under the same reaction conditions described above [Pd(PPh_3)_4/Et_3N/DMAP/DMF, 80 °C, 48 h, CO (30 atm)]. Surprisingly, 1 (2,2) having C₂ chains in the both side wings was obtained after cleavage from the polymer-support (Br₂-CH₂Cl₂). It is conceivable that *trans*-esterification of the initial product 16 with the



Scheme 4 The final step for the solid-phase synthesis of bananashaped molecule 1(2,8) by way of palladium-catalyzed carbonylation. *Reagents and conditions:* (i) E1 (m = 2) (0.2 M), Pd(PPh₃)₄ (0.01 M), NEt₃ (0.3 M), DMAP (0.1 M), CO (30 atm), DMF, 48 h; (ii) Br₂-CH₂Cl₂, rt, 30 min.

acylpalladium intermediate formed from E1 (m = 2) would occur in the presence of base under heating conditions leading to 17. After optimization of the reaction conditions, it was found that the *trans*-esterification was suppressed when the reaction was carried out at room temperature. Ultimately, the desired five-ring bent molecule 1(2,8) was provided in 65% overall yield with 94% selectivity.

On the basis of the above solid-phase synthesis, we constructed a 16-member combinatorial library of ester-type banana-shaped molecules 1 by a split & pool method utilizing radiofrequency tags.²¹ Sixteen MicroKans[™] each containing 30 mg of PS-DES resin (6) were pooled and used together in a single flask in the synthesis of 12. Then, the MicroKans were decoded and split into four parts. The carbonylation of fragment D1-D4 with 12 was performed in four individual autoclaves and the MicroKans were pooled together for washing and drying. After removal of the MEM group in a single flask, the MicroKans were decoded and split into four parts. The carbonylation of E1-E4 was accomplished in four individual autoclaves and the MicroKans were pooled for washing and drying. Finally, the sixteen MicroKans were decoded and were treated with Br₂ in parallel. After purification of the crude products by gel permeation chromatography (GPC), a 16-member library of banana-shaped molecules 1(m,n) (m = 2, 4, 6, 8 and n = 2, 4, 6, 8 were isolated in 41–90% overall yields. The phase transition behaviors of all synthetic compounds 1(m,n)measured on cooling by using a polarized optical microscopy (POM) are summarized in Table 1.

When (m + n) is smaller than 6, the compounds show a direct transition into crystalline phase except $\mathbf{1}(2,6)$ which also does not exhibit a mesophase. In addition, all compounds showing mesomorphic phase sequence exhibit at least one smectic banana phase $(\text{Sm})^{12}$ and a monotropic transition behavior except for $\mathbf{1}(4,4)$ and $\mathbf{1}(6,4)$ which show enantiotropic property. The unsymmetrical effect on the terminal alkyl chains $(m \neq n)$ is so great that it eventually affects not only the transition temperatures but the phase transition behavior. Among homologues with same number of (m + n), the lowering effect of transition temperature for $\mathbf{1}(m \neq n)$ was

Table 1 Phase transition temperature of banana-shaped molecules1(m,n)

$(m,n)^a$	Yield (%)	Phase and phase transition temp./°C
(2,2)	82	Cr•120•Iso
(2,4)	53	Cr•97•Iso
(4,2)	49	Cr•95•Iso
(4,4)	90	$Cr \bullet 59 \bullet Sm \bullet 120 \bullet Iso^{c}$
(2,6)	61	Cr•95•Iso
(6,2)	67	Cr•70•Sm•103•N•104•Iso ^d
(2,8)	65	Cr•85•N•98•Iso ^d
(8,2)	73	$Cr \bullet 90 \bullet N \bullet 97 \bullet Iso^d$
(4,6)	50	$Cr \bullet 69 \bullet Sm \bullet 98 \bullet Iso^d$
(6,4)	49	$Cr \bullet 44 \bullet Sm \bullet 98 \bullet Iso^{c}$
$(6,6)^{b}$	85	$Cr \bullet 94 \bullet Sm \bullet 95 \bullet Iso^d$
(4,8)	61	$Cr \bullet 63 \bullet Sm \bullet 70 \bullet Iso^d$
(8,4)	63	$Cr \bullet 55 \bullet Sm \bullet 83 \bullet Iso^d$
(6,8)	53	$Cr \bullet 62 \bullet Sm \bullet 73 \bullet N \bullet 81 \bullet Iso^d$
(8,6)	41	Cr•65•Sm2•71•Sm1•73•N•80•Iso ^d
$(8,8)^{b}$	78	$Cr \bullet 69 \bullet N \bullet 83 \bullet Iso^d$

^{*a*} The *m* and *n* indicate number of carbons in the terminal alkyl chains. ^{*b*} Ref. 14. ^{*c*} Enantiotropic. ^{*d*} Monotropic.

significant when compared with symmetric 1(m = n). More interestingly, it has been found that for the compounds with a big difference between *m* and *n*, for example (8,2), (2,8) and (6,2), an additional nematic phase (N) could be derived over the smectic range. In addition to the report that a nematic phase could be obtained by an increase of bending angle,²² this clearly indicates that the appearance of a nematic phase for bent-shaped molecules can also be achieved by a significant unsymmetrical effect in the length of the terminal alkyl moieties.

In summary, we have demonstrated the rapid synthesis of a 16-member combinatorial library of ester-type Br-substituted banana-shaped molecules **1** utilizing palladium-catalyzed carbonylation on a polymer-support and preliminary results on their mesophase behavior. This synthetic method can apply to the introduction of a halogen atom in the central core and modification of the side wings including alkyl chain lengths in both sides, individually. We are currently investigating the properties of the library **1**.

This work was supported by Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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