ca. 10^9, equivalent to 12-13 kcal/mol. A substantial fraction of this rate acceleration is clearly due to hydrogen bonding of Tyr-14 to the developing negative charge. A mutant enzyme in which Tyr-14 has been changed to Phe shows a rate decrease of ca. 10^5-fold relative to the wild-type enzyme, demonstrating the importance of this group.[26] An additional source of the enzymatic rate acceleration is the decrease in molecularity in the KSI reaction, resulting in an entropic advantage for proton transfer.[31] Finally, Benisek's group has shown that Asp-38 may be intrinsically hyperreactive; thus, carbodiimide-catalyzed amidation of KSI with cystamine gives modification of Asp-38 at a rate about 100-fold faster than modification of other carboxyl groups of the enzyme.[32] Although the source of this enhanced reactivity is not apparent, it could be an important contributor to the impressive value of k_{cat}.

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(32) Benisek, W. F.; Ogez, J. R.; Smith, S. B. *Ann. N.Y. Acad. Sci.* **1980**, *346*, 115.

Experimental Section

All materials have been described previously.[9b] Ultraviolet kinetic measurements, except for k_{-1}, were performed at 25.0 ± 0.4 °C with a Gilford 2400 spectrophotometer as described previously.[9b] Measurements of k_{-1} were made in the following way. The dienolate ion $\mathbf{2}^-$ was prepared by mixing a 5×10^{-4} M solution of **1** in 20% methanol/water with an equal volume of 0.1 M sodium hydroxide with the two syringes in drive 1 of a HiTech PQ/SF-53 stopped-flow spectrophotometer at 25.0 °C. After a 0.5-s delay, the dienolate solution was rapidly mixed with buffer solution in a 1:5 ratio, with drive 2 of the spectrophotometer, to give the dienol **2**. The loss of absorbance due to the dienol was monitored as a function of time at 238 nm for 5-9 half-lives of reaction.

Enolization rate constants were determined with a General Electric GN-500 spectrometer (500.11 MHz, ^{1}H), equipped with a variable-temperature probe set at 25 °C, with a concentration of **1** of 86 mM. Integration was carried out automatically at 20-25 time intervals corresponding to 2-8 half-lives of reaction. The 4α- and 4β-hydrogens of **1** were assigned by a combination of HMQC, COSY, and NOESY as described previously for **3**.[10]

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A CD Method for Determination of the Absolute Stereochemistry of Acyclic Glycols. 1. Application of the CD Exciton Chirality Method to Acyclic 1,3-Dibenzoate Systems

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Abstract: To determine the absolute configuration and conformation of chiral acyclic 1,3-glycols, the CD exciton chirality method has been applied to various acyclic 1,3-diesters with *p*-bromobenzoate, *p*-chlorobenzoate, or benzoate chromophore. Acyclic *anti*-1,3-dibenzoates exhibit typical exciton split CD Cotton effects, the sign of which agrees with the sign of the screw sense between two benzoate chromophores in the conformation expanded in a zigzag form. For example, the CD spectrum of bis(*p*-bromobenzoate) (2*S*,4*S*)-**2** shows first the positive and then secondly the negative Cotton effects: λ_{ext} 252.5 nm, $\Delta\epsilon$ +26.5 and λ_{ext} 236.0 nm, $\Delta\epsilon$ −9.1, A = +35.6. On the other hand, *syn*-1,3-dibenzoates exhibit no exciton split Cotton effects irrespective of the asymmetric structure. Instead the CD spectra of *syn*-dibenzoates show a weak single Cotton effect: e.g., (2*S*,4*R*)-**5**, λ_{ext} 238.0 nm, $\Delta\epsilon$ −1.7. Other 1,3-dibenzoates composed of primary and secondary alcoholic benzoates exhibit exciton split CD Cotton effects of half intensity in comparison with those of *anti*-1,3-dibenzoates: e.g., 1,3-bis(*p*-bromobenzoate) (*S*)-**1**, λ_{ext} 252.6 nm, $\Delta\epsilon$ +13.9 and λ_{ext} 235.9 nm, $\Delta\epsilon$ −3.9, A = +17.8. These results provided the CD method for determination of the absolute stereochemistry of acyclic 1,3-glycols.

The CD exciton chirality method for determination of absolute stereochemistry on the basis of the mechanism of a chiral exciton coupling between two or more chromophores has been extensively applied to various natural products and chiral synthetic organic compounds.[2] The exciton chirality method, however, has been mainly applied to cyclic compounds except for a few examples of acyclic dibenzoate, dibenzamide, and benzoate-benzamide systems.[3-5] Other examples[6] of acyclic systems are acyclic allylic benzoates, the absolute configuration of which has been determined by the application of the allylic benzoate method.[7] The main reason why the exciton chirality method has been rarely applied to acyclic compounds is that the conformation of acyclic systems is, in general, more complex than that of cyclic systems. On the other hand, much attention has been focussed on many natural products having a polyhydroxylated chain such as polyene macrolide antibiotics because of their important biological activity.[8-11] Furthermore, the asymmetric synthesis of acyclic compounds has

(1) (a) Tohoku University. (b) Adam Mickiewicz University. (c) Hoechst Japan Ltd.
(2) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, and Oxford University Press: Oxford, 1983.
(3) McGahren, W. J.; Ellestad, G. A.; Morton, G. O.; Kunstzmann, M. P.; Mullen, P. *J. Org. Chem.* **1973**, *38*, 3542.
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(11) Lancelin, J.-M.; Paquet, F.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 2827.

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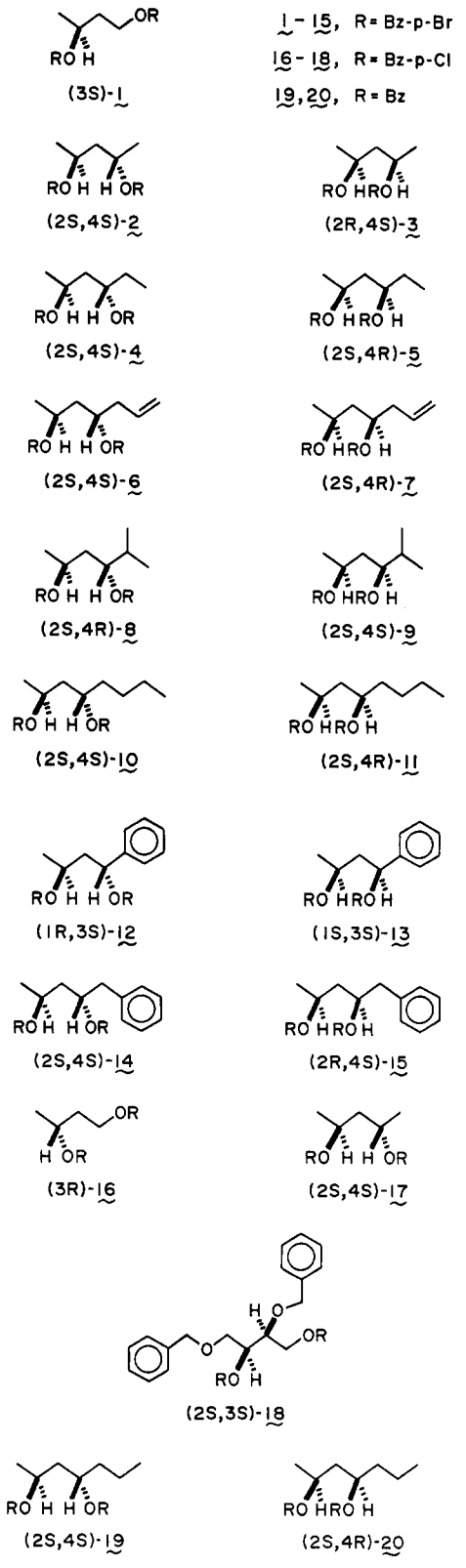
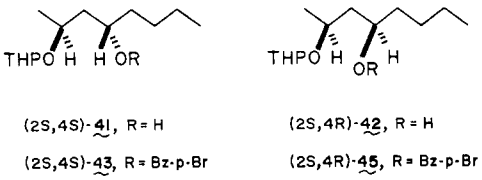
Chart I



been remarkably advanced. Particularly, new methods for the synthesis of chiral acyclic 1,3-polyols have been recently developed for the purpose of the total synthesis of polyene macrolides.[12,13] Therefore, it became very important to develop new methods for determination of the absolute stereochemistry of acyclic compounds. For example, on the basis of the chemical conversion and ^{1}H NMR studies, Oishi reported a method for determination of the absolute configuration of acyclic 1,3-polyols.[14]

Chart II



We have studied the applicability of the CD exciton chirality method to acyclic dibenzoates and already reported a part of the results in a preliminary form.[15] Since then, attention has been focussed on the application of the CD exciton method to acyclic compounds. Nakanishi reported a simple method for assigning relative and absolute configurations of acyclic 1,2,3-triols by use of the fingerprint CD Cotton effects due to the nondegenerate exciton interaction between 9-anthracenecarboxylate and *p*-methoxycinnamate chromophores.[16] Meguro also reported the applications of the dibenzoate chirality method to glycerols and related acyclic alcohols.[17] In this paper, we focus on the systematic applications of the CD exciton chirality method to acyclic 1,3-dibenzoates by use of *p*-bromobenzoate, *p*-chlorobenzoate, and benzoate chromophores (Chart I). It was clarified that acyclic 1,3-dibenzoates exhibited intense exciton split CD Cotton effects, from the sign of which the absolute stereochemistry of acyclic 1,3-glycols could be determined.

Results and Discussion

Syn and Anti Relative Configurations of Acyclic 1,3-Dibenzoates. The definition of the absolute configuration by the *R* and *S* nomenclature is universal and has been extensively used. However, the *R* and *S* method is sometimes inconvenient to express the absolute configuration of a group of compounds. For example, in the case of 2,4-pentanediyl bis(*p*-bromobenzoates), (2*S*,4*S*)-**2** is the optically active isomer, while (2*R*,4*S*)-**3** is the meso and optically inactive isomer. On the other hand, in the case of 5-methyl-2,4-hexanediyl bis(*p*-bromobenzoates), (2*S*,4*R*) isomer **8** corresponds to the optically active form, while the other isomer (2*S*,4*S*)-**9** is classified into the category of meso-type compound because the absolute configuration at the two benzoate groups of **9** in space is the same as that of **3**. Therefore, the *R* and *S* nomenclature is inadequate to distinguish the two groups of the optically active form and the meso form. In such a case, the following nomenclature of syn and anti configurations[18] is more useful than the *R* and *S* method; when the molecular skeletal chain is extended in a zigzag form in a single plane, if the two benzoate groups are on the same side, it is defined as a syn configuration. If the two benzoate groups are on opposite sides, it is defined as an anti configuration. So, in addition to the *R* and *S* nomenclature, the syn and anti nomenclature was also employed in this paper.

Synthesis of Optically Active Acyclic 1,3-Dibenzoate Compounds. Various chiral acyclic 1,3-dibenzoates were synthesized starting from (*S*)-(−)-ethyl 3-hydroxybutanoate (**21**), which was easily obtained by the method of baker's yeast reduction[19] of ethyl acetoacetate (Chart I and Scheme I). Alcohol (−)-**21** was protected as tetrahydropyranyl ether (THP ether), and the ester moiety was reduced to alcohol, which was then oxidized to an aldehyde giving 3-(tetrahydropyranyloxy)butanal, **24**. In order

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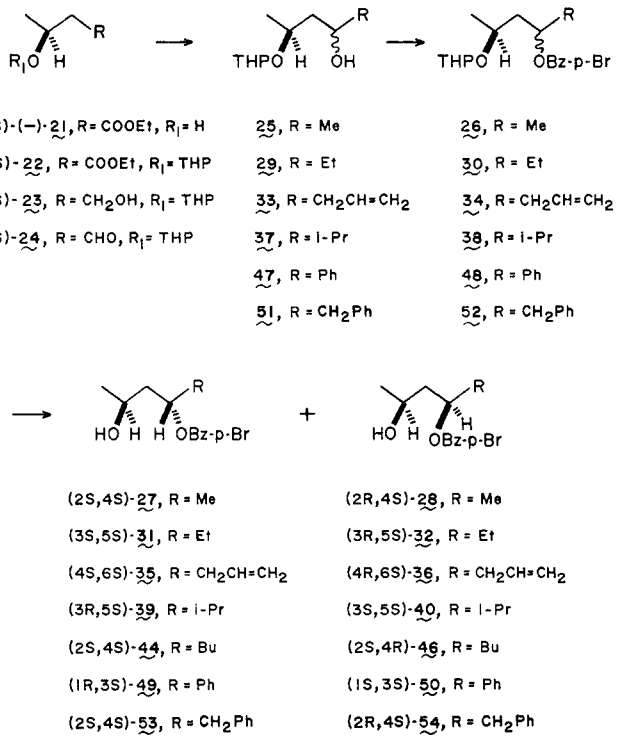
Scheme I



to synthesize 1,3-glycol dibenzoates with various chain lengths and substituents, aldehyde **24** was subjected to the reactions with various Grignard reagents or alkyllithium reagents. To make a separation of the mixture of two diastereomers formed, the obtained THP ether–alcohols were converted to THP ether–(*p*-bromobenzoates), which were then hydrolyzed with pyridinium *p*-toluenesulfonate in ethanol to give alcohol–mono(*p*-bromobenzoates). The mixture of two diastereomers of the syn and anti series could be easily separated at the stage of alcohol–mono(*p*-bromobenzoates) by HPLC methods (silica gel, hexane/EtOAc), and, in general, the anti isomers were eluted earlier than the syn isomers. Each isomer obtained was then benzoylated to afford bis(*p*-bromobenzoate). In the case of 2,4-octanediol system, two diastereomers could be separated by the HPLC method at the stage of THP ether–alcohols **41** and **42** (Chart II).

The relative stereochemistry of syn and anti isomers was easily and unambiguously determined by ^{1}H NMR spectroscopy. For example, the ^{1}H NMR spectrum of *anti*-2,4-pentanediyl bis(*p*-bromobenzoate) (**2**) exhibits the two methylene protons at the 3-position as a triplet (δ 2.05, 2 H, t, J = 6.1 Hz) because of its C_2 symmetrical structure. On the other hand, the ^{1}H NMR of syn isomer **3** shows the corresponding methylene protons as two sets of multiplets (δ 1.94, 1 H, ddd, J = 14.0, 5.3, 5.3 Hz and δ 2.29, 1 H, ddd, J = 14.0, 7.0, 7.0 Hz), because the two methylene protons at the 3-position are not equivalent to each other. On the basis of similar arguments, the stereochemistry of other 1,3-dibenzoates was determined; the anti isomers show the two methylene protons as one set of triplets, although the two protons are not equivalent to each other in a strict sense (see Experimental Section). The methylene protons of syn isomers appear as two sets of multiplets.[20] In the case of bis(*p*-bromobenzoate) **14**, the relative and absolute stereochemistry was also determined by the X-ray crystallographic method as described below. Other 1,3-bis(*p*-chlorobenzoates) and 1,3-dibenzoates were also prepared (Tables II and III).

Conformation of Acyclic anti-1,3-Dibenzoates and Exciton Chirality. In order to determine the absolute configuration of acyclic 1,3-dibenzoates by the application of the CD exciton chirality method, it is crucial to know the rotational conformation of the acyclic systems. In the ^{1}H NMR spectra of all of the anti isomers listed in Table I, the two methylene protons at the central

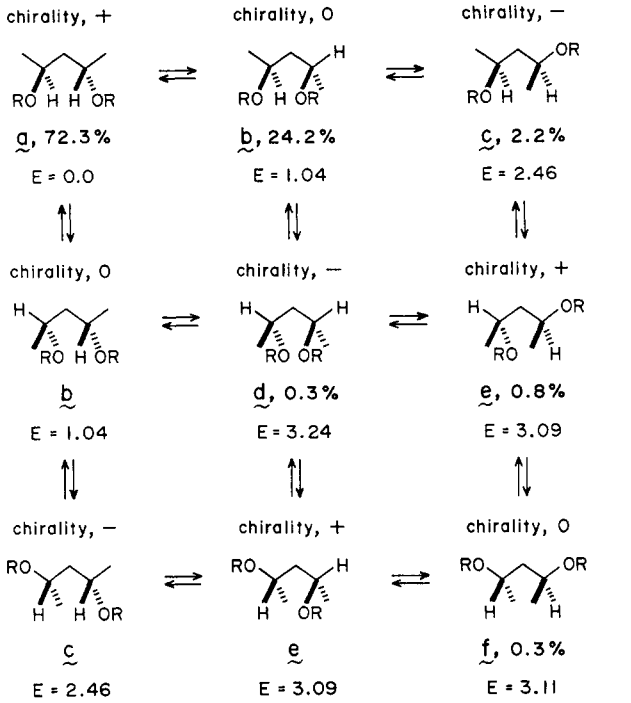
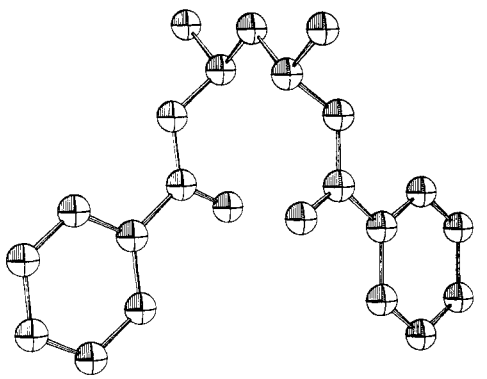


Figure 1. The rotational conformation, exciton chirality, and calculated steric energy and population at 20 °C of *anti*-(2*S*,4*S*)-2,4-pentanediyl dibenzoate.



anti-(2S,4S)

Figure 2. Stereoscopic view of the stable conformation of (2*S*,4*S*)-2,4-pentanediyl dibenzoate calculated by molecular mechanics.

position appear as a triplet (J = 6.1–6.6 Hz; see Experimental Section), which means that the molecules behave almost like a free rotamer at room temperature. Namely the time scale of the rotation is faster than the NMR time scale, so the problem to be solved is the estimation of the population of each rotamer.

In order to know the most stable rotational conformation and its energy level, we performed the molecular mechanics calculation of (2*S*,4*S*)-2,4-pentanediyl dibenzoate by use of the MMPI program[21] (Figure 1). Instead of bis(*p*-bromobenzoate), we adopted unsubstituted dibenzoate as a model compound for the sake of simplicity. As seen in Figure 1, six rotational conformers can exist. Among them, the most stable conformer is **a** in which the skeletal chain takes a zigzag form in an almost single plane (Figure 2). The two benzoate chromophores are close to each other in space and constitute a positive exciton chirality. The dihedral angle between two alcoholic C–O bonds is about 115°. The population of conformer **a** at 20 °C was calculated to be 72.3% by the simple approximation of the Boltzmann distribution on the basis of the steric energy.

The second stable conformer is **b** which is higher in energy by 1.04 kcal/mol than **a**: the population of **b** at 20 °C, 24.2% (Figure

(20) See similar results for other compounds reported in ref 8.

(21) Allinger, N. L. *QCPE* **1976**, *11*, 318; QCPE Program No. 318.

Table I. UV and CD Spectra of Acyclic 1,3-Bis(*p*-bromobenzoates)[a,b]

		in ethanol			in hexane	
compd	syn or anti	UV, λ_{max}, nm (ϵ)	CD, λ_{ext}, nm ($\Delta\epsilon$)	*A* value	CD, λ_{ext}, nm ($\Delta\epsilon$)	*A* value
(3*S*)-**1**		243.0 (34900)	252.6 (+13.9) 235.9 (−3.9)	+17.8	252.3 (+13.8) 234.6 (−3.8)	+17.6
(2*S*,4*S*)-**2**	anti	243.0 (35600)	252.5 (+26.5) 236.0 (−9.1)	+35.6	252.6 (+26.6) 236.4 (−8.9)	+35.5
(2*R*,4*S*)-**3**	syn	243.6 (36300)				
(2*S*,4*S*)-**4**	anti	244.0 (32800)	252.0 (+24.5) 236.0 (−9.3)	+33.8	251.3 (+26.6) 235.0 (−9.9)	+36.5
(2*S*,4*R*)-**5**	syn	243.0 (35000)	238.0 (−1.7)		235.2 (−1.3)	
(2*S*,4*S*)-**6**	anti	244.8 (36200)	252.6 (+28.4) 236.0 (−11.0)	+39.4	252.0 (+28.6) 235.9 (−11.2)	+39.8
(2*S*,4*R*)-**7**	syn	243.8 (36000)			243.0 (+1.7)	
(2*S*,4*R*)-**8**	anti	243.5 (36600)	251.9 (+26.4) 236.0 (−9.3)	+35.7	252.2 (+28.1) 236.0 (−10.4)	+38.5
(2*S*,4*S*)-**9**	syn	242.8 (34900)	241.8 (−2.2)		239.4 (−1.0)	
(2*S*,4*S*)-**10**	anti	244.0 (36100)	252.5 (+24.7) 236.1 (−9.7) [251.9 (+32.3) [234.9 (−12.8)][c]	+34.4 +45.1][c]	252.1 (+25.1) 236.1 (−9.7)	+34.8
(2*S*,4*R*)-**11**	syn	242.9 (34000)	240.5 (−1.5) 213.6 (+1.2) [237.0 (−3.3)][c]		249.5 (+1.4)	
(1*R*,3*S*)-**12**	anti	245.2 (38300)	253.2 (+18.4) 237.5 (−13.4)	+31.8	253.1 (+18.9) 237.0 (−14.3)	+33.2
(1*S*,3*S*)-**13**	syn	244.4 (39300)	241.5 (+9.3)		241.5 (+8.8)	
(2*S*,4*S*)-**14**	anti	244.4 (34500)	253.5 (+22.1) 237.0 (−12.3)	+34.4	252.5 (+24.4) 237.3 (−13.7)	+38.1
(2*R*,4*S*)-**15**	syn	243.0 (35500)	240.5 (+4.1)		241.8 (+3.1)	

[a] R = *p*-Bromobenzoyl. [b] Measured at 20 °C. [c] CD measured in ethanol at −73 °C.

1). In the conformer **b**, the two benzoate groups are almost parallel to each other and therefore make no exciton chirality. The third stable conformer **c** is higher in energy by 2.46 kcal/mol than **a**: the population of **c** at 20 °C, 2.2%. The two benzoate chromophores constitute a negative exciton chirality. Since the distance between two benzoate chromophores in **c** is longer than the corresponding interchromophoric distance in **a**, the CD Cotton effect due to the conformer **c** would be weaker than that due to **a**. These studies on the population and exciton CD Cotton effects of each conformer led to the conclusions that the preferred conformer **a** governs the sign of CD Cotton effects of acyclic *anti*-1,3-dibenzoates. Since the ^{1}H NMR coupling constant data of other *anti*-bis(*p*-bromobenzoates) are similar to those of anti isomer **2** as discussed above, it is reasonable to consider that the sign of CD Cotton effects of other *anti*-1,3-dibenzoates is similarly governed by the exciton chirality of the preferred conformer corresponding to **a**.

Absolute Configuration and Crystalline State Conformation of (2*S*,4*S*)-1-Phenyl-2,4-pentanediyl Bis(*p*-bromobenzoate) (14) as Determined by the X-ray Method. *anti*-Bis(*p*-bromobenzoate) **14** crystallized as large colorless prisms (mp 93–95 °C), although most of the other acyclic 1,3-bis(*p*-bromobenzoates) synthesized were obtained as syrup. The crystals were found to be orthorhombic, and the space group was $P2_12_12_1$: a = 15.248 Å, b = 24.985 Å, c = 6.261 Å, vol = 2385.4 Å^3, ρ(calcd) = 1.521 g/cm^3, ρ(obsd) = 1.519 g/cm^3. The crystal structure was solved by direct methods and by successive Fourier synthesis. The least-squares refinement of positional and thermal parameters, including anomalous scattering factors, led to the final convergence with R = 0.0438. The relative and absolute configurations obtained were consistent with those obtained from the ^{1}H NMR spectral data and the synthetic studies. The (2*S*,4*S*) absolute stereochemistry of **14** was thus established.

The molecular conformation of **14** in a crystaline state is illustrated in Figure 3. The aliphatic skeletal chain makes a zigzag form in an almost single plane, while the phenyl group is completely out of the plane. The two benzoate chromophores clearly constitute a positive exciton chirality; the dihedral angle between two alcoholic C–O bonds of ester groups is about 154°, which

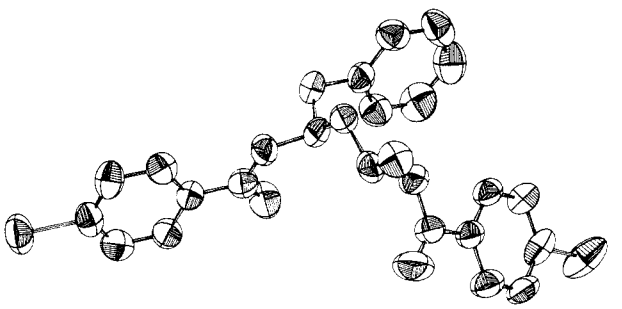


Figure 3. ORTEP drawing of the absolute configuration and crystalline conformation of (2*S*,4*S*)-1-phenyl-2,4-pentanediyl bis(*p*-bromobenzoate) (**14**).

deviates a little from the angle of 120° found in an ideal zigzag form in a single plane. Thus the positive exciton chirality between two benzoate chromophores is seen also in a crystalline state.

Conformation of Acyclic *syn*-1,3-Dibenzoates. In order to obtain the knowledge on the rotational conformation of acyclic *syn*-1,3-dibenzoates, the molecular mechanics calculation was performed for a model compound of *syn*-(2*R*,4*S*)-2,4-pentanediyl dibenzoate, although the compound is optically inactive because of the meso structure. As shown in Figure 4, the most stable conformer is **a**, in which the skeletal chain takes a zigzag form in a single plane and the two benzoate chromophores are parallel to each other, so the exciton chirality is nil. The energy gap between the most stable conformer **a** and the next one is 2.56 kcal/mol, from which the population of conformer **a** at 20 °C was calculated to be 95.5‰. The second stable conformers are **b** and **b′**: the population at 20 °C, 1.2%. The two conformers **b** and **b′** are mirror images of each other; conformer **b** has a negative exciton chirality, whereas the other conformer **b′** has a positive exciton chirality, so both conformers counteract mutual optical activity. The same is true in the case of conformers of higher energy level.

If the molecule has an asymmetrical structure as seen in the

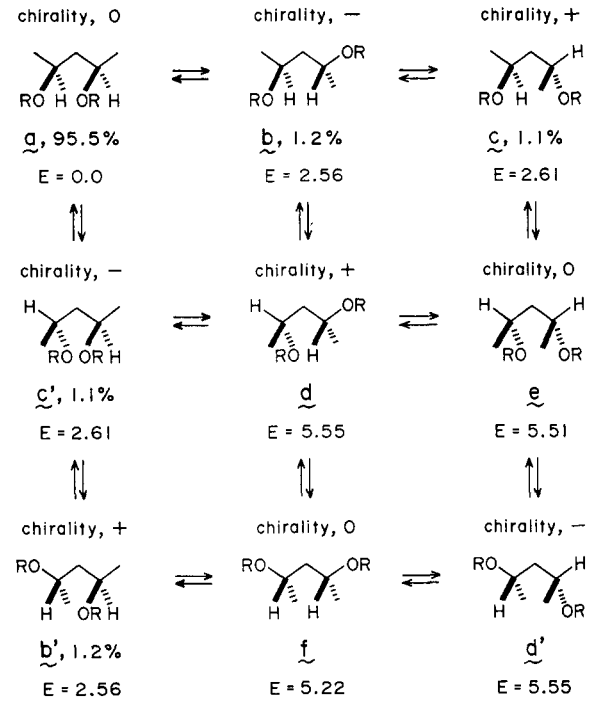


Figure 4. The rotational conformation, exciton chirality, and calculated steric energy and population at 20 °C of *syn*-(2*R*,4*S*)-2,4-pentanediyl dibenzoate.

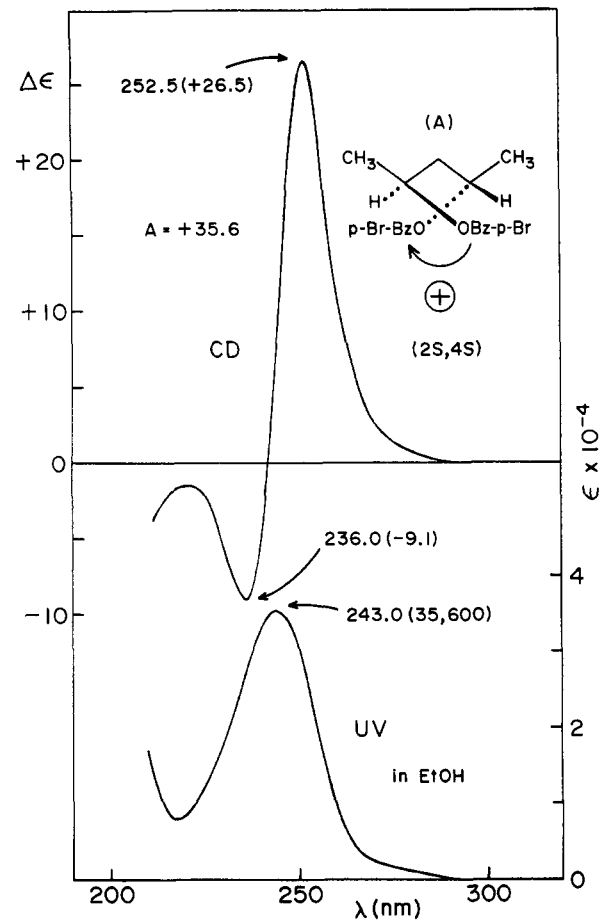


Figure 5. CD and UV spectra of *anti*-(2*S*,4*S*)-2,4-pentanediyl bis(*p*-bromobenzoate) (**2**) in ethanol.

case of *syn*-1,3-bis(*p*-bromobenzoates) **5**, **7**, **9**, **11**, **13**, and **15**, the populations of the conformers corresponding to **b** and **b'** would be different from each other because of the different energy levels; therefore, the conformers analogous to **b** and **b'** might not be able to counteract their mutual CD activity in a strict sense. However, such a difference in the populations is negligible because of their having a smaller population. The physical properties of the molecules would depend mainly on the preferred conformer corresponding to **a**. In fact, irrespective of the difference in the structure of the skeletal chain, the ^{1}H NMR coupling constant data of the central methylene protons of compounds **5**, **7**, **9**, **11**, **13**, and **15** are very similar to those of the meso compound **3**. For example, compound **15** exhibits δ 1.96 (1 H, ddd, J = 14.4, 5.0, 5.0 Hz) and 2.25 (1 H, ddd, J = 14.4, 7.5, 7.5 Hz), while compound **3** shows δ 1.94 (1 H, ddd, J = 14.0, 5.3, 5.3 Hz) and 2.29 (1 H, ddd, J = 14.0, 7.0, 7.0 Hz); see Experimental Section for other compounds. These coupling constants are directly correlated with the rotational conformation under discussion. These results lead to the conclusion that the conformational behavior of optically active syn isomers resembles that of the meso compound **3**. In other words, it is hence implied that the CD activity of *syn*-1,3-bis(*p*-bromobenzoates) **5**, **7**, **9**, **11**, **13**, and **15** would be almost zero like the *meso*-1,3-bis(*p*-bromobenzoate) **3**.

Circular Dichroism Spectra and Absolute Stereochemistry of Acyclic 1,3-Dibenzoates. (a) *anti*-Dibenzoates. Acyclic *anti*-1,3-dibenzoates clearly exhibit the exciton split CD Cotton effects in the region of the intrachromophoric charge transfer or ^1L_a transition of the benzoate chromophore (Table I). For example, the CD spectrum of *anti*-(2*S*,4*S*)-2,4-pentanediyl bis(*p*-bromobenzoate) (**2**) in ethanol shows first the positive and then secondly the negative Cotton effects (λ_{ext} 252.5 nm, $\Delta\epsilon$ +26.5 and λ_{ext} 236.0 nm, $\Delta\epsilon$ −9.1, A = +35.6) in the region of the $\pi \rightarrow \pi^*$ transition (λ_{max} 243.0 nm, ϵ 35 600) (Figure 5). The exciton CD spectrum is only slightly affected by the change of solvent from ethanol to hexane (in hexane, λ_{ext} 252.6 nm, $\Delta\epsilon$ +26.6 and λ_{ext} 236.4 nm, $\Delta\epsilon$ −8.9, A = +35.5). As discussed above, the sign and amplitude of exciton CD Cotton effects are governed mainly by the exciton chirality of conformer **a**. In the case of the anti (2*S*,4*S*) isomer, the preferred conformer **a** has a positive exciton chirality. The observed CD spectra of **2** are thus consistent with the prediction.

The CD spectra of other *anti*-bis(*p*-bromobenzoates) **4**, **6**, **8**, **10**, **12**, and **14** in ethanol similarly exhibit exciton CD Cotton effects of first positive and then secondly negative signs (Table I and Figure 6). The A value, CD amplitude of exciton Cotton effects, is almost constant and distributed in the range of +34 to +39, irrespective of the difference in the structure of the skeletal chain. The A value (+31.8) of **12** is a little deviated from the average values because the neighboring phenyl group interacts with the dibenzoate system. Since the A value of the exciton CD Cotton effects of cyclic 1,3-bis(*p*-bromobenzoates) is roughly 16–28, the observed A values are larger than those of common 1,3-bis(*p*-bromobenzoates). This phenomenon means that the two benzoate chromophores of acyclic *anti*-1,3-dibenzoates are close in space to each other. The CD amplitude becomes a little larger in hexane than in ethanol: the A values in hexane, +35 to +40.

The temperature dependence of the exciton CD Cotton effects of *anti*-bis(*p*-bromobenzoate) ((2*S*,4*S*)-**10**) was studied by the measurement of CD spectra in ethanol at −73 °C (Table I). The CD intensity observed was corrected for a contraction in volume. Although the sign, shape, and position of the Cotton effects remain unchanged, the A value at −73 °C becomes larger than at room temperature: λ_{ext} 251.9 nm, $\Delta\epsilon$ +32.3 and λ_{ext} 234.9 nm, $\Delta\epsilon$ −12.8, A = +45.1 at −73 °C; λ_{ext} 252.5 nm, $\Delta\epsilon$ +24.7 and λ_{ext} 236.1 nm, $\Delta\epsilon$ −9.7, A = +34.4 at +20 °C. The increase of the CD intensity at low temperature can be reasonably explained by the conformational analysis described above. Namely, the preferred rotational conformer corresponding to **a** which has a positive exciton chirality is located at the lowest energy level. Therefore, by lowering the temperature, the population of the conformer analogous to **a** increases and hence the CD intensity becomes larger.[22] The studies of the temperature dependence thus support

(22) In the case of (2*S*,4*S*)-**2**, the population of major conformer **a** at −73 °C is calculated to be 86.8%. Therefore, by lowering temperature from 20 °C to −73 °C, the population of conformer **a** and hence the CD intensity increase by 1.2 times (= 86.8/72.3). This calculated value is close to the value of the increase of CD intensity (1.3 = 45.1/34.4) observed for (2*S*,4*S*)-**10**.

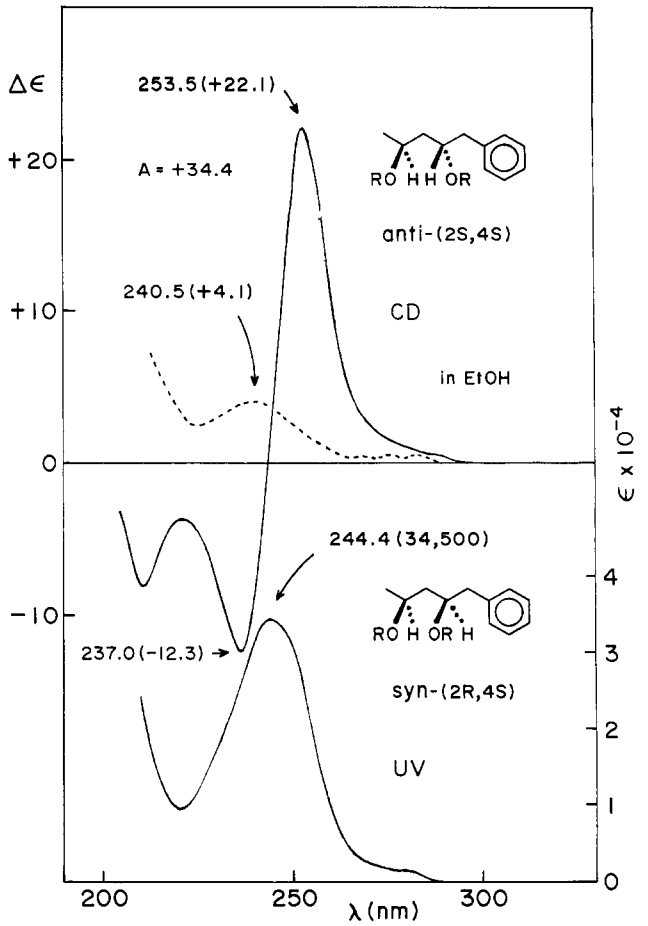


Figure 6. CD and UV spectra of *anti*-(2*S*,4*S*)-1-phenyl-2,4-pentanediyl bis(*p*-bromobenzoate) (**14**) (solid lines) and CD spectrum of *syn*-(2*R*,4*S*)-**15** (dotted line) in ethanol.

Table II. UV and CD Spectra of Acyclic 1,3-Bis(*p*-chlorobenzoates) in 1,4-Dioxane[a]

compd	syn or anti	UV, λ_{ext}, nm (ϵ)	CD, λ_{ext}, nm ($\Delta\epsilon$)	*A* value
(3*R*)-**16**		240.0 (33 800)	247.0 (−7.6) 229.0 (+2.1)	−9.7
(2*S*,4*S*)-**17**	anti	240.0 (33 100)	248.0 (+18.0) 231.0 (−4.8)	+22.8
(2*S*,3*S*)-**18**		241.0 (35 200)	249.0 (+9.1) 231.0 (−5.3)	+14.4

[a] R = *p*-chlorobenzoyl.

the conformational analysis described above.

The CD spectra of *anti*-1,3-bis(*p*-chlorobenzoate) **17** and 1,3-dibenzoate **19** similarly show exciton Cotton effects of positive chirality (Tables II and III). The results discussed here lead to the conclusion that *anti*-1,3-dibenzoates with a clockwise screw sense between two benzoate chromophores exhibit first the positive and then secondly the negative CD Cotton effects (Figure 7). On the other hand, *anti*-1,3-dibenzoates with a counterclockwise screw sense give negative first and positive second CD Cotton effects.

(b) *syn*-1,3-Dibenzoates. It is interesting that in contrast to the case of *anti*-1,3-dibenzoates, all of the CD spectra of *syn*-1,3-bis(*p*-bromobenzoates) **5**, **7**, **9**, **11**, **13**, and **15** show only a weak

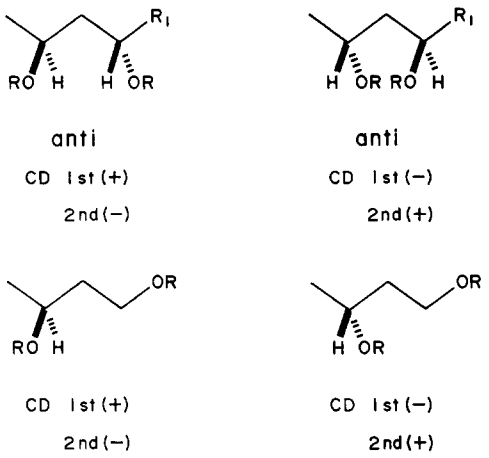


Figure 7. The sign of exciton CD Cotton effects and absolute configuration of acyclic 1,3-dibenzoates, where OR is benzoate and R_1 is the aliphatic or the aromatic group, respectively.

single Cotton effect around 240 nm, instead of exciton split CD Cotton effects (Table I). For example, *syn*-bis(*p*-bromobenzoate) (2*R*,4*S*)-**15** exhibits a positive Cotton effect in ethanol: λ_{ext} 240.5 nm, $\Delta\epsilon$ +4.1 (Figure 6). The CD Cotton effect is little affected by the change of solvent from ethanol to hexane: λ_{ext} 241.8 nm, $\Delta\epsilon$ +3.1 in hexane. The same is true in the case of other *syn*-1,3-dibenzoates (Table I). In the case of *syn*-(1*S*,3*S*)-**13**, the CD intensity (λ_{ext} 241.5 nm, $\Delta\epsilon$ +9.3) is a little larger than that of others. This is due to the interaction between phenyl and benzoate chromophores.

As discussed in the section of the conformational analysis of *syn*-1,3-dibenzoates, the behavior of the syn compounds is similar to that of the meso compound **3**, and hence it was expected that the CD Cotton effects of syn compounds would be very weak. This prediction is clearly validated by the CD data of *syn*-1,3-bis(*p*-bromobenzoates) listed in Table I. However, it is difficult to correlate these CD data with absolute configurations, because the sign of the weak single Cotton effect is variant depending on the structure.

The CD spectrum of syn compound (2*S*,4*R*)-**11** was measured at low temperature: λ_{ext} 237.0 nm, $\Delta\epsilon$ −3.3 at −73 °C in ethanol; λ_{ext} 240.5 nm, $\Delta\epsilon$ −1.5 at room temperature in ethanol. The CD spectrum remained almost unchanged; exciton split CD Cotton effects were not observed even at such a low temperature. This phenomenon is in line with the results of conformational analysis of syn compounds described above. An increase in the population of the most stable conformer at low temperature does not give rise to exciton split CD Cotton effects, because the major conformer corresponding to **a** has no exciton chirality as shown in Figure 4.

(c) 1,3-Dibenzoates with a Single Chirality. The ^{1}H NMR spectrum of (*S*)-1,3-butanediyl bis(*p*-bromobenzoate) (**1**) shows the central methylene protons as a quartet at δ 2.67 (J = 6.4 Hz), methylene protons at the 1-position as a triplet at δ 4.45 (J = 6.4 Hz), and the methyne proton at the 3-position as a sextet at 5.36 (J = 6.4 Hz). These data indicate that the molecule behaves like a free rotamer. Since compound **1** has only one chiral center of *S* configuration, the molecule may be treated as half of the *anti*-bis(*p*-bromobenzoate) (2*S*,4*S*)-**2**. It is quite interesting that the CD spectrum of (3*S*)-**1** actually exhibits exciton split Cotton effects of the same sign as that of (2*S*,4*S*)-**2** but of half intensity: compound **1**, λ_{ext} 252.6 nm, $\Delta\epsilon$ +13.9 and λ_{ext} 235.9 nm, $\Delta\epsilon$ −3.9,

Table III. UV and CD Spectra of Acyclic 1,3-Dibenzoates[a]

		in ethanol			in hexane	
compd	syn or anti	UV, λ_{max}, nm (ϵ)	CD, λ_{ext}, nm ($\Delta\epsilon$)	*A* value	CD, λ_{ext}, nm ($\Delta\epsilon$)	*A* value
(2*S*,4*S*)-**19**	anti	229.0 (25 200)	235.5 (+16.4) 219.0 (−4.3)	+20.7	234.9 (+13.5) 218.6 (−3.9)	+17.4
(2*S*,4*R*)-**20**	syn	228.8 (25 300)	226.0 (−1.3)		230.0 (+0.8)	

[a] R = benzoyl.

A = +17.8 in ethanol. Almost the same CD spectrum was observed in hexane (Table I).

Bis(*p*-chlorobenzoate) (3*R*)-**16** also exhibits exciton split CD Cotton effects, the intensity of which is weaker than that of bis(*p*-bromobenzoate) **1**. The signs of the Cotton effects observed, of course, reflect the absolute configuration of the single chiral center. The interesting example is the case of compound (2*S*,3*S*)-**18** which has two benzyloxy groups. Although the molecule has two chiral centers, it is classified in the category of 1,3-dibenzoate with a single chiral center. Irrespective of such a complex structure, the CD spectrum of **18** shows simple exciton split Cotton effects which are similar to those of compound **16**. The sign of the Cotton effects observed is easily correlated with the absolute configuration of the chiral center to which the benzoate group is attached as shown in Figure 7.

Concluding Remarks

The CD spectra of *anti*-1,3-dibenzoates and 1,3-dibenzoates with a single chiral center show exciton split Cotton effects, from the sign of which the absolute configuration can be determined as summarized in Figure 7. In the case of *syn*-1,3-dibenzoates, the CD spectra show a weak single Cotton effect, instead of exciton split Cotton effects. Therefore, to determine the absolute configuration of *syn*-1,3-glycols, it is desirable to chemically correlate the *syn*-1,3-glycols with *anti*-1,3-dibenzoates or 1,3-dibenzoates with a single chirality shown in Figure 7.[23]

Experimental Section

General Procedures. Physical and Spectroscopic Data. Melting points are uncorrected. IR spectra were obtained as KBr disks, neat, or $CHCl_3$ solutions by using a Jeol JIR-100, a Hitachi 285, or a Perkin-Elmer 580 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Jeol PMX-60 SI, a Jeol FX90Q, a Jeol PS-100, or a Bruker AC250T spectrometer, and all NMR data are reported in ppm (δ) downfield from tetramethylsilane. Optical rotations $[\alpha]_D$ were measured on a JASCO DIP-4S spectropolarimeter. UV spectra were recorded on a JASCO UVDEC-505, a JASCO Ubest-50, a Cary 118C, or a Shimadzu 160 spectrophotometer. CD spectra were measured on a JASCO J-400X or a Jobin-Yvon Dichrograph III spectrometer. MS spectra were obtained with a Jeol JMS DX-300/JMA-3100/3500 spectrometer by the electron ionization procedure (70 eV), unless otherwise noted. The purity of all title compounds was shown to be ≥95% by ^1H NMR, TLC, HPLC, and/or elemental analysis.

(S)-(−)-Ethyl 3-Hydroxybutanoate (21). Compound **21** was prepared from ethyl acetoacetate by the method of baker's yeast reduction:[19] $[\alpha]_D$ +36.1° (*c* 2.483, $CHCl_3$), 96% ee; [lit.[19] $[\alpha]_D$ +32.7° (*c* 2.50, $CHCl_3$), 87% ee].

(*S*)-1,3-Butanediyl Bis(*p*-bromobenzoate) (1). (*S*)-(+)-1,3-Butanediol (0.087 g, 0.97 mmol, prepared from (*S*)-(−)-ethyl 3-hydroxybutanoate, **21**) was benzoylated to yield **1** (0.419 g, 95%) as crystals: mp 60–61 °C; IR (KBr) ν_{max} 2997, 2942, 1716, 1589, 1286, 1101, 1011, 754, 683, 476 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.37 (3 H, d, J = 6.4 Hz), 2.67 (2 H, q, J = 6.4 Hz), 4.45 (2 H, t, J = 6.4 Hz), 5.36 (1 H, sextet, J = 6.4 Hz), 7.57 (4 H, d, J = 8.0 Hz), 7.80 (4 H, d, J = 8.0 Hz); high-resolution mass spectrum calcd for $C_{18}H_{16}{}^{81}Br_2O_4$ 457.93769, found 457.93269; calcd for $C_{18}H_{16}{}^{81}Br^{79}BrO_4$ 455.93966; found 455.93994; calcd for $C_{18}H_{16}{}^{79}Br_2O_4$ 453.94163, found 453.94246. Anal. Calcd for $C_{18}H_{16}Br_2O_4$: C, 47.40; H, 3.54. Found: C, 47.01; H, 3.62.

(*S*)-3-(3,4,5,6-Tetrahydro-2*H*-pyran-2-yloxy)butanal (24). A mixture of alcohol (*S*)-**23** (5 g, 28.7 mmol), pyridinium dichromate (54.1 g, 144 mmol), and dry dichloromethane (300 mL) was stirred under nitrogen at room temperature for 3 days. The reaction mixture was subjected to a short column chromatography on silica gel (diethyl ether) giving **24** (5.21 g, 100%) as an oil: IR (neat) ν_{max} 2930, 2860, 1725, 1440, 1380, 1285, 1260, 1200, 1130, 1075, 1020, 1000 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (1.5 H, d, J = 6.2 Hz), 1.34 (1.5 H, d, J = 6.2 Hz), 1.5–2.0 (6 H, m), 2.6 (2 H, m), 3.3–4.6 (3 H, m), 4.91 (1 H, br s), 9.78 (1 H, br s).

(2ξ,4*S*)-4-(3,4,5,6-Tetrahydro-2*H*-pyran-2-yloxy)-2-pentanol (25). To a solution of aldehyde (*S*)-**24** (0.169 g, 0.981 mmol) in dry diethyl ether (8.0 mL) cooled in an ice-bath was added dropwise a solution of methyllithium (1.6 M, 3.5 mL, 5.6 mmol) in diethyl ether. After being stirred at room temperature for 1.5 h, the reaction mixture was treated with aqueous ammonium chloride and extracted with diethyl ether. The ethereal layer was washed with brine and evaporated giving **25** (0.161 g, 87%) as a syrup: ^1H NMR (60 MHz, $CDCl_3$) δ 1.17 (3 H, d, J = 6.1 Hz), 1.27 (3 H, d, J = 6.1 Hz), 1.4–2.0 (8 H, m), 3.5–4.5 (4 H, m), 4.5–4.9 (1 H, m).

(2*S*,4*S*)- and (2*R*,4*S*)-4-Hydroxy-2-pentanyl *p*-Bromobenzoates (27) and (28). THP ether (2ξ,4*S*)-**26** (0.190 g, 0.512 mmol) was hydrolyzed. The crude product was subjected to a high-performance liquid chromatography (HPLC) on silica gel (hexane/EtOAc, 5:1) to yield two diastereomeric benzoates. The first fraction to be eluted gave (2*S*,4*S*)-**27** (0.060 g, 41%) as a syrup: ^1H NMR (60 MHz, $CDCl_3$) δ 1.20 (3 H, d, J = 6.0 Hz), 1.39 (3 H, d, J = 6.0 Hz), 1.7–1.9 (2 H, m), 2.91 (1 H, br s), 3.66 (1 H, sextet, J = 6.0 Hz), 5.40 (1 H, sextet, J = 6.0 Hz), 7.54 (2 H, d, J = 8.4 Hz), 7.89 (2 H, d, J = 8.4 Hz). The second fraction to be eluted afforded (2*R*,4*S*)-**28** (0.063 g, 43%) as a syrup: ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (3 H, d, J = 6.1 Hz), 1.30 (3 H, d, J = 6.1 Hz), 1.7–2.2 (2 H, m), 2.30 (1 H, s), 3.99 (1 H, sextet, J = 6.1 Hz), 5.33 (1 H, sextet, J = 6.1 Hz), 7.56 (2 H, d, J = 9.0 Hz), 7.91 (2 H, d, J = 9.0 Hz).

(2*S*,4*S*)-2,4-Pentanediyl Bis(*p*-bromobenzoate) (2). Monobenzoate (2*S*,4*S*)-**27** (0.072 g, 0.25 mmol) was converted to **2** (0.072 g, 61%), a syrup: IR (neat) ν_{max} 2980, 1720, 1589, 1483, 1398, 1284, 1273, 1173, 1115, 1103, 1068, 1012, 849, 756 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.36 (6 H, d, J = 6.1 Hz), 2.05 (2 H, t, J = 6.1 Hz), 5.22 (2 H, sextet, J = 6.1 Hz), 7.38 (4 H, d, J = 8.4 Hz), 7.69 (4 H, d, J = 8.4 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.50, 41.94, 68.45, 127.92, 129.26, 131.00, 131.54, 165.20; UV (hexane) λ_{max} 243.8 nm (ϵ 38 100); high-resolution mass spectrum, calcd for $C_{19}H_{18}{}^{81}Br_2O_4$ 471.95334, found 471.95331; calcd for $C_{19}H_{18}{}^{81}Br^{79}BrO_4$ 469.95531, found 469.95494; calcd for $C_{19}H_{18}{}^{79}Br_2O_4$ 467.95728, found 467.95679. Anal. Calcd for $C_{19}H_{18}Br_2O_4$: C, 48.54; H, 3.86; Br, 33.99. Found: C, 48.47; H, 3.86; Br, 33.79.

(2*R*,4*S*)-2,4-Pentanediyl Bis(*p*-bromobenzoate) (3). Benzoylation of monobenzoate (2*R*,4*S*)-**28** (0.079 g, 0.28 mmol) gave **3** (0.107 g, 82%) as crystals: mp 71–72 °C; IR (KBr) ν_{max} 2980, 1718, 1589, 1485, 1398, 1286, 1176, 1117, 1082, 1014, 910, 845, 754, 681 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.37 (6 H, d, J = 6.0 Hz), 1.94 (1 H, ddd, J = 14.0, 5.3, 5.3 Hz), 2.29 (1 H, ddd, J = 14.0, 7.0, 7.0 Hz), 5.26 (2 H, sextet, J = 6.1 Hz), 7.38 (4 H, d, J = 8.5 Hz), 7.72 (4 H, d, J = 8.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.35, 41.98, 69.27, 127.99, 129.24, 131.02, 131.58, 165.20; UV (hexane) λ_{max} 243.6 nm (ϵ 39 000); high-resolution mass spectrum calcd for $C_{19}H_{18}{}^{81}Br_2O_4$ 471.95334, found 471.95631; calcd for $C_{19}H_{18}{}^{81}Br^{79}BrO_4$ 469.95531, found 469.95528; calcd for $C_{19}H_{18}{}^{79}Br_2O_4$ 467.95728, found 467.95704. Anal. Calcd for $C_{19}H_{18}Br_2O_4$: C, 48.54; H, 3.86; Br, 33.99. Found: C, 48.45; H, 3.96; Br, 33.72.

(2*S*,4*S*)-2,4-Hexanediyl Bis(*p*-bromobenzoate) (4). Benzoylation of monobenzoate (3*S*,5*S*)-**31** (0.030 g, 0.10 mmol) gave **4** (0.038 g, 79%) as a syrup: IR ($CHCl_3$) ν_{max} 2950, 2900, 1710, 1585, 1480, 1390, 1270, 1170, 1110, 1100, 1010, 845 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 (3 H, t, J = 7.4 Hz), 1.36 (3 H, d, J = 6.4 Hz), 1.72 (2 H, quintet, J = 7.2 Hz), 2.03 (2 H, t, J = 6.5 Hz), 5.20 (2 H, sextet, J = 6.9 Hz), 7.44 (4 H, d, J = 8.1 Hz), 7.75 (4 H, d, J = 8.1 Hz); UV (hexane) λ_{max} 243.0 nm (ϵ 37 200); high-resolution mass spectrum calcd for $C_{20}H_{20}{}^{81}Br_2O_4$ 485.96899, found 485.96618; calcd for $C_{20}H_{20}{}^{81}Br^{79}BrO_4$ 483.97096, found 483.96851; calcd for $C_{20}H_{20}{}^{79}Br_2O_4$ 481.97293, found 481.97015.

(2*S*,4*R*)-2,4-Hexanediyl Bis(*p*-bromobenzoate) (5). Monobenzoate (3*R*,5*S*)-**32** (0.020 g, 0.067 mmol) was converted to **5** (0.027 g, 85%), a syrup: IR ($CHCl_3$) ν_{max} 2950, 2910, 1710, 1585, 1480, 1390, 1270, 1110, 1100, 1065, 1010, 845 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 (3 H, t, J = 7.6 Hz), 1.39 (3 H, d, J = 6.4 Hz), 1.78 (2 H, quintet, J = 6.5 Hz), 1.95 (1 H, ddd, J = 14.6, 5.7, 4.9 Hz), 2.28 (1 H, ddd, J = 14.6, 7.6, 7.6 Hz), 5.1–5.4 (2 H, m), 7.48 (2 H, d, J = 8.7 Hz), 7.49 (2 H, d, J = 8.7 Hz), 7.81 (2 H, d, J = 8.7 Hz), 7.82 (2 H, d, J = 8.7 Hz); UV (hexane) λ_{max} 243.0 nm (ϵ 37 600).

(2*S*,4*S*)-6-Heptene-2,4-diyl Bis(*p*-bromobenzoate) (6). Alcohol (4*S*,6*S*)-**35** (0.061 g, 0.195 mmol) was benzoylated to give **6** (0.092 g, 95%) as a syrup: IR (neat) ν_{max} 2980, 1720, 1591, 1483, 1398, 1273, 1173, 1115, 1103, 1068, 1012, 847, 756 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.37 (3 H, d, J = 6.1 Hz), 2.10 (2 H, t, J = 6.1 Hz), 2.49 (2 H, t, J = 6.1 Hz), 5.0–5.5 (4 H, m), 5.79 (1 H, dddd, J = 17.3, 9.1, 6.8, 6.8 Hz), 7.45 (4 H, d, J = 8.6 Hz), 7.78 (4 H, d, J = 8.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.44, 38.97, 39.43, 68.39, 70.59, 118.57, 127.90, 127.99, 129.08, 129.26, 130.98, 131.00, 131.51, 131.55, 132.85, 165.14, 165.18; UV (hexane) λ_{max} 243.8 nm (ϵ 39 000). Anal. Calcd for $C_{21}H_{20}Br_2O_4$: C, 50.83; H, 4.06; Br, 32.21. Found: C, 51.07; H, 4.07; Br, 31.90.

(2*S*,4*R*)-6-Heptene-2,4-diyl Bis(*p*-bromobenzoate) (7). Alcohol (4*R*,6*S*)-**36** (0.429 g, 1.37 mmol) was benzoylated to afford **7** (0.654 g,

(23) The present exciton CD method for acyclic systems would prove to be useful, even for determination of the absolute configuration of natural products with an *all-syn*-1,3-polyol chain, if compounds can be converted to proper dibenzoates exhibiting exciton CD Cotton effects as shown in Figure 7.

96%) as a syrup: IR (neat) ν_{max} 2980, 1720, 1591, 1483, 1398, 1271, 1173, 1115, 1103, 1068, 1012, 847, 756 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.38 (3 H, d, J = 6.0 Hz), 1.98 (1 H, ddd, J = 14.4, 5.0, 5.0 Hz), 2.27 (1 H, ddd, J = 14.4, 7.7, 7.7 Hz), 2.48 (2 H, dd, J = 6.6, 6.8 Hz), 5.0–5.4 (4 H, m), 5.83 (1 H, dddd, J = 17.1, 9.6, 6.8, 6.8 Hz), 7.48 (2 H, d, J = 8.8 Hz), 7.49 (2 H, d, J = 8.8 Hz), 7.82 (4 H, d, J = 8.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.28, 38.85, 39.57, 69.38, 71.54, 118.60, 127.93, 128.04, 129.04, 129.20, 130.97, 131.00, 131.50, 131.57, 132.77, 165.12, 165.17; UV (hexane) λ_{max} 243.8 nm (ϵ 39 100). Anal. Calcd for $C_{21}H_{20}Br_2O_4$: C, 50.83; H, 4.06; Br, 32.21. Found: C, 51.13; H, 4.10; Br, 31.97.

(2*S*,4*R*)-5-Methyl-2,4-hexanediyl Bis(*p*-bromobenzoate) (8). Alcohol (3*R*,5*S*)-**39** (0.065 g, 0.21 mmol) was benzoylated to yield **8** (0.088, g, 86%) as a syrup: IR (neat) ν_{max} 2966, 2933, 2875, 1720, 1591, 1483, 1398, 1273, 1173, 1117, 1103, 1068, 1012, 846, 756, 683 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.7 Hz), 0.98 (3 H, d, J = 6.7 Hz), 1.59 (3 H, d, J = 6.1 Hz), 1.8–2.2 (1 H, m), 2.05 (2 H, t, J = 6.1 Hz), 5.0–5.4 (1 H, m), 7.44 (2 H, d, J = 9.0 Hz), 7.45 (2 H, d, J = 9.0 Hz), 7.78 (4 H, d, J = 9.0 Hz); UV (hexane) λ_{max} 243.0 nm (ϵ 36 800); MS m/z 500, 498, 596.

(2*S*,4*S*)-5-Methyl-2,4-hexanediyl Bis(*p*-bromobenzoate) (9). Benzoylation of alcohol (3*S*,5*S*)-**40** (0.042 g, 0.13 mmol) gave **9** (0.057 g, 86%) as fine needles: mp 49–51 °C; IR (KBr) ν_{max} 2962, 2875, 1714, 1589, 1483, 1396, 1346, 1273, 1238, 1174, 1119, 1090, 1066, 1012, 957, 845, 756, 683, 474 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 6.6 Hz), 0.99 (3 H, d, J = 6.6 Hz), 1.40 (3 H, d, J = 6.0 Hz), 1.8–2.2 (1 H, m), 1.96 (1 H, ddd, J = 14.6, 5.7, 3.4 Hz), 2.29 (1 H, ddd, J = 14.6, 8.4, 6.2 Hz), 5.1–5.4 (2 H, m), 7.45 (2 H, d, J = 8.3 Hz), 7.49 (2 H, d, J = 8.3 Hz), 7.77 (2 H, d, J = 8.3 Hz), 7.81 (2 H, d, J = 8.3 Hz); UV (hexane) λ_{max} 242.6 nm (ϵ 37 400); MS m/z 500, 498, 496.

(2*S*,4*S*)-2,4-Octanediyl Bis(*p*-bromobenzoate) (10). Monobenzoate (2*S*,4*S*)-**44** (0.062 g, 0.19 mmol) was benzoylated to give **10** (0.093 g, 94%) as a syrup: IR (neat) ν_{max} 2956, 2931, 2872, 1720, 1591, 1483, 1398, 1273, 1173, 1115, 1101, 1068, 1012, 847, 756, 683 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.89 (3 H, br t, J = 6.1 Hz), 1.36 (3 H, d, J = 6.0 Hz), 1.2–1.5 (4 H, m), 1.6–1.9 (2 H, m), 2.07 (2 H, br t, J = 6.1 Hz), 5.22 (2 H, sextet, J = 6.1 Hz), 7.38 (4 H, d, J = 8.5 Hz), 7.73 (4 H, d, J = 8.5 Hz); UV (hexane) λ_{max} 243.0 nm (ϵ 35 300); high-resolution mass spectrum calcd for $C_{22}H_{24}{}^{81}Br_2O_4$ 514.00029, found 514.00129; calcd for $C_{22}H_{24}{}^{81}Br^{79}BrO_4$ 512.00226, found 512.00266; calcd for $C_{22}H_{24}{}^{79}Br_2O_4$ 510.00423, found 510.00369.

(2*S*,4*R*)-2,4-Octanediyl Bis(*p*-bromobenzoate) (11). Alcohol (2*S*,4*R*)-**46** (0.092 g, 0.28 mmol) was benzoylated to afford **11** (0.114 g, 80%) as a syrup: IR (neat) ν_{max} 2956, 2931, 2860, 1722, 1591, 1483, 1398, 1269, 1173, 1117, 1101, 1068, 1012, 847, 756, 683 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.87 (3 H, br t, J = 6.2 Hz), 1.38 (3 H, d, J = 6.1 Hz), 1.2–1.5 (4 H, m), 1.6–1.9 (2 H, m), 1.90 (1 H, ddd, J = 14.5, 5.0, 4.5 Hz), 2.27 (1 H, ddd, J = 14.5, 7.4, 7.4 Hz), 5.1–5.4 (2 H, m), 7.48 (2 H, d, J = 8.2 Hz), 7.49 (2 H, d, J = 8.2 Hz), 7.82 (2 H, d, J = 8.2 Hz), 7.83 (2 H, d, J = 8.2 Hz); UV (hexane) λ_{max} 243.0 nm (ϵ 37 700); high-resolution mass spectrum calcd for $C_{22}H_{24}{}^{81}Br_2O_4$ 514.00029, found 514.00143; calcd for $C_{22}H_{24}{}^{81}Br^{79}BrO_4$ 512.00226, found 512.00320; calcd for $C_{22}H_{24}{}^{79}Br_2O_4$ 510.00423, found 510.00469.

(1*R*,3*S*)-1-Phenyl-1,3-butanediyl Bis(*p*-bromobenzoate) (12). Alcohol (1*R*,3*S*)-**49** (0.157 g, 0.449 mmol) was benzoylated to give **12** (0.193 g, 81%) as a syrup: IR (neat) ν_{max} 2980, 1720, 1589, 1483, 1398, 1271, 1173, 1115, 1101, 1068, 1012, 847, 754, 698, 683 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.41 (3 H, d, J = 6.2 Hz), 2.39 (2 H, t, J = 6.2 Hz), 5.36 (1 H, sextet, J = 6.2 Hz), 6.15 (1 H, t, J = 6.2 Hz), 7.27 (5 H, br s), 7.45 (4 H, d, J = 8.1 Hz), 7.77 (2 H, d, J = 8.1 Hz), 7.83 (2 H, d, J = 8.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.49, 42.47, 68.51, 73.52, 126.30, 127.96, 128.17, 128.72, 128.96, 129.19, 131.02, 131.11, 131.54, 131.65, 139.98, 164.87, 165.18; UV (hexane) λ_{max} 244.4 nm (ϵ 39 700); MS m/z 534, 532, 530. Anal. Calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79; Br, 30.03. Found: C, 54.04; H, 3.77; Br, 30.33.

(1*S*,3*S*)-1-Phenyl-1,3-butanediyl Bis(*p*-bromobenzoate) (13). Alcohol (1*S*,3*S*)-**50** (0.212 g, 0.607 mmol) was benzoylated to yield **13** (0.237 g, 73%) as a syrup: IR (neat) ν_{max} 2980, 1722, 1591, 1483, 1398, 1269, 1173, 1115, 1101, 1066, 1012, 847, 756, 700, 683 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.41 (3 H, d, J = 6.1 Hz), 2.28 (1 H, ddd, J = 13.8, 7.0, 7.0 Hz), 2.68 (1 H, ddd, J = 13.8, 7.2, 7.2 Hz), 5.21 (1 H, sextet, J = 6.1 Hz), 6.16 (1 H, t, J = 6.4 Hz), 7.32 (5 H, br s), 7.49 (4 H, d, J = 8.6 Hz), 7.80 (2 H, d, J = 8.6 Hz), 7.87 (2 H, d, J = 8.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.30, 42.45, 69.14, 74.29, 126.38, 128.01, 128.20, 128.36, 128.74, 128.94, 129.16, 131.03, 131.10, 131.57, 131.66, 139.65, 164.87, 165.09; UV (hexane) λ_{max} 244.2 nm (ϵ 41 300); MS m/z 534, 532, 530. Anal. Calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79; Br, 30.03. Found: C, 54.01; H, 3.77; Br, 30.31.

(2*S*,4*S*)-1-Phenyl-2,4-pentanediyl Bis(*p*-bromobenzoate) (14). Alcohol (2*S*,4*S*)-**53** (0.093 g, 0.26 mmol) was benzoylated to give **14** (0.105 g, 75%) as crystals: mp 93–95 °C; IR (KBr) ν_{max} 3028, 2937, 1718, 1589, 1483, 1398, 1354, 1273, 1174, 1115, 1103, 1057, 1011, 958, 850, 758, 700, 685 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.33 (3 H, d, J = 6.7 Hz), 2.06 (2 H, br t, J = 6.6 Hz), 2.96 (1 H, dd, J = 13.4, 6.6 Hz), 3.10 (1 H, dd, J = 13.4, 5.9 Hz), 5.1–5.6 (2 H, m), 7.22 (5 H, s), 7.43 (2 H, d, J = 8.8 Hz), 7.44 (2 H, d, J = 8.8 Hz), 7.72 (2 H, d, J = 8.8 Hz), 7.74 (2 H, d, J = 8.8 Hz); UV (hexane) λ_{max} 243.6 nm (ϵ 38 500). Anal. Calcd for $C_{25}H_{22}Br_2O_4$: C, 54.97; H, 4.06; Br, 29.26. Found: C, 54.84; H, 4.24; Br, 29.53.

X-ray Crystallography of (2*S*,4*S*)-1-Phenyl-2,4-pentanediyl Bis(*p*-bromobenzoate) (14). Colorless single crystals were obtained by crystallization of *p*-bromobenzoate **14** from a concentrated solution in ethyl acetate: mp 93–95 °C. A crystal (dimension 0.25 × 0.30 × 0.29 mm) was selected for data collection and mounted on a Rigaku AFC-6B automated four-circle diffractometer. The crystal was found to be orthorhombic, and unit cell parameters and the orientation matrix were obtained. Data collection was carried out by using a 2θ–θ scan: formula, $C_{25}H_{22}Br_2O_4$; formula weight, 546.25; space group, $P2_12_12_1$; a = 15.248 (1) Å, b = 24.985 (2) Å, c = 6.261 (1) Å; vol = 2385.4 (4) $Å^3$; Z = 4; ρ(obsd) = 1.519 g/cm^3; ρ(calcd) = 1.521 g/cm^3; diffractometer, Rigaku AFC-6B; radiation, Cu K_α (1.541 78 Å); monochrometer, graphite crystal; linear absorption coefficient, 45.693 cm^{-1}; temperature, 20 °C; scan type, 2θ–θ; scan speed, 2.0°/min; scan range, 1.2° + 0.5° tan θ; 2θ scan limits, 2.0–130.0°; standard reflections, 3 per 50 reflections; indices, (3,5,0), (0,4,1), (2,0,1); crystal stability, no indication of standard reflection decay during data collection; total reflections scanned, 2546; unique data $F_o > 3.0\sigma(F_o)$, 2037.

The positions of the two bromine atoms were at first found by direct methods, and then those of the remaining non-hydrogen atoms were found by successive Fourier synthesis. Absorption correction was made by using the data of face indices and the size of the crystal. All hydrogen atoms were placed in idealized positions. Block diagonal least-squares refinement of positional parameters, anisotropic thermal parameters for non-hydrogen atoms, and isotropic parameters for hydrogen atoms, including anomalous scattering factors of bromine, oxygen, and carbon atoms, led to the final convergence with R = 0.0438 (final no. of variables, 369) for the 2*S*,4*S* absolute configuration, while a similar calculation for the mirror image structure gave R = 0.0487. So, the absolute stereochemistry of **14** was determined to be 2*S*,4*S* as illustrated in Figure 3.

(2*R*,4*S*)-1-Phenyl-2,4-pentanediyl Bis(*p*-bromobenzoate) (15). Alcohol (2*R*,4*S*)-**54** (0.070 g, 0.19 mmol) was benzoylated to yield **15** (0.0948 g, 90%) as a syrup: IR (neat) ν_{max} 3088, 3028, 2978, 2931, 1724, 1589, 1483, 1454, 1398, 1263, 1173, 1080, 1011, 847, 754, 700, 683, 627 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.36 (3 H, d, J = 6.2 Hz), 1.96 (1 H, ddd, J = 14.4, 5.0, 5.0 Hz), 2.25 (1 H, ddd, J = 14.4, 7.5, 7.5 Hz), 3.03 (1 H, dd, J = 13.5, 6.0 Hz), 3.04 (1 H, dd, J = 13.5, 6.0 Hz), 5.2–5.6 (2 H, m), 7.23 (5 H, s), 7.47 (2 H, d, J = 8.6 Hz), 7.48 (2 H, d, J = 8.6 Hz), 7.79 (4 H, d, J = 8.6 Hz); UV (hexane) λ_{max} 243.3 nm (ϵ 39 100).

(*R*)-1,3-Butanediyl Bis(*p*-chlorobenzoate) (16). (*R*)-1,3-Butanediol (Aldrich, 82% ee) was benzoylated to afford **16** as crystals: mp 60–61 °C; IR ν_{max} 1708, 1590, 1285, 1265, 1085, 1010, 845, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3 H, d, J = 6.5 Hz), 2.16 (2 H, q, J = 6.5 Hz), 4.44 (2 H, t, J = 9.0 Hz), 7.91 (2 H, d, J = 9.0 Hz), 7.94 (2 H, d, J = 9.0 Hz); $[\alpha]^{20}_D$ +72.8° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{16}Cl_2O_4$: C, 58.82; H, 4.39. Found: C, 58.71; H, 4.47.

(2*S*,4*S*)-2,4-Pentanediyl Bis(*p*-chlorobenzoate) (17). (2*S*,4*S*)-Pentanediol (Aldrich) was benzoylated to give **17** as crystals: mp 40–41 °C; IR ν_{max} 1710, 1590, 1280, 1095, 840, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (6 H, d, J = 6.0 Hz), 2.08 (2 H, t, J = 6.0 Hz), 5.30 (2 H, sextet, J = 6.0 Hz), 7.31 (4 H, d, J = 8.5 Hz), 7.87 (4 H, d, J = 8.5 Hz); $[\alpha]^{20}_D$ +165.3° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{18}Cl_2O_4$: C, 59.80; H, 4.76. Found: C, 59.80; H, 4.87.

(2*S*,3*S*)-2,4-Bis(benzyloxy)-1,3-butanediyl Bis(*p*-chlorobenzoate) (18). 2,4-Di-*O*-benzyl-L-threitol was benzoylated to give **18** as syrup: IR ν_{max} 1720, 1590, 1260, 1100, 1010, 845, 750, 730, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (1 H, dd, J = 10.4, 5.5 Hz), 3.83 (1 H, dd, J = 10.4, 4.7 Hz), 4.16 (1 H, ddd, J = 6.0, 5.9, 4.6 Hz), 4.46 (1 H, dd, J = 11.8, 6.0 Hz), 4.51 (1 H, d, J = 12.0 Hz), 4.52 (1 H, dd, J = 11.8, 4.6 Hz), 4.56 (1 H, d, J = 12.0 Hz), 4.68 (1 H, d, J = 12.0 Hz), 4.76 (1 H, d, J = 12.0 Hz), 5.55 (1 H, ddd, J = 5.9, 5.5, 4.7 Hz), 7.27 (10 H, s), 7.38 (2 H, d, J = 8.7 Hz), 7.41 (2 H, d, J = 8.7 Hz), 7.88 (2 H, d, J = 8.7 Hz), 7.97 (2 H, d, J = 8.7 Hz); $[\alpha]^{20}_D$ +29.1° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{32}H_{28}Cl_2O_6$: C, 66.26; H, 4.87. Found: C, 65.96; H, 4.81.

(2*S*,4*S*)-2,4-Heptanediyl Dibenzoate (19). A mixture of olefin (2*S*,4*S*)-**6** (0.217 g, 0.437 mmol), palladium on charcoal (5%, 0.018 g), and ethanol (8 mL) was stirred under hydrogen for 3 h. After removal of the catalyst by filtration, the mixture was evaporated to dryness. The residue was chromatographed on silica gel (hexane/EtOAc 10:1) to yield

19 (0.141 g, 94%) as a syrup: IR (neat) ν_{max} 2960, 2873, 1716, 1450, 1313, 1279, 1113, 1099, 1070, 1026, 710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.94 (3 H, br t, J = 6.0 Hz), 1.40 (3 H, d, J = 6.4 Hz), 1.2-2.0 (4 H, m), 2.10 (2 H, t, J = 6.0 Hz), 5.29 (2 H, sextet, J = 6.1 Hz), 7.2-7.6 (6 H, m), 7.97 (4 H, br d, J = 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.96, 18.49, 20.56, 36.76, 40.36, 68.45, 71.41, 128.20, 128.23, 129.51, 129.56, 130.52, 130.62, 132.67, 132.71, 166.00, 166.07; UV (hexane) λ_{max} 227.4 nm (ϵ 25 700). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.12. Found: C, 74.17; H, 7.15.

(2*S*,4*R*)-2,4-Heptanediyl Dibenzoate (20). Olefin (2*S*,4*R*)-**7** (0.221 g, 0.445 mmol) was similarly reduced to yield **20** (0.145 g, 96%) as a syrup: IR (neat) ν_{max} 2960, 2873, 1716, 1450, 1313, 1275, 1099, 1070, 1026, 712 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.92 (3 H, br t, J = 6.1 Hz), 1.41 (3 H, d, J = 6.2 Hz), 1.2-2.4 (6 H, m), 5.2-5.6 (2 H, m), 7.2-7.6 (6 H, m), 8.02 (4 H, br d, J = 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.91, 18.46, 20.28, 36.52, 40.23, 69.01, 71.84, 128.27, 128.31, 129.55, 129.60, 130.46, 130.55, 132.78, 132.83, 165.98, 166.16; UV (hexane) λ_{max} 227.6 nm (ϵ 26 200). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.12. Found: C, 74.34; H, 7.12.

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Supplementary Material Available: Synthetic procedure and spectral data of compounds which are not described in the Experimental Section (9 pages). Ordering information is given on any current masthead page.

Total Synthesis of Calicheamicinone: New Arrangements for Actuation of the Reductive Cycloaromatization of Aglycon Congeners

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Abstract: The total synthesis of *dl*-calicheamicinone (**1**) has been accomplished. The key elements of the synthesis were (i) an application of the Becker-Adler reaction to reach compound **91**, (ii) an application of the concept of in situ protection to deliver lithiated enediyne **35** to a ketone group in the nominal presence of an aldehyde, (iii) an apparently stereospecific aldol-like cyclization of **93** to reach **94**, (iv) intramolecular Emmons-like closure (cf. **102** to **103**), (v) exploitation of vinylogous urethane character to provide stabilization to an otherwise labile primary enamine (see compound **104**), and (vi) generation of an allylic thiolate and its conversion to the allylic trisulfide emanating from the C_1 bridge (see transformation **111** → **112**). Much of the strategy used in the synthesis of **1** had been worked out in a synthesis of the descarbamate system **9**. The propensity for reductive cycloaromatization of calicheamicin has been simulated with these simpler substrates (see compounds **9**, **68**, **115**, **117**, **124**, and its unstable reduction product).

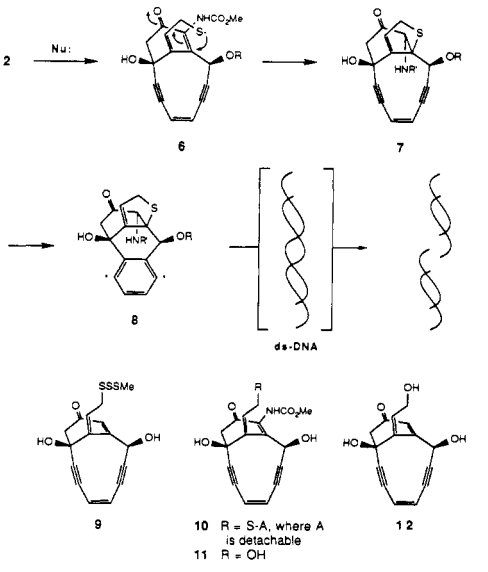
Background and Synthetic Strategy

It is not uncommon for the discovery of a class of compounds of novel structure to provide impetus for new research in organic chemistry. One need only reflect on the enormous impact occasioned by the discovery of steroids, terpenes, and alkaloids (not to mention carbohydrates, proteins, and nucleic acids) to appreciate this connectivity.[1] The recent advent of a new class of antibiotics featuring a confluence of olefinic and acetylenic functionality is likely to provide new challenges for organic chemists. Four such compounds (**2**-**5**) have been fully characterized, and they all exhibit remarkably potent cytotoxicity.[2] The possibility of exploiting the high cell-killing potential of **2**-**5** for cancer chemotherapy has evoked interdisciplinary efforts in the biomedical sciences (Chart I).

The cytotoxic properties of these substances are perceived to involve a bionucleophile-induced series of bond reorganizations leading to aromatic diyl species (vide infra) with DNA-damaging ability via cleavage of carbon-hydrogen bonds of deoxyribose residues. The resultant DNA species, bearing anomalous carbon appendages, could well be less subject to normal repair mechanisms.[3]

One might question whether such drugs can exhibit useful indices of selectivity based solely on the increased vulnerability of rapidly proliferating cells to cytotoxic agents.[4a] Conceivably, a better understanding of the way in which these compounds are

Scheme I



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