

Highly efficient chiral resolution and determination of absolute configuration of 2-alkanols by using a cyclopenta[*b*]furan derivative[☆]

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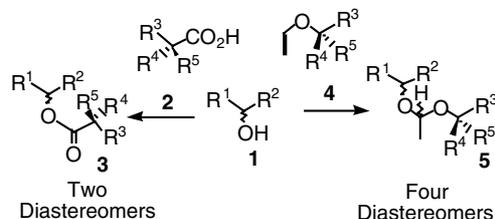
Received 8 November 2003; revised 15 December 2003; accepted 18 December 2003

Abstract—The reaction of 3a-benzhydryl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan and various 2-alkanols in the presence of a catalytic amount of pyridinium 4-toluenesulfonate in dichloromethane gave 3a-benzhydryl-6a-(1-methyl-alkoxy)-hexahydrocyclopenta[*b*]furan in more than 90% chemical yields. The resulting diastereomeric mixture is easily separable on silica gel chromatography because of the large ΔR_f value (briefly 0.1). Absolute configuration of the 2-alkanols can be easily estimated by the chemical shifts of ¹H and ¹³C NMR of methyne group of the benzhydryl moiety.

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One of the most efficient methods of resolving an enantiomeric mixture of amines or acids is by recrystallization as their diastereomeric salts using an optically pure counterpart.¹

However, such routes are not available in the resolution of alcohols, and therefore alcohols (e.g., **1**) are often derivatized with an optically active acyl compound (e.g., **2**) to prepare a diastereomeric mixture of esters (e.g., **3**),



Scheme 1.

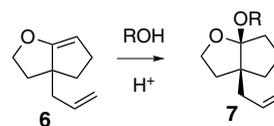
Keywords: Chiral resolution; Acetal; Thin layer chromatography; Alkenyl ether.

[☆] Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.12.104

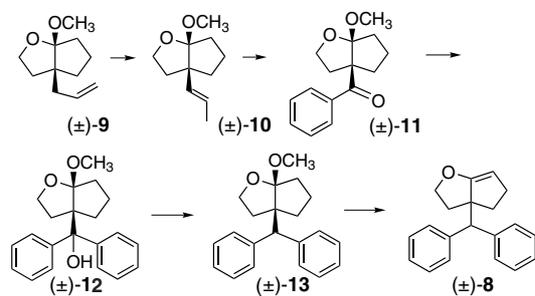
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which is then resolved by recrystallization or chromatography (Scheme 1).^{1,2} An alternate approach to resolve chiral alcohols is by the formation of acetals (e.g., **5**) with chiral *alkenyl ethers* (e.g., **4**); however, this method has not been widely reported.³ One of the serious problems of this method is the lack of control of the stereochemistry of the newly formed acetal **5**; separation by recrystallization or chromatography of the *four* diastereomers of **5** is impractical. However, if the newly formed acetal carbon could be stereospecifically controlled, alkenyl ethers could prove to be useful chiral resolving agents, since the protection/deprotection reactions often proceed in excellent yields and under mild acidic conditions.⁴

We have previously reported on the stereospecific transformation of tetrahydrocyclopenta[*b*]furan **6** to *cis*-hexahydrocyclopenta[*b*]furan **7** (Scheme 2).⁵ This stereospecificity was strongly supported by experimental measurements of their heat of formations; with a



Scheme 2.

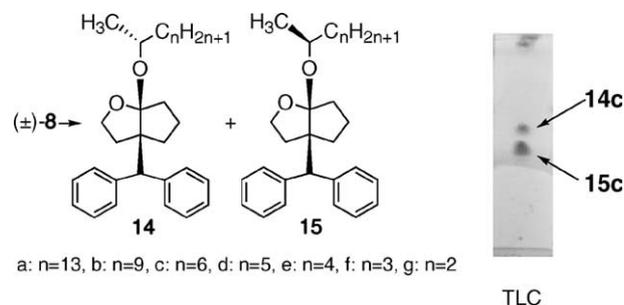


Scheme 3.

difference of 6.21 kcal/mol, *cis*-[3.3.0]bicyclooctane was more stable than the corresponding *trans*-isomer.⁶

Herein, we report on an efficient chiral resolution of 2-alkanols using a novel alkenyl ether derivative of tetrahydrocyclopenta[*b*]furan **8**. The synthesis of racemic (\pm)-**8** from (\pm)-**9**⁵ is shown in Scheme 3. Acetal (\pm)-**9** was refluxed in benzene in the presence of a catalytic amount of PdCl₂(C₆H₅CN)₂⁷ to afford corresponding disubstituted olefin **10** in 80% isolated yield. Alkene **10** was then treated with ozone, followed by the addition of dimethyl sulfide to yield the corresponding aldehyde, which was subsequently used without further purification. 1,2-Addition of phenylmagnesium bromide to the aldehyde, followed by oxidation of the resulting secondary alcohol using pyridinium dichromate, afforded ketone **11** in 45% overall yield from **9**. An addition reaction between phenylmagnesium bromide and ketone **11** afforded *tert*-alcohol **12** in 79% yield, which was treated with lithium metal in ammonia to yield diphenylmethane derivative (\pm)-**13** in 78% yield. Acetal (\pm)-**13** was transformed to alkenyl ether (\pm)-**8** in 82% yield using similar reaction conditions as for compound **6**.⁵

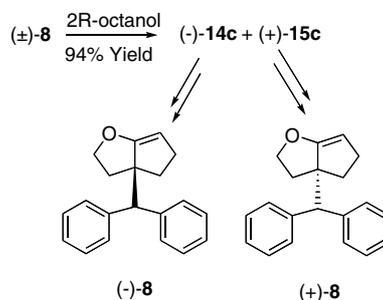
Consequently, using newly synthesized (\pm)-**8**, we embarked upon studies of the protection reactions of 2-alkanols (Scheme 4). Typically, the reactions were carried out in dichloromethane at room temperature, and in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). During the silica gel thin layer chromatography (TLC)⁸ identification procedures using hexane/toluene⁹ (3:2) as the eluent, ΔR_f value of 0.1 between **14c** and **15c** (obtained from 2-octanol) was observed. We were surprised at the relatively large ΔR_f



Scheme 4.

value since the 2-hexyl moiety has neither π -orbital nor polar groups, which were presumably essential for efficient separation.¹ To further determine whether similarly efficient separation can be obtained from other 2-alkanols, we undertook a TLC study of a series of **14** and **15**. Distinctive features of the chemical shifts of **14** and **15** were also noted, and as shown in Table 1, the following relationships were observed: (1) the longer the carbon chain length, the greater the ΔR_f value, (2)¹⁰ the singlet peak of HCPH₂ of **14** always appears in lower field than the corresponding peak of **15** does in ¹H NMR, and (3)¹⁰ peak of HCPH₂ of **14** always appears in higher field than the corresponding peak of **15** does in ¹³C NMR. It is important to note that the HCPH₂ and HCPH₂ NMR signals appeared away from other potentially interfering peaks, thus providing a facile method to observe the differences.¹¹

Since ΔR_f between (\pm)-**14c** and (\pm)-**15c** are large enough, and (*R*)-2-octanol is commercially available, it is obvious



Scheme 5.

Table 1. ΔR_f values and the differences of typical distinctive feature of chemical shift between **14** and **15**

Acetals	<i>n</i> ^a	ΔR_f	Eluent ^b	¹ H NMR ^c (14/15)	¹³ C NMR ^d (14/15)
14a/15a	13	0.153	120/100	4.57/4.55	69.4/70.6
14b/15b	9	0.147	125/100	4.57/4.55	69.3/70.6
14c/15c	6	0.099	150/100	4.57/4.55	69.3/70.6
14d/15d	5	0.091	175/100	4.57/4.55	69.4/70.6
14e/15e	4	0.082	200/100	4.57/4.55	69.3/70.6
14f/15f	3	0.045	200/100	4.57/4.55	69.1/70.4
14g/15g	2	0.000	200/100	ND ^e	ND ^e

^a *n* of R¹ = C_{*n*}H_{2*n*+1}.

^b Eluent = hexane/toluene.

^c Chemical shift of HCPH₂.

^d Chemical shift of HCPH₂.

^e Not determined.

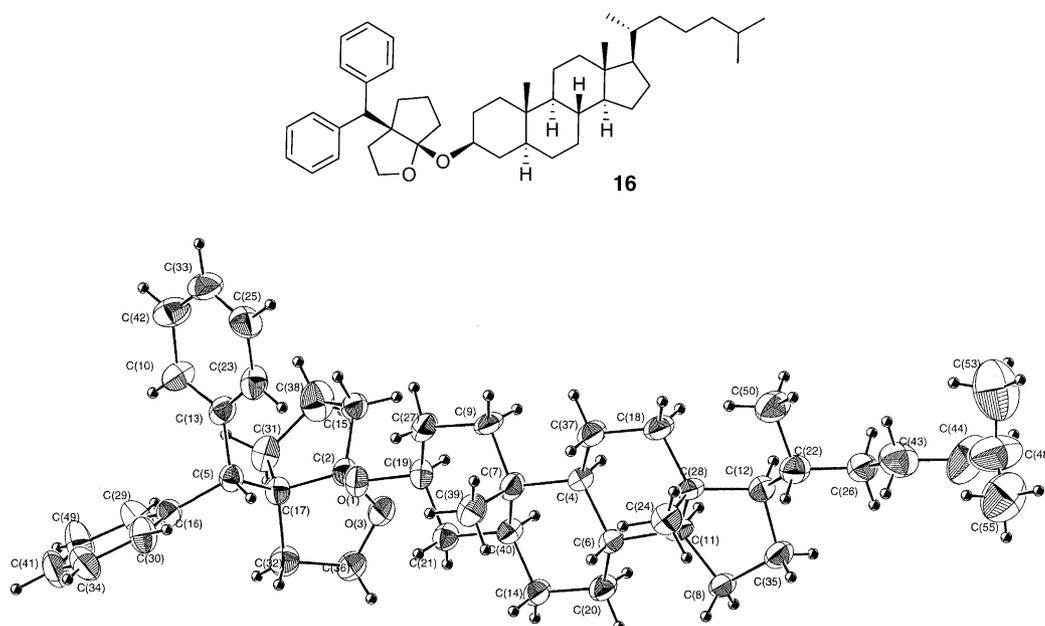


Figure 1.

that (\pm)-**8** can be practically resolved by (*R*)-2-octanol. Thus we prepared (+)-**8** and (–)-**8** as shown in Scheme 5. The reaction of (\pm)-**8** and (*R*)-2-octanol yielded a diastereomeric mixture of (–)-**14c** ($[\alpha]_D^{25} -153^\circ$) and (+)-**15c** ($[\alpha]_D^{25} +119^\circ$) in 94% combined yield with 1:1 molar ratio, which were easily separated using silica gel column chromatography. Transformation of (–)-**14c** was carried out in methanol in the presence of a catalytic amount of PPTS in to yield (–)-**13** ($[\alpha]_D^{25} -208^\circ$ (*c* 0.80, CHCl_3)) in 82% yield, along with the quantitative recovery of (*R*)-2-octanol. Transformation of acetal (–)-**13** to (–)-**8** ($[\alpha]_D^{25} -142^\circ$ (*c* 0.138, benzene)) was carried out in the same manner as (\pm)-**13** to (\pm)-**8**. Similarly, (+)-**8** ($[\alpha]_D^{25} +142^\circ$ (*c* 0.138, benzene)) was obtained from (+)-**15c**.

The absolute configuration at the *cis*-junction of the tetrahydrocyclopenta[*b*]furan skeleton was determined using X-ray analysis of **16**, which was synthesized from (+)-**15c** and cholestanol¹² (Fig. 1). The results proved that (+)-**8** and (–)-**8** correspond to the (*S*)- and (*R*)-configurations, respectively. Using *R*-(–)-**8**, TLC of the (*R*)-2-alkanol derivatives was reproducibly observed higher than the (*S*)-2-alkanol derivatives.

All the acetals that are described herein were shown to be adequately stable under conditions of silica gel column chromatography. The protection/deprotection reactions of 2-alkanol adducts of **8** proceeded in excellent yields under mild acidic conditions. The stability under silica gel column chromatographic conditions and mildness of the protection/deprotection reactions were identical to those of ethyl vinyl ether or dihydrofuran,¹³ both of which have often been used in organic synthesis.⁴

Based on these encouraging results, we are continuing our studies to survey the chiral resolutions of various asymmetric alcohols, in hopes of defining the scope of

the novel chiral resolving agent **8**, as well as the factor responsible for the highly efficient separation.

Supplementary material

IR, ¹H NMR, ¹³C NMR, HRMS data or elementary analyses of all compounds, and X-ray analysis of **16** are available.

Acknowledgements

We thank Ms. Hiroko Takao, Dr. Hiroshi Imagawa, Professor Takumichi Sugihara, and Professor Mugio Nishizawa in Tokushima Bunri University for the measurement of X-ray of **16**. We are grateful to Professor Takenori Kusumi of the University of Tokushima for helpful suggestions and discussions. This work was in part supported by research grants from Nippon Zeon Co. Ltd, and Faculty of Pharmaceutical Sciences, The University of Tokushima.

References and notes

- (a) Yamamoto, C.; Yoshio Okamoto, Y.; Thomas Schmidt, T.; Jäger, R.; Vögtle, F. *J. Am. Chem. Soc.* **1997**, *119*, 10547–10548; Okamoto, Y.; Osa, T.; Nakai, T.; Nohira, H.; Murakami, N.; Yamada, H. Resolution of Optical Isomers. In *Kikan Kagaku Sousetsu 6*; Japan Chemical Society, 1998; (b) Ingersoll, A. W. In *The Resolution of Alcohols. Organic Reactions*; Wiley: NY, 1994; Vol. 2, Chapter 9, p 376.
- (a) Kouda, K.; Ooi, T.; Kaya, K.; Kusumi, T. *Tetrahedron Lett.* **1996**, *37*, 6347–6350; (b) Kasai, Y.; Watanabe, M.; Harada, N. *Chirality* **2003**, *15*, 295–299.

- Wuts, P. G. M.; Bigelow, S. S. *J. Chem. Soc., Chem. Commun.* **1984**, 736–737; Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkne, H. *Chem. Ber.* **1988**, *121*, 1231–1239; Linderman, R. J.; Cusack, K. P.; Jaber, M. R. *Tetrahedron Lett.* **1996**, *37*, 6649–6652; Lainé, D.; Fujita, M.; Lay, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1639–1645; Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron Lett.* **1982**, *23*, 1921–1924.
- Greene, T. W.; Wuts, P. M. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: NewYork, 1999, pp 17–148.
- Nemoto, H. *Tetrahedron Lett.* **1994**, *42*, 7785–7788.
- Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566–8575.
- Golborn, P.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870–2875.
- TLC used in all the experimental was obtained from Merck (1.05715.0009, Silica gel 60F₂₅₄).
- In addition to hexane/toluene, we also surveyed various eluent systems, such as hexane/ether, hexane/ethyl acetate, hexane/dichloromethane, and hexane/chloroform. However, since these solvents resulted identical R_f values for **14c** and **15c**, we used the hexane/toluene eluent system for all subsequent TLC procedures.
- At first, we simply observed ΔR_f value of the diastereomers produced from (\pm)-**8** and various (\pm)-2-alkanols. Then, we prepared optically active **14** and **15** by the reaction of either (\pm)-**8** and optically active 2-alkanols, or optically active **8** and DL-2-alkanols. Accordingly, all the relative and absolute configurations of **14** and **15** were determined.
- A typical example of publication describing the determination of absolute configuration using the formation of diastereomers: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
- Alcohol exchange reaction was used, catalyzed by K-10. Taniguchi, T.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synlett* **1999**, 1247–1248.
- In our TLC studies of the diastereomeric mixture of THP-protected 2-octanol, we did not observe a pair of distinct spots (hexane/toluene). In contrast, ΔR_f value of the two diastereomers produced from (\pm)-**6** and various (\pm)-2-alkanols, was comparable to the ΔR_f value of **14** and **15**. Accordingly, the large ΔR_f value could be produced by the skeleton of hexahydrocyclopenta[b]furan.