A Method for the Synthesis of 3a-Aryl-Substituted Cyclopenta[1,2-*b*]furan Derivatives

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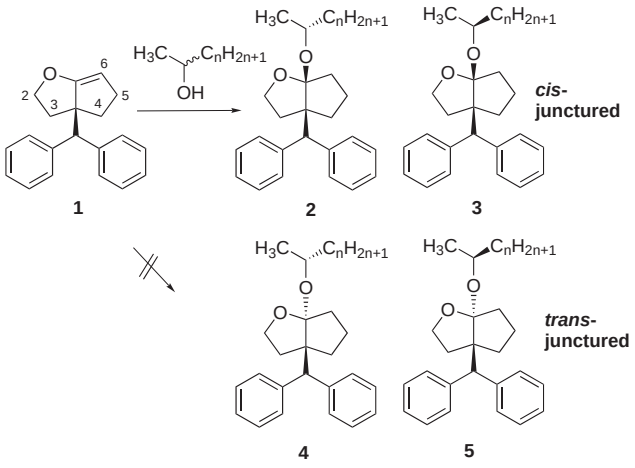
Abstract: An alternative method for the synthesis of cyclopenta[1,2-*b*]furan (CPF) derivatives, which show promise as chiral resolving agents, was developed. Various CPF derivatives, aryl-substituted at the 3a-position, can be synthesized via Suzuki–Miyaura coupling reaction.

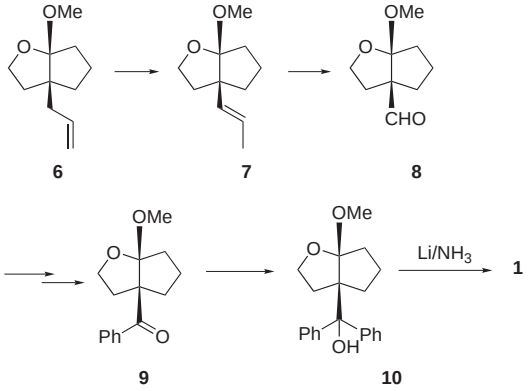
Key words: cyclopenta[1,2-*b*]furan, chiral resolution, divergent synthesis, secondary alcohols, acetals

Optically pure secondary alcohols are important components in the production of pharmaceuticals, perfumes, displays of electronics, and synthetic intermediates.[1] We have described the preparation of a diastereomeric mixture of the *cis*-fused acetals **2** and **3** produced from a dl-2-alkanol and 3a-benzhydryl-2,3,4,5,3a-pentahydrocyclopenta[1,2-*b*]furan (**1**, CPF-Bzh) in the presence of a catalytic amount of an acid (Scheme 1).[2] The facile separation of **2** and **3** by silica gel column chromatography demonstrated that **1** can act as an efficient chiral resolving agent[3] for 2-alkanols. Such stereospecific control of the acetal carbon[4] affords an easy and practical separation process.



Scheme 1 Previously reported reaction of 1 with 2-alkanols.

To the best of our knowledge, the formation of *trans*-fused diastereomers **4** and **5** has yet to be observed. Not even trace amounts of *trans*-fused diastereomer have been detected for the synthetic intermediates **6**–**10** (Scheme 2).[4] It is reasonable to assume, therefore, this stereospecific controlled *cis*-fused relative stereochemistry strongly depends upon cyclopenta[1,2-*b*]furan (CPF) framework, rather than the nature of the 3a-side chain. Accordingly, CPF derivatives with different side chains can serve as efficient and perhaps unique chiral resolving agents.



Scheme 2 Previously reported synthetic route of **1**.

Several problems are associated with the previous synthetic route for **1**. First, the transformation from **6** to **1** requires numerous steps. Secondary, the allyl group of **6**, which was introduced for the convenience of palladium-catalyzed reaction from **12** to **13**,[5] limits the introduction of various side chains in place of allyl group (Scheme 3).

Herein, we report an alternative method for the divergent synthesis of CPF derivatives (Scheme 4). Nucleophilic addition of 4-bromophenyllithium to cyclopentanone at –78 °C for 4 hours, followed by dehydration of the resulting tertiary alcohol with *p*-toluenesulfonic acid gave **14** in 77% yield. Treatment of **14** with hydrogen peroxide and formic acid in well-stirred benzene–water at 35 °C for 4 hours gave **15** in 45% yield. The conditions for these two reactions were based on the reported procedures for 2-phenylcyclopenta-1-one.[5] Attempts to alkylate the enolate from **15** included the use of lithium-, sodium-, potassium hexamethyl disilazide, lithium diisopropylamide, and sodium hydride as the base. These reactions, however, resulted in the formation of unidentified products; moreover, compound **15** was not quantitatively recovered. Subsequently, the successful alkylation of **15** involved the

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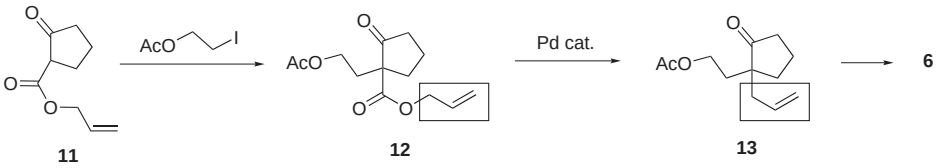
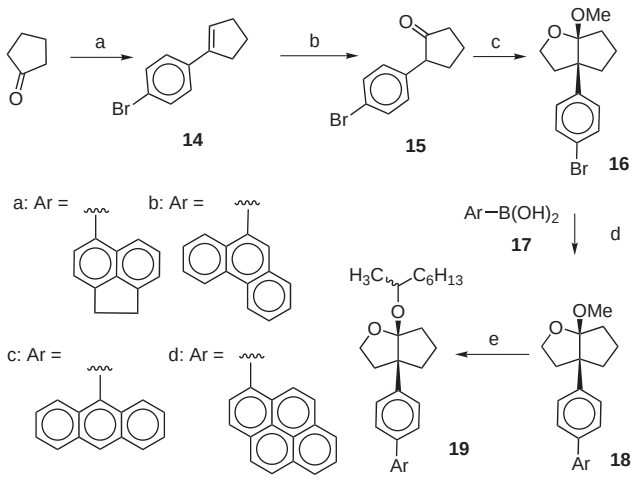


Scheme 3 Previously reported preparation of **6** having CPF framework.

use of 2-bromoethyl acetate with sodium hydroxide and tetrabutylammonium iodide in refluxing and vigorously stirred biphasic benzene–water solution. Formation of a carbon–carbon bond occurred only at the benzylic position probably because the pK_a value of **15** at the benzylic methyne is expected to be lower than at the opposite side of methylene. Finally, the crude mixture was treated with *p*-toluenesulfonic acid in methanol to give a desired CPF derivative **16** (55% overall yield from **15**).



Scheme 4 An alternative method for the synthesis of CPF derivatives **18**. *Reagents and conditions*: a) 4-BrC_6H_4Li in THF, –78 °C to r.t., 4 h; *p*-TsOH in benzene, reflux, 3.5 h; b) H_2O_2–HCO_2H, 35 °C, 4 h; c) $BrCH_2CH_2OAc/Bu_4NI/NaOH$, in benzene–$H_2O$, reflux, 6 h; *p*-TsOH in MeOH, reflux, 5 h; d) $Pd(OAc)_2/Na_2CO_3/PPh_3$ in PrOH–H_2O, reflux, 5 h; e) 2-octanol (2 equiv) in toluene at reflux, PPTS, 3 h.

In our synthetic scheme, bromide **16** serves as the diverging intermediate for the synthesis of **18** with various aryl groups. Accordingly, the synthesis of compounds **18a**–**d** were carried out using the corresponding arylboronic acids **17a**–**d** via Suzuki–Miyaura coupling reaction.[6] Details of a typical experimental procedure are as follows: a mixture of **16** (2.00 g, 6.53 mmol), **17b** (1.90 g, 8.49 mmol), palladium acetate (15 mg, 0.065 mmol), triphenylphosphine (52 mg, 0.198 mmol), and sodium carbonate (8 mL of a 2 M solution in H_2O, 9.43 mmol) in propanol (25 mL) was refluxed with stirring for 5 hours. The resulting mixture was poured into water (50 mL), then extracted with diethyl ether (3×15 mL). The combined organic layers were washed with water, brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 9:1) to give **18b** as a colorless solid (2.00 g, 4.96 mmol, 76% yield).

To assess its ability as a chiral resolving agent, **18**[7] was converted into a mixture of two diastereomers of acetal **19**[8] using 2-octanol. The reaction was carried out in toluene at reflux in the presence of a catalytic amount of pyridinium *p*-toluene sulfonate.

The chemical yields form **17** to **18**, **18** to **19**, and ΔR_f values of **19a**–**d** by silica gel thin layer chromatography[9] are listed in Table 1. For comparison, the ΔR_f value of a mixture of diastereomers, 1a-(2-octyloxyl)-substituted acetals, which were prepared from **1**, **6**, **7** and **16**, are also included. Among the derivatives, three show improved efficiencies as chiral resolving agents in comparison to **1** (entries 2–4).

Table 1 The ΔR_f Value of **19** Eluted with Hexane–Toluene (1:1), Chemical Yields from **17** to **18**, and from **18** to **19**

Entry	Acetal	Yield from **17** to **18** (%)	Yield from **18** to **19** (%)	ΔR_f of two diastereomeric acetals **19**
1	**18a**	74	68	0.083
2	**18b**	76	67	0.121
3	**18c**	37	76	0.110
4	**18d**	65	72	0.113
5	**1**	–	–	0.099
6	**6**	–	–	0.100
7	**7**	–	–	0.100
8	**16**	–	–	0.000

In conclusion, an alternative route for the synthesis of CPF derivatives bearing 3a-aryl substituent[10] was developed. Consequently, several new CPF derivatives, which show promise as chiral resolving agents, were synthesized. Additional divergent syntheses of various CPF derivatives and their evaluation are currently underway.

Acknowledgment

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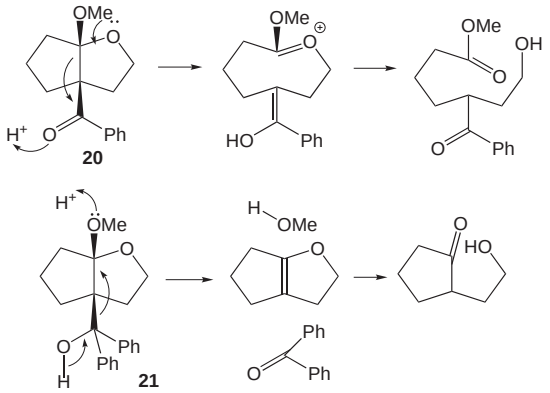
(7) We did not carry out the transformation reaction from **18** to the corresponding alkenyl ethers for the following reasons. 1) In a cooperative work with Zeon Corporation, exhaustive optimizations in industrial-scale were carried out for alcohol exchange reaction of acetal **6** and various dl-secondary alcohols. As a result, several dl-alcohols were converted to the corresponding diastereomers in excellent yields with high cost performance. Thus, priority of the optimization of acetal exchange reaction in laboratory scale is low. 2) We attempted the transformation reaction from **20** or **21** to the corresponding alkenyl ethers, and the carbon–carbon bond cleavage reactions were observed as shown in the following scheme. Conversely, we consider that possibility of such cleavage reactions for **18a**–**d** is very low (Scheme 5).



Scheme 5

(8) In the case of **2** and **3** (CPF-Bzh derivatives of 2-alkanols), the absolute configuration of the 2-alkoxy position can be empirically determined by the chemical shift of benzylic position, which appears around at δ = 4.5–4.6 ppm as a clear singlet in ^{1}H NMR and around at δ = 60–71 ppm in ^{13}C NMR. In contrast, no such peak was observed in ^{1}H NMR and ^{13}C NMR of **19**.

(9) TLC used in all the experimental was obtained from Merck (1.05715.0009, silica gel 60F254).

(10) Data of four CPF derivatives synthesized by Suzuki–Miyaura coupling reaction and their synthetic intermediates are as following.
Compound **14**: colorless crystals; mp 94–95 °C (hexane). FT-IR (KBr): 3053, 2953, 2843, 1902, 1619, 1585, 1486 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 6.17 (s, 1 H), 2.68–2.63 (m, 2 H), 2.53–2.48 (m, 2 H), 2.01 (td, *J* = 14.8, 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3 (C), 135.7 (C), 131.2 (2 × CH), 127.1 (2 × CH), 127.0 (CH), 120.5 (C), 33.5 (CH_2), 33.2 (CH_2), 23.4 (CH_2). HRMS (EI): *m/z* calcd for $C_{11}H_{11}Br$ [M$^+$]: 222.0044; found: 222.0060. Anal. Calcd for $C_{11}H_{11}Br$: C, 59.22; H, 4.97. Found: C, 58.91; H, 4.94.
Compound **15**: colorless oil. FT-IR (KBr): 3029, 2966, 2876, 1899, 1741, 1589, 1488, 1402 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 3.26 (dd, *J* = 11.4, 8.0 Hz, 1 H), 2.51–2.42 (m, 2 H), 2.31–2.21 (m, 1 H), 2.18–2.10 (m, 1 H), 2.08–2.00 (m, 1 H), 1.95–1.85 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.0 (C), 137.1 (C), 131.5 (2 × CH), 129.7 (2 × CH), 120.7 (C), 54.6 (CH), 38.2 (CH_2), 31.4 (CH_2), 20.8 (CH_2). HRMS (EI): *m/z* calcd for $C_{11}H_{11}BrO$ [M$^+$]: 237.9993; found: 237.9996.
Compound **16**: colorless crystals; mp 48–49 °C (hexane). FTIR (KBr, $CHCl_3$): 2955, 2829, 1489, 1316 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 4.05 (t, *J* = 7.2 Hz, 2 H), 3.20 (s, 3 H), 2.49–2.42 (m, 1 H), 2.29–2.22 (m, 2 H), 1.98–1.89 (m, 3 H), 1.83–1.76 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4 (C), 130.8 (2 × CH), 129.1 (2 × CH), 119.8 (C), 118.1 (C), 66.2 (CH_2), 58.6 (C), 50.9 (CH_3), 40.3 (CH_2), 38.1 (CH_2), 34.3 (CH_2), 21.4 (CH_2). HRMS (EI): *m/z* calcd for $C_{14}H_{17}BrO_2$ [M$^+$]: 296.0412; found: 296.0402. Anal. Calcd for $C_{14}H_{17}BrO_2$: C, 56.58; H, 5.77. Found: C, 56.43; H, 5.67.
Compound **18a**: colorless solid; mp 155–156 °C (EtOAc–hexane). FT-IR (KBr): 3027, 2948, 2880, 2829, 1605, 1515, 1495, 1447, 1426, 1366 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.0 Hz, 1 H), 7.52–7.47 (m, 4 H), 7.41 (d, *J* = 7.2 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 12.4 Hz, 1 H), 7.29 (d, *J* = 12.4 Hz, 1 H), 4.15–4.06 (m, 2 H), 3.41 (s, 4 H), 3.27 (s, 3 H), 2.62–2.55 (m, 1 H), 2.37–2.27 (m, 2 H), 2.13–1.98 (m, 3 H), 1.94–1.80 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0 (C), 145.3 (C), 143.1 (C), 139.5 (C), 137.4 (C), 135.4 (C), 129.7 (C), 129.1 (2 × CH), 128.5 (CH), 127.8 (CH), 127.2 (2 × CH), 121.0 (C), 119.1 (CH), 118.4 (CH), 66.2 (CH_2), 58.8 (C), 50.9 (CH_3), 40.7 (CH_2), 38.1 (CH_2), 34.4 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 21.5 (CH_2). HRMS (EI): *m/z* calcd for $C_{26}H_{26}O_2$ [M$^+$]: 370.1933; found: 370.1953. Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.29; H, 7.07. Found: C, 84.56; H, 7.21.
Compound **18b**: colorless solid; mp 144–145 °C (EtOAc–hexane). FT-IR (KBr): 2950, 2881, 2828, 2244, 1610, 1510, 1492, 1450, 1317 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 8.0 Hz, 1 H), 8.70 (d, *J* = 8.0 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.68–7.57 (m, 4 H), 7.54–7.47 (m, 5 H), 4.16–4.07 (m, 2 H), 3.29 (s, 3 H), 2.64–2.57 (m, 1 H), 2.39–2.28 (m, 2 H), 2.15–2.00 (m, 3 H), 1.92–1.82 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5 (C), 138.6 (C), 138.1 (C), 131.6 (C), 131.1 (C), 130.6 (C), 129.8 (C), 129.5 (2 × CH), 128.6 (CH), 127.5 (CH), 127.2 (2 × CH), 127.0 (CH), 126.7 (CH), 126.43 (CH), 126.36 (2 × CH), 122.8 (CH), 122.5 (CH), 118.4 (C), 66.3 (CH_2), 58.9 (C), 51.0 (CH_3), 40.7 (CH_2), 38.2 (CH_2), 34.4 (CH_2), 21.5 (CH_2). HRMS (EI): *m/z* calcd for $C_{28}H_{26}O_2$ [M$^+$]: 394.1933; found: 394.1954. Anal. Calcd for $C_{28}H_{26}O_2$: C, 85.25; H, 6.64. Found: C, 85.60; H, 6.85.

Compound **18c**: colorless solid; mp 225–226 °C (EtOAc–hexane). FT-IR (KBr): 3048, 2971, 2886, 2830, 1815, 1621, 1514, 1441, 1412, 1362, 1319 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.0 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 4.21–4.11 (m, 2 H), 3.32 (s, 3 H), 2.71–2.63 (m, 1 H), 2.46–2.40 (m, 1 H), 2.38–2.31 (m, 1 H), 2.22–2.04 (m, 3 H), 2.00–1.85 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 (C), 137.0 (C), 135.9 (C), 131.4 (2 × C), 130.7 (2 × CH), 130.3 (2 × C), 128.2 (2 × CH), 127.2 (2 × CH), 127.0 (2 × CH), 126.4 (CH), 125.1 (2 × CH), 125.0 (2 × CH), 118.5 (C), 66.4 (CH_2), 59.0 (C), 51.0 (CH_3), 41.1 (CH_2), 38.2 (CH_2), 34.7 (CH_2), 21.6 (CH_2). HRMS (EI): *m/z* calcd for $C_{28}H_{26}O_2$ [M^+]: 394.1933; found: 394.1954. Anal. Calcd for $C_{28}H_{26}O_2$: C, 85.25; H, 6.64. Found: C, 85.20; H, 6.77.

Compound **18d**: light yellow crystals; mp 196–197 °C (EtOAc–hexane). FT-IR (KBr): 2955, 2828, 1917, 1796, 1601, 1584, 1520, 1499, 1402 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 9.2 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 8.14 (t, *J* = 8.0 Hz, 2 H), 8.05 (s, 2 H), 8.00–7.95 (m, 3 H), 7.57–7.52 (m, 4 H), 4.16–4.06 (m, 2 H), 3.30 (s, 3 H), 2.64–2.57 (m, 1 H), 2.38–2.28 (m, 2 H), 2.15–2.00 (m, 3 H), 1.93–1.81 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4 (C), 138.5 (C), 137.8 (C), 131.4 (C), 131.0 (C), 130.4 (C), 130.0 (2 × CH), 128.4 (C), 127.6 (CH), 127.4 (CH), 127.28 (3 × CH), 127.26 (CH), 127.24 (C), 125.9 (CH), 125.5 (CH), 124.95 (CH), 124.9 (C), 124.7 (CH), 124.6 (CH), 118.4 (C), 66.3 (CH_2), 58.9 (C), 51.0 (CH_3), 40.7 (CH_2), 38.2 (CH_2), 34.4 (CH_2), 21.5 (CH_2). HRMS (EI): *m/z* calcd for $C_{30}H_{26}O_2$ [M^+]: 418.1933; found: 418.1941. Anal. Calcd for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 85.93; H, 6.37.