New Method of Kinetic Resolution of Axially Chiral Biaryl Compounds Using a Sugar Template

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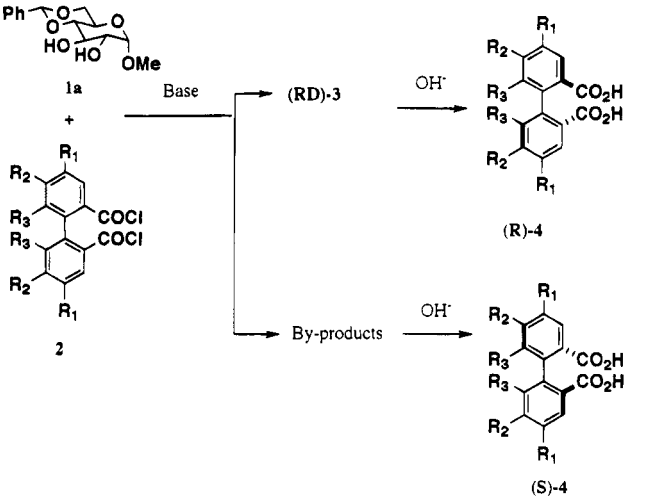
Chiral biaryl units are present in a wide range of compounds both natural and synthetic. Because of their pharmacological activity and use as chiral catalysts for asymmetric syntheses, the need for a simple synthetic route to axially chiral biaryls is great.[1,2] In synthesizing an ellagitannin natural product,[3] we made the interesting observation that the esterification of racemic biphenyldicarboxylic acid with a glucose derivative occurred diastereoselectively. This means that the optical resolution of axially chiral biaryls can be realized through the esterification of a racemic biaryl dicarboxylic acid with a sugar template, if the diastereoselectivity can be controlled (Scheme 1). Because the synthesis of a racemic compound is often so much easier than enantioselective synthesis, optical resolution still plays a very important role in the preparation of axially chiral biaryl compounds. We wish to report a new method of optical resolution for axially chiral biaryls based on this simple concept.

Initially, we attempted an optical resolution using hexamethoxydiphenic acid as a model compound.[4] Use of acyl chloride **2a** (R^1, R^2, R^3 = OMe) was found to be essential for effective esterification,[5] and its level of diastereoselectivity was examined under various reaction conditions. A survey of the effect of solvent in the presence of several types of bases is summarized in Table 1. The reaction product was mainly the cyclized compound **3**, with a fair amount of **5** as a major byproduct and small amounts of other products which we assumed to be oligomeric ester compounds. Although byproducts were formed in this reaction, isolation of the target product, **3**, was accomplished very easily by silica gel thin layer chromatography (TLC) or flash column chromatography. Ester **3** was subjected to hydrolysis using anhydrous potassium hydroxide (potassium *tert*-butoxide, H_2O, THF),[6] to yield diphenic acid **4** for assignment of the absolute configuration by comparison of the specific rotation with that found in the literature.[7] Optically pure hexamethoxydiphenic acid, (*R*)-**4**, was obtained from (*RD*)-**3**, and (*S*)-**4** was obtained from (*SD*)-**3**. Optical resolution of hexamethoxydiphenic acid was thus accomplished through esterification using sugar template **1a**.

Scheme 1. Concept of the Present Optical Resolution of Axially Chiral Biaryls



We speculated that (*SD*)-**3** should be obtained preferentially from this reaction because the (*S*)-isomer of diphenic acid is a component of natural ellagitannins.[8] However, in most cases (*RD*)-**3** proved to be the major product. MM2 calculations on the model compound cyclic ester **3** suggested that (*SD*)-**3** was preferable to (*RD*)-**3** from the standpoint of steric energy.[9] It was assumed that the diastereoselectivity did not depend on thermodynamic differences between the two atropisomers but on kinetic differences in the intramolecular cyclization. A strong base, therefore, would promote high diastereoselection through kinetically-controlled cyclization. As can be seen in Table 1, use of a stronger base than triethylamine was essential in order to obtain **3** diastereoselectively. The best results occurred when the reaction was carried out using sodium hydride as a base and toluene as a solvent at room temperature (entry 9). Use of an excess amount of sugar **1a** was essential to obtain (*RD*)-**3** in good yield (entries 10 and 11). In particular, the reaction was completed rapidly when 2 equiv of **1a** were used, giving (*RD*)-**3** in 38% yield, which corresponded to a 76% theoretical yield (entry 11). The conditions of entry 11 are thus recommended for practical use, though this did not provide the best selectivity. In addition, dilute reaction conditions were found to be superior to concentrated conditions as shown in entries 11 and 12. Because product **3** is easily crystallized, pure (*RD*)-**3** was obtained from the product isolated under the reaction conditions in entry 11 without a tedious separation of (*RD*)-**3** and (*SD*)-**3**. The use of DMAP and t-BuOK caused a drastic reduction in diastereoselectivity (entries

(1) For leading references for both the synthesis and natural occurrence of biaryls see: (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Hattori, T.; Goto, J.; Miyano, S. *J. Synth. Org. Chem., Jpn.* **1992**, *50*, 986. References cited therein.

(2) The recent synthetic strategies for axially chiral biaryl compounds are summarized in three general types. For examples, see the following: (1) Nucleophilic aromatic substitution: (a) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655. (b) Jung, M. E.; Kim, C.; Bussche, L. *J. Org. Chem.* **1994**, *59*, 3248. (c) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732. (d) Hattori, T.; Suzuki, T.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1375. (2) Oxidative coupling: (e) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567. (f) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357. (g) Osa, T.; Kashiwagi, Y. Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535. Optical resolution of racemic compounds: (h) Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *J. Org. Chem.* **1994**, *59*, 5748. (i) Miyano, S.; Koike, N.; Hattori, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1899. (j) Lin, G.; Liu, S.-H.; Chen, S.-J.; Wu, F.-C.; Sun, H.-L. *Tetrahedron Lett.* **1993**, *34*, 6057.

(3) Ellagitannins are galloyl esters of glucose and found in plants. They are known for interesting biological activity such as anti HIV activity. Nonaka, G.; Nishioka, I.; Nishizawa, M.; Yamagishi, T.; Kashiwada, Y.; Dutschman, G. E.; Bondner, A. J.; Kikuskie, R. E.; Cheng, Y.-E.; Lee, K.-H. *J. Nat. Prod.* **1990**, *53*, 587.

(4) Prepared easily from commercially ellagic acid in three steps with 34% overall yield.

(5) We initially utilized dicyclohexylcarbodiimide (DCC)-mediated esterification of hexamethoxydiphenic acid with sugar **1a**, but the desired cyclic ester **3** was obtained in low yield.

(6) This reagent gave biphenic acid in superior yield to other reagents tested such as lithium hydroxide and sodium hydroxide: Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577. Gassman, P. G.; Schenk, W. N. *Ibid.* **1977**, *42*, 918.

(7) Schmidt, O. T.; Demmler, K. *Liebigs Ann. Chem.* **1952**, *576*, 85.

(8) Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1765.

(9) "Extended MM2 program" (CAChe Scientific, version 3.0) was employed to calculate the steric energy of (RD)-**3** (46.267 kcal/mol) and (SD)-**3** (42.566 kcal/mol).

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Table 1. Diastereoselective Esterification of Acyl Chloride 2a with Sugar 1a[a]

entry	base	amt of **1a**[b]	solvent (concn, M)	time (h)	temp (°C)	(*RD*)-**3**[c] (%)	(*SD*)-**3**[c] (%)	ratio ((*RD*)-**3**:(*SD*)-**3**)
1	Et_3N	1.0	CH_2Cl_2 (0.01 M)	46	rt	30	9	3.3:1
2	Et_3N	1.0	CH_2Cl_2 (0.01 M)	44	reflux	42	34	1.3:1
3	Et_3N	1.0	CH_2Cl_2 (0.5 M)	6	rt	40	4	10:1
4	Et_3N	1.0	CH_2Cl_2 (0.05 M)	6.5	−78 to rt	46	5	8.8:1
5	Et_3N	1.0	Et_2O (0.01 M)	111	rt	13	10	1.3:1
6	Et_3N	1.0	THF (0.01 M)	125	rt	6	24	1:4.4
7	Et_3N	1.0	PhH (0.01 M)	106	rt	30	2	16:1
8	Et_3N	1.0	$PhCH_3$ (0.01 M)	11	−78 to rt	28	0.4	78:1
9	NaH	1.0	$PhCH_3$ (0.01 M)	16.5	rt	44	trace[d]	>900:1
10	NaH	1.5	$PhCH_3$ (0.01 M)	17	rt	74	trace[d]	>1500:1
11	NaH	2.0	$PhCH_3$ (0.01 M)	2.5	rt	76	2	38:1
12	NaH	2.0	$PhCH_3$ (0.5 M)	3.5	rt	72	5	14:1
13	NaH	2.0	$PhCH_3$ (0.005 M)	5	rt	74	4	19:1
14	tBuOK	2.0	$PhCH_3$ (0.01 M)	5	rt	56	4	13:1
15	DMAP	2.0	$PhCH_3$ (0.01 M)	36	rt	54	44	1.2:1
16	NaH	2.0	PhH (0.01 M)	1.5	rt	60	trace[d]	>1200:1
17	NaH	2.0	THF (0.01 M)	1.5	rt	44	4	12:1
18	NaH	2.0	Et_2O (0.01 M)	11	rt	42	trace[d]	>800:1
19	NaH	2.0	DMF (0.01 M)	66	rt	8	1	5.2:1

[a] Reaction conditions: amount of the base was 2.1 equiv, relative to the sugar **1a**. [b] Equivalent relative to acyl chloride **2a**. [c] Isolated yield based on acyl chloride **2a**. Yield is shown as a calculated value relative to the theoretical yield because the starting acyl chloride was a racemic state. The minimum weight of the balance employed was 0.05 mg. [d] There was no detectable amount of (*SD*)-**3**, though it seemed to be present on the TLC plate.

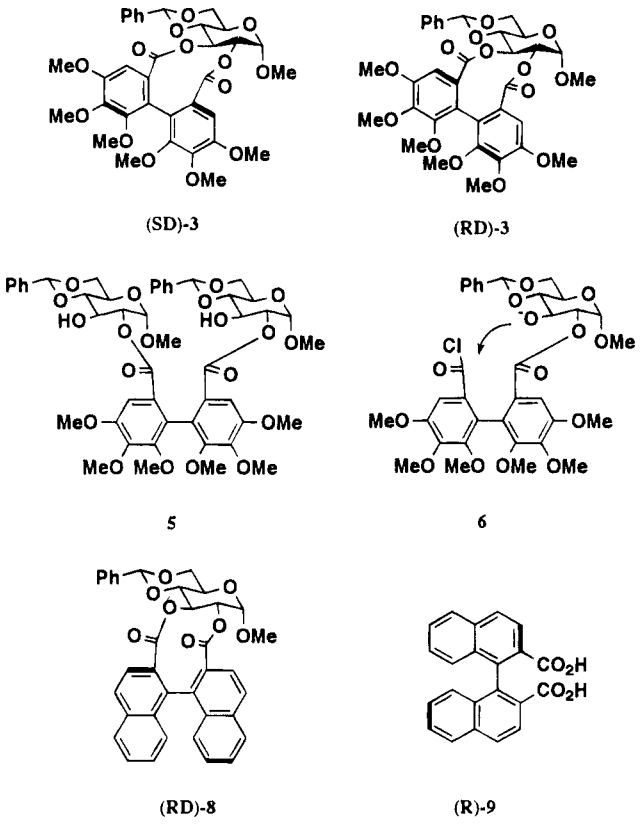

Figure 1.

14 and 15). Because compound **5** was obtained as the major byproduct, we assumed that the reaction took place first at the C-2 position of **1a** and that this was followed by the intramolecular esterification. Although we also tested three other types of sugar templates, methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**1b**), methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**1c**), and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**1d**), for their reaction with acyl chloride **2a**, less effective results were obtained in all cases.[10] Sugar **1a** is sterically much bulkier than the others and seems to better promote production of the cyclized product (*RD*)-**3**.

(10) Ratio of RD-**3**/SD-**3**: for **1b**, 25/1; **1c**, 6.5/1; **1d**, no cyclized product **3** was obtained.

We applied our methodology to the kinetic resolution of axially chiral binaphthyl compounds which are most frequently used as catalysts for asymmetric reactions.[11] Racemic 1,1′-binaphthyl-2,2′-dicarboxyl chloride (**7**) was subjected to optical resolution using sugar template **1a**. The reaction proceeded with excellent diastereoselectivity, giving (*RD*)-**8** in 35% yield, which corresponds to 70% theoretical yield, with none of the diastereoisomer. Optically pure binaphthyldicarboxylic acid (*R*)-**9** was then prepared from (*RD*)-**8** by hydrolysis, in quantitative yield. Optically pure (*S*)-**9**[12] was obtained from the byproducts by hydrolysis and subsequent recrystallization from a mixed solvent of hexane and ether in 25% yield, which corresponds to 50% theoretical yield.

It should be emphasized that the concept of our optical resolution is based on kinetically-controlled intramolecular ester cyclization. This methodology should therefore be applicable to a wide variety of axially chiral biaryl compounds. The chiral template is a sugar derivative which, because of its hydrophilicity, is easily removed from the reaction mixture after hydrolysis simply by washing with water. This template is also an inexpensive, commercially available compound, and the reaction can be carried out easily without any special equipment, though chromatographic separation may be necessary. This new methodology should prove to be very useful in the preparation of a variety of types of optically pure axially chiral biaryls. Further study of the scope and limitations of this reaction will reveal its full potential.

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Supporting Information Available: General experimental and characterization data (14 pages).

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(11) For examples, see: (a) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *Ibid.* **1992**, *114*, 4418. (c) Sasai, H.; Arai, T.; Shibasaki, M. *Ibid.* **1994**, *116*, 1571.

(12) Kanoh, S.; Hongoh, Y.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1032.