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Synchronized stereocontrol of planar chirality by crystallization-induced asymmetric transformation

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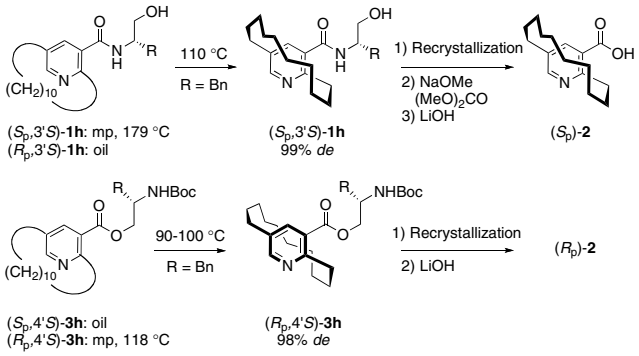
ABSTRACT

Synchronized stereocontrol of two planar-chiral units was accomplished by using crystallization-induced asymmetric transformation (CIAT) of cyclophane-type bridged bisnicotinate derivatives **5b** and **7**. After screening various linkers, (*S*)-2-amino-1-butanol and (*S*)-*tert*-leucinol were found to be the most effective for CIAT of the corresponding bridged bisnicotinate **5b** and **7**, respectively, whose diastereomeric ratio finally reached 97% and 88%, respectively.

Planar-chiral organic molecules represented by cyclophanes[1,2] and other related compounds[3] are recently becoming attractive targets for organic chemists because of their potent and characteristic functionality as distinctive chiral sources for asymmetric reactions.[4] However, research on that area has been still underdeveloped according to the limited numbers of efficient synthetic routes to access such chiral molecules.[5,6] We had previously reported new synthetic methods for [*n*](2,5)cyclophane-3-carboxylates (or bridged benzoates)[7] and for [*n*](2,5)pyridinophane-3-carboxylates (or bridged nicotinates)[8] and also their stereocontrol of planar chirality via crystallization-induced asymmetric transformation (CIAT)[7,9] and adsorption-induced asymmetric transformation (AIAT).[10] In these transformations, linkers derived from amino alcohols play a key role in forming hydrogen bonds at amide functionality and neighboring stereochemistry at chiral centers on the auxiliary transfers to the configuration of planar chirality accumulated in (S_p,3′*S*)-**1h** (R = Bn)[9] or (R_p,4′*S*)-**3h** (R = Bn)[11] with 99% or 98% *de*, respectively (Scheme 1). On the other hand, only a little is known about asymmetric transformation concerning simultaneous stereocontrol of multi chiral centers[6] and, therefore, we turned our attention to seeking stereocontrol of multi planar chirality by using single asymmetric center. For achieving such stereocontrol in pyridinophane systems, we have synthesized bridged bisnicotinic acid derivatives **5a**–**h** whose two planar-chiral units are linked together with the chiral amino alcohols (*S*)-**4a**–**h**. We describe here the first synchronized stereocontrol of planar chirality via CIAT: a dynamic 'induced-fit' of two independent atropisomeric units in a crystal field.

Syntheses of bisnicotinic acid derivatives **5a**–**h** are described in Scheme 2. Since the compounds **5a**–**h** are generally inseparable



Scheme 1. Synthesis of chiral bridged nicotinic acid (S_p)-**2** and (R_p)-**2** via crystallization-induced asymmetric transformation.

mixtures of each stereoisomer due to their similar polarity, we initially synthesized every single diastereoisomer of **5a**–**h** independently for examining their physical states to find out a suitable candidate for the synchronized stereocontrol. The reaction of amino alcohol (*S*)-**4a**–**h** with 1.5 equiv amount of (*S*)-methyl [10](2,5)pyridinophane-3-carboxylate [(S_p)-**2** in Scheme 1] in the presence of EDC·HCl salt and a catalytic amount of DMAP resulted in the formation of ca. 1/1 mixture of (S_p,3′*S*,S_p)-**5a**–**h** and (S_p,3′*S*)-**1a**–**h**. Similarly, (*S*)-**4a**–**h** reacted with 1.5 equiv amount of (R_p)-**2** afforded (R_p,3′*S*,R_p)-**5a**–**h** and (R_p,3′*S*)-**1a**–**h**. After separation of the mono- and bis-nicotinate derivatives, the latter mono-nicotinamide derivatives (S_p,3′*S*)-**1a**–**h** and (R_p,3′*S*)-**1a**–**h** were treated with (R_p)-**2** and (S_p)-**2**, respectively, to furnish the rest of the diastereomers, (S_p,3′*S*,R_p)-**5a**–**h** and (R_p,3′*S*,S_p)-**5a**–**h**. Melting points of these bridged bisnicotinate derivatives were tabulated in Table 1.

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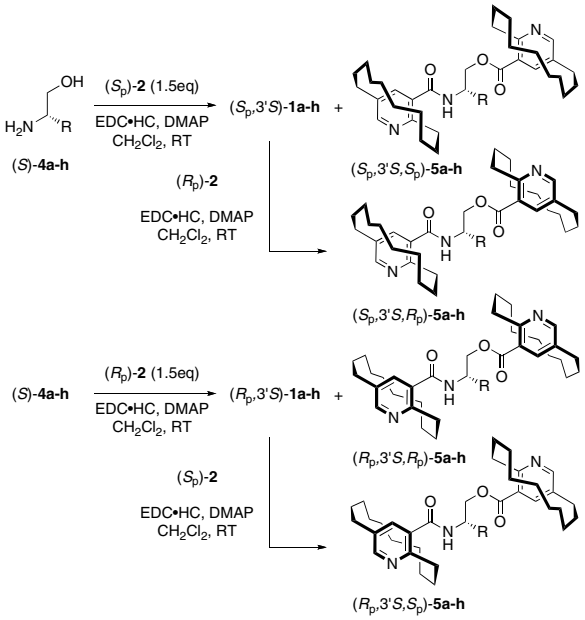


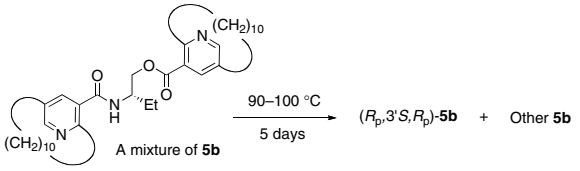
Scheme 2. Syntheses of chiral bridged bisnicotinate derivatives **5a**–**h**.

All the compounds of **5a**–**h** are desired solid molecules except (S_p,3′*S*,R_p)-**5a**, but the melting points of **5a**,**d**,**f**–**h** are not high enough (less than 59 °C) to keep a solid state at such temperatures for CIAT that allow rope-skipping isomerization of the planar-chiral moieties (usually above 80–90 °C). On the other hand, compounds **5b**,[12] **5c**, and **5e**, simply having a series of linear alkyl groups on the linker, share a similarity in common that there are only one diastereoisomer each which has significantly higher melting point as compared to those of the other three isomers. Among compounds **5c** and **5e**, the compounds (S_p,3′*S*,R_p)-**5c,e** fulfill the prerequisite for crystal growth by CIAT; however, those compounds incorporate a pair of (R_p)- and (S_p)-bridged nicotinate units, leading to racemic **2**. On the other hand, it is noteworthy that (R_p,3′*S*,R_p)-**5b**, derived from (*S*)-(+)-2-amino-1-butanol [(*S*)-**4b**], incorporates two identical (R_p)-configurations even with a higher melting point by more than 100 °C. Therefore, we chose a diastereomeric mixture of **5b** to explore CIAT to (R_p,3′*S*,R_p)-**5b** with synchronized stereocontrol of planar chirality.

A 1/1/1/1 mixture of the four diastereoisomers **5b** was simply prepared from dehydrocondensation of (*S*)-**4b** with two equivalent amounts of (±)-**2** in 89% yield. Table 2 summarizes the results of thermal asymmetric transformation of **5b**. After heating the mixture without solvent for one day at 90 °C, the relative amount of (R_p,3′*S*,R_p)-**5b** whose initial ratio was statistical 25% largely increased to 43% and those of the other three isomers decreased to 57% (entry 1). Further successive heating of the mixture at 100 °C slowly but steadily amplified the fraction of (R_p,3′*S*,R_p)-**5b** in accordance with acceleration of the rope-skipping isomerization (entries 2–4). The ratio eventually reached 97% among all the four stereoisomers, which is worth being 96% ee of (R_p)-**2** (entry 5).[13] It is indeed that the 97% grade of **5b** afford (R_p)-**6** with 97% ee in 99% yield by clean removal of the amino alcohol linker with sodium methoxide/dimethyl carbonate reagents (Scheme 3).[14]

Surprisingly, heating the 1/1/1/1 mixture at 100 °C from the beginning seems to be inappropriate to complete the asymmetric transformation: the major isomer reached at most 80% even after 10 days. This indicates that initial temperature control is extremely important to achieve high stereoselectivity of the synchronized stereocontrol of **5b**.

Table 2
Synchronized stereocontrol of planar-chiral nicotinate **5b**[a]



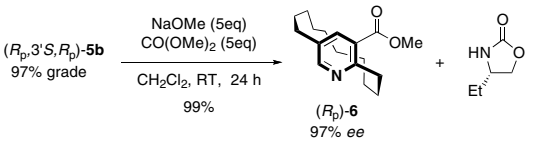
Entry	*t* d[b]	*T* (°C)	(R_p,3′*S*,R_p)-**5b**[c] (%)
1	1	90	43[d]
2	2	100	76
3	3	100	90
4	4	100	92.5
5	5	100	97

[a] Heat isomerization was carried out by using a glass tube oven (Shibata Scientific Technology, Ltd) known as a Kugelrohr apparatus.
[b] Cumulative reaction time for CIAT.
[c] The ratio was determined by HPLC. For conditions, see Ref. 13.
[d] Determined by using ^{1}H NMR.

Table 1
Physical properties of bridged bisnicotinate derivatives **5a**–**h**

Compound	R	Configuration[a]	Mp (°C)	Compound	R	Configuration[a]	Mp (°C)
5a	Me	(S_p,3′*S*,S_p)	53.0–54.0	**5e**	Bu	(S_p,3′*S*,S_p)	38.0–39.0
		(S_p,3′*S*,R_p)	Oil			(S_p,3′*S*,R_p)	**114.0–115.0**
		(R_p,3′*S*,S_p)	33.0–33.5			(R_p,3′*S*,S_p)	34.0–35.0
		(R_p,3′*S*,R_p)	48.1–48.5			(R_p,3′*S*,R_p)	42.0–43.0
5b	Et	(S_p,3′*S*,S_p)	44.5–45.1	**5f**	*i*-Bu	(S_p,3′*S*,S_p)	47.5–48.5
		(S_p,3′*S*,R_p)	48.5–49.5			(S_p,3′*S*,R_p)	53.5–54.5
		(R_p,3′*S*,S_p)	44.0–44.8			(R_p,3′*S*,S_p)	48.0–49.0
		(R_p,3′*S*,R_p)	**143.5–144.0**			(R_p,3′*S*,R_p)	52.0–53.0
5c	Pr	(S_p,3′*S*,S_p)	43.0–44.0	**5g**	*t*-Bu	(S_p,3′*S*,S_p)	56.0–56.8
		(S_p,3′*S*,R_p)	**128.5–129.5**			(S_p,3′*S*,R_p)	55.0–56.0
		(R_p,3′*S*,S_p)	43.0–44.0			(R_p,3′*S*,S_p)	53.0–54.0
		(R_p,3′*S*,R_p)	49.5–50.5			(R_p,3′*S*,R_p)	58.0–59.0
5d	*i*-Pr	(S_p,3′*S*,S_p)	52.5–53.5	**5h**	Bn	(S_p,3′*S*,S_p)	48.7–50.4
		(S_p,3′*S*,R_p)	41.5–42.5			(S_p,3′*S*,R_p)	47.5–50.0
		(R_p,3′*S*,S_p)	48.2–49.0			(R_p,3′*S*,S_p)	50.8–52.6
		(R_p,3′*S*,R_p)	48.5–49.2			(R_p,3′*S*,R_p)	51.3–53.1

[a] Configuration of **5a**–**h** is expediently shown in a bracket from left to right indicating (1) configuration of nicotinamide moiety with subscript 'p' standing for planar chirality, (2) central chirality on linker at 3′ position, and (3) configuration of nicotinate moiety.



Scheme 3. Synthesis of bridged nicotinate (R_p)-**6** by removal of chiral auxiliary from (R_p,3′*S*,R_p)-**5b**.

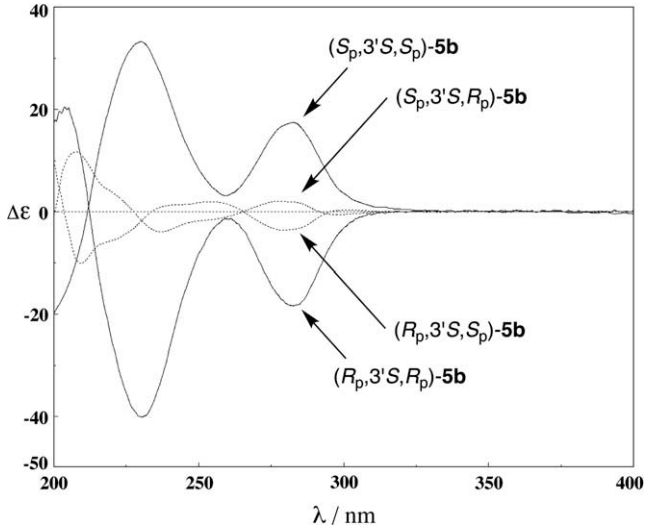
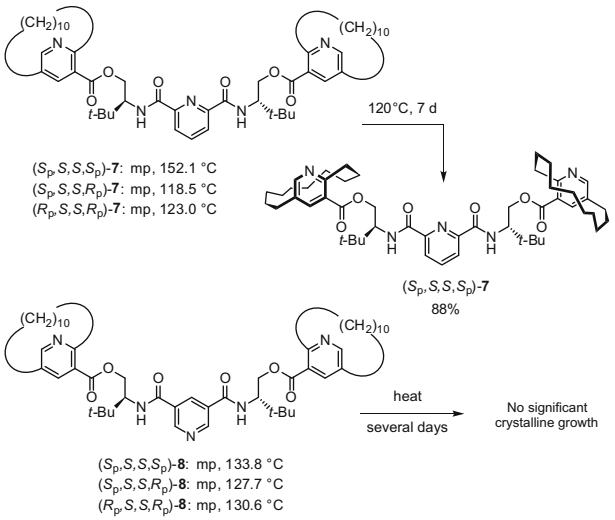


Figure 1. CD spectra of bridged bisnicotinate derivatives **5b**.

Figure 1 depicted CD spectrum of each diastereoisomer of **5b** to demonstrate that its line shape is dependent upon absolute configuration regarding the planar-chiral moieties (Fig. 1).[12] The compounds (S_p,3′*S*,S_p)- and (R_p,3′*S*,R_p)-**5b** comprising the two identical planar-chiral units (i.e., $2 \times S_p$ or $2 \times R_p$) exhibit two strong CD bands at 230 and 283 nm with either two positive or two negative intensities. On the other hand (S_p,3′*S*,R_p)- and (R_p,3′*S*,S_p)-**5b** having a pair of the opposite planar-chiral units (i.e., one each of S_p and R_p) showed three weaker CD bands at 208, 235–260, and 277–280 nm regions with either positive–negative–positive or negative–positive–negative intensity. These observations are in good accordance with usefulness of CD spectra for structural elucidation of the related chiral cyclophane molecules.[7,9] It is of interest to note that those spectra are nearly superimposable on sum spectra of the corresponding nicotinamide **1b** (R = Et)[9] and nicotinate **3b** (R = Et),[15] indicating that intensities of $\Delta\varepsilon$ are approximately additive.

We have also designed some other candidates such as C_2-symmetric bispyridinophane **7**[16] and **8** having longer linkers derived from pyridinedicarboxylic acids and two identical amino alcohol units (Scheme 4). These compounds were synthesized by stepwise condensation of (*S*)-**4g** and the corresponding dicarboxylic acid chlorides derived from pyridine-2,6-dicaroboxylic and pyridine-3,5-dicarboxylic acids, respectively, followed by standard EDC dehydration with (±)-**2**. After screening the compounds **7** and a couple of related analogues with different substituents on linkers, we found that *tert*-butyl group is the best choice for CIAT since one of the three possible diastereoisomers, namely (S_p,*S*,*S*,S_p)-**7**, exhibits a significantly higher melting point than those of the other isomers and are apparently worth being examined for synchronized stereocontrol. Indeed, heat isomerization of a 1/2/1 diastereomeric mixture of **7** initiated a crystal growth of (S_p,*S*,*S*,S_p)-**7** at 120 °C and its percentage among all the three isomers reached 88% in a week.[17] The hydrolysis of the final mixture with LiOH liberated



Scheme 4. Bridged bisnicotinate derivatives **7** and **8** and the synchronized stereocontrol of **7**.

the accumulated planar-chiral units to give bridged nicotinate (S_p)-**6** with 87% ee in 90% yield as well as the recovery of the linker, N^2,N^6-bis((*S*)-1-hydroxy-3,3-dimethyl-2-butanyl)pyridine-2,6-dicarboxamide, in quantitative yield. On the other hand, each isomer of bispyridinophane **8** did not show any significant difference in melting points and, thereby, no significant crystal growth was observed with stereocontrol of planar chirality.

Consequently, we have accomplished synchronized stereocontol of two planar-chiral units by CIAT method accumulating the same atropisomeric configuration in the crystalline bispyridinophane compounds, **5b** and **7** as the first examples of multi-stereocontrol of planar chirality.

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12. *Selected spectral data for (S_p,3′*S*,S_p)*-**5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.13 (m, 1H), 0.35 (m, 1H), 0.38–0.90 (m, 16H), 0.95–1.29 (m, 8H), 1.31–1.48 (m, 4H), 1.10 (t, *J* = 7.8 Hz, 3H), 1.49–1.95 (m, 4H), 2.54–2.90 (m, 6H), 3.25 (ddd, *J* = 12.7, 6.8, 4.4 Hz, 1H), 3.75 (ddd, *J* = 10.7, 5.8, 4.4 Hz, 1H), 4.35–4.62 (m, 3H), 5.88 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 8.42 (d, *J* = 1.9 Hz, 1H), 8.47 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ = 168.4, 166.8, 161.5, 157.2, 152.1, 150.6, 138.8, 135.5, 134.7, 134.6, 131.8, 124.8, 77.2, 66.3, 50.7, 36.1, 35.1, 31.9, 31.8, 28.3, 28.2, 28.1, 27.82, 27.81, 27.7, 27.6, 27.5, 26.4, 26.38, 26.27, 25.24, 25.2, 24.8, 24.6, 24.4, 10.5; CD (CH_3CN): λ_{ext} = 283 ($\Delta\varepsilon$ + 17.5), 260 (+3.1), 230 (+33.3). For (S_p,3′*S*,R_p)-**5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.13 (m, 1H), 0.35 (m, 1H), 0.38–0.90 (m, 16H), 0.95–1.29 (m, 8H), 1.10 (t, *J* = 5.3 Hz, 3H), 1.31–1.48 (m, 4H), 1.49–1.95 (m, 4H), 2.51–2.92 (m, 6H), 3.25 (ddd, *J* = 12.7, 7.8, 4.4 Hz, 1H), 3.75 (ddd, *J* = 10.2, 6.3, 3.9 Hz, 1H), 4.42–4.59 (m, 3H), 5.83 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ = 168.2, 166.8, 161.2, 157.2, 151.9, 150.4, 138.7, 135.1, 134.5, 134.4, 131.4, 124.8, 77.0, 66.0, 50.5, 35.9, 34.9, 31.7, 31.6, 28.1, 28.0, 27.8, 27.7, 27.65, 27.6, 27.5, 27.4, 26.24, 26.23, 26.1, 25.1, 24.9, 24.6, 24.4, 24.2, 10.3; CD (CH_3CN): λ_{ext} = 277 ($\Delta\varepsilon$ + 2.1), 237 (−3.9), 208 (+11.7). For (R_p,3′*S*,S_p)-**5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.13 (m, 1H), 0.35 (m, 1H), 0.38–0.90 (m, 16H), 0.95–1.29 (m, 8H), 1.08 (t, *J* = 5.3 Hz, 3H), 1.31–1.48 (m, 4H), 1.49–1.95 (m, 4H), 2.54–2.90 (m, 6H), 3.25 (ddd, *J* = 12.7, 8.8, 4.4 Hz, 1H), 3.75 (ddd, *J* = 10.2, 6.3, 3.9 Hz, 1H), 4.45–4.62 (m, 3H), 5.87 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 8.42 (d, *J* = 2.5 Hz, 1H), 8.47 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ = 168.4, 167.0, 161.5, 157.6, 152.2, 150.6, 138.8, 135.1, 134.7, 134.5, 131.7, 124.8, 77.2, 66.3, 50.7, 36.2, 35.0, 31.9, 31.8, 28.3, 28.2, 28.0, 27.88, 27.85, 27.7, 27.5, 26.43, 26.4, 26.38, 26.3, 25.24, 25.2, 24.7, 24.6, 24.4, 10.5; CD (CH_3CN): λ_{ext} = 280 ($\Delta\varepsilon$ −4.7), 240 (+2.6), 208 (−21.1). (R_p,3′*S*,R_p)-**5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.13 (m, 1H), 0.35 (m, 1H), 0.38–0.90 (m, 16H), 0.95–1.29 (m, 8H), 1.05 (t, *J* = 6.9 Hz, 3H), 1.31–1.48 (m, 4H), 1.49–1.95 (m, 4H), 2.54–2.90 (m, 6H), 3.25 (ddd, *J* = 12.7, 7.8, 3.9 Hz, 1H), 3.75 (ddd, *J* = 10.8, 6.9, 4.0 Hz, 1H), 4.55–4.62 (m, 3H), 5.88 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ = 168.5, 167.1, 161.5, 157.5, 152.2, 150.6, 138.9, 135.2, 134.7, 134.5, 131.8, 124.9, 77.2, 66.2, 50.7, 36.2, 35.0, 32.0, 31.9, 29.7, 28.3, 28.1, 27.88, 27.82, 27.7, 27.5, 26.8, 26.4, 26.38, 26.3, 25.3, 25.2, 24.8, 24.7, 24.5, 10.4; CD (CH_3CN): λ_{ext} = 283 ($\Delta\varepsilon$ −18.4), 261 (−1.3), 230 (−40.1), 203.7 (+20.5).
13. HPLC analysis showed that the final mixture contained 96.9% of (R_p,3′*S*,R_p)-**5b**, 1.5% of (S_p,3′*S*,R_p)-**5b**, 0.9% of (S_p,3′*S*,S_p)-**5b**, and 0.7% of (R_p,3′*S*,S_p)-**5b** (column: Chiralcel OD, Dicel Chemical Industries, Ltd; Mobile phase: 5% IPA in hexane; flow rate: 2.0 mL/min; oven temperature: 25 °C).
14. (a) Kanomata, N.; Maruyama, S.; Tomono, K.; Anada, S. *Tetrahedron Lett.* **2003**, *44*, 3599–3603; (b) Miao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662–7671.
15. *CD spectral data for (S_p, 4′*S*)*-**3b**: CD (CH_3CN): λ_{ext} = 283 ($\Delta\varepsilon$ +8.4), 261 (+2.2), 232 (+23.6), 203 (−24.5). For (R_p, 4′*S*)-**3b**: CD (CH_3CN): λ_{ext} = 283 ($\Delta\varepsilon$ −6.9), 262 (−1.7), 232 (−20.3), 205 (+18.7).
16. *Selected spectral data for (S_p,*S*,*S*,S_p)*-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.20 (m, 2H), 0.21 (m, 2H), 0.31 (m, 2H), 0.45–0.60 (m, 6H), 0.60–0.75 (m, 4H), 0.75–1.01 (m, 6H), 1.02–1.25 (m, 4H), 1.13 (s, 18H), 1.34 (m, 2H), 1.54 (m, 2H), 1.72 (m, 2H), 2.49–2.66 (m, 6H), 3.58 (ddd, *J* = 12.6, 6.9, 4.1 Hz, 2H), 4.36–4.48 (m, 4H), 4.81–4.89 (m, 2H), 7.83 (d, *J* = 2.4 Hz, 2H), 7.94 (t, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 10.0 Hz, 2H), 8.26 (d, *J* = 7.6 Hz, 2H), 8.36 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.4 (2C), 25.0 (2C), 26.1 (2C), 26.3 (2C), 26.7 (6C), 27.5 (2C), 27.6 (2C), 27.8 (2C), 28.1 (2C), 31.7 (2C), 34.3 (2C), 35.6 (2C), 57.4 (2C), 64.0 (2C), 125.1 (4C), 134.5 (2C), 138.8 (2C), 138.9, 148.5 (2C), 152.0 (2C), 161.2 (2C), 163.4 (2C), 167.2 (2C); CD (MeCN): λ_{ext} = 285 ($\Delta\varepsilon$ +26.5), 262 (+10.1), 231 (+51.5). For (S_p,*S*,*S*,R_p)-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.17 (m, 1H), −0.05 (m, 1H), 0.20–0.45 (m, 4H), 0.45–0.65 (m, 10H), 0.80–1.02 (m, 6H), 1.02–1.20 (m, 4H), 1.13 (s, 9H), 1.14 (s, 9H), 1.30–1.35 (m, 2H), 1.51–1.57 (m, 2H), 1.69–1.75 (m, 2H), 2.49–2.66 (m, 6H), 3.49–3.54 (m, 2H), 4.43–4.45 (m, 4H), 4.84–4.90 (m, 2H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.94 (dd, *J* = 8.0, 7.6 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 9.6 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.2, 24.4, 25.2, 25.5, 26.0, 26.2, 26.5 (2C), 26.7 (3C), 26.9 (3C), 27.5, 27.6, 27.8, 27.9, 28.0, 28.1, 28.2 (2C), 31.5, 31.7, 34.1, 34.2, 35.8, 36.1, 57.1, 57.2, 64.0, 64.1, 124.8, 125.0, 129.8, 129.9, 133.0, 133.2, 134.5, 138.7, 138.8, 150.2, 150.5, 152.0, 152.4, 161.5, 161.6, 164.5, 164.9, 167.2, 167.6; CD (MeCN): λ_{ext} = 285 ($\Delta\varepsilon$ +8.4), 270 (+4.6), 253 (+7.2). For (R_p,*S*,*S*,R_p)-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = −0.08 (m, 2H), 0.25–0.40 (m, 4H), 0.50–0.60 (m, 6H), 0.67–0.75 (m, 4H), 0.80–0.95 (m, 6H), 1.00–1.20 (m, 4H), 1.12 (s, 18H), 1.20–1.39 (m, 4H), 1.55–1.68 (m, 4H), 2.47–2.58 (m, 4H), 2.64 (m, 2H), 3.51 (ddd, *J* = 12.6, 6.9, 4.1 Hz, 2H), 4.41–4.48 (m, 4H), 4.92 (m, 2H), 7.80 (d, *J* = 2.3 Hz, 2H), 7.93 (t, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 10.0 Hz, 2H), 8.23 (d, *J* = 7.8 Hz, 2H), 8.34 (d, *J* = 2.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.4 (2C), 25.1 (2C), 26.2 (2C), 26.3 (2C), 26.7 (2C), 27.6 (6C), 27.8 (4C), 28.1 (2C), 31.7 (2C), 34.4 (2C), 35.9 (2C), 57.4 (2C), 63.9 (2C), 125.0 (4C), 134.3 (2C), 138.7 (2C), 138.9, 148.6 (2C), 151.8 (2C), 160.9 (2C), 163.7 (2C), 167.8 (2C); CD (MeCN): λ_{ext} = 282 ($\Delta\varepsilon$ −14.8), 259 (+3.9), 233 (−60.5).
17. The final mixture after the heat isomerization consists of 87.7% of (S_p,*S*,*S*,S_p)-**7**, 11.5% of (S_p,*S*,*S*,R_p)-**7**, and 0.8% of (R_p,*S*,*S*,R_p)-**7**. The ratio was determined by HPLC analysis using CHIRALPAK IA, Dicel Chemical Industries, Ltd, with hexane/ethyl acetate (2/1) as a mobile phase (flow rate: 1.0 mL/min; oven temperature: 40 °C).