Asymmetric Synthesis of 6,6′-Dialkoxy-2,2′-biphenyldiols by Using Menthone as a Chiral Template

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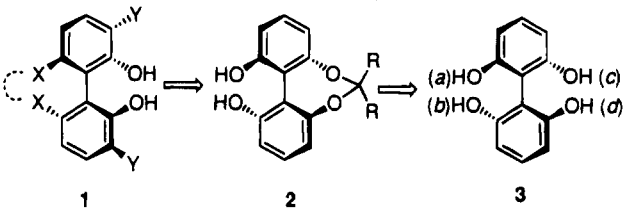
Received September 12, 1994®

Summary: Acetalization of prochiral 2,2′,6,6′-biphenyltetrol with *l*-menthone proceeds in an enantiodifferentiating manner to give isomenthonide **5a** of *S*-axial chirality as a major product, which can be used as a general intermediate for asymmetric synthesis of a series of (*S*)-6,6′-dialkoxy-2,2′-biphenyldiols **9a–f**.

Complexes of 2,2′-dihydroxybiaryls with Lewis acids, in particular those of 1,1′-bi-2-naphthol, have been utilized as chiral catalysts in a variety of enantioselective syntheses.[1,2] Recently, attention has been focused on improvement of their performance by modification of a parent structure. Successful results have been reported by increasing the asymmetry around the hydroxy groups via introducing proper substituents at the adjacent positions.[2,3] The stereochemical features of dihydroxybiaryls **1**, and their Lewis acid complexes, are also governed by substituents attached at the 6 and 6′ positions which control torsional angle ω for the benzene rings (Scheme 1). However, the effect of torsional angles has not been studied previously due to the lack of a general method for the preparation of axially chiral 2,2′-biphenyldiols with optional substituents at the 6 and 6′ positions.[4]

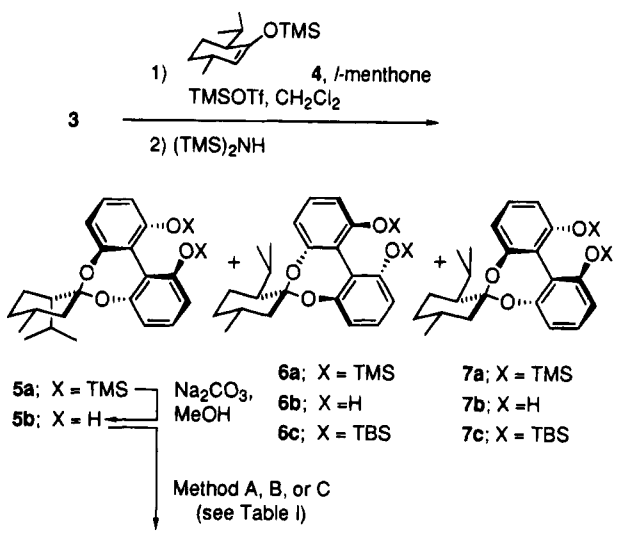
Acetal **2** is a candidate for a common intermediate of 6,6′-disubstituted 2,2′-biphenyldiols. Moreover, **2** was anticipated to be synthesized from achiral precursor, 2,2′,6,6′-biphenyltetrol (**3**),[5] by an enantiogroup selective acetalization[6] between the hydroxy groups a and b (or c and d). We wish to report herein a group selective acetalization of **3** with *l*-menthone and use of the resulting acetal **5b** in asymmetric synthesis of a series of 6,6′-dialkoxy-2,2′-biphenyldiols **9a–g** whose torsional angles

Scheme 1



1 2 3

Scheme 2



8a; R = Bn
8b; R = Ph
8c; R---R = -$(CH_2)_3$-
8d; R---R = -$(CH_2)_4$-
8e; R---R = -$(CH_2)_5$-
8f; R---R = -$(CH_2)_6$-

9a; R = Bn
9b; R = Ph
9c; R---R = -$(CH_2)_3$-
9d; R---R = -$(CH_2)_4$-
9e; R---R = -$(CH_2)_5$-
9f; R---R = -$(CH_2)_6$-

are controlled by the alkoxy (or methylenedioxy) groups attached at the 6 and 6′ positions (Scheme 2).

Attempted acetalization of the tetrakis(TMS) ether of **3** with *l*-menthone catalyzed by TMSOTf resulted in recovery of the starting materials. We recently reported an efficient method for the preparation of menthonides by acid-catalyzed reaction of 1,3-diols and *l*-menthone enol silyl ether **4**, where facile acetalization takes place between the initially produced, partially silylated derivatives of the diols and *l*-menthone.[7] The method was successfully employed in the acetalization of **3** (Scheme

® Abstract published in *Advance ACS Abstracts,* November 15, 1994.

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Table 1. Asymmetric Synthesis of 6,6′-Dialkoxy-2,2′-biphenyldiols 9a–f

	etherification				removal of menthone[b]			
entry	reagent	method[a]	product	yield (%)	product	yield (%)	ee[c] (%)	$[\alpha]_D$
1	BnBr	A	**8a**	91	**9a**	97	97	+60.0 (0.70, EtOH)
2	$Ph_3Bi(OAc)_2$	B	**8b**	48	**9b**	96	96	+80.0 (0.52, EtOH)
3	$Br(CH_2)_3Br$	C	**8c**	83	**9c**	100	80	+169 (1.06, THF)
4	$Br(CH_2)_4Br$	C	**8d**	82	**9d**	97	98	+141 (0.60, THF)
5	$Br(CH_2)_5Br$	C	**8e**	70	**9e**	82	98	+189 (0.98, THF)
6	$Br(CH_2)_6Br$	C	**8f**	40	**9f**	100	99	+152 (0.77, EtOH)

[a] Method A: 4 equiv of the reagent, NaOH (3 equiv), $Bn(Et)_3NBr$ (0.5 equiv), CH_2Cl_2, H_2O, rt, 18 h. Method B: 4 equiv of the reagent, Cu powder (1.3 equiv), benzene, 50 °C, 26 h. Method C: a DMF solution (0.1 M) of the reagent (1.0 equiv) was slowly added to a suspension of **5b** and K_2CO_3 (2.3 equiv) in DMF (0.04 M) at 80 °C during 2–4 h, and the mixture was stirred further for 2 h. [b] Concentrated HCl–THF–MeOH (1:4:2), rt, 2–5 h. [c] Ee was determined by HPLC analysis with a Chiracel OD column.

2). For separation, the resulting mixture was subsequently treated with $(TMS)_2NH$. Flash chromatography of the crude products gave a 15:1 mixture of **5a** and **7a** in 45% yield and **6a** in 16% yield. Pure **5a** was obtained by a single recrystallization of the mixture from methanol. Desilylation (K_2CO_3, MeOH) of **5a** gave acetal **5b** quantitatively.[8]

Structural determination of the major product **5a** was made by X-ray analysis.[9] The analysis disclosed that **5a** is an isomenthonide of *S* axial chirality in which the isopropyl group takes an unusual axial position. The structure of the second major product **6a** was determined to be the menthonide of *R* chirality by X-ray diffraction analysis of the TBS ether derivative **6c**.[9] Minor product **7a** was assigned tentatively to a menthonide of *S*-chirality based on the observed rapid interconversion of hydroxy derivatives **6b** and **7b** at rt. Desilylation of both **6a** and **7a** resulted in the formation of the same 2.6:1 mixture of **6b** and **7b**.[10] Resilylation of the mixture ($(TMS)_2NH$, TMSOTf, CH_2Cl_2, rt) afforded TMS ethers **6a** (69%) and **7a** (24%).

Although (1*R*,4*R*)-isomenthone is formed reversibly in an acid-catalyzed acetalization with *l*-menthone, we have never observed the formation of the thermodynamically less stable[11] isomenthonides in our previous study on acetalization of 1,*n*-alkanediols.[6] In the acetalization of **3**, formation of menthonides **6a** and **7a** is unfavorable probably due to a repulsive interaction between the isopropyl group and the benzene ring and the relatively more stable isomenthonide **5a** was formed as a major product. Formation of the diastereomeric isomenthonide of *R* chirality in which unfavorable interaction exists between the axial isopropyl group and the benzene ring was not observed.

Reactions of **5b** with benzyl bromide afforded **8a** in high yields (entry 1 in Table 1). Diphenylation of **5b** was achieved by using an organobismuth reagent developed by Barton et al. (entry 2).[12] Axially chiral biphenyls **8c–f** with $-O(CH_2)_nO-$ (n = 3–6) bridges were prepared by intermolecular cyclization of **5a** with the corresponding 1,ω-dibromoalkanes (entries 3–6).[13] The reactions were carried out under high dilution conditions by adding a solution of the dibromoalkanes slowly using a syringe pump.

Hydrolysis of **8a–f** under acidic conditions afforded chiral biphenyldiols **9a–f** in high yields. The enantiomeric purities of these compounds were high (>95% ee) except for the trimethylenedioxy derivative[14] **9c**. A separate experiment showed that **9c** did not racemize under these conditions, suggesting that **8c** underwent partial racemization under the acidic conditions.[15] The biphenyldiols **9a–f** are thermally stable during practical use. Thus, no detectable racemization was observed upon heating **9a,b** in ethanol at 60 °C for 18 h. Slow racemization was observed at 111 °C in toluene; the enantiomeric purities of **9a**, **9b**, and **9d** were reduced to 86% (after 15 h), 81% (after 12 h), and 87% ee (after 6 h), respectively.

Each of the chiral biphenyldiols synthesized in the present study has a unique structure related to its torsional angle. Use of their Lewis acid complexes in catalytic asymmetric reactions is now underway.

Acknowledgment. This work was supported partially by a Grant-in-Aid from the Japan Ministry of Education, Science, and Culture.

Supplementary Material Available: Experimental procedures, spectral data for the intermediates and products, and ORTEP drawings of **5a** and **6c** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Harada, T.; Tanaka, S.; Oku, A. *Tetrahedron* **1992**, *48*, 8621.

(8) Experimental procedure for the preparation of acetal **5b**: To a stirred suspension of biphenyltetrol **3** (1.00 g, 4.59 mmol) in CH_2Cl_2 (9.2 mL) at −85 °C was added enol silyl ether **4** (2.8 mL, 11 mmol), *l*-menthone (0.56 mL, 3.2 mmol), and TMSOTf (1.8 mmol) in that order. The mixture was allowed to warm to −20 °C and stirred for 20 h at this temperature. Hexamethyldisilazane (3.9 mL, 19 mmol) was added, and the mixture was stirred further for 1 h at rt. The resulting mixture was diluted with hexane, poured into water, and extracted twice with hexane. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Unreacted *l*-menthone was recovered by vacuum distillation (bath temperature 60 °C). The residue was purified by silica gel flash chromatography (gradient elution from benzene/hexane 10/90 to 25/75 and then ethyl acetate/hexane 50/50) to give, in the order of elution, the tetrakis(TMS) ether of **4** (0.55 g, 23%), a 15:1 mixture of **5a** and **7a** (1.04 g, 45%), and **6a** (0.36 g, 16%). Recrystallization of a mixture of **5a** and **7a** from methanol gave pure **5a** (mp 96–7 °C). To a stirred solution of **5a** (2.6 g, 5.2 mmol) in methanol (52 mL) at rt was added potassium carbonate (2.2 g, 16 mmol). After being stirred for 5 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ether and washed successively with 1 N aq HCl and with brine. The concentrate from the dried (Na_2SO_4) organic layer was purified by silica gel flash chromatography (ethyl acetate/hexane = 10/90) to give **5b** (1.8 g, 98%).

(9) The authors have deposited atomic coordinates for **5a** and **6c** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(10) TBS ethers **6c** and **7c** were prepared by silylation (TBSCl, imidazole, DMF) of the mixture in 59% and 23% yields, respectively.

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(14) Enantiomerically pure **9c** $[\alpha]^{25}_D$ +220 (*c* 1.11, THF) was obtained by recrystallization from methanol.

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