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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 159–165

Synthesis and characterization of asymmetric *o*- and *m*-nitrobenzoic acids with a 1,3-benzodioxole skeleton

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Received 4 October 2003; accepted 18 October 2003

Abstract—Asymmetric *o*- and *m*-nitrobenzoic acids with a 1,3-benzodioxole skeleton have been synthesized and characterized. The synthesis involved nitration at either the C-5 or C-6 position of 2-*tert*-butyl-2-methyl-1,3-benzodioxole-4-carboxylate derived from catechol. These were then resolved with chiral solid-phased HPLC columns into each of enantiomers (>99% ee), which were characterized by circular dichroism. The (*S*)-enantiomers were also obtained by fractional crystallization of the precursor prior to the nitration. When applied as chiral derivation agents for alcohols and amines, *m*-nitrobenzoic acid showed notable ability to separate the enantiomers in both HPLC and NMR analyses. On the other hand, ^{1}H NMR and X-ray data of their ester and amide derivatives strongly suggested that the *o*-nitrobenzoic acid would serve as a fluorescent building block useful for the assembly of β-peptide linkages with a defined conformation.

1. Introduction

1,3-Benzodioxoles occur widely in plant products,[1] some of which are known to show potent antioxidant and antibacterial activities.[2] Although the skeleton per se of **1** ($R^1 = R^2 = H$, Fig. 1) is achiral, a new class of chiral 1,3-benzodioxoles has recently been proposed by one of us,[3] which possesses a stereogenic center at the C-2 position. This design is based on the unique structure of 2,2-substituted-1,3-benzodioxole **1** ($R^1 \neq R^2$), which provides prochiral positions on the aromatic ring. This means that an aromatic substitution reaction gives the corresponding asymmetric 1,3-benzodioxole. For example, carboxylation of **1** ($R^1 = {}^t$Bu, $R^2 = $ Me) with *n*-butyl lithium and solid CO_2 gave optically active (*S*)-**2** [(*S*)-**2**-*tert*-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid] after resolution with a chiral amine (cinchonidine).[3,4] The use of 3-methyl catechol instead of catechol gave (*S*)-**2** in a simpler manner. The combination of the 2-substituent groups can be varied via the use of different ketones for the condensation with catechols.

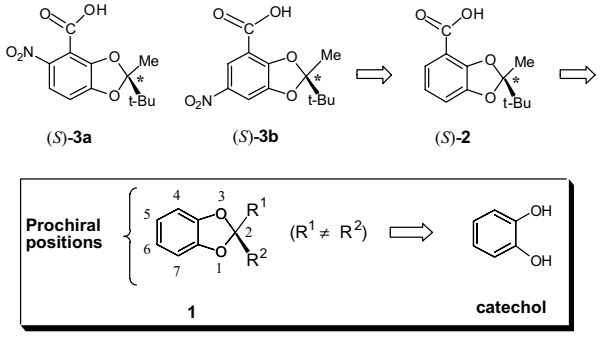

Figure 1. Asymmetric 1,3-benzodioxoles built up from catechol.

The chiral benzoic acid (*S*)-**2**, its esters, and amides are all fluorescent (Ex. ca. 310 nm, Em. ca. 370 nm). Thus, compound (*S*)-**2** serves as a fluorescent chiral agent that has had applications shown in many analytical studies.[5] Along with our continuing studies on the design and application of artificial glycoconjugates,[6] our interests have also been directed to the function of (*S*)-**2** showing stable fluorescence under various physiological conditions.[7] In the present study, we extend the skeleton of (*S*)-**2** to chiral nitrobenzoates (*S*)-**3a** and (*S*)-**3b**.

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doi:10.1016/j.tetasy.2003.10.030

It is obvious that the nitrobenzoic acids, possessing both amino and carboxyl functions, are versatile synthetic intermediates. It is known that *o*- and *m*-nitrobenzoic acids provide such artificial β- and γ-peptide linkages showing unique conformational and physicochemical properties.[8] In the present study, we envisage that the chiral nitrobenzoates will be useful not only for analytical purposes but also for the assembly of fluorescent glycosyl peptide linkages. Herein, we describe the synthesis of (*S*)-**3a** and (*S*)-**3b** starting from *rac*-**2**, the resolution, absolute configuration, conformational, and preliminary functions as chiral reagents and peptide building blocks.

2. Results and discussion

2.1. Nitration reactions of *rac*-2 and (*S*)-2

Theoretically, three mono-nitro derivatives (*o*-, *m*-, and *p*-) can be obtained from *rac*-**2**. We examined the nitration reaction of *rac*-**2** at different temperatures with nitronium tetrafluoroborate (NO_2BF_4)[9] (Table 1).

Table 1. Nitration reactions of *rac*-**2** using NO_2BF_4[a]

Solvent	Temperature (°C)	Ratio of *rac*-**3a** and *rac*-**3b**[b]	Total yield[c] (%)
Sulfolane	60	71/29	72
	40	65/35	80
	30	60/40	84
Acetonitrile	20–25	86/14	80
	0	65/35	88
	−8	60/40	92

[a] Reaction was carried out using *rac*-**2** (300 mg) and the nitronium salt (1.1 equiv, 0.5 M in sulfolane) until *rac*-**2** was consumed (for 1–1.5 h).
[b] Determined by ^{1}H NMR spectroscopy of the mixture before purification by silica gel column chromatography. A *p*-nitro isomer could not be detected in the products.
[c] Isolated yield after purification with silica gel column.

When 1.1 equiv of the nitrating agent was applied to *rac*-**2**, a mixture of *rac*-**3a** and *rac*-**3b** was obtained in good yield (72–92%) together with a dinitro derivative in a trace amount. No *p*-nitro isomer was detected in any reaction. If the usual electrophilic substitution was assumed, *m*-directed nitration might have predominated. Thus, the observed regioselectivity disclosed the unusual case that *o*-nitration was preferential over *m*-nitration particularly at elevated temperatures. This meant that the substrate *rac*-**2** reacts via an alternative nitration pathway. When the reaction was carried out at temperatures higher than 0 °C, the reaction mixture gave a deep green color.

It is known that aryl compounds with a low oxido-redox potential take a radical nitration pathway that involves electron transfer to the nitrium cation.[10] The redox potential of *rac*-**2** was measured to be 1.06 V with cyclic voltametry against Ag/AgCl electrode. The value was lower than that of 1,3-dimethyl-naphthalene (1.60 V) that has been reported to take the radical pathway.[10] Thus, it is obvious that the nitration of *rac*-**2**, at elevated temperatures, takes the radical pathway giving the *o*-nitro isomer as the major product.

When the nitration was conducted with (*S*)-**2** in sulfolane at 30 °C, a mixture of (*S*)-**3a** and (*S*)-**3b** was derived in the ratio of 60:40 (in 84% total yield). However, this reaction caused partial racemization in the products in different degrees between (*S*)-**3a** and (*S*)-**3b**. The racemization was more pronounced for (*S*)-**3a** (20% ee determined by HPLC analysis under the conditions cited in Table 2) than (*S*)-**3b** (47% ee). This indicated that a part of the racemization occurred after the nitration. The reagent (*S*)-**2** was stable under both acidic and basic conditions employed for the derivation of alcohols and amides.[5] These facts allowed us to assume that the radical pathway might also give a radical species at the C-2 stereogenic center causing racemization. On the other hand, when the nitration was performed at −40 °C in CH_3CN, (*S*)-**3a** and (*S*)-**3b** were obtained from (*S*)-**2** in ca. 1:1 ratio (>99% ee, 92% yields) without racemization. In this case, the reaction mixture did not show the deep green color that seems to show the occurrence of the radical pathway.

Table 2. Resolution of **2**, **3a**, and **3b** with chiral phase HPLC columns[a]

Agents	Retention times (min)		
	r_1	r_2	R_s[b]
rac-**2**	9.37	9.37	0
	(11.65	12.60	1.78)[c]
rac-**3a**	14.33	15.12	0.88
	(48.56	52.63	1.46)[d]
rac-**3b**	11.45	12.83	1.95

[a] Chiralpak AD (Daicel Co. Ltd.). Elution: *n*-hexane–2-PrOH–TFA = 90:10:0.1; flow rate = 0.5 mL/min.
[b] R_s = resolution factors = $2 \times (r_2 - r_1)$/(sum of band width of the two HPLC peaks).
[c] Separated by Chiralcel OD (Daicel Co. Ltd.).
[d] Eluted with *n*-hexane–2-PrOH–TFA = 98:2:0.1; flow rate = 0.6 mL/min.

2.2. Resolution and chiroptical properties

From a variety of methods to resolve racemic carboxylic acids into the enantiomers, a series of asymmetric 1,3-benzodioxole-4-carboxylic acids including (*S*)-**2** has been resolved by fractional crystallization with cinchonidine or analogous chiral amines.[6] On the other hand, we encountered the problem that the synthetic route was not adaptable for the resolution of *rac*-**3a** and *rac*-**3b**. Iterative experiments using cinchonidine and quindine for the resolution failed. Thus, it is of practical importance to establish a more general method for the resolution of asymmetric 1,3-benzodioxoles.

In this section, we examined chiral phase HPLC columns developed by Okamoto et al.[11] for the resolution of *rac*-**2**, *rac*-**3a**, and *rac*-**3b**. After finding the optimal HPLC conditions, *rac*-**3a** and *rac*-**3b** were resolved using

a Chiralpak AD column (Daicel Co. Ltd.) and a mixture of trifluoroacetic acid (TFA), *n*-hexane, and 2-PrOH (0.1:90:10) as the mobile phase (Table 2). Here, the use of TFA was essential for the resolution, otherwise, the HPLC gave broad and complicated chromatograms due probably to the formation of carboxyl dimers in both diastereomeric and enantiomeric relations. Under the optimized conditions, every enantiomer component in *rac*-**3a** and *rac*-**3b** was separated with high enantiomeric purity (>99% ee). For the HPLC resolution of *rac*-**2**, the above column was not effective but was successfully replaced with an alternative column of Chiralcel OD (Daicel Co. Ltd.).

Since the absolute configuration of (*S*)-**2** had already been established by X-ray analysis,[12] the absolute configurations of (*S*)-**3a** and (*S*)-**3b** derived from (*S*)-**2** were also determined. Here, circular dichroic (CD) spectroscopy was applied to correlate the absolute configuration with CD signals. The CD spectra of (*S*)-**3a** and its antipode (*R*)-**3a** derived by the chiral HPLC separation gave three main bands at ca. 230, 300, and 360 nm. The *m*-nitro isomer **3b** gave similar CD bands at ca. 240, 290, and 340 nm with a much lower intensity than those of the *o*-nitro isomer **3a**. The CD band at ca. 230 nm of **3b** was ambiguous due to a noisy response associated with a strong UV absorption in this region, while the band ca. 350 nm was of diagnostic value to be correlated with the absolute configuration (Fig. 2).

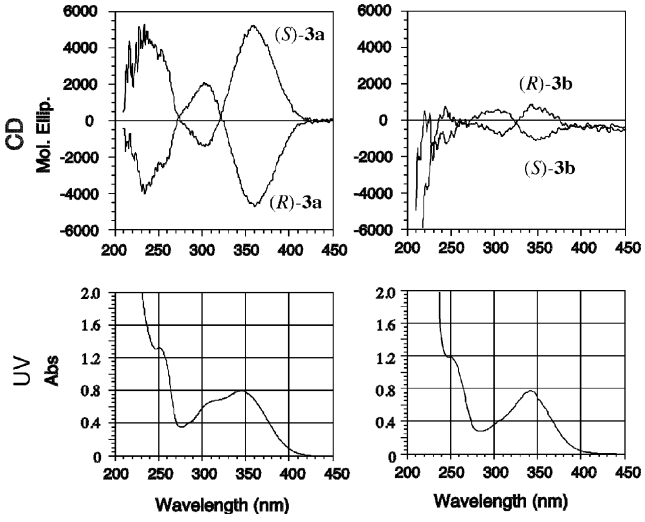

Figure 2. CD and UV spectra of asymmetric nitrobenzoic acids (MeOH).

The CD bands of (*S*)-**3b** were very weak and similar to those of (*S*)-**2**($[\theta]_{max}$ +1800, 318 nm).[3] This indicated that the two alkyl groups at C-2 made minor perturbations to the 1,3-benzodioxole-4-carboxylate chromophore. On the other hand, the strong couplet CD bands of (*S*)-**3a** strongly suggested that the chromophore might permit a helical distortion. This assumption is based on an exciton CD coupling mechanism[13] and a MNDO calculation of 1,3-benzodioxoles reported by Vidal et al.[14] who predicted that the skeleton of 1,3-benzodioxole was distorted to some extent from a planar Kekule-type benzene ring. It is highly probable that compound (*S*)-**3a**, with repulsive interactions between *o*-nitro and carboxylate groups in the vicinity, may take a non-coplanar 1,3-benzodioxole to show the exciton coupling CD bands.

2.3. Evaluations of (*S*)-3a and (*S*)-3b as chiral reagents

The chemical function of (*S*)-**3a** and (*S*)-**3b** stems from their ability to induce chirality into the second achiral or chiral molecule via an ester or amide linkage. This function can be applied, for example, to separate enantiomeric alcohols and amines using the usual HPLC and NMR methods under achiral conditions.[5] In order to evaluate this function in a simple way, *rac*-**3a** and *rac*-**3b** were coupled with either racemic 1-phenylethanol or 1-phenylethylamine. The mixtures of the diastereomers, composed of (*R*,*S*)/(*S*,*S*)- and (*S*,*R*)/(*R*,*R*)-isomers, were subjected to the analyses with achiral phased HPLC and ^{1}H NMR. In order to correlate the HPLC elution orders with relative configurations, optically active (*S*)-**3a** (50% ee) and (*S*)-**3b** (20% ee) were also coupled with (*S*)-1-phenylethylamine (95% ee).

The coupling reactions were performed via the activation of carboxyl group with hexafluoropropene–diethylamine complex.[16] Every coupling reaction afforded the corresponding diastereomeric esters and amides in high yields (>80%). The results of HPLC and ^{1}H NMR analyses are summarized in Tables 3 and 4. Here, it is assumed that (*S*)-**3a** and (*S*)-**3b** can be applied for the separation of the racemic alcohol and amine. This assumption is valid for the present case that the HPLC and NMR studies were carried out under achiral conditions using chiral reagents with established configurations.

Table 3. HPLC separation of enantiomeric alcohol and amine labeled with 1,3-benzodioxole-based chiral reagents[a]

Agents	1-Phenylethanol[b]			1-Phenylethylamine[c]		
	r_1[d]	r_2[d]	R_s	r_1[d]	r_2[d]	R_s
(*S*)-**2**	9.94	9.94	0	10.98	12.05	2.47
(*S*)-**3a**	20.99	22.18	1.86	19.53	20.66	1.36
(*S*)-**3b**	17.44	18.84	2.53	12.27	15.23	7.05

[a] Separated on achiral silica HPLC columns (Shiseido Co. Ltd.).
[b] Eluted with *n*-hexane–ethyl acetate = 95:5 at flow rate 0.6 mL/min.
[c] Eluted with *n*-hexane–ethyl acetate = 80:20 at flow rate 0.6 mL/min.
[d] r_1,r_2 = retention times (min) of each diastereomer. For (*S*)-**2** and (*S*)-**3b**, r_1 = (*S*,*S*), r_2 = (*S*,*R*)-isomers. For (*S*)-**3a**, r_1 = (*S*,*R*), r_2 = (*S*,*S*)-isomers. The assignment may be reversed for 1-phenylethanol.

The HPLC data indicates that (*S*)-**3b** has a higher ability to separate enantiomeric alcohols and amines than (*S*)-**2**. (*S*)-**3a** showed higher activity than (*S*)-**2** for 1-phenylethanol but not for the amine. The enhanced activity of (*S*)-**3a** and (*S*)-**3b** for the alcohol is of practical significance because (*S*)-**2** and other commercially available chiral agents tend to show poor activity for the resolution of alcohols. Here, it is noteworthy that the enhanced activity summarized in Table 3 corresponds well with the resolution of *rac*-**2**, *rac*-**3a**, and *rac*-**3b**

Table 4. ^{1}H NMR separation of enantiomeric alcohol and amine labeled with 1,3-benzodioxole chiral reagents[a]

Agents	1-Phenylethanol (ΔHz[b])		1-Phenylethylamine (ΔHz[b])	
	Δ^tBu	ΔMe	Δ^tBu	ΔMe
(*S*)-**2**	+8.0	−7.0	+31.0	−24.0
(*S*)-**3a**	+14.5	+14.0	−5.0	+8.5
(*S*)-**3b**	+8.5	−6.0	+36.5	−27.5

[a] Measured at 500 MHz in $CDCl_3$ (digital resolution = 0.2 Hz); temperature = 22–24 °C.

[b] Chemical shift difference: $\Delta Hz = [\delta$ (ppm) $(R,S) - \delta$ (ppm) $(S,S)] \times 500$. For 1-phenylethanol, the relative chemical shifts for the assignments of (+ or −) signs are ambiguous and may be reversed.

themselves confirmed by chiral phased HPLC columns (Table 2); *rac*-**3a** and *rac*-**3b** were more easily resolved than *rac*-**2**. This suggests that the chiral HPLC methods are more useful in determining the ability of the chiral acids to separate enantiomeric alcohols and amines.

^{1}H NMR spectroscopy provided a facile way to analyze enantiomeric components. In the present case, the 1,3-benzodioxole-based agents (*S*)-**3a** and (*S*)-**3b** possessing *t*-Bu and Me groups at C-2 give their sharp signals at ca. δ 1.0 ppm and δ 1.5 ppm, respectively. These are useful in discriminating between enantiomers, as summarized in Table 4. The ^{1}H NMR data (500 MHz, digital resolution ±0.2 Hz) indicated that (*S*)-**2** and (*S*)-**3b** showed a tendency similar to each other. On the other hand, (*S*)-**3a** showed a largely different behavior as can be seen from the fact that it shows a higher separation for the alcohol rather than the amine. The high resolution for the alcohol was in good agreement with the HPLC analysis as mentioned above (Table 3). The unique behavior of (*S*)-**3a** seems to arise from the stereo- and electrostatic repulsion between the *o*-nitro and 4-carbonyl group leading to the flexible conformation around the two functional groups.

2.4. Conformational property of amide linkages constructed with (*S*)-3a and (*S*)-3b

Previous results have demonstrated that both (*S*)-**3a** and (*S*)-**3b** serve as chiral discriminating reagents useful for enantiomeric alcohols and amines. The results have also shown that (*S*)-**3a** and (*S*)-**3b** behave differently as the chiral reagents. For example, the latter showed much higher activity in separating the enantiomers of 1-phenylethylamine than (*S*)-**3a** and (*S*)-**2** in the HPLC analysis. The stronger activity seems ascribable to a stable conformation around the 4-carbamide linkage constructed from (*S*)-**3b** and the amine.

X-ray crystalline analysis for an L-phenylalanine derivative of (*S*)-**2**[12] had disclosed that the 4-carbamide moiety takes a coplanar conformation, in which an intra-molecular hydrogen bond is observed between the N–H and O-3. The 4-carbamide derived from (*S*)-**3b** is assumed to take a similar conformation as depicted in Figure 3, since the *m*-nitro group has little effect on the conformation. This assumption was supported by the ^{1}H NMR data of the 1-phenylethylamide derivative of (*S*)-**3b**. The ^{1}H signal of the N–H proton shifted to a lower magnetic field (δ 7.38 ppm) than that of the corresponding amide protons of (*S*)-**3a** (6.08 ppm) similarly to the case of (*S*)-**2** (δ 7.22 ppm). The deshielding effect should arise from the intra-molecular hydrogen bond as depicted in Figure 3. The stable conformation locates the phenyl and *t*-Bu in a *cis*-relation for the (*S*,*R*)-diastereomer (a), while it locates them in a *trans*-relation for the (*S*,*S*)-isomer (b).

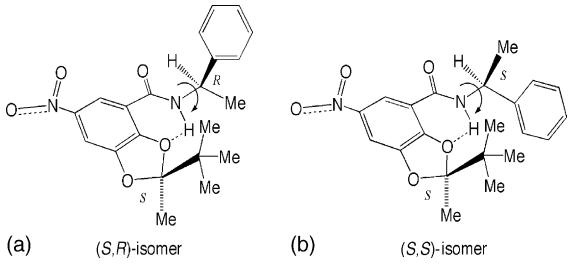

Figure 3. Proposed conformations at the amide linkage of two diastereoisomers derived from (*S*)-**3b** and 1-phenylethylamine.

As discussed in the HPLC study (Table 3), the (*S*,*S*)-diastereomer derived from (*S*)-**3b** was eluted faster than the (*S*,*R*)-isomer section under normal phased conditions. The eluting order was rationalized with the conformations depicted in Figure 3. That is, the (*S*,*R*)-isomer, possessing a less hindered face, can move more slowly and adsorb much better on the silica than the (*S*,*S*)-isomer. The ^{1}H NMR data can be also interpreted. In this case, the magnetic anisotropy of the 1-phenyl group appears in different ways between the two diastereomers: the (*S*,*R*) and (*S*,*S*)-diastereomers permit anisotropic deshielding at the *t*-Bu and Me groups, respectively.

When applied as a chiral reagent, (*S*)-**3a** behaved differently from (*S*)-**2** and (*S*)-**3b**. As judged from the ^{1}H chemical shift of N–H (δ 6.08 ppm), the 4-carbamide linkage in the 1-phenylethylamine derivative was free from the intra-molecular hydrogen bond. It is obvious that the electrostatic repulsion between *o*-nitro and 4-carbamide and groups did not allow the amide to take a coplanar conformation. On the other hand, when the *o*-nitro group in *rac*-**3a** was converted into the acetamido group in **4a** (Fig. 4), a drastic change in the conformation occurred. The X-ray crystallographic data of **4a**[15] indicated that both of the 4-carboxylate ester and acetamide groups are in a coplanar conformation, where an intra-molecular hydrogen bond is observed between the N–H and 4-C=O. This means that the electrostatic repulsion in **3a** is released after the conversion to **4a** with the *o*-acetamido group giving a stable conformation.

Though none of *o*-nitrobenzoic acid, its esters, and amides were fluorescent, the conversion of the *o*-nitro group was found to recover the fluorescence of 1,3-benzodioxole-4-carboxylates (Fig. 5) at a longer wavelength region (Ex. 350 nm, Em. 445 nm), than that of **2**. The wavelength region, applicable to fluorescence

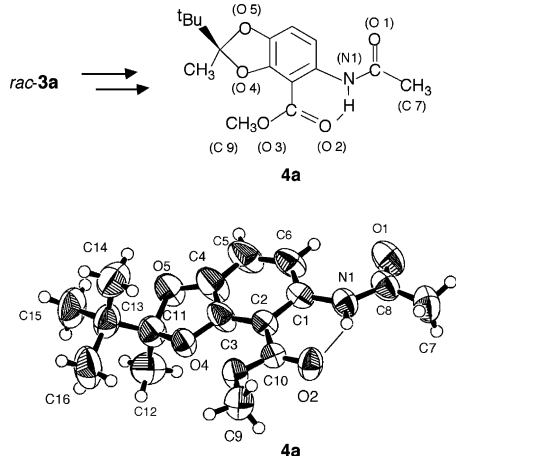

Figure 4. ORTEP structure of *o*-acetamido derivative **4a**.[15]

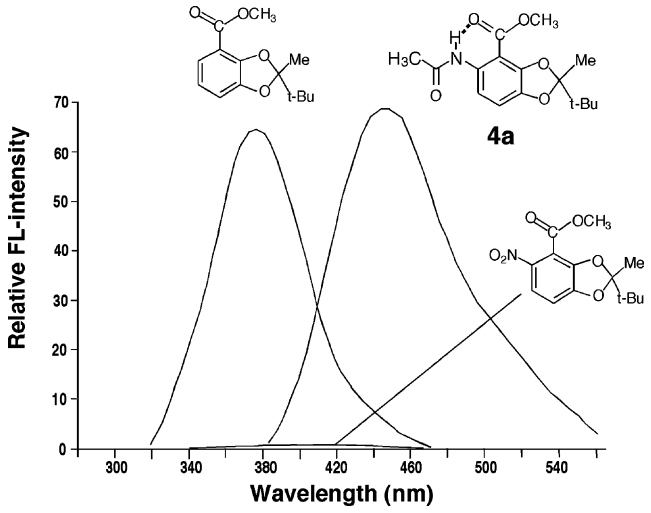

Figure 5. Fluorescence spectra of *o*-substituted 1,3-benzodioxole-4-carboxylates (MeOH) (methyl ester of **2**: Ex. 315 nm; methyl ester of **3a**: Ex. 320–350 nm; **4a**: 350 nm).

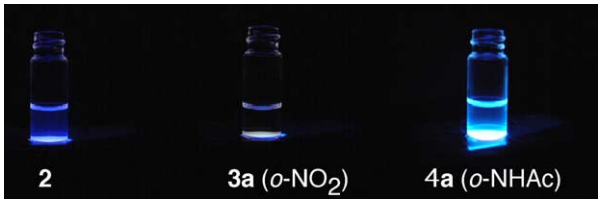

Figure 6. Fluorescence of **2** and **4a** in MeOH solution (ca. 1 mM) as visualized under UV light.

microscopy, extended the potential use of the 1,3-benzodioxole fluorophore. These results support that the *o*-nitrobenzoic acid **3a** or (*S*)-**3a** is useful for the assembly of fluorescent β-peptide linkages showing a well-defined conformation property[17] (Fig. 6).

3. Conclusion

We have demonstrated that chiral *o*- and *m*-nitrobenzoates with a 1,3-benzodioxole skeleton are available extending the concept of asymmetric 1,3-benzodioxoles. In the primary function as chiral reagents, the *m*-nitro benzoic acid showed a notable activity to separate enantiomeric alcohol and amines. The *o*-nitro isomer showed a drastic conformational and fluorescent change when converted to an *o*-acetamido derivative. These results suggest that the asymmetric *o*- and *m*-nitrobenzoic acids have high potential in both analytical and synthetic applications. We speculate that they will be useful as fluorescent reagents for the assembly of highly functional glyco-peptide conjugates and reagents. A study along this line is currently in progress and will be reported elsewhere.

4. Experimental

^{1}H NMR spectra were measured on a Varian INOVA-500 (500 MHz) or Varian Mercury-300 (300 MHz) at ambient temperature in $CDCl_3$ using an internal TMS standard unless otherwise stated. FT-IR spectra (JASCO FT/IR-230), UV spectra (JASCO V-530, MeOH), and CD spectra (JASCO J-725, MeOH) were measured in conventional ways at room temperature. X-ray crystallographic data were obtained on a Rigaku AFC7R diffractometer and the details cited reported in Ref. 15. Racemic TBMB carboxylic acid *rac*-**2** and (*S*)-TBMB carboxylic acid (*S*)-**2** were prepared by reported methods from either catechol or 3-methyl catechol.[3,4] Nitronium tetrafluoroborate (0.5 M solution in sulfolane) was purchased from Aldrich Chemical Company Inc. Hexafluoropropene–diethylamine complex (HFPDA) was purchased from Tokyo Kasei Kogyo in Tokyo. The other chemicals and solvents were commercially available and used without further purification.

4.1. Nitration of *rac*-2

A solution of *rac*-**2** (300 mg, 1.27 mmol) in sulfolane (6 mL) was stirred for 15 min at 30 °C under nitrogen atmosphere. To the mixture was added NO_2BF_4 [0.5 M in sulfolane, 2.79 mL (1.1 equiv)]. The mixture was stirred for 1 h at 30 °C, poured into water (100 mL), and extracted with *n*-hexane–ethyl acetate (4:1, v/v). The combined extracts were washed with water and dried over $MgSO_4$. After removing the solvents, the residue was purified by silica gel column chromatography [chloroform–methanol–acetic acid, 100:1:1.5 (v/v)] to afford *rac*-**3a** (180 mg, 50.1%) and *rac*-**3b** (122 mg, 34.1%). *rac*-**3a**: mp 163–164 °C. ^{1}H NMR δ 1.098 (9H, s, *t*-Bu), 1.684 (3H, s, Me), 6.809 (1H, d, $J = 8.7$ Hz, H-7), 7.686 (1H, d, $J = 8.4$ Hz, H-6). IR (KBr) 1716 (CO), 1529 (NO_2), 1336 (NO_2). HR-MS calcd for $C_{13}H_{15}O_6N$ (281.0899), found: 281.0865. *rac*-**3b**: sublimated point 186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.119 (9H, s, *t*-Bu), 1.714 (3H, s, Me), 7.719 (1H, d, $J = 2.1$ Hz, H-7), 8.454 (1H, d, $J = 2.1$ Hz, H-5). IR (KBr) 1697 (CO), 1531 (NO_2), 1338 (NO_2). HR-MS calcd for $C_{13}H_{15}O_6N$ (281.0899), found: 281.0889.

4.2. Nitration of (*S*)-2

A solution of (*S*)-**2** (>99% ee, 150 mg, 0.64 mmol) in acetonitrile (30 mL) was stirred for 15 min at −40 °C under nitrogen atmosphere. To the mixture was added NO_2BF_4 [0.5 M in sulfolane, 1.27 mL (1.0 equiv)]. The mixture was stirred for 1 h at −40 °C, poured into water (100 mL), and extracted with *n*-hexane–ethyl acetate (4:1, v/v). The combined extracts were washed with water and dried over $MgSO_4$. After removing the solvents, the residue was purified by silica gel column chromatography [chloroform–methanol–acetic acid, 100:1:1.5 (v/v) and toluene–methanol, 20:1 (v/v)] to afford (*S*)-**3a** [>99% ee, 80.6 mg, 50%, $[\alpha]_D^{22}$ +16.6 (*c* 0.1, MeOH)] and (*S*)-**3b** [>99% ee, 54.5 mg, 35%, $[\alpha]_D^{22}$ +15.4 (*c* 0.1, MeOH)]. Enantiomeric purity was determined by ^{1}H NMR spectroscopy of the cinchonidine salt.

4.3. Derivation of 3a and 3b with 1-phenylethanol and 1-phenylethylamine

A mixture of (*S*)-**3a** (47% ee) or *rac*-**3a** (3 mg, 0.01 mmol) and hexafluoropropene–diethylamine complex (HFPDA, 5.8 μL, 1.5 equiv) in toluene (2 mL) was stirred for 1 h. The reaction mixture was washed with satd $NaHCO_3$ and water and then dried over $MgSO_4$. The filtrate solution was concentrated, and the residue dissolved in CH_2Cl_2 (1 mL), and used as a reagent solution. In the same manner, the reagent solutions of *rac*-**3b** and *rac*-**2** were prepared. A mixture of 1-phenylethylamine (2.0 equiv, or 1-phenylethanol), triethylamine (2.0 equiv), and *N*,*N*-dimethylaminopyridine (DMAP, 0.2 equiv) were dissolved in CH_2Cl_2 (2 mL) under nitrogen atmosphere and mixed with the reagent solution (2.0 equiv). The mixture was stirred for 3 h and concentrated. The residue was purified by silica gel column chromatography to give a pair of diastereomeric amides or esters (>80% yields). 1-Phenylethylamide of *rac*-**2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.034 and 1.096 (9H×2, s, *t*-Bu), 1.581 and 1.590 (3H×2, d, $J = 7.0$ Hz, CH_3), 1.587 and 1.635 (3H×2, s, TBMB–Me), 5.299 (2H, m), 6.832–6.882 (4H, m, H-6 and H-7), 7.240–7.281 (2H, m), 7.321–7.385 (8H, m), 7.39 (2H, br, NH), 7.489–7.511 (2H, m, H-5). EI-MS 340 $[M]^+$, 283 $[M-57]^+$.

Phenylethylamide of *rac*-**3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.058 and 1.068 (9H×2, s, *t*-Bu), 1.621 and 1.638 (3H×2, s, TBMB–Me), 1.637 and 1.649 (3H×2, s, CH_3), 5.412 (2H, m), 6.059 and 6.101 (1H×2, br d, $J = 20.5$ Hz, NH), 6.755 and 6.757 (1H×2, d, $J = 8.5$ Hz, H-7), 7.276–7.292 (2H, m), 7.333–7.369 (4H, m), 7.427–7.457 (4H, m), 7.655 and 7.681 (1H×2, d, $J = 8.5$ Hz, H-6). EI-MS 384 $[M]^+$, 327 $[M-57]^+$. 1-Phenylethylamide of *rac*-**3b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.040 and 1.113 (9H×2, s, *t*-Bu), 1.605 and 1.614 (3H×2, d, $J = 6.5$ Hz, CH_3), 1.664 and 1.719 (3H×2, s, TBMB–Me), 5.298 and 5.308 (1H×2, m), 7.224 (2H, br t, $J = 7.0$ Hz, NH), 7.269–7.318 (2H, m), 7.355–7.371 (4H, m), 7.677 and 7.680 (1H×2, d, $J = 2.5$ Hz, H-7), 8.547 and 8.551 (1H×2, d, $J = 2.5$ Hz, H-5). EI-MS 384 $[M]^+$, 327 $[M-57]^+$.

1-Phenylethyl ester of *rac*-**2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.096 and 1.112 (9H×2, s, *t*-Bu), 1.611 and 1.625 (3H×2, s, TBMB–Me), 1.633 and 1.641 (3H×2, d, $J = 6.0$ Hz, CH_3), 6.125 (2H, dd, $J = 6.5$ Hz, 13.0 Hz), 6.758–6.791 (2H, m, H-6), 6.847–6.867 (2H, m, H-7), 7.270–7.302 (2H, m), 7.324–7.367 (4H, m), 7.359–7.380 (2H, m, H-5), 7.462–7.494 (4H, m). EI-MS 339 $[M]^+$, 282 $[M-57]^+$. 1-Phenylethyl ester of *rac*-**3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.026 and 1.055 (9H×2, s, *t*-Bu), 1.605 and 1.633 (3H×2, s, TBMB–Me), 1.686 and 1.695 (3H×2, d, $J = 6.5$ Hz, CH_3), 6.209 and 6.217 (1H×2, dd, $J = 6.5$ Hz, 13.0 Hz), 6.766 and 6.767 (1H×2, d, $J = 8.5$ Hz, H-7), 7.276–7.317 (2H, m), 7.328–7.372 (4H, m), 7.412–7.438 (4H, m), 7.701 and 7.726 (1H×2, d, $J = 8.5$ Hz, H-6). EI-MS 385 $[M]^+$, 328 $[M-57]^+$. 1-Phenylethyl ester of *rac*-**3b**:^{1}H NMR (500 MHz, $CDCl_3$) δ 1.101 and 1.118 (9H×2, s, *t*-Bu), 1.668 and 1.679 (3H×2, d, $J = 6.5$ Hz, CH_3), 1.681 and 1.693 (3H×2, s, 2-Me), 6.143 and 6.145 (1H×2, dd, $J = 6.5$ Hz, 13.0 Hz), 7.290–7.332 (2H, m), 7.345–7.390 (4H, m), 7.445–7.477 (4H, m), 7.670 and 7.673 (1H×2, d, $J = 2.5$ Hz, H-7), 8.411 and 8.416 (1H×2, d, $J = 3.0$ Hz, H-5). EI-MS 385 $[M]^+$, 328 $[M-57]^+$.

4.4. Methyl 5-acetamide-2-*tert*-butyl-2-methyl-1,3-benzodioxole-4-carboxylate (*rac*-4a)

A mixture of *rac*-**3a** (100 mg, 0.355 mmol) and the hexafluoropropene–diethylamine complex (HFPDA, 193 μL, 1.5 equiv) in toluene (8 mL) was stirred for 1 h. To the mixture were added methanol (0.3 mL), triethylamine (294 μL, ca. 6 equiv), and DMAP (8.7 mg, 0.2 equiv). After 5 h, the mixture was washed with satd $NaHCO_3$ and water, and then dried over $MgSO_4$. The solution was filtrated and concentrated, and the residue then purified by column chromatography on silica gel to give a methyl ester of *rac*-**3a** (84 mg, 82%): mp 87–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.075 (9H, s, *t*-Bu), 1.651 (3H, s, Me), 3.953 (3H, s, COOMe), 6.777 (1H, d, $J = 8.5$ Hz, H-7), 7.715 (1H, d, $J = 9.0$ Hz, H-6). IR (KBr) 1745 (C=O), 1529 (NO_2), 1334 (NO_2). EI-MS 295 $[M]^+$, 238 $[M-57]^+$.

This ester (80 mg, 0.271 mmol) was hydrogenated in methanol (8 mL) with $Pd(OH)_2$/C at room temperature under atmospheric pressure. After 3 h, the reaction mixture was filtered, treated with acetic anhydride (0.5 mL), and stirred for 30 min. After removing the solvents, the residue was purified by silica gel column chromatography [toluene–ethyl acetate, 10:1 (v/v)]. **4a** (81 mg, 97%): mp 94–95 °C. ^{1}H NMR (300 MHz, CDCl3) δ 1.061 (9H, s, *t*-Bu), 1.574 (3H, s, Me), 2.188 (3H, s, Ac), 3.922 (3H, s, COOMe), 6.839 (1H, d, $J = 9.0$ Hz, H-7), 8.016 (1H, d, $J = 8.4$ Hz, H-6), 10.62 (1H, br s, NH). HR-MS calcd for $C_{16}H_{21}O_5N$ (307.1420), found: 307.1418.

Acknowledgements

A part of this study was supported in part by a grant from the 21st Century COE program 'Nature-Guided

Materials Processing' of the Ministry of Education, Culture, Sport, Science and Technology of Japanese Government.

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