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An efficient method for the synthesis of hydrocyclopenta[1,2-*b*]furan with various side chains at 3a-position

Weihui Zhong, Jun Xie, Xian Peng, Tomoyuki Kawamura and Hisao Nemoto*

Division of Pharmaceutical Chemistry, Institution of Health Biosciences, Graduate School of The University of Tokushima, 1-78, Sho-machi, Tokushima 770-8505, Japan

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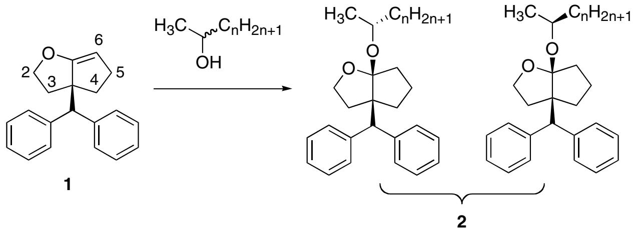
Abstract—(3a*S**,1a*R**)-1a-Methoxy-3a-methoxycarbonyl-2,3,4,5,6,3a-hexahydrocyclopenta[1,2-*b*]furan was prepared in 96% overall yield from 2-methoxycarbonylated cyclopenta-1-one in two steps. This furan derivative is used as a divergent intermediate in the synthesis of our originally designed chiral resolving agents having various substitutions. During the preliminary evaluation of divergent synthetic products, it was discovered that 3a-(fluoren-9-ylidenemethyl)-2,3,4,5,3a-pentahydrocyclopenta[1,2-*b*]furan, was a remarkably improved chiral resolving agent for secondary alcohols.

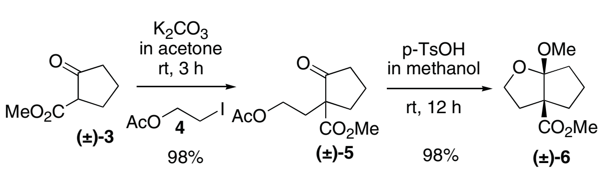
Chiral resolution is one of the major methods[1–4] used to obtain optically active secondary alcohols. The availability of these compounds is important in the production of pharmaceutical products, perfumes, displays of electronics, and various synthetic intermediates.[5] We have reported chiral resolution of *dl*-2-alkanols by using 3a-benzhydryl-2,3,4,5,3a-pentahydrocyclopenta[1,2-*b*]-furan **1** (CPF-Bzh)[6] via a mixture of two (not four) cis-fused diastereomeric acetals[7] **2**, which were easily separated by the usual method of silica gel chromatography (Scheme 1).[8] However, many steps were required for the synthesis of **1**,[8] and three intricate reactions[9] (two of palladium-catalyzed reactions and an ozonolysis) were involved. Furthermore, for the sake of high performance of chiral resolution, there are no grounds for choice of Bzh group. Thus, a novel, more efficient synthetic route should be developed to produce CPF derivatives having various side chains, in order to achieve a highly efficient chiral resolution.



Scheme 1.

We report here, the syntheses of new derivatives **7**–**9** in short steps, and their performance with respect to chiral resolution (Scheme 2). The intermediate **6**, which occurs at the diverging point for the synthesis of various CPF derivatives, was obtained from commercially available material **3** in two steps, so that this synthesis could be easily carried out on a large scale. Alkylation of **4** to **3** with suspended potassium carbonate gave **5** in 98% yield. Treatment of **5** with a catalytic amount of *p*-toluene sulfonic acid (*p*-TsOH) in methanol gave **6** in 98% yield.

Next, we examined transformation reactions in which various substitutions were made at the methoxycarbonyl group of **6**. To simplify the design of compounds that would influence the chiral resolving property through the side chains, we synthesized preliminary compounds



Scheme 2. Rt = room temperature.

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* Corresponding author. Tel./fax: +81 88 633 7284; e-mail: nem@ph.tokushima-u.ac.jp

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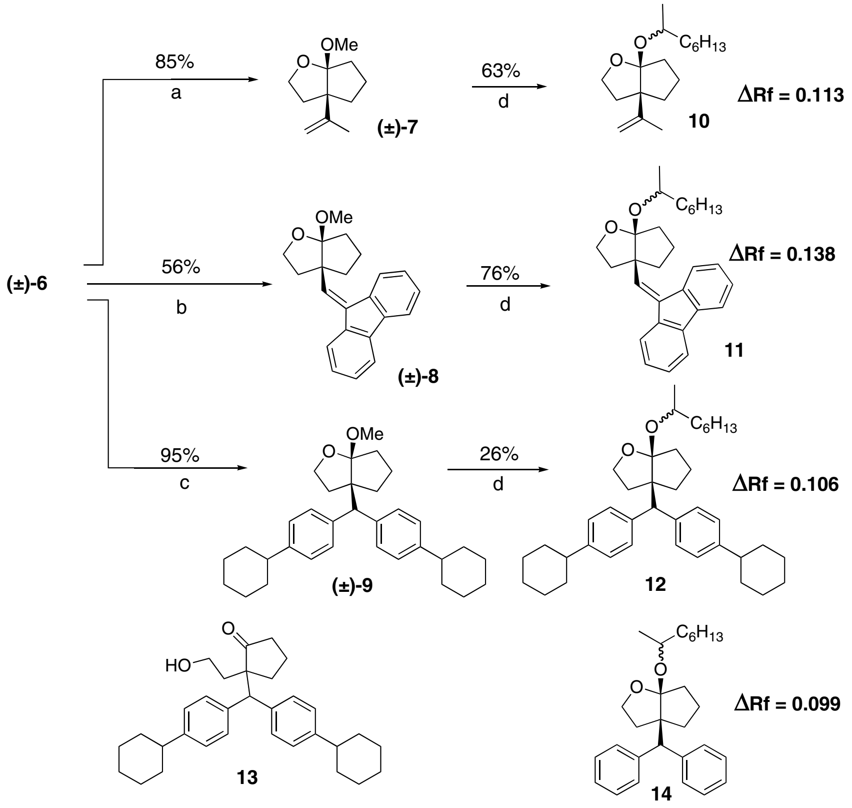


Scheme 3. Reagents and conditions: (a) MeLi in THF, 0 °C, 1 h, methanesulfonyl chloride in pyridine, 0 °C, 1 h; (b) diisobutylaluminium hydride in THF, 2 h, 0 °C, 9-lithiofluorene in THF, 60 °C, 6 h; (c) $6C_6H_5C_6H_5Li$ in THF, 2 h, 0 °C, Li/NH_3, 1 h, Pd/C, H_2 in AcOEt, 1 h; (d) 2-octanol (1.1 equiv), pyridinium *p*-toluenesulfonate in toluene, reflux, 3 h.

having various side chains without an asymmetric center or a geometrical isomer at the double bond (Scheme 3).

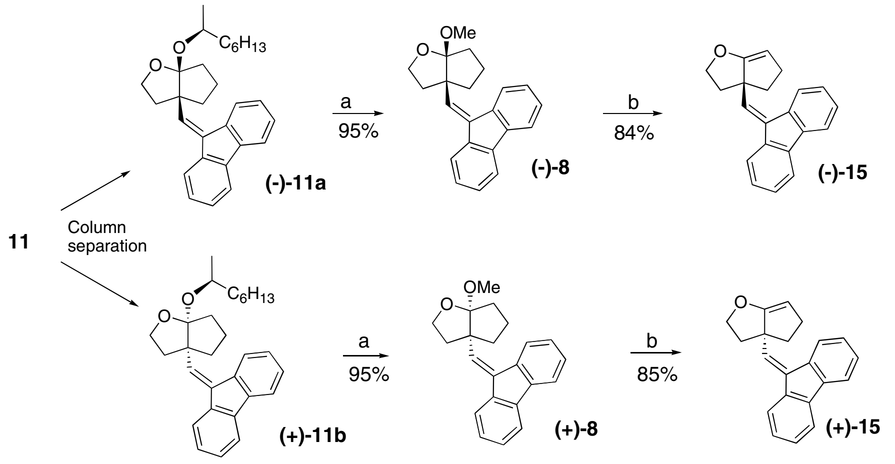
Double alkylations of **6** with methyllithium followed by elimination of the resulting hydroxyl group via mesylate gave **7** in 85% yield. Reduction of **6** with DIBAL-H in THF at −78 °C followed by addition of 9-lithiofluorene to the resulting aldehyde gave **8** in 95% yield. Addition of two 4-phenylphenyllithium to the ester **6** followed by the treatment with Li/NH_3 gave **9** in 56% overall yield from **6**.

Acid-catalyzed alcohol-exchange reactions were examined for their ability to substitute the methoxy group for the 2-octyloxy group of **7**–**9**, and evaluate the properties of the resulting molecules. The corresponding diastereomeric acetals **10** and **11** were obtained from **7** and **8** in toluene in the presence of a catalytic amount of pyridinium 4-toluenesulfonate (PPTS) after reflux for 3 h, giving yields of 63% and 76% yield, respectively (Scheme 3). However, the alcohol exchange reaction gave **12** from **9** in low yield along with several unidentified byproducts including probably keto alcohol **14**. This occurred even though many conditions were attempted at varying temperatures, acid catalysts, solvents, and so on, probably because of steric hindrance due to the side chain. The ΔR_f values of the obtained diastereomers on silica gel thin-layer chromatography (TLC)[10] are appended in Scheme 3. Fortunately, in spite of the preliminary survey, the ΔR_f value of newly synthesized compounds **10**, **11**, and **12** (0.113, 0.138, and 0.106, respectively) were larger than the previously reported ΔR_f value of **13** (0.099).[8] This indicates a possibility that additional improved chiral resolving agents[11] may be discovered via the divergent intermediate **6**.

Since the largest ΔR_f value among all the compounds examined was recorded by using **8**, optically active **15** was prepared to examine the ΔR_f value of a diastereomeric acetal with various secondary alcohols (Scheme 4). The diastereomeric mixture of acetal **11** prepared from (−)-2*R*-octanol and (±)-**8**, was separated by silica gel column chromatography. The less polar compound (−)-**11a** ($[\alpha]_D^{20}$ −59.1, *c* 1.50, $CHCl_3$) was transformed to (−)-**8** ($[\alpha]_D^{20}$ −42.1, *c* 0.247, $CHCl_3$) with methanol in the presence of a catalytic amount of PPTS. The acetal (−)-**8** was converted to the alkenyl ether (−)-**15** ($[\alpha]_D^{20}$ −9.5, *c* 0.647, $CHCl_3$) with acetyl chloride, followed by treatment with triethylamine[8] in 84% yield. Transformation of the corresponding enantiomer from (−)-**11b** ($[\alpha]_D^{20}$ +0.8, *c* 1.44, $CHCl_3$) to (+)-**15** ($[\alpha]_D^{20}$ +9.5, *c* 0.962, $CHCl_3$) was also carried out by the same procedure.

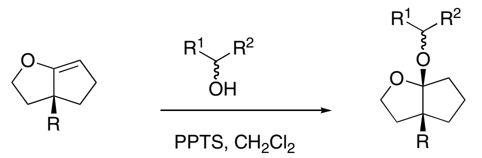
A survey of the chiral resolving property of (−)-**15** is shown in Table 1 and compared with that of ordinary alkenyl ether (−)-**1**.

All of the ΔR_f values obtained from a mixture of two diastereomers **17**, which were derived from **15** and 2-alk-



Scheme 4. Reagents and conditions: (a) *p*-TsOH in methanol, rt, 1 h; (b) AcCl in $CHCl_3$, rt, 20 h, Et_3N in CH_2Cl_2, reflux, 2 h.

Table 1. ΔR_f values of two diastereomers on TLC[8]



(-)-1: R = benzhydryl
(-)-15: R = fluoren-9-ylidenemethyl

16: R = benzhydryl
17: R = fluoren-9-ylidenemethyl

Entry	Secondary alcohol ($R^1CH(OH)R^2$)		ΔR_f of **16**	ΔR_f of **17**
	R^1	R^2		
1	CH_3	C_3H_7	0.045	0.053
2	CH_3	C_4H_9	0.082	0.090
3	CH_3	C_5H_{11}	0.091	0.111
4	CH_3	C_9H_{19}	0.147	0.156
5	CH_3	$C_{13}H_{27}$	0.153	0.168
6	β-Naphthyl	C_3H_7	0.000	0.050
7	C_6H_5	$(CH_2)_3CO_2Me$	0.000	0.050

Eluent: hexane–toluene = 1:1 (entries 1–6).
Eluent: hexane–ethyl acetate = 5:1 (entry 7).

anols (entries 1–5 and appended value in Scheme 3 for 2-octanol) were larger than the corresponding **16** obtained from **1**. We next have examined certain secondary alcohols bearing an aromatic ring. By using **1**, only one spot was observed on TLC (entries 6 and 7). In contrast, by using **15**, two distinct spots corresponding to the diastereomers were clearly observed on TLC.

In conclusion, we have developed a more efficient route for the synthesis of CPF derivatives via **6**, and a promising new CPF derivative **15**, and this method has a remarkably improved chiral resolving property.[11] We are now in a position to carry out further divergent syntheses of various CPF derivatives and evaluate their properties.

Acknowledgments

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Supplementary data

All the detailed descriptions of experimental procedures, full characterization of compounds, and determination of absolute configuration of (−)-**15** and (+)-**15**. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.164.

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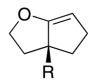
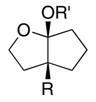
6. In this paper, 'CPF derivative' indicates both 3a-*R*-2,3,4,5,3a-pentahydrocyclopenta[1,2-*b*]furan (alkenyl ether form, CPF-*R*), and 3a-*R*-5a-OR′-perhydrocyclopenta[1,2-*b*]furan (acetal form, *R*′O-CPF-*R*).


CPF-R


R'O-CPF-R

7. Chiral resolution of *dl*-alcohol via diastereomeric esters has been a major method. An example via esters: Kasai, Y.; Naito, J.; Kuwahara, S.; Watanabe, M.; Ichikawa, A.;

Harada, N. *J. Synth. Org. Chem., Jpn. (Yuuki Gousei Kagaku Kyoukai-shi, Special Issue in Eng.)* **2004**, *62*, 1114–1127; A rare example via acetal: Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron Lett.* **1982**, *23*, 1921–1924.

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9. The intermediate, ozonide, is an explosive chemical, and has very low energical efficiency for the generation of ozone gas. Therefore, ozonolysis is very unsuitable step for the industrial scale. In the cases of palladium-catalyzed reactions, recovery of expensive transition-metal is often required for economical reason.
10. TLC used in all the experimental was obtained from Merck (1.05715.0009, Silica gel 60F254).
11. Our chiral resolving method has been carried out in Zeon Corporation and separation of several hundred kilograms of diastereomers has been demonstrated even when non-polar solvents were used. During the industrial scale work, we observed that ΔR_f value of TLC correlates closely with practical separating efficiency.