Enantioselective Construction and Utilization of 2-(Cyclohex-2-enyl)phenols

Hiroyuki Konno and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Fax +81-22-217-6845

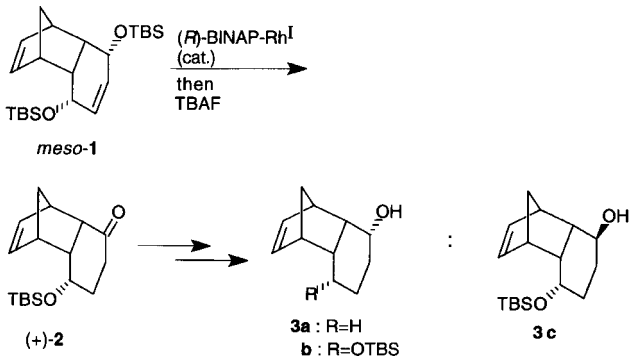
E-mail konol@mail.cc.tohoku.ac.jp

Received 22 May 1998

Abstract: Enantioselective construction of 2-(cyclohex-2-enyl)phenols from chiral equivalents of cyclohex-2-enols has been investigated by employing a concurrent retro-Diels-Alder reaction and Claisen rearrangement protocol. Utilizing the enantiomerically pure product obtained, the first enantiocontrolled synthesis of a phenolic natural sesquiterpene (+)-curcudiol, isolated from the marine sponge *Didiscus flavus*, has been demonstrated.

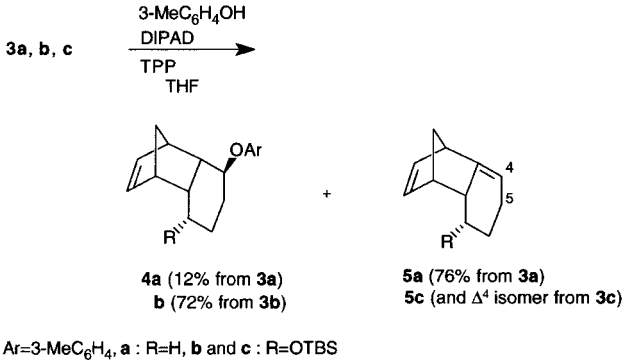
We have encountered[1] difficulties in preservation of the original chiral integrity of chiral allyl alcohols in their conversion into chiral 2-allylphenols[2] through a sequential Mitsunobu aryl ether formation[3,4] and Claisen rearrangement.[5,6] The enantiomeric purities of the products were diminished considerably in both the ether formation[4,7] and the rearrangement steps. In relation to our recent development[8] of a chiral building block serving as chiral cyclohexenone, we examined the synthesis of chiral 2-(cyclohex-2-enyl)phenols using the chiral cyclohexenone synthon to extend its synthetic utility as the chiral cyclohexenol equivalent. We wish to report here an enantio- and stereoselective construction of 2-(6-*tert*-butyldimethylsiloxy-2-cyclohexenyl)phenol and its conversion into a natural phenolic sesquiterpene (+)-curcudiol isolated from the marine sponge *Didiscus flavus*.[9]

Since one major factor leading to loss of the original enantiomeric purity was due to the racemization in the Mitsunobu coupling using allylic alcohols,[4] we first examined the coupling between 3-methylphenol and each of the three non-allylic chiral cyclohexanols serving as chiral cyclohex-2-enols to avoid the allylic racemization. Thus, the enantiomerically pure ketone (+)-**2**, obtained by a chiral BINAP-Rh^{I}-catalyzed asymmetrization[8] of the *meso*-endiol *bis*-silyl ether **1**, was first transformed into the three substrates, chiral cyclohex-2-enol equivalent **3a** and *syn*-1,4 and *anti*-1,4 substituted chiral cyclohex-2-enol equivalents, **3b** and **3c** (Scheme 1).



Scheme 1

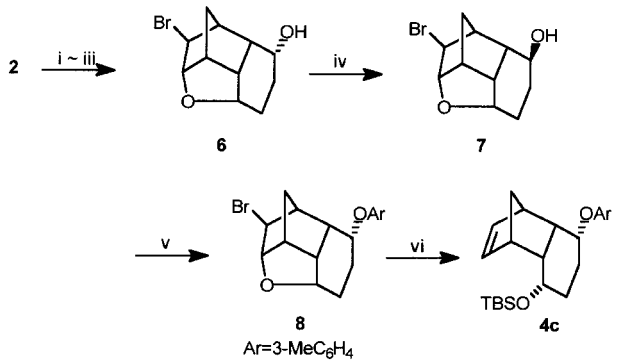
The Mitsunobu reaction of these non-allylic alcohols with 3-methylphenol was carried out in the presence of two equivalents each of diisopropyl azodicarboxylate (DIPAD) and triphenylphosphine (TPP) in THF. Only the *endo*-alcohol **3b**, m.p. 128–130 °C, $[\alpha]_D^{29}$ –16.9 (*c* 1.1, $CHCl_3$), carrying a *syn*-4-substituent furnished the expected *exo*-aryl ether **4b**, $[\alpha]_D^{34}$ +33.6 (*c* 1.2, $CHCl_3$), carrying an *anti*-4-substituent in satisfactory yield (72%) as the single product. Dehydration prevailed in the reaction of the *endo*-alcohol **3a**, $[\alpha]_D^{32}$ –43.7 (*c* 0.6, $CHCl_3$), not carrying a 4-substituent to give the elimination product **5a** in 76% yield as a volatile oil and only 12% yield of the desired *exo*-ether **4a**, $[\alpha]_D^{26}$ +7.2 (*c* 2.5, $CHCl_3$), was generated. In the reaction of the *exo*-alcohol **3c** carrying an *anti*-4-substituent, dehydration occurred exclusively to afford a mixture of the two regioisomeric olefins, **5c** and its Δ^4-isomer, without generation of the aryl ether **4c** having the *exo-syn*-1,4-stereochemistry. The observed specific ether formation in the reaction of the *endo*-alcohol **3b** may be due to the steric repulsion between the *endo-syn*-1,4-substituents which alleviates the antiperiplanar hydrogen and oxygen-phosphorus disposition appropriate for the E2-elimination. Meanwhile, with **3a** and **3c** which do not have the 1,4-steric interaction, the elimination rather than the substitution occurs to give the olefins as observed (Scheme 2).



Scheme 2

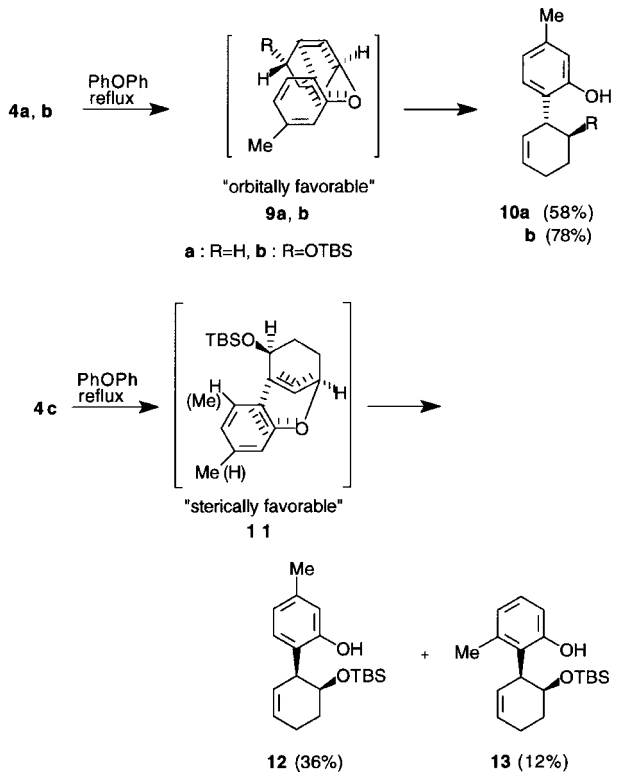
We next examined the thermolysis of the aryl ethers. For comparison, we prepared the *endo*-aryl ether **4c**, which could not be obtained directly from **3c**, by employing an alternative way from the same keto-ether **2**. Thus, **2**, after desilylation, was exposed to NBS to form the bromo ketone having an ether linkage which was then reduced from the convex face to give the bromohydrin **6**, m.p. 133–134 °C, $[\alpha]_D^{31}$ +103.0 (*c* 1.1, $CHCl_3$). The Mitsunobu reaction of **6** with 4-nitrobenzoic acid,[10] followed by the hydrolysis of the resulting benzoate gave the *exo*-alcohol **7**, $[\alpha]_D^{29}$ +67.2 (*c* 1.4, $CHCl_3$), which on the second Mitsunobu reaction furnished the *endo*-aryl ether **8** as the single stereoisomer. During these two-fold Mitsunobu inversions, dehydration did not take place at all, supporting the above-mentioned 1,4-repulsion explanation. On reductive cleavage of the bromo-ether functionality followed by silylation of the secondary hydroxy group, **8** yielded the *endo*-aryl ether **4c**, $[\alpha]_D^{30}$ +10.0 (*c* 1.4, $CHCl_3$), bearing a *syn*-4-substituent (Scheme 3).

With the three substrates in hand, thermolysis was carried out in boiling diphenyl ether to initiate the concurrent retro-Diels-Alder reaction and Claisen rearrangement.[11] Thermolysis of **4a** was completed within 30 min to give the 2-(cyclohex-2-enyl)phenol **10a**, $[\alpha]_D^{28}$ +102.1 (*c* 0.2, $CHCl_3$), as the single product in 58% yield, whose enantiomeric purity was determined to be 97% ee by hplc using a chiral column



Reagents and conditions: i) Bu_4NF. ii) NBS. iii) $NaBH_4$ (69%). iv) 4-$NO_2C_6H_4CO_2H$, DIPAD, TPP then dil. NaOH (86%). v) 3-MeC_6H_4OH, DIPAD, TPP. vi) (a) Zn, AcOH (cat.), EtOH, reflux, (b) TBS-Cl, imidazole, (82% from 7)

Scheme 3



Scheme 4

(CHIRALCEL OJ, 5% Pr^{i}OH-hexane) indicating about 1.5% loss of the original chiral integrity of the starting keto-ether **2**. The reaction was found to proceed most easily with **4b**, having no significant 1,4-interaction, to give 5-methyl-2-(6-siloxycyclohex-2-enyl)phenol **10b**, $[\alpha]_D^{31}$ –24.6 (*c* 0.5, $CHCl_3$), stereo- and regioselectively, in 78% yield as the single product within 30 min. In a shorter reaction time (~ 5 min), a separable mixture of **10b** and the aryl cyclohex-2-enyl ether **9b**, $[\alpha]_D^{33}$ +89.1 (*c* 0.7, $CHCl_3$), was obtained though the reaction could not be terminated definitely at the retro-Diels-Alder stage. Since none of the stereoisomers could be detected by hplc [after desilylation: Microsorb(Si), 1% Pr^{i}OH-hexane] in the reaction of **9b**, it was presumed that the original chiral integrity originated from the keto-ether **2** was preserved in the product **10b**. On the other hand, the thermolysis of the *endo*-aryl ether **4c** having a considerable 1,4-interaction took a longer reaction time to give a separable 6:1 mixture of 5-methyl-2-(6-siloxycyclohex-2-enyl)phenol **12** and 3-methyl-2-(6-siloxycyclohex-2-enyl)phenol **13** in 45% total yield after 2.5 h. Although the reaction proceeded stereoselectively as none of the stereoisomers of **12** and **13** were detected by hplc analysis [after desilylation: Microsorb(Si), 1% Pr^{i}OH-hexane], it lost regioselectivity to some extent. The observed differences in the regioselectivity among the allyl aryl ethers **4a**, **b** and **4c** were presumed to be due to the stereochemistry of the 4-substituent: **4a**, **b**, without having 1,4-interaction, were allowed to take the orbitally favorable chair-like transition states[12] **9a**, **b** in the Claisen rearrangement to give the single products **10a**, **b**, respectively, while **4c**, having a considerable 1,4-interaction, was forced to take sterically favorable two boat-like transition states **11** to give rise to the mixture of the two regioisomers **12** and **13** (Scheme 4).

Having concluded the cyclohexenylphenol **10b** to be the only compound accessible practically from the keto-ether **2** via the *syn*-4-substituted cyclohex-2-enol equivalent **3b** through the Mitsunobu reaction and the concurrent retro-Diels-Alder and Claisen reaction, we explored its utilization as a chiral building block for the enantiocontrolled construction of a natural phenolic sesquiterpene (+)-curcudiol **19** isolated from the marine sponge *Didiscus flavus*.[9] Thus, the phenol **10b** was first transformed into the methyl ether **14**, $[\alpha]_D^{27}$ +131.7 (*c* 0.3, $CHCl_3$), in 72% yield, which was sequentially transformed into the monopivalate **15**, $[\alpha]_D^{29}$ –18.4 (*c* 0.9, $CHCl_3$), in 73% yield through one-flask ozonolysis and reduction followed by specific monoacylation. Reductive removal[13] of the primary hydroxy functionality of **15** via the tosylate afforded **16**, $[\alpha]_D^{27}$ –12.3 (*c* 0.3, $CHCl_3$), whose secondary oxygen functionality was removed via the xantate[14] to give the primary alcohol **17**, $[\alpha]_D^{31}$ +5.6 (*c* 0.5, $CHCl_3$), in 62% overall yield after reductive deacylation. Enantiomeric purity of **17** was determined to be >99% ee by hplc using a chiral column (CHIRALCEL OJ, 3% Pr^{i}OH-hexane). By employing a sequence of reactions involving oxidation, ether cleavage and esterification, **17** was converted to the penultimate ester **18**, $[\alpha]_D^{32}$ +20.7 (*c* 0.2, $CHCl_3$), which was treated with excess methylmagnesium iodide to accomplish the first enantiocontrolled synthesis[15] of (+)-curcudiol **19**, $[\alpha]_D^{30}$ +9.9 (*c* 0.2, $CHCl_3$), [natural: $[\alpha]_D^{22}$ +9.2 (*c* 10.8, $CHCl_3$)]. Overall yield of **19** from **17** was 44% (Scheme 5).

In summary, it was concluded that only the chiral cyclohex-2-enol equivalent **3b** bearing a *syn*-4-substituent was tolerable under the Mitsunobu reaction and the concurrent retro-Diels-Alder and Claisen rearrangement reaction protocol to give the 2-(cyclohex-2-enyl)phenol **10b** satisfactorily without losing the original chiral integrity[16] of the chiral starting material **2**.

References and Notes

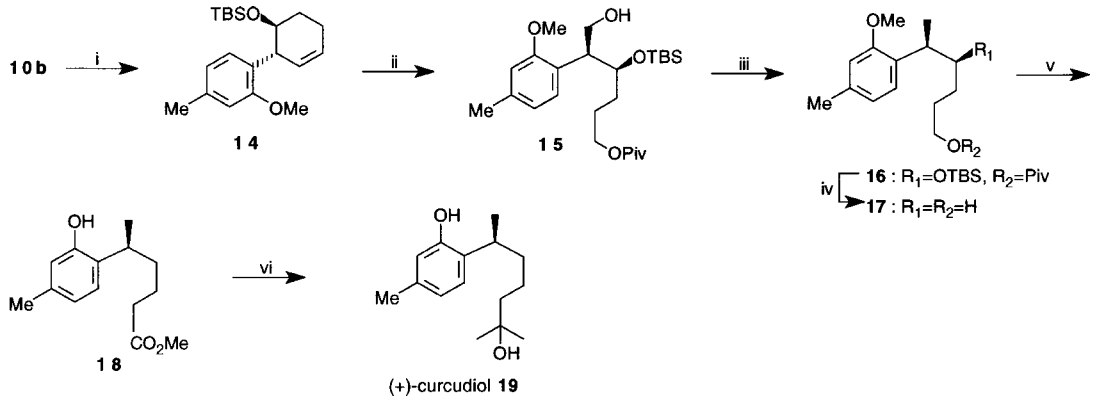
(1) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2447.

(2) Goering, H. L.; Kimoto, W. I. *J. Am. Chem. Soc.*, **1965**, *87*, 1748.

(3) Pertinent reviews, see: Mitsunobu, O. *Synthesis* **1981**, 1. Hughes, D. L. *Org. React.* **1992**, *42*, pp. 335-656. Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127.

(4) A discussion on the Mitsunobu reaction of cyclic allylic alcohols, see: Shull, B. K.; Sakai, T.; Nichols, J. B.; Koreeda, M. *J. Org. Chem.* **1997**, *62*, 8294.

(5) Pertinent reviews, see: Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. Wipf, P. In "*Comprehensive Organic Synthesis*" Trost, B. M.; Fleming, I.; Paquette, L. A. Eds. Pergamon Press, Oxford, **1991**, *5*, pp. 827-874.



Reagents and conditions: i) MeI, NaH, THF (72%). ii) (a) O_3, then $NaBH_4$, MeOH-CH_2Cl_2, (b) Piv-Cl, pyridine (73%). iii) (a) TsCl, pyridine, (b) $NaBH_4$, DMSO (93%). iv) (a) HF, MeCN, (b) CS_2, MeI, NaH, (c) Bu_3SnH, AIBN (cat.), (d) $LiAlH_4$ (62%). v) (a) PDC, DMF, (b) BBr_3 then CH_2N_2 (59%). vi) MeMgI, THF (75%).

Scheme 5

(6) Quite recently, a catalytic asymmetric protocol for the formation of allyl aryl ethers and their Claisen rearrangements has been disclosed, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1998**, *120*, 815.

(7) Sakagami, H.; Samizu, K.; Kamikubo, T.; Ogasawara, K. *Synlett* **1996**, 163.

(8) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287.

(9) Wright, A. E.; Pomponi, S. A.; McConnell, O. J.; Kohmoto, S.; McCarthy, P. J. *J. Nat. Prod.* **1987**, *50*, 976.

(10) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett*. **1991**, *32*, 3017.

(11) Sugahara, T.; Ogasawara, K. *Synlett* **1996**, 319.

(12) Fleming, I. In *Frontier Orbitals and Organic Chemical Reactions*, J. Wiley & Sons, London, **1976**.

(13) Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081.

(14) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc*., Perkin Trans 1, **1975**, 1574. Barton, D. H. R.; Crich, D.; Löbberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329.

(15) Racemic synthesis of curcudiol, see: Ono, M.; Yamamoto, Y.; Todoroki, R.; Akita, H. *Heterocycles* **1994**, *37*, 181.

(16) The corresponding cyclopent-2-enyl ether lost some of the original chiral integrity under the same concurrent retro-Diels-Alder and Claisen conditions, see: Sugahara, T.; Ogasawara, K. *Tetrahedron*: *Asymmetry* in press.