Asymmetric Synthesis of Axially Chiral Biaryls via Desymmetrization of 2,2′,6,6′-Tetrahydroxybiphenyl Using 1,4-Di-*O*-benzyl-L-threitol as a Chiral Template

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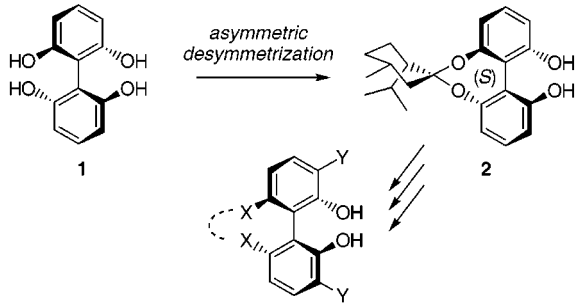
Sequential etherification of 2,2′,6,6′-tetrahydroxybiphenyl (**1**) with 1,4-di-*O*-benzyl-L-threitol under Mitsunobu conditions gives desymmetrized biphenyldiol **9** of *S*-axial chirality exclusively. Cyclization of **9** with 1,*ω*-dibromoalkanes followed by removal of the chiral auxiliary yields (*S*)-2,2′-biphenyldiols **14** with alkylenedioxy bridges at the 6 and 6′ positions. (*S*)-6,6′-Dialkyl- and -diphenyldiols **20** are obtained in an efficient manner via Pd(0)-catalyzed cross-coupling of bis(triflate) derivative **17** with organozinc reagents. Bis(triflate) **17** also serves as an intermediate for asymmetric synthesis of axially chiral biphenyldicarboxylic acid **23**, terphenylcarboxylic acid **28**, lactone **26**, and lactam **30**.

Introduction

Axially chiral biaryl compounds have become increasingly important as ligands for a variety of effective chiral catalysts[1] and as pharmacologically potent natural products.[2] For this reason, much attention has been focused on their enantioselective syntheses.[3] Most of the reported methods rely on intra- or intermolecular biaryl-coupling reactions in which the absolute configuration of the axially chiral structure is controlled when a stereogenic biaryl bond is formed. Recently, we introduced a conceptually different approach based on asymmetric desymmetrization[4] in which differentiation of enantiotopic groups of prochiral biaryl compounds leads to the generation of axial chirality.[5,6] Thus, we reported that prochiral 2,2′,6,6′-tetrahydroxybiphenyl (**1**) is converted to (*S*)-diols **2** with 69% diastereoselectivity through enantiodifferentiating acetalization with *l*-menthone (Scheme 1). One of the advantages of the approach is that desymmetrized derivatives of tetrol **1** can be transformed to a variety of biaryl compounds. Indeed, we reported that a series of substituted 2,2′-biphenyldiols are readily accessible through the functional group transformation and through the directed ortho functionalization of (*S*)-diol **2**.

Scheme 1



Although asymmetric desymmetrization through acetalization with *l*-menthone is straightforward, formation of the diastereotopic byproducts that should be removed proved particularly problematic upon scale-up. Herein, we wish to report a general and practical method for the asymmetric synthesis of axially chiral biaryls via asymmetric desymmetrization of tetrol **1** using 1,4-di-*O*-benzyl-L-threitol as a chiral template. The desym-

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(5) For a similar approach, see: Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

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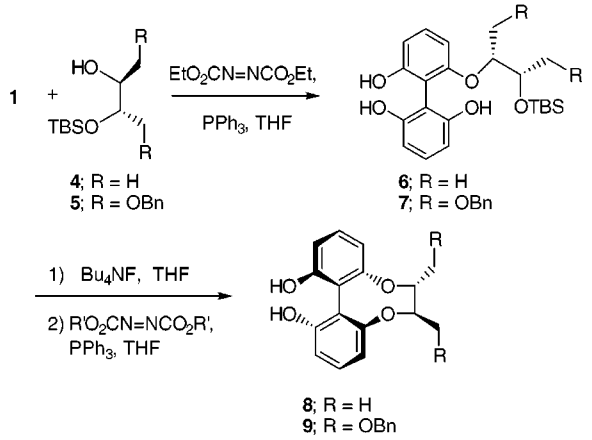
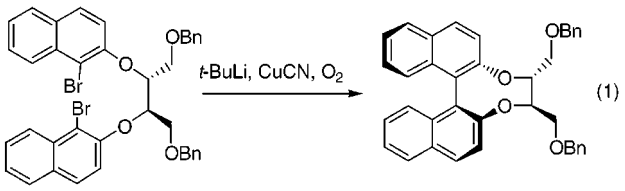
Scheme 2



metrization proceeds stereoselectively without forming diastereotopic byproducts and the resulting chiral biaryldiol **9** serves as a versatile intermediate for asymmetric synthesis of biaryl compounds possessing not only hydroxy but also other functionalities.[7]

Results and Discussion

Recently, Lipshutz et al. have reported a highly stereoselective intramolecular coupling of **3** where two aryl units are connected through a chiral 1,2-dioxy moiety (eq 1).[8,9] Their report prompted us to examine a possible use of a chiral 1,2-diol as a template in asymmetric desymmetrization of tetrol **1**. To assess the degree of stereoselectivity, we first examined desymmetrization of **1** by using (2*R**,3*R**)-2,3-butanediol (Scheme 2). Treatment of tetrol **1** with mono-TBS derivative **4** under the conditions of the Mitsunobu etherification[10] (diethyl azodicarboxylate (DEAD), PPh_3, THF) afforded monoether **6** in 52% yield. After deprotection of the TBS group with Bu_4NF (80% yield), the resulting alcohol was again subjected to the Mitsunobu reaction. The intramolecular cyclization proceeded smoothly to give **8** in 67% yield. Stereoselectivity of the cyclization was high; formation of the diastereomer was not detected by ^1H NMR analysis of the crude product.



3

Being encouraged by high selectivity observed, we then examined the use of (2*S*,3*S*)-1,4-di-*O*-benzyl-L-threitol as a chiral template that can be removed after desymmetrization. The chiral diol was prepared from L-tartaric acid according to the reported procedure[11] and was converted to the monosilyl ether **5** in 77% yield. Mitsunobu etherification of tetrol **1** with **5** using DEAD proceeded with inversion of stereochemistry to give monoether **7** in 94% yield. Deprotection of **7** (97%) and subsequent cyclization under the Mitsunobu conditions using dimethyl azodicarboxylate (DMAD)[12] furnished desymmetrization product **9** with *S*-axial chirality and with (*R*,*R*)-auxiliary group[13] exclusively as colorless crystals in 90% yield.

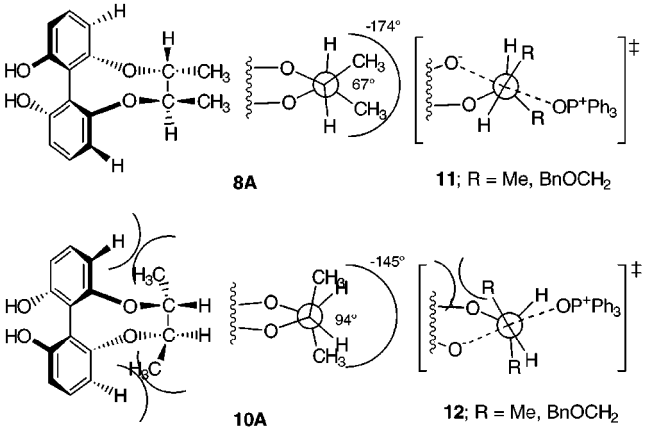


Figure 1.

To gain information on the origin of high stereoselectivity observed, MO (PM3)[14] calculations were carried out for dimethyl derivative **8** and the corresponding diastereomer **10** (Figure 1). The calculations showed that **8A** and **10A** are the most stable conformers for **8** and **10**, respectively. Conformer **8A** was calculated to be 2.57 kcal/mol more stable than conformer **10A**. Both conformers have a similar C_2-symmetrical conformation of the 1,4-dioxocane ring. Two methyl groups in **8A** locate approximately in the gauche position (a dihedral angle Me−C−C−Me = 67°). On the other hand, the deviation of the two groups from the anti position is considerable for **10A** (dihedral angle Me−C−C−Me = −145°), suggesting that a repulsive interaction between the benzene ring and the methyl group is the major factor for the unstability of **10A**. It is most likely that the stereoselectivity of the second Mitsunobu cyclization is controlled kinetically. Assuming an S_N2-type transition-state model **11** and **12**,[10b] the exclusive formation of **8** or **9** through **11** can be rationalized by a similar, but more pronounced, unfavorable interaction between the R (Me or $BnOCH_2$) group and the benzene ring in **12**.

Intermolecular cyclization of diol **9** with 1,ω-dibromoalkanes in the presence of K_2CO_3 in DMF gave biphenyls **13a**−**e** with $-O(CH_2)_nO-$ (n = 4, 5, 6, 7, and 10) bridges (eq 2, Table 1). The reactions were carried out under high dilution conditions by adding the dibromoalkanes slowly during 5−6 h at 80 °C by using a syringe pump. It should

(7) For a preliminary report of a portion of this work, see: Harada, T.; Tuyet, T. M. T.; Hashimoto, K.; Hatsuda, M.; Oku, A. *Synlett* **1997**, 1246.

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(12) DMAD in place of DEAD has an advantage that byproduct hydrazine can be removed by aqueous extraction. We would like to thank Professor Toshikazu Takata of Osaka Prefecture University for this information.

(13) The absolute configuration of the chiral template L-threitol derivative undergoes inversion through sequential Mitsunobu etherification. The term "chiral auxiliary" used through out this paper indicates the resulting template-derived moiety of (*R*,*R*)-configuration.

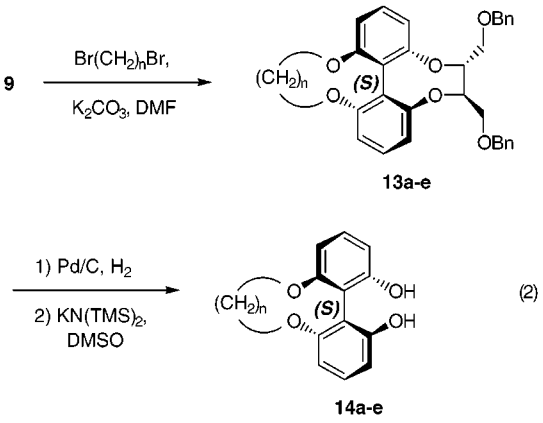
(14) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209, 221.

Table 1. Asymmetric Synthesis of (*S*)-Biphenyldiols 14a−e

		etherification		removal of auxiliary		
entry	*n*	product	yield (%)	product	yield (%)	ee (%)
1	4	**13a**	84	**14a**	100	98[a]
2	5	**13b**	77	**14b**	95	>95[b]
3	6	**13c**	73	**14c**	99	>95[b]
4	7	**13d**	53	**14d**	100	98[a]
5	10	**13e**	29	**14e**	92	>95[b]

[a] Ee was determined by LC analysis using a Chiracel OD column. [b] Ee was determined by ^{1}H NMR analysis of the mono-MTPA derivatives.

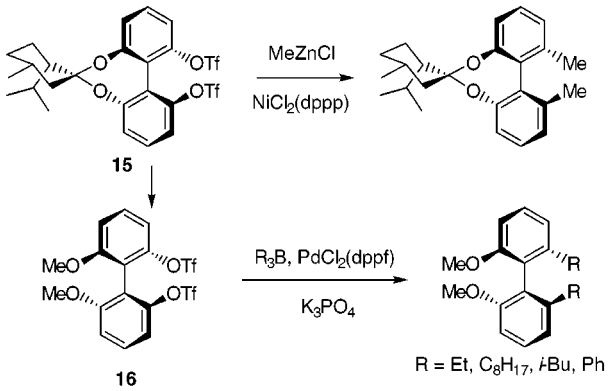
be noted that the efficiency of the cyclization is higher than that observed in a related reaction of acetal derivative **2**.[5c] Thus, for example, hexamethylenedioxy derivative **13c** was obtained in 73% yield (entry 3), while under similar conditions, the reaction of acetal **2** with 1,6-dibromohexane gave the corresponding product in 56% yield. Even 16-membered macrocyclic product **10e** with a decamethylenedioxy bridge could be prepared albeit in lower yield (entry 5). The improvement in the yields is probably due to the wider biaryl torsional angle in **9** in comparison with that in **2**.



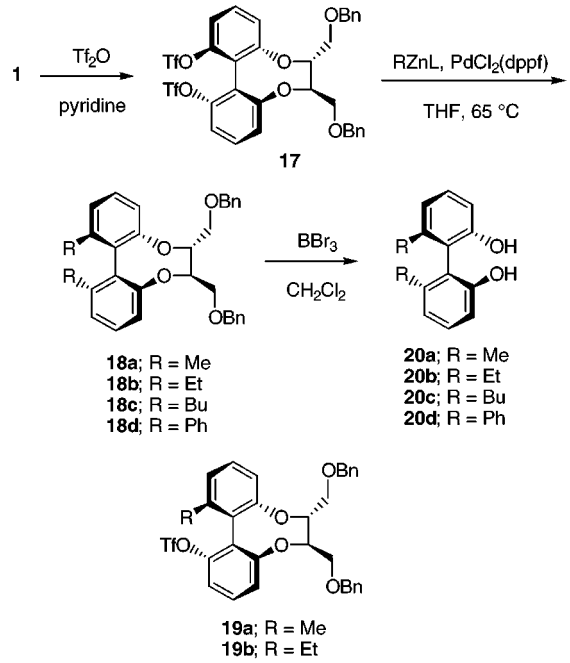
The chiral auxiliary in cyclization products **13a−e** could be removed efficiently in two steps. Thus, hydrogenolysis (H_2, 10% Pd/C, EtOH) and treatment of the potassium alkoxides of the resulting diols in DMSO at 50 °C furnished (*S*)-biphenyldiols **14a−e**[15] of high enantiomeric purities in high yields (Table 1). Use of the potassium salts in DMSO is essential. When sodium as a counterion or THF as a solvent was employed, the reaction was sluggish, and prolonged heating at higher temperatures resulted in considerable racemization of the products.[16]

Palladium- and nickel-catalyzed cross-coupling is one of the efficient methods for the preparation of regioselectively substituted arenes.[17] Recent advances in the successful use of aryl triflates as substrates has expanded the utility of the reaction[18] because of the diversity of available hydroxyarenes and the simple conversion of them to aryl triflates.[19] In our previous work, we examined cross-coupling of bis(triflate) **15** (Scheme 3).[5b] Although dimethylation of **15** with MeZnCl proceeded efficiently in the presence of $NiCl_2$(dppp), the reaction with other organometallics such as Et_2Zn, EtMgBr, and PhZnCl did not afford the corresponding coupling products in appreciable yields. The biaryl moiety in **15** is fixed with a relatively narrow torsional angle, and the reaction may be hampered due to steric hindrance. We anticipated that bis(triflate) **17** with a larger torsional angle possesses higher reactivity in cross-coupling and may serve as a versatile intermediate for asymmetric synthesis of axially chiral biaryldiols.

Scheme 3



Scheme 4



Bis(triflate) **17** was prepared in 90% yield by the treatment of biphenyldiol **9** with triflic anhydride in pyridine (Scheme 4). Cross-coupling of **17** with MeZnCl (6 equiv) was first examined in the presence of $NiCl_2$(dppp) (40 mol %) in refluxing THF. The reaction gave dialkylation product **18a**[20] and the monoalkylation product **19a** in 65% and 12% yields, respectively, together with recovery of **17** (Table 2, entry 1). Under these conditions, reaction with Me_2Zn also gave a similar result (entry 2). On the other hand, reaction with EtZnCl was sluggish, affording diethylation product **18b** only in 5%

(15) Absolute configuration of **14a−c** was confirmed by comparing their specific rotations to those reported previously.[5c]

(16) For the thermal stability of axial chirality of **14**, see ref 5c.

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(19) Stang, P. J.; Hanack, H. Subramanian, L. R. *Synthesis* **1982**, 85.

Table 2. Cross-Coupling Reaction of Bis(triflate) 17[a]

entry	reagent	catalyst	mol %	time (h)	yield (%) 18a,b	19a,b	17
1	MeZnCl	$NiCl_2$(dppp)	40	18	65	12	5
2	Me_2Zn	$NiCl_2$(dppp)	40	16	56	13	7
3	EtZnCl	$NiCl_2$(dppp)	40	23	5	20	70
4[b]	Et_3B	$PdCl_2$(dppf)[c]	10	20	34	35	11

[a] All reactions were carried out at 65 °C in THF by using an organozinc reagent (6 equiv) or Et_3B (5 equiv). [b] K_3PO_4 (3 equiv) and KBr (2.5 equiv) was used. [c] The catalyst was treated with DIBALH before use.

Table 3. Palladium-Catalyzed Cross-Coupling Reaction of Bis(triflate) 17 with Organozinc Reagents[a]

entry	reagent	equiv	mol % of $PdCl_2$(dppf)	time (h)	product	yield (%)
1	EtZnCl	6	10	17	**18b**	100
2	EtZnCl	3	5	37		96
3	Et_2Zn	6	10	18		66
4	Et_2Zn	6	10	45		95
5[b]	MeZnCl	4	5	20	**18a**	99
6[b]	Me_2Zn	6	5	15		94
7[c]	Me_2Zn	3	5	23		5
8	BuZnCl	4	5	20	**18c**	90
9	PhZnCl	4	5	24	**18d**	89

[a] All reactions were carried out in THF at 66 °C. [b] $PdCl_2$(dppf) was treated with DIBALH before the coupling reaction. [c] Mono methylation product **19** was in 20% yield together with the recovery of **17** (65%).

yield (entry 3). The Suzuki−Miyaura cross-coupling[21] of **17** with Et_3B also did not give a satisfactory result (entry 4).

Hayashi et al. reported that $PdCl_2$(dppf) is an efficient catalyst for cross-coupling of bromoarenes with organozinc reagents.[22] We found that dialkylation of bis(triflate) **17** also proceeds in an efficient manner by using $PdCl_2$(dppf) in combination with organozinc reagents (Table 3). Thus, **18b** was obtained in quantitative yield when **17** was treated with EtZnCl (6 equiv) and $PdCl_2$(dppf) (10 mol %) in refluxing THF for 17 h (entry 1). Amounts of the organozinc reagent and the catalyst could be reduced to 3 equiv and 5 mol %, respectively, by carrying out the reaction for a longer time (entry 2). Cross-coupling with Et_2Zn was slightly slow but gave **18b** also in high yield (entry 4). $PdCl_2$(dppf)-catalyzed cross-coupling was equally applicable to other alkylzinc (entries 5−8) and arylzinc reagents (entry 9) to give the corresponding products **18a**,**c**,**d** in high yields. For generation of an active Pd(0) complex, pretreatment of $PdCl_2$(dppf) with DIBALH was required in the reaction with MeZnCl and Me_2Zn (e.g., entries 6 vs 7).

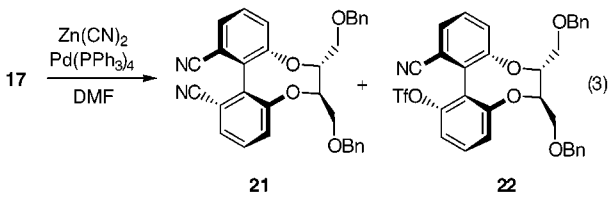
6,6′-Disubstituted (*S*)-biphenyldiols **20a**−**d** were prepared in a single step by removing the chiral auxiliary from **18a**−**d**. Thus, treatment of **18a**−**d** with BBr_3 in CH_2Cl_2 at room temperature for 20 h furnished enantiomerically pure (>95% ee) **20a**−**d**[23] in high yields (**20a**, 100%; **20b**, 76%; **20c**, 77%; **20d**, 83%). We have previously reported asymmetric synthesis of **20** via the Suzuki−Miyaura cross-coupling of 6,6′-dimethoxy bis(triflate) **16**, which was prepared from bis(triflate) **15** in two steps (Scheme 3).[5b] From the preparative point of view, the present method is considerably more straightforward than the previous one. In the cross-coupling of **16**, reduction of the TfO group took place as a side reaction.[5b] The absence of such reduction byproducts is another advantage of the present method.

Table 4. Palladium-Catalyzed Cyanation of Bis(triflate) 17[a]

entry	concentration (M)	*T* (°C)	product yield (%) 21	22	17
1	0.5	120	43	37	15
2	0.8	120	50	32	10
3	1.0	150	86		
4[b]	0.8	120	18	44	38

[a] Unless otherwise noted, reactions were carried out by using 2.0 equiv of $Zn(CN)_2$ and 10 mol % of $Pd(PPh_3)_4$ in DMF for 16 h. [b] The reaction was carried out by using 3 mol % of $Pd(PPh_3)_4$ for 3 h.

Recently, it has been revealed that cyanation[25] as well as amination[26] of aryl triflates is catalyzed also by palladium complexes. We anticipated that bis(triflate) **17** may also serve as an intermediate for the asymmetric synthesis of functionalized biphenyls by using these reactions. Cyanation reaction of **17** was carried out by using $Zn(CN)_2$ in combination with $Pd(PPh_3)_4$ (10 mol %) in DMF (eq 3, Table 4).[25c] Although a considerable amount of monocyano derivative **22** was produced as a byproduct in the reaction at 0.5 M at 120 °C (entry 1), dicyano derivative **21** was obtained in higher yield in similar reactions at higher concentration (entry 2). The best yield of 86% was achieved when the reaction was carried out at 1.0 M at 150 °C for 16 h (entry 3). Because monocyano derivative **22** shows a reactivity similar to that of **17**, it was difficult to obtain **22** selectively, especially at higher conversion. Reaction for 3 h with a reduced amount of the catalyst gave **21** in 44% yield with the 38% recovery of **17** (entry 4).



Treatment of dicyano derivative **21** with aqueous KOH in refluxing ethoxyethanol for 10 h gave dicarboxylic acid **23** and amidocarboxylic acid **24** in 47% and 38% yield, respectively (eq 4). Prolonged reaction did not improve the yield of **23**. However, a separate treatment of **24** under similar conditions afforded **23** in 72% yield. Hydrolysis of monocyano derivative **22** proceeded effectively to give hydroxycarboxylic acid **25** (eq 5). Since **25** was prone to be converted to lactone **26** during isolation by silica gel column chromatography, it was isolated as the lactone

(20) X-ray analysis performed on **18a** further verified the *S*-axial chirality of the desymmetrization product **9**. See the Supporting Information for details.

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(22) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(23) The absolute configuration of **20a**,**b** was confirmed by comparing their specific rotations to those reported previously.[5b,24]

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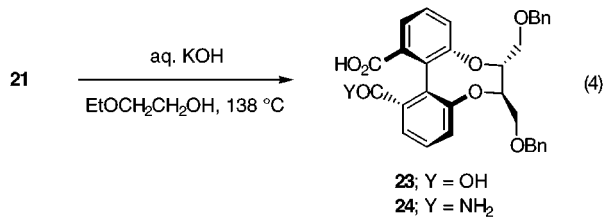
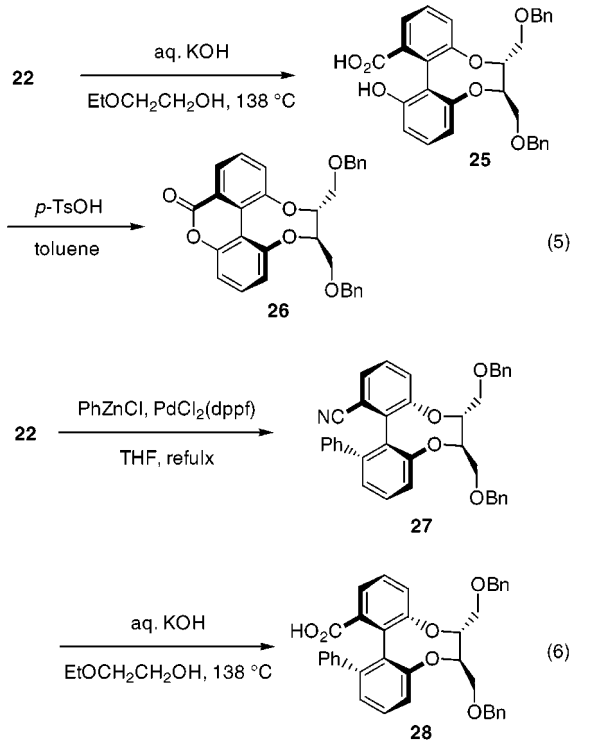
(26) (a) Wolfe, J. P.; Buchbald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268. (c) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.

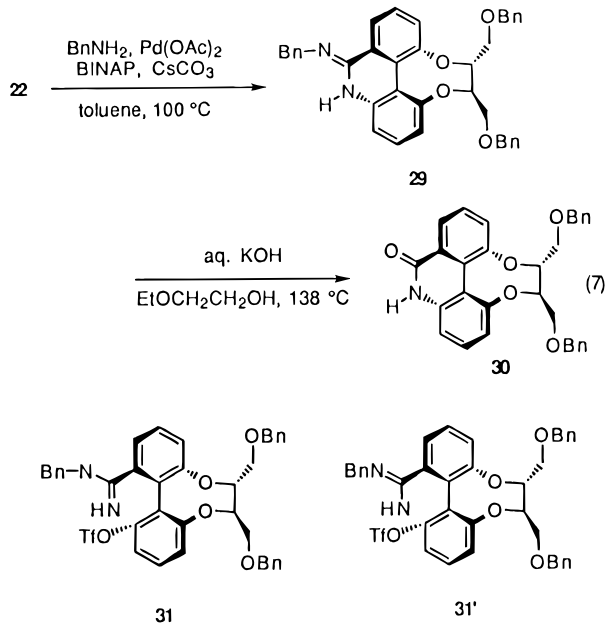
after treatment of the crude product with *p*-TsOH in toluene (80% overall yield).



Palladium-catalyzed cross-coupling of monocyano derivative **22** followed by hydrolysis would afford axially chiral 2′-substituted biphenylcarboxylic acids. Indeed, $PdCl_2$(dppf)-catalyzed cross-coupling of **22** with PhZnCl gave terphenyl **27** in 95% yield (eq 6). Although the cyano group of **27** is sterically hindered due to the neighboring phenyl group, hydrolysis of **27** proceeded smoothly to give terphenylcarboxylic acid **28** in 55% yield.



Axially chiral biphenyls with 2′-amino and 2-carboxylic acid groups is of interest as a new type amino acid component for peptide synthesis and as chiral ligands. To convert monocyano derivative **22** to the corresponding amino acid, palladium-catalyzed amination was examined under the conditions reported by Buchwald et al.[26c] When **22** was treated with benzylamine in the presence of $Pd(OAc)_2$ (5 mol %), (*S*)-BINAP (7.5 mol %), and Cs_2CO_3 in toluene at 100 °C, a normal amination product was not produced at all but cyclic amidine **29** was obtained unexpectedly in 57% yield. The formation of **29** can be explained by the initial reaction of benzylamine at the cyano group to form intermediates **31** and/or **31′**, which undergo intramolecular cross-coupling to give **29**. The structure of the product was verified by the fact that hydrolysis under basic conditions afforded lactam **30** in 67% yield. Unfortunately, **30** is rather stable, and the formation of amino acid derivative was not detected under these conditions.



We have described a practical and general method for asymmetric synthesis of axially chiral biaryl compounds based on asymmetric desymmetrization. Sequential etherification of 2,2′,6,6′-tetrahydroxybiphenyl (**1**) with 1,4-di-*O*-benzyl-L-threitol under the Mitsunobu conditions gave desymmetrized biphenyldiol **9** of *S*-axial chirality exclusively. Biphenyldiol **9** was proved to be a versatile intermediate for asymmetric synthesis of a variety of biaryl compounds. Cyclization of **9** with 1,*ω*-dibromoalkanes followed by removal of the chiral auxiliary yielded (*S*)-2,2′-biphenyldiols **14a**−**e** with alkylenedioxy bridges at the 6 and 6′ positions. (*S*)-6,6′-Dialkyl- and (*S*)-6,6′-dialkylbiphenyldiol **20a**−**d** could be prepared in an efficient manner via $PdCl_2$(dppf)-catalyzed cross-coupling of bis(triflate) derivative **17** with organozinc reagents. It was also demonstrated that bis(triflate) **17** serves as an intermediate for asymmetric synthesis of axially chiral biphenyldicarboxylic acid **23**, terphenylcarboxylic acid **28**, lactone **26**, and lactam **30**.

Experimental Section

General Methods. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75.6 MHz, respectively. All commercially available reagents were used without further purification unless otherwise noted. THF and toluene were distilled from sodium benzophenone ketyl. DMF, DMSO, and pyridine were distilled from CaH_2. Commercial anhydrous $ZnCl_2$ was dried in vacuo at 100 °C for 10 h over P_2O_5. All reactions were performed under nitrogen or argon atmosphere. Organic extracts were dried over Na_2SO_4. Flash chromatography was conducted on silica gel (Wakogel C-300).

(2*S*,3*S*)-1,4-Dibenzyloxy-3-(*tert*-butyldimethylsiloxy)-2-butanol (5). To a solution of 1,4-di-*O*-benzyl-L-threitol[11] (9.07 g, 30.0 mmol) and imidazole (2.94 g, 43.2 mmol) in DMF (30 mL) was added *tert*-butyldimethylchlorosilane (5.65 g, 37.5 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was poured into water and extracted three times with ether. The dried organic layers were concentrated in vacuo. The residue was purified by flash chromatography (5−30% ethyl acetate in hexane) to give 9.39 g (75%) of **5**: ^1H NMR δ 0.05 (3H, s,), 0.06 (3H, s), 0.87 (9H, s), 2.47 (1H, d, J = 7.8 Hz), 3.46 (1H, dd, J = 5.7, 9.3 Hz), 3.49 (2H, d, J = 6.3 Hz), 3.58 (1H, dd, J = 6.0, 9.3 Hz), 3.87 (1H, m), 3.98 (1H, dt. J = 2.7, 6.0 Hz), 4.51 (2H, s), 4.54 (2H, s), 7.25−7.34 (10H, m); IR (liquid film) 3470 (br), 1100, 835, 700 cm^{-1}.

6′-[(1*R*,2*S*)-4-Benzyloxy-2-(*tert*-butyldimethylsilyloxy)-1-(benzyloxymethyl)propyloxy]-2,2′,6-biphenyltriol (7). To a solution of biphenyltetrol **1**[27] (1.75 g, 8.00 mmol), monosilyl ether **5** (4.02 g, 9.65 mmol), and triphenylphosphine (3.15 g, 12.0 mmol) in THF (60 mL) at 0 °C was slowly added a THF (20 mL) solution of diethyl azodicarboxylate (DEAD) (1.9 mL, 12 mmol) during 3 h. After the addition, the mixture was stirred further at 0 °C for 1 h and then at 40 °C for 14 h. The mixture was poured into water, acidified with 1 N aqueous HCl, and extracted twice with ethyl acetate. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (20−50% ethyl acetate in hexane) gave 4.64 g (94%) of **7**: ^{1}H NMR δ −0.17 (3H, s), −0.71 (3H, s), 0.75 (9H, s), 3.38 (2H, d J = 5.5 Hz), 3.61 (1H, dd, J = 7.2, 10.8 Hz), 3.68 (1H, dd, J = 3.1, 10.8 Hz), 3.98 (1H, br q, J = ca. 4 Hz), 4.38 (1H, d, J = 11.7 Hz), 4.43 (2H, s), 4.58 (1H, d, J = 11.7 Hz), 4.76 (1H, dt, J = 3.6, 7.4 Hz), 5.03 (2H, s), 5.67 (1H, s), 6.62 (1H, br d, J = 7.9 Hz), 6.65 (1H, br d, J = 7.9 Hz), 6.72 (1H, d, J = 8.2 Hz), 6.79 (1H, d, J = 8.2 Hz), 7.15−7.35 (12H, m); IR (neat film) 3420 (br), 835, 780, 735, 700 cm^{-1}.

6′-[(1*R**,2*S**)-2-(*tert*-Butyldimethylsilyloxy)-1-methylpropyloxy]-2,2′,6-biphenyltriol (**6**) was prepared from tetrol **1** and TBS ether **4** in 52% yield by a procedure similar to that described above. **6**: ^{1}H NMR δ −0.09 (3H, s), 0.01 (3H, s), 0.81 (9H, s), 1.01 (3H, d, J = 6.3 Hz), 1.18 (3H, d, J = 6.3 Hz), 3.74 (1H, dq, J = 4.2, 6.3 Hz), 4.29 (3H, dq, J = 4.2, 6.3 Hz), 4.85 (1H, br s), 4.98 (1H, br s), 5.44 (1H, br s), 6.63 (1H, br d, J = ca. 8 Hz), 6.65 (1H, br d, J = ca. 8 Hz), 6.67 (1H, br d, J = ca. 8 Hz), 6.71 (1H, br d, J = ca. 8 Hz), 7.22 (1H, t, J = 8.4 Hz), 7.31 (1H, t, J = 8.4 Hz).

Cyclization Product 9. To a solution of **7** (4.22 g, 6.84 mmol) in THF (34 mL) at 0 °C was added Bu_4NF (14 mL, 1 M in THF, 14 mmol). After being stirred at room temperature for 4 h, the reaction mixture was poured into 1 N aqueous HCl and extracted three times with ethyl acetate. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (50−70% ethyl acetate in hexane) gave 3.33 g (97%) of the desilylation product: ^{1}H NMR δ 2.6 (1H, br), 3.36 (1H, dd, J = 6.6, 9.8 Hz), 3.45 (1H, dd, J = 4.1, 9.8 Hz), 3.64 (1H, dd, J = 5.8, 10.8 Hz), 3.72 (1H, dd, J = 3.8, 10.8 Hz), 3.92 (1H, dt, J = 4.1, 5.9 Hz), 4.42 (4H, br s), 4.57 (1H, dt, J = 4.0, 5.8 Hz), 5.2 (3H, br), 6.59 (1H, br d, J = 8.2 Hz), 6.62 (1H, br d, J = 8.2 Hz), 6.73 (2H, d, J = 8.3 Hz), 7.1−7.35 (12H, m); ^{13}C NMR δ 62.25, 68.81, 69.93, 70.12, 73.28, 78.35, 106.42, 107.37, 107.78, 108.62, 108.85, 109.68, 127.56, 127.63, 127.69, 127.77, 128.31, 128.31, 130.13, 130.63, 137.50, 137.69, 154.60, 155.05, 155.51, 156.95; IR (KBr disk) 3250 (br), 780, 740, 700 cm^{-1}; MS m/z (relative intensity) 502 (M$^+$, 68), 411 (16), 291 (23), 218 (100); HRMS calcd for $C_{30}H_{30}O_7$ 502.1992, found 502.1984.

To a solution of the desilylation product (2.45 g, 4.87 mmol) and triphenylphosphine (3.83 g, 14.6 mmol) in THF (200 mL) at 0 °C was added slowly a THF (45 mL) solution of dimethyl azodicarboxylate (DMAD) (3.56 g, 40% in toluene; 9.74 mmol) during 3 h. After the addition, the mixture was stirred at room temperature for 14 h and then concentrated in vacuo. The residue was subjected to flash chromatography (15−50% ethyl acetate in hexane). A fraction containing cyclization product **9** was collected and washed twice with water to remove 1,2-dicarbomethoxyhydrazine. The solution was dried and concentrated in vacuo to give 2.12 g (90%) of **9**: mp 138−139 °C (recrystallized from EtOH); $[\alpha]^{30}_D$ +8.5 (*c* 1.20, $CHCl_3$); ^{1}H NMR δ 3.60 (2H, ddd, J = 2.4, 3.4, 10.9 Hz), 3.73 (2H, br, d, J = ca. 11 Hz), 4.19 (2H, m), 4.52 (2H, d, J = 12.0 Hz), 4.58 (2H, d, J = 12.0 Hz), 6.10 (2H, br s), 6.74 (2H, dd, J = 1.0, 8.2 Hz), 6.83 (2H, dd, J = 1.0, 8.2 Hz), 7.20 (2H, t, J = 8.2 Hz), 7.27−7.37 (10H, m); ^{13}C NMR (125.8 MHz) δ 70.21, 73.64, 84.89, 113.04, 114.70, 115.35, 127.77 (2C), 128.42, 129.99, 137.66, 153.29, 159.77; IR (KBr disk) 3180 (br), 1235, 1050, 790, 745, 695 cm^{-1}; MS m/z (relative intensity) 484 (M$^+$, 4), 287 (7), 91 (100); HRMS calcd for $C_{30}H_{28}O_6$ 484.1886, found 484.1886. Anal. Calcd for $C_{30}H_{28}O_6$: C, 74.36; H, 5.82. Found: C, 74.61; H, 5.72.

Cyclization product **8** was prepared from **6** via 6′-[(1*R**,2*S**)-2-hydroxy-1-methylpropyloxy]-2,2′,6-biphenyltriol in 54% overall yield by a procedure similar to that described above. 6′-[(1*R**,2*S**)-2-Hydroxy-1-methylpropyloxy]-2,2′,6-biphenyltriol: ^{1}H NMR δ 1.00 (3H, d, J = 6.3 Hz), 1.18 (3H, d, J = 6.3 Hz), 2.2 (1H, br), 3.82 (1H, m), 4.38 (1H, dq, J = 2.9, 6.3 Hz), 4.9 (1H, br), 5.1 (1H, br), 5.35 (1H, br), 6.62 (1H, d, J = 8.5 Hz), 6.64 (1H, d, J = 8.5 Hz), 6.65 (1H, d, J = 8.5 Hz), 6.74 (1H, d, J = 8.5 Hz), 7.23 (1H, t, J = 8.4 Hz), 7.33 (1H, t, J = 8.2 Hz). Cyclization product **8**: ^{1}H NMR δ 1.36 (6H, m), 3.89 (2H, m), 6.78 (2H, d, J = 8.1 Hz), 6.80 (2H, d, J = 8.4 Hz), 7.25 (2H, t, J = 8.2 Hz); FT-IR (KBr disk) 3300 (br), 1052, 793, 754, 721 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.55; H, 6.04.

General Procedure for Intermolecular Cyclization of 9. To a solution of **9** (1.0 mmol) in DMF (25 mL) at room temperature was added K_2CO_3 (2.3 mmol). A solution of a 1,ω-dibromoalkane (1.0 mmol) in DMF (10 mL) was added slowly to the resulting suspension during 5−6 h at 80 °C by using a syringe pump. The reaction mixture was stirred further for 3 h at this temperature. The resulting mixture was poured into water and extracted twice with benzene. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (10−30% ethyl acetate in hexane) gave 6,6′-alkylenedioxy derivatives **13a**−**e**.

6,6′-Tetramethylenedioxy derivative 13a: ^{1}H NMR δ 1.75−2.0 (4H, m), 3.63 (2H, br d, J = ca. 10 Hz), 3.74 (2H, br d, J = ca. 10 Hz), 4.1−4.25 (4H, m), 4.44 (2H, br d, J = ca. 11 Hz), 4.60 (4H, br s), 6.87 (2H, d, J = 8.7 Hz), 6.89 (2H, d, J = 8.7 Hz), 7.25−7.35 (12H, m); ^{13}C NMR δ 26.90, 70.47, 70.88, 73.49, 84.87, 111.67. 115.18, 118.85, 127.49, 127.53, 128.27, 128.89, 138.03, 157.82, 159.74; IR (neat film) 1060, 790, 725, 695 cm^{-1}; MS m/z (relative intensity) 538 (M$^+$, 23), 355 (70), 192 (100); HRMS calcd for $C_{34}H_{34}O_6$ 538.2356, found 538.2366.

6,6′-Pentamethylenedioxy derivative 13b: ^{1}H NMR δ 1.67 (2H, m), 1.82 (4H, m), 3.62 (2H, m), 3.73 (2H, m), 4.11 (4H, m), 4.29 (2H, m), 4.58 (4H, s), 6.76 (2H, d, J = 8.4 Hz), 6.83 (2H, d, J = 8.1 Hz), 7.25 (2H, t, J = 8.2 Hz), 7.3−7.35 (10H, m); ^{13}C NMR δ 24.99, 26.56, 67.72, 70.69, 73.64, 84.98, 107.97, 114.29, 117.30, 127.56, 127.64, 128.35, 128.99, 138.13, 156.95, 159.84; IR (KBr disk) 1185, 780, 740, 725, 700 cm^{-1}; MS m/z (relative intensity) 552 (M$^+$, 78), 444 (12), 200 (55), 91 (100); HRMS calcd for $C_{35}H_{36}O_6$ 552.2512, found 552.2506.

6,6′-Hexamethylenedioxy derivative 13c: ^{1}H NMR δ 1.54 (4H, m), 1.72 (4H, m), 3.60 (2H, m), 3.71 (2H, m), 3.98 (2H, m), 4.1−4.4 (4H, m), 4.57 (4H, s), 6.73 (2H, d, J = 8.3 Hz), 6.82 (2H, d, J = 8.0 Hz), 7.2−7.35 (12H, m); ^{13}C NMR δ 24.06, 25.95, 66.64, 70.76, 73.65, 85.15, 106.82, 113.84, 117.41, 127.57, 127.65, 128.35, 129.12, 138.13, 156.95, 159.93; IR (KBr disk) 1060, 785, 740, 700 cm^{-1}; MS m/z (relative intensity) 566 (M$^+$, 75), 367 (25), 91 (100); HRMS calcd for $C_{36}H_{38}O_6$ 566.2669, found 566.2661.

6,6′-Heptamethylenedioxy derivative 13d: ^{1}H NMR δ 1.25−1.9 (10H, m), 3.61 (2H, m), 3.72 (2H, br d, J = ca. 11 Hz), 3.95−4.00 (2H, m), 4.05−4.15 (4H, m), 4.60 (4H, br s), 6.71 (2H, br d, J = 8.1 Hz), 6.83 (2H, br d, J = 8.1 Hz) 7.25−7.35 (12H, m, including t (2H, J = 8.1 Hz) at 7.27); ^{13}C NMR δ 24.48, 25.14, 26.59, 67.03, 70.71, 73.63, 85.13, 106.51, 113.57, 117.06, 127.61, 127.67, 128.37, 129.19, 138.06, 157.49, 159.78; IR (KBr disk) 1100, 780, 740, 720, 695 cm^{-1}; MS m/z (relative intensity) 580 (M$^+$, 42), 368 (95), 236 (100); HRMS calcd for $C_{37}H_{40}O_6$ 580.2825, found 580.2829.

6,6′-Decamethylenedioxy derivative 13e: mp 140−142 °C (recrystallized from ethyl acetate and hexane); ^{1}H NMR δ 1.40 (8H, m), 1.64 (4H, m), 3.59 (2H, m), 3.71 (2H, m), 3.86 (4H, br t, J = ca. 6.5 Hz), 4.10 (2H, m), 4.56 (4H, s), 6.75 (2H, d, J = 8.4 Hz), 6.82 (2H, d, J = 7.9 Hz), 7.25 (2H, t, J = 8.0 Hz), 7.3−7.35 (10H, m); ^{13}C NMR δ 23.84, 25.57, 25.57, 27.79, 68.88, 70.75, 73.64, 85.08, 108.65, 114.07, 118.10, 127.61, 127.68, 128.37, 129.04, 138.08, 158.26, 159.62; IR (KBr disk) 1090, 785, 740, 700 cm^{-1}; MS m/z (relative intensity) 622 (M$^+$, 100), 425 (17); HRMS calcd for $C_{40}H_{46}O_6$ 622.3296, found 622.3289.

(27) Lindsten, G.; Wennerstorm, O.; Isaksson, R. *J. Org. Chem.* **1987**, *52*, 547.

General Procedure for the Synthesis of (*S*)-2,2′-Biphenyldiols 14a−e. A mixture of **13a**−**e** (1 mmol) and Pd/C (10%, 270 mg) in ethanol (100 mL) was vigorously stirred under H_2 atmosphere at room temperature for 12−16 h. The mixture was filtered through a pad of cellulose, and the filtrate was concentrated in vacuo. To a DMSO (20 mL) solution of the resulting oil at room temperature was added $KN(TMS)_2$ (10 mL, 1 M in THF, 10 mmol). After being stirred at 50 °C for 7 h, the mixture was poured into 1 N aqueous HCl and extracted twice with ethyl acetate. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (30−50% ethyl acetate in hexane) gave (*S*)-biphenyldiols **14a**−**c**[5c] and **14d**,**e**.

The ee values of **14a**,**d**,**e** and **14b**,**c** were established by HPLC analyses using Chiracel OD column and by ^{1}H NMR analysis of the mono-MTPA derivatives, respectively. Mono-(*R*)-MTPA ester of **14b**: ^{1}H NMR δ 1.4−1.55 (2H, m), 1.6−1.75 (4H, m), 3.28 (3H, br s), 3.52 (1H, br s), 4.0−4.1 (2H, m), 4.25−4.4 (2H, m), 6.52 (1H, dd, J = 0.6, 8.1 Hz), 6.58 (1H, br d, J = ca. 8 Hz), 6.76 (1H, br d, J = ca. 8 Hz), 6.99 (1H, br d, J = ca. 8 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.25−7.45 (6H, m) [a minor diastereomer resonated at δ 3.30 (3H, br s) and 6.82 (1H, br d, J = ca. 8 Hz)]. Mono-(*R*)-MTPA ester of **14c**: ^{1}H NMR δ 1.3−1.4 (4H, m), 1.5−1.7 (4H, m), 3.20 (3H, br s), 3.9−4.0 (1H, m), 4.0−4.25 (3H, m), 4.91 (1H, br s), 6.53 (1H, br d, J = *ca.* 8 Hz), 6.56 (1H, br d, J = ca. 8 Hz), 6.72 (1H, br d, J = ca. 8 Hz), 6.96 (1H, br d, J = ca. 8 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.3−7.4 (5H, m), 7.40 (1H, t, J = 8.1 Hz) [a minor diastereomer resonated at δ 3.27 (3H, br s) and 4.81 (1H, br s)].

(*S*)-6,6′-Heptamethyledioxy-2,2′-biphenyldiol (14d): mp 221−222 °C (recrystallized from benzene); $[\alpha]^{33}_D$ +89.0 (*c* 0.78, EtOH); ^{1}H NMR δ 1.2−1.4 (4H, m), 1.4−1.6 (2H, m), 1.6−1.85 (4H, m), 3.95−4.05 (2H, m), 4.05−4.15 (2H, m), 5.00 (2H, br s), 6.53 (2H, br d, J = 8.1 Hz), 6.64 (2H, br d, J = 8.1 Hz), 7.24 (2H, t, J = 8.1 Hz); ^{13}C NMR δ 25.04, 25.24, 26.29, 67.51, 104.10, 106.80, 108.01, 130.32, 154.92, 157.91; IR (KBr disk) 3420 (br), 1190, 780, 735 cm^{-1}; MS *m*/*z* (relative intensity) 314 (M^+, 100), 218 (86), 200 (31); HRMS calcd for $C_{19}H_{22}O_4$ 314.1516, found 314.1517. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.56; H, 7.12.

(*S*)-6,6′-Decamethylenedioxy-2,2′-biphenyldiol (14e): mp 131−132 °C (recrystallized from benzene); $[\alpha]^{32}_D$ −165 (*c* 0.56, EtOH); ^{1}H NMR δ 1.0−1.35 (12H, m), 1.5−1.6 (4H, m), 3.9−4.15 (4H, m), 5.38 (2H, br s), 6.64 (2H, br d, J = 8.1 Hz), 6.72 (4H, d, J = 8.1 Hz), 7.26 (2H, t, J = 8.1 Hz); ^{13}C NMR (125.8 MHz) δ 24.27, 25.71, 26.65, 27.73, 68.26, 105.78, 109.16, 109.96, 130.02, 155.63, 156.54; IR 3470 (br), 1190, 1080, 780, 725 cm^{-1}; MS *m*/*z* (relative intensity) 356 (M^+, 100), 218 (90), 200 (34); HRMS calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1986. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.94; H, 7.842.

(*S*)-Bis(triflate) 17. Trifluoromethanesulfonic anhydride (1.1 mL, 6.6 mmol) was added to a solution of **6** (1.06 g, 2.19 mmol) in pyridine (4.4 mL) at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was diluted with ether, poured into 1 N aqueous HCl, and extracted twice with ether. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (30% ethyl acetate in hexane) gave 1.48 g (90%) of **17**: $[\alpha]^{33}_D$ +17.9 (*c* 1.23, EtOH); ^{1}H NMR δ 3.65 (2H, br d, J = ca. 11 Hz), 3.73 (2H, br d, J = ca. 11 Hz), 4.16 (2H, m), 4.58 (4H, br s), 7.25 (2H, dd, J = 0.9, 8.4 Hz), 7.28−7.38 (12H, m), 7.51 (2H, t, J = 8.4 Hz); ^{13}C NMR δ 69.90, 73.64, 85.84, 117.59, 118.31, (q, J = 321 Hz), 120.19, 122.56, 127.71, 127.83, 128.46, 131.26, 137.66, 146.90, 160.38; IR (neat film) 795, 750, 695 cm^{-1}; MS *m*/*z* (relative intensity) 748 (M^+, 1), 657 (37), 551 (39), 91 (100); HRMS calcd for $C_{32}H_{26}O_{10}F_6S_2$ 748.0871, found 748.0870.

General Procedure for Palladium-Catalyzed Cross-Coupling of Bis(triflate) 17 with Organozinc Reagents. A solution of RZnCl (R = Me, Bu, Ph) was prepared by treatment of a THF (8 mL) solution of $ZnCl_2$ (4.0 mmol) with RLi (4.0 mmol) (MeLi; 1 M in ether, BuLi; 1.6 M in hexane, PhLi; 1 M in cyclohexanes−ether) at 0 °C for 15 min. A solution of EtZnCl was prepared by treatment of a THF (8 mL) solution of $ZnCl_2$ (2.0 mmol) with Et_2Zn (2.0 mmol) (1 M in hexane) under similar conditions. To a suspension of **17** (1.0 mmol) and $PdCl_2$(dppf) (0.05 mmol) in THF (20 mL) at 0 °C was added a THF solution of RZnCl (4.0 mmol). For the reaction with MeZnCl, the solution was treated with DIBALH (0.10 mL, 1 M in hexane, 0.10 mmol) at 0 °C for 10 min before the addition of MeZnCl. After being stirred at 65 °C for 20−37 h, the resulting mixture was diluted with ether, poured into aqueous NH_4Cl, and extracted twice with ether. The organic layers were washed with aqueous $NaHCO_3$, dried, and concentrated in vacuo. Purification of the residue by flash chromatography (2−30% ethyl acetate in hexane) gave dialkylation products **18a**−**d**.

6,6′-Dimethyl derivative 18a: mp 101−102 °C (recrystallized from ethyl acetate and hexane); ^{1}H NMR δ 2.17 (6H, s), 3.59 (2H, br d, J = ca. 10 Hz), 3.70 (2H, br d, J = ca. 10 Hz), 4.11 (2H, m), 4.57 (4H, br s), 7.06 (4H, d, J = 7.8 Hz), 7.25 (2H, t, J = 7.8 Hz), 7.3−7.4 (10H, m); ^{13}C NMR δ 19.72, 70.65, 73.55, 85.65, 119.08, 125.90, 127.63, 127.63, 128.32, 128.61, 130.21, 137.61, 137.94, 159.14; IR (KBr disk) 1095, 790, 760, 740, 700 cm^{-1}; MS *m*/*z* (relative intensity) 480 (M^+, 45), 389 (13), 91 (100); HRMS calcd for $C_{32}H_{32}O_4$ 480.2302, found 480.2305.

6,6′-Diethyl derivative 18b: ^{1}H NMR δ 1.03 (6H, t, J = 7.5 Hz), 2.2−2.6 (4H, m), 3.63 (2H, br d, J = ca. 11 Hz), 3.71 (2H, br d, J = ca. 11 Hz), 4.11 (2H, m), 4.58 (4H, br s), 7.09 (2H, br d, J = 7.5 Hz), 7.13 (2H, br d, J = 7.5 Hz), 7.3−7.4 (12H, m); ^{13}C NMR δ 15.01, 26.13, 70.72, 73.50, 85.69, 119.19, 123.79, 127.56, 127.64, 128.30, 128.86, 129.41, 138.03, 143.49, 159.24; IR (KBr disk) 1090, 755, 735, 695 cm^{-1}; MS *m*/*z* (relative intensity) 508 (M^+, 66), 311 (34), 91 (100); HRMS calcd for $C_{34}H_{36}O_4$ 508.2615, found 508.2609.

6,6′-Dibutyl derivative 18c: ^{1}H NMR δ 0.73 (6H, t, J = 7.2 Hz), 1.13 (4H, sextet, J = 7.2 Hz), 1.25−1.5 (4H, m), 2.4−2.6 (4H, m), 3.64 (2H, br d, J = ca. 11 Hz), 3.71 (2H, br d, J = ca. 11 Hz), 4.11 (2H, m), 4.59 (4H, br s), 7.07 (2H, br d, J = 7.5 Hz), 7.09 (2H, br d, J = 7.5 Hz), 7.25−7.34 (12H, m); ^{13}C NMR δ 13.67, 22.17, 32.81, 33.16, 70.72, 73.48, 85.64, 119.12, 124.46, 127.57, 127.66, 128.33, 128.67, 129.84, 138.10, 142.26, 159.27; IR (neat film) 1100, 765, 735, 700 cm^{-1}; MS *m*/*z* (relative intensity) 564 (M^+, 34), 367 (28), 91 (100); HRMS calcd for $C_{38}H_{44}O_4$ 564.3241, found 564.3243.

6,6′-Diphenyl derivative 18d: ^{1}H NMR δ 3.72 (2H, br d, J = ca. 11 Hz), 3.80 (2H, br d, J = ca. 11 Hz), 4.29 (2H, m), 4.65 (4H, br s), 6.44 (4H, br d, J = ca. 7 Hz), 6.9−7.0 (6H, m), 7.05 (2H, br t, J = ca. 7 Hz), 7.25−7.40 (14 H, m); ^{13}C NMR δ 70.69, 73.66, 85.58, 120.75, 125.84, 126.06, 127.21, 127.71, 127.74, 128.73, 129.14, 137.97, 140.54, 142.67, 159.94; IR (neat film) 1900, 735, 695 cm^{-1}; MS *m*/*z* (relative intensity) 604 (M^+, 74), 407 (22), 91 (100); HRMS calcd for $C_{42}H_{36}O_4$ 604.2613, found 604.2617.

Monomethylation product 19a: ^{1}H NMR δ 2.23 (3H, s), 3.6−3.8 (4H, m), 4.1−4.2 (2H, m), 4.56 (4H, br s), 7.05−7.1 (2H, m), 7.18 (1H, d, J = 8.4 Hz), 7.25−7.45 (13H, m); MS *m*/*z* (relative intensity) 614 (M^+, 20), 523 (22), 91 (100); HRMS calcd for $C_{32}H_{29}O_7F_3S$ 614.1586, found 614.1581.

Monoethylation product 19b: ^{1}H NMR δ 1.10 (2H, t, J = 7.5 Hz), 2.45 (1H, dq J = 7.5 and 15.0 Hz), 2.64 (1H, dt, J = 7.5 and 15.0 Hz), 3.6−3.8 (4H, m), 4.05−4.2 (2H, m), 4.56 (2H, br s), 4.57 (2H, br s), 7.06 (1H, br d, J = ca. 8 Hz), 7.15−7.2 (2H, m), 7.25−7.45 (13H, m); MS *m*/*z* (relative intensity) 628 (M^+, 14), 503 (49), 91 (100); HRMS calcd for $C_{33}H_{31}O_7F_3S$ 628.1742, found 628.1729.

General Procedure for the Synthesis of (*S*)-2,2′-Biphenyldiols 20a−d. To a solution of **17a**−**d** (1.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added BBr_3 (1.7 mL, 18.0 mmol). After being stirred for 8−10 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, poured into ice, and extracted twice with ether. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (5−30% ethyl acetate in hexane) gave **20a**[24] and **20b**−**d**. Their ee values were established by HPLC analyses using Chiracel OD column.

(*S*)-6,6′-Diethyl-2,2′-biphenyldiol (20b): mp 93−95 °C (recrystallized from hexane); $[\alpha]^{35}_D$ −55.3° (*c* 1.03, EtOH); ^{1}H NMR δ 1.06 (6H, t, J = 7.5 Hz), 2.29 (4H, q, J = 7.5 Hz), 4.72

(2H, br s), 6.90 (2H, d, J = 8.1 Hz), 6.97 (2H, d, J = 7.5 Hz), 7.31 (2H, t, J = 7.8 Hz); ^{13}C NMR δ 14.52, 26.08, 113.09, 118.83, 120.66, 130.19, 145.01, 153.84; IR (KBr disk) 3400 (br), 800, 750 cm^{-1}; MS m/z (relative intensity) 242 (M^+, 68), 213 (100); HRMS calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1316. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.30; H, 7.37.

(*S*)-6,6′-Dibutyl-2,2′-biphenyldiol (20c): mp 48−49 °C (recrystallized from hexane) $[\alpha]^{22}_D$ −28.3 (c 1.13, EtOH); ^{1}H NMR δ 0.77 (6H, t, J = 7.2 Hz), 1.15−1.25 (4H, m), 1.41 (4H, quintet, J = 7.2 Hz), 2.2−2.3 (4H, m), 4.73 (2H, s), 6.88 (2H, d, J = 7.5 Hz), 6.94 (2H, d, J = 8.2 Hz), 7.28 (2H, t, J = 7.8 Hz); ^{13}C NMR δ 13.71, 22.51, 32.34, 32.75, 113.00, 118.85, 121.42, 130.09, 143.76, 153.83; FT-IR (KBr disk) 3490 (br), 3420 (br), 796, 741 cm^{-1}; MS m/z (relative intensity) 298 (M^+, 68), 241 (100); HRMS calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1913. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.10; H, 8.87.

(*S*)-1,1′:2′,1″:2″,1‴-Quaterphenyl-3′,6″-diol (20d): mp 135−136 °C (recrystallized from benzene); $[\alpha]^{25}_D$ −86.3 (c 1.02, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.27 (2H, br s), 6.67 (4H, br d, J = ca.8 Hz), 6.86 (2H, dd, J = 0.9, 7.6 Hz), 7.04 (1H, dd, J = 0.9, 8.2 Hz), 7.08 (4H, br t, J = ca. 8 Hz), 7.16 (2H, br t, J = ca. 8 Hz), 7.33 (2H, br t, J = ca. 8 Hz); ^{13}C NMR δ 114.39. 119.33, 122.76, 126.57, 127.29, 128.69, 130.05, 140.04, 144.01, 154.30; IR (KBr disk) 3580, 3400 (br), 755, 700 cm^{-1}; MS m/z (relative intensity) 338 (M^+, 100), 281 (18); HRMS calcd for $C_{24}H_{18}O_2$ 338.1307, found 338.1308.

6,6′-Dicyano Derivative 21 (Table 4, Entry 3). A mixture of bis(triflate) **17** (0.15 g, 0.19 mmol), $Zn(CN)_2$ (47 mg, 0.40 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) in DMF (0.2 mL) was stirred at 150 °C for 16 h. The resulting mixture was diluted with ethyl acetate, poured into aqueous $NaHCO_3$, and extracted three times with ethyl acetate. The dried organic layers were concentrated in vacuo. The residue was purified by flash chromatography (15−40% ethyl acetate in hexane) to give 84 mg (86%) of **21**: ^{1}H NMR (500 MHz) δ 3.60 (2H, br td, J = *c*a. 1.5, 10.2 Hz), 3.75 (2H, br d, J = 10.2 Hz), 4.17 (2H, m), 4.55 (2H, d, J = 12.1 Hz), 4.62 (2H, d, J = 12.1 Hz), 7.3−7.4 (10H, m), 7.50 (2H, dd, J = 1.0, 8.1 Hz), 7.57 (2H, t, J = 8.0 Hz), 7.65 (2H, dd, J = 1.0, 7.5 Hz); ^{13}C NMR (125.8 MHz) δ 69.69, 73.74, 85.39, 113.91, 117.38, 127.44, 127.73, 127.94, 128.50, 129.55, 131.25, 131.48, 137.39, 159.03; IR (KBr disk) 2240, 805, 740, 700 cm^{-1}; MS m/z (relative intensity) 502 (M^+, 2), 411 (62), 305 (42), 91 (100); HRMS calcd for $C_{32}H_{26}N_2O_4$ 502.1892, found 502.1884.

Monocyano Derivative 22 (Table 4, Entry 4). A mixture of bis(triflate) **17** (0.45 g, 0.60 mmol), $Zn(CN)_2$ (0.14 g, 1.2 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) in DMF (0.5 mL) was stirred at 120 °C for 3 h. Aqueous workup similar to that described above and purification of the crude products by flash chromatography (10−30% ethyl acetate in hexane) gave, in the order of elution, **17** (171 mg, 38%), **22** (165 mg, 44%), and **21** (54 mg, 18%). **22**: ^{1}H NMR (500 MHz) δ 3.6−3.7 (2H, m), 3.75 (1H, br d, J = ca. 10 Hz), 3.82 (1H, br d, J = ca. 10 Hz), 4.22 (2H, br s), 4.59 (1H, d, J = 12.1 Hz), 4.61 (2H, br s), 4.67 (1H, d, J = 12.1 Hz), 7.3−7.45 (12H, m), 7.55−7.65 (4H, m); ^{13}C NMR (125.8 MHz) δ 69.70 (2C), 73.57, 73.62, 85.49, 85.58, 113.99, 117.31, 118.22, 118.23 (q, J = 329.9 Hz), 122.59, 122.63, 125.74, 127.55, 127.67, 127.80, 127.85, 128.24, 128.41, 128.43, 128.88, 131.24, 131.40, 137.43, 137.53, 146.64, 159.50, 159.89; IR (KBr disk) 2230, 1220, 1140, 800, 735 cm $^{-1}$; MS m/z (relative intensity) 625 (M^+, 1), 534 (58), 428 (32), 91 (100); HRMS calcd for $C_{32}H_{26}NO_7F_3S$ 625.1382, found 625.1382.

Dicarboxylic Acid 23. Dicyano derivative **21** (0.26 g, 0.52 mmol) was treated with KOH (1.02 g, 18.17 mmol) in water (0.5 mL) and 2-ethoxyethanol (0.8 mL) at 138 °C for 10 h. The resulting mixture was diluted with water, poured into 1 N aqueous HCl, and extracted three times with ethyl acetate. The organic layers were dried and concentrated in vacuo. The residue was purified by chromatography (40−70% ethyl acetate in hexane) to give, in the order of elution, dicarboxylic acid **23** (131 mg, 47%) and amidocarboxylic acid **24** (109 mg, 38%). Hydrolysis of **24** under similar conditions gave **23** in 72% yield. **23**: mp 240−241 °C (recrystallized from ethyl acetate and hexane); $[\alpha]^{25}_D$ +97.9 (c 0.515, $CHCl_3$); ^{1}H NMR (500 MHz) δ 3.62 (2H, br d, J = ca. 11 Hz), 3.69 (2H, br d, J = ca. 11 Hz), 4.17 (2H, m), 4.57 (4H, br s), 7.3−7.35 (10H, m), 7.45 (4H, m), 7.94 (2H, m), 12.6 (2H, br); ^{13}C NMR (125.8 MHz) δ 70.41, 73.72, 85.72, 127.03, 127.06, 127.67, 127.75, 128.43, 129.17, 130.26, 130.67, 137.79, 158.68, 172.44; FT-IR (KBr disk) 3450 (br), 1697, 729, 767, 698 cm^{-1}; MS m/z (relative intensity) 540 (M^+, <1), 431 (46), 91 (100); HRMS calcd for $C_{32}H_{28}O_8$ 540.1784, found 540.1801. Anal. Calcd for $C_{32}H_{28}O_8$: C, 71.10; H, 5.22. Found: C, 71.18; H, 5.49. **24**: ^{1}H NMR (500 MHz) δ 3.63 (2H, m), 3.71 (2H, br d, J = ca. 10 Hz), 4.15 (2H, br s), 4.58 (4H, br s), 6.06 (2H, br s), 6.76 (1H, br s), 7.30−7.38 (15H, m), 7.73 (1H, br t, J = ca. 4.5 Hz); ^{13}C NMR (125.8 MHz) δ 70.41, 70.41, 73.69, 73.69, 85.27, 85.62, 123.75, 124.50, 126.20, 126.75, 127.71, 128.22, 128.43, 129.51, 129.53, 129.68, 136.55, 137.79, 137.82, 158.39, 158.66, 170.88, 172.31; FT-IR (KBr disk) 3490 (br), 3390 (br), 3205 (br), 1709, 1651, 768, 735, 698 cm^{-1}; MS m/z (relative intensity) 521 ($M^+ - H_2O$, 20), 430 (31), 91 (100); HRMS calcd for $C_{32}H_{27}NO_6$ ($M^+ - H_2O$) 521.1839, found 521.1829.

Lactone 26. Monocyano derivative **22** (0.14 g, 0.22 mmol) was treated with KOH (0.89 g, 15 mmol) in water (0.5 mL) and 2-ethoxyethanol (0.8 mL) first at room temperature for 1 h and then at 138 °C for 10 h. The resulting mixture was poured into 1 N aqueous HCl and extracted three times with ethyl acetate. The organic layers were dried and concentrated in vacuo. The reside was dissolved in toluene (3 mL) containing *p*-toluenesulfonic acid monohydrate and heated at 50 °C for 4 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (3−5% ethyl acetate in benzene) gave 86 mg (80%) of **26**: mp 124−124.5 °C (recrystallized from EtOH); $[\alpha]^{23}_D$ −55.0 (c 0.695, $CHCl_3$); ^{1}H NMR (500 MHz) δ 3.69 (2H, br s), 3.80 (2H, br s), 4.48 (2H, br), 4.55 (2H, br d, J = ca. 11 Hz), 4.64 (2H, br d, J = ca. 11 Hz), 7.13 (1H, br d, J = ca. 8 Hz), 7.15 (1H, br d, J = ca. 8 Hz), 7.3−7.4 (11H, m), 7.51 (1H, br t, ca. 8 Hz), 7.61 (1H, br d, ca. 8 Hz), 8.18 (1H, br d, J = ca. 8 Hz); ^{13}C NMR (125.8 MHz) δ 73.51, 123.56, 127.75, 127.86, 128.27, 128.43, 129.39, 129.98, 137.46, 151.27, 160.88 (other resonances were too broad to be observed); FT-IR (KBr disk) 1728, 735, 696 cm^{-1}; MS m/z (relative intensity) 494 (M^+, 30), 297 (20), 91 (100); HRMS calcd for $C_{31}H_{26}O_6$ 494.1729, found 494.1725. Anal. Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 74.95; H, 5.36.

6-Cyano-6′-phenyl Derivative 27. Cross coupling of **22** with PhZnCl was carried out according to a procedure similar to that described for **17**. Purification of the crude products by flash chromatography (5% ethyl acetate in benzene) gave **27** in 95% yield: ^{1}H NMR (500 MHz) δ 3.66 (1H, br d, J = ca. 11 Hz), 3.70 (1H, br d, J = ca. 11 Hz), 3.80 (2H, br d, J = ca. 11 Hz), 3.82 (2H, br d, J = ca. 11 Hz), 4.25 (2H, m), 4.59 (1H, d, J = 12.1 Hz), 4.54 (2H, br s), 4.56 (1H, d, J = 12.1 Hz), 7.21 (1H, dd, J = 1.0, 7.6 Hz), 7.24 (4H, m), 7.28 (1H, dd, J = 1.0, 7.6 Hz), 7.35−7.45 (8H, m), 7.50 (1H, dd, J = 1.0, 7.6 Hz), 7.53 (1H, t, J = 7.6 Hz); ^{13}C NMR (125.8 MHz) δ 70.02, 70.26, 73.63, 73.63, 85.17, 85.76, 114.23, 117.63, 120.97, 126.19, 126.85, 126.90, 127.65, 127.70, 127.77, 127.80, 128.41, 128.86, 129.55, 130.36, 130.74, 134.62, 137.61, 137.63, 139.87, 143.14, 159.08, 159.69; IR (KBr disk) 2220, 760, 730, 695 cm-^{1}; MS m/z (relative intensity) 553 (M^+ 32), 462 (14), 91 (100); HRMS calcd for $C_{37}H_{31}NO_4$ 553.2253, found 553.2263.

Terphenyl Carboxylic Acid 28. The acid was obtained in 55% yield by hydrolysis of **27** by a procedure similar to that described for the preparation of diacid **23**. **28**: $[\alpha]^{25}_D$ −72.8 (c 0.86, $CHCl_3$); ^{1}H NMR (500 MHz) δ 3.65−3.75 (2H, m), 3.75−3.8 (2H, m), 4.2−4.3 (2H, m), 4.61 (2H, br s), 4.64 (2H, br s), 6.2 (1H, br), 6.96 (2H, br d, J = ca. 7 Hz), 7.13 (1H, br s, J = ca. 7 Hz), 7.15 (1H, br d, J = ca. 7 Hz), 7.18 (2H, br t, J = ca. 7 Hz), 7.25 (1H, br s, J = ca. 7 Hz), 7.3−7.5 (14H, m); ^{13}C NMR (125.8 MHz) δ 70.39, 70.64, 73.72, 73.75, 85.10, 85.85, 120.92, 125.87, 126.02, 126.27, 126.64, 127.78, 127.80, 127.82, 128.47, 128.90, 129.66, 130.26, 131.34, 131.81, 137.88, 140.24, 142.84, 158.46, 159.73, 171.04; FT-IR (KBr disk) 3500 (br), 1693, 764,

700 cm^{-1}; MS *m*/*z* (relative intensity) 572 (M^+, 50), 503 (7), 91 (100); HRMS calcd for $C_{37}H_{32}O_6$ 572.2199, found 572.2207.

Cyclic Amidine Derivative 29. To a mixture of $Pd(OAc)_2$ (6 mg, 0.03 mmol), BINAP (25 mg, 0.04 mmol), and Cs_2CO_3 (0.24 g, 0.75 mmol) at room temperature was added a toluene (1 mL) solution of **22** (0.33 g, 0.53 mmol) and benzylamine (0.1 mL, 1.1 mmol). The mixture was stirred first at room temperature for 0.5 h and then at 100 °C for 16 h. The reaction mixture was diluted with ethyl acetate, poured into aqueous $NaHCO_3$, and extracted three times with ethyl acetate. The dried organic layers were concentrated in vacuo. Purification of the residue by flash chromatography (30−60% ethyl acetate in hexane) gave 176 mg (57%) of **29**: ^{1}H NMR (500 MHz) δ 3.72 (2H, m), 3.87 (2H, br s), 4.49 (2H, m), 4.55−4.75 (4H, m), 4.9−5.05 (4H, m), 5.75 (1H, br s), 7.12 (1H, br d, J = ca. 7.5 Hz), 7.3−7.4 (12H, m), 7.45−7.65 (8H, m); ^{13}C NMR (125.8 MHz) δ 69.78, 73.59, 116.96, 121.75, 127.41, 127.62, 127.70, 127.74, 128.89, 128.43, 128.66, 128.83, 137.84, 139.14, 152.61 (other resonances were too broad to be observed); FT-IR (KBr disk) 3400 (br), 1649, 1521, 1250, 723, 696 cm^{-1}; MS *m*/*z* (relative intensity) 582 (M^+, 84), 360 (57), 91 (100); HRMS calcd for $C_{38}H_{34}N_2O_4$ 582.2518, found 582.2515.

Lactam 30. The compound was obtained in 67% yield by hydrolysis of **29** by a procedure similar to that described for the preparation of diacid **23**. **30**: mp 118−119 °C (recrystallized from benzene and hexane); $[\alpha]^{24}_D$ −152 (*c* 0.87, $CHCl_3$); ^{1}H NMR (500 MHz) δ 3.73 (2H, br dd, J = ca. 6, 11 Hz), 3.86 (2H, br δ J = ca. 11 Hz), 4.47 (2H, br), 4.61 (2H, br d, J = ca. 12 Hz), 4.68 (2H, br d, J = ca. 12 Hz), 7.10 (1H, br d, J = ca. 7.5 Hz), 7.21 (1H, br d, J = ca. 7.5 Hz), 7.3−7.45 (11H, m), 7.58 (1H, br t, J = ca. 7.5 Hz), 7.62 (1H, br t, J = ca. 7 Hz), 8.36 (1H, br d, J = ca. 7.5 Hz), 11.47 (1H, br s); ^{13}C NMR (125.8 MHz) δ 69.6 (br), 73.58, 89.0 (br), 111.5 (br), 116.8 (br), 123.2 (br), 126.9 (br), 127.72, 127.77, 128.43, 129.69, 136.98, 137.69, 126.0 (br), 157.1 (br), 163.05, 171.14 (other resonances were too broad to be observed); FT-IR (KBr disk) 3185 (br), 1664, 738, 698 cm^{-1}; MS *m*/*z* (relative intensity) 493 (M^+, 71), 296 (10), 91 (100); HRMS calcd for $C_{31}H_{27}NO_5$ 493.1889, found 493.1880. Anal. Calcd for $C_{31}H_{27}NO_5$: C, 75.44; H, 5.51; N, 2.84. Found: C, 75.26; H, 5.65; N, 2.77.

Supporting Information Available: X-ray crystallographic data for **18a** and ^{1}H NMR spectra of compounds **5**−**7**, **13a**−**e**, **17**, **18a**−**d**, **19a**,**b**, **20d**,**e**, **21**, **22**, **24**, and **27**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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