Tetrahedron Letters 49 (2008) 7074–7077

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Highly stereoselective iminopinacol coupling of chiral aromatic imines derived from di- and tripeptides

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ARTICLE INFO

*Article history:*
Received 28 August 2008
Revised 25 September 2008
Accepted 26 September 2008
Available online 1 October 2008

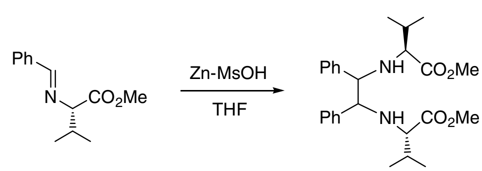
*Keywords:*
Iminopinacol coupling
1,2-Diamine
Dipeptide
Tripeptide
Zinc

ABSTRACT

The reduction of aromatic imines prepared from (*S*)-Ile-(*S*)-Ile-OMe, (*S*)-Val-(*S*)-Val-OMe, and (*S*)-Val-(*S*)-Val-(*S*)-Val-OMe with Zn–MsOH in THF gave $C_2$-symmetric (*R,R*)-diamines in high yields and stereoselectivities.

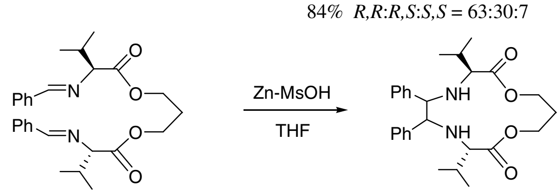


Reductive homocoupling of imines (iminopinacol coupling) is well known as a useful tool for the synthesis of symmetrical 1,2-diamines.[1] Although a number of methods have been reported for this purpose, most of them were nondiastereoselective.[2] Recently, some studies on the diastereoselective iminopinacol coupling of chiral imines have been reported.[3] We have also reported the stereoselective inter- and intramolecular coupling of chiral aromatic imines prepared from (*S*)-valine (Eqs. 1 and 2).[4] The intermolecular coupling of aromatic imine derived from (*S*)-valine methyl ester gave the corresponding dimer as a mixture of three diastereomers (*R,R*:*R,S*:*S,S* = 63:30:7) (Eq. 1). On the other hand, the reductive intramolecular coupling of bis(imino ester) gave the macrocyclic diamine in *R,R*:*R,S*:*S,S* = 91:9:0 ratio (Eq. 2). We report herein the highly diastereoselective intermolecular iminopinacol coupling of chiral aromatic imines derived from di- and tripeptide methyl esters with Zn–MsOH (Eq. 3). It was found that the yield and stereoselectivity of the hydrodimers was strongly affected by reaction temperature. It is noted that the reductive coupling of the imine prepared from (*S*)-Ile-(*S*)-Ile-OMe with Zn–MsOH in THF at −50 °C gave the corresponding *R,R*-dimer stereospecifically (99% selectivity). This reaction provides a convenient method for the synthesis of a new class of $C_2$-symmetric chiral 1,2-diamines from readily available di- and tripeptides.



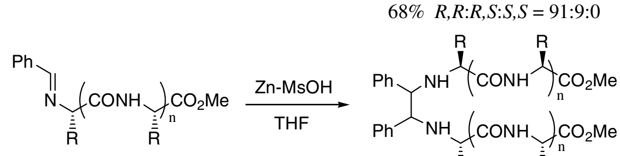
(1)

84% *R,R*:*R,S*:*S,S* = 63:30:7



(2)

68% *R,R*:*R,S*:*S,S* = 91:9:0



(3)

R = *i*-Pr, *sec*-Bu, *i*-Bu
n = 1, 2

First, we attempted the reductive coupling of chiral aromatic imine **1a**, derived from (*S*)-Val-(*S*)-Val-OMe and benzaldehyde, with zinc powder (5 equiv) as a reducing agent in the presence of MsOH (5 equiv) in THF or DMF, according to the previously reported method.[4] The results are summarized in Table 1. The yield and diatereoselectivity of hydrodimer 2a increased with a decrease in temperature accompanying a decrease in the yield of simply

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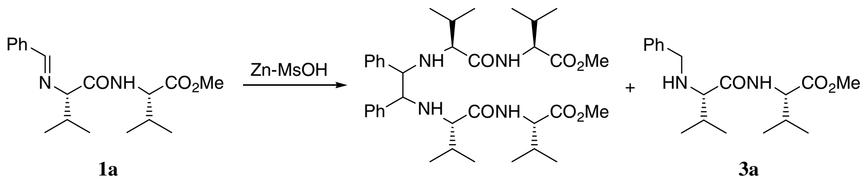
0040-4039/$ - see front matter 
doi:10.1016/j.tetlet.2008.09.149

**Table 1**
Reductive coupling of **1a** to **2a**[a]




| Run | Solvent | Temp (°C) | Time (h) | % Yield[b] of **2a** | *R,R*:*R,S*:*S,S*[c] in **2a** | % Yield[b] of **3a** |
|---|---|---|---|---|---|---|
| 1 | THF | 25 | 2 | 49 | 75:18:8 | 36 |
| 2 | THF | 0 | 12 | 63 | 82:12:6 | 23 |
| 3 | THF | −20 | 24 | 69 | 88:12:6 | 14 |
| 4 | THF | −30 | 24 | 82 | 90:7:3 | 10 |
| 5 | THF | −40 | 24 | 85 | 94:4:2 | 5 |
| 6 | THF | −50 | 48 | 90 | 95:3:2 | 0 |
| 7 | THF | −60 | 72 | <10[d] | 95:3:2 | 0 |
| 8 | DMF | 0 | 12 | 82 | 25:47:28 | 0 |
| 9 | DMF | −50 | 24 | 83 | 57:28:15 | 0 |

[a] Reaction was carried out using 1.0 mmol of **la**, 5.0 mmol of MsOH, 5.0 mmol of zinc powder, and 10 mL of solvent.
[b] Isolated yields.
[c] Determined by $^1$H NMR spectra (Ref. 6).
[d] More than 90% of **1a** was recovered.

reduced amine **3a** (runs 1–6). When the reaction was carried out at −50 °C for 48 h in THF, the dimer 2a was obtained in 90% yield and *R,R*:*R,S*:*S,S* = 95:3:2 ratio (run 6).[5,6] Of the three diastereomers of **2a**, the major isomer could be isolated by column chromatography and its stereoconfiguration was determined to be *R,R* by X-ray crystallographic analysis (Fig. 1).[7] The reaction at −60 °C was very slow due to low solubility of **1a** and afforded a poor yield of **2a** even after 72 h (run 7). As a solvent, THF is much superior to DMF in the stereoselectivity of **2a** (runs 8 and 9).

The reduction of aromatic imines **1b** and **1c**, derived from (*S*)-Ile-(*S*)-Ile-OMe and (*S*)-Leu-(*S*)-Leu-OMe, respectively, was carried out under the same conditions as those in Table 1 (Table 2). The reaction of **1b** at −50 °C in THF gave hydrodimer **2b** in 94% yield and *R,R*:*R,S*:*S,S* = 99:1:0 ratio (run 2). The major isomer of **2b** was further purified by recrystallization and its stereochemistry was confirmed to be *R,R*-dimer by X-ray crystallography (Fig. 2).[7] The elevation of reaction temperature (run 1) and the use of DMF as a solvent in place of THF (run 3) brought about a decrease of the stereoselectivity in **2b**. On the other hand, the reduction of **1c** gave dimer 2c in low stereoselectivitity (*R,R*:*R,S*:*S,S* = 62:11:27), even though the reaction was carried out at −50 °C in THF (run 5).

Next, we tried the reductive coupling of imines **4a** and **4b** prepared from tripeptides of (*S*)-valine and (*S*)-isoleucine, respectively (Table 3). In these substrates, the reduction did not proceed below −40 °C in THF because of low solubility of **4a**,**b**. The best result for the hydrocoupling of **4a** was obtained by the reduction at −30 °C in THF; hydrodimer **5a** was formed in 91% yield and *R,R*:*R,S*:*S,S* = 94:5:1 ratio (run 2). However, the stereoselectivities in the reductive coupling of **4b** (runs 4–6) were not so high in comparison to those of **4a** (runs 1–3); the reaction of **4b** at −30 °C in THF gave hydrodimer **5b** in 82% yield and *R,R*:*R,S*:*S,S* = 80:18:2 ratio (run 5). The major dimers of **5a** and **5b** were isolated by recrystallization and confirmed to be *R,R* by comparison with authentic samples prepared from (***R*,*R***)**-2a** and (***R*,*R***)**-2b** by usual peptide chain elongation.

This reaction is conveniently applicable to the gram-scale synthesis of chiral *R,R*-dimers. In fact, the reaction of 10 g (28.9 mmol) of **1b** with Zn–MsOH in THF at −50 °C and subsequent recrystallization of a crude product gave 8.5 g of pure (***R*,*R***)**-2b** as a white solid. Similarly, 7.2 g of (***R*,*R***)-**5a** was obtained by the reaction of 10 g (24.0 mmol) of **4a** in THF at −30 °C and following recrystallization.

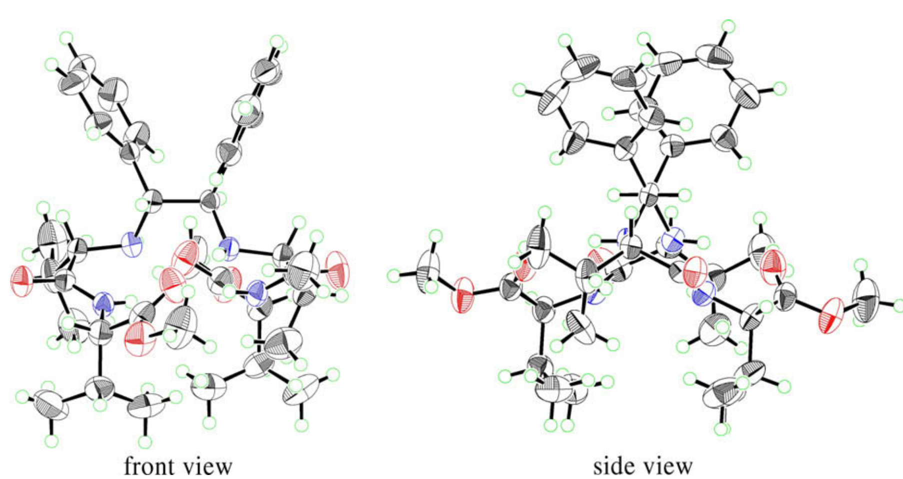
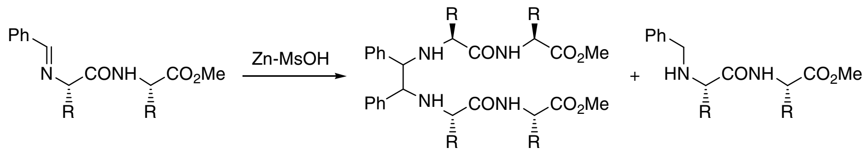



**Figure 1.** X-ray crystal structure (ortep) of (***R*,*R***)**-2a**.

**Table 2**
Reductive coupling of **1b**,**c** to **2b**,**c**[a]




**1b** (R = *sec*-Bu)
**1c** (R = *i*-Bu)
**2b**
**2c**
**3b**
**3c**

| Run | R | Solvent | Temp (°C) | Time (h) | % Yield[b] of **2** | *R*,*R*:*R*,*S*:*S*,*S*[c] in **2** | % Yield[b] of **3** |
|---|---|---|---|---|---|---|---|
| 1 | *sec*-Bu | THF | −30 | 24 | **2b** 83 | 95:4:1 | **3b** 5 |
| 2 | *sec*-Bu | THF | −50 | 48 | **2b** 94 | 99:1:0 | **3b** 0 |
| 3 | *sec*-Bu | DMF | −50 | 24 | **2b** 87 | 70:19:11 | **3b** 0 |
| 4 | *i*-Bu | THF | −30 | 24 | **2c** 54 | 52:20:28 | **3c** 19 |
| 5 | *i*-Bu | THF | −50 | 48 | **2c** 67 | 62:11:27 | **3c** 0 |
| 6 | *i*-Bu | DMF | −50 | 24 | **2c** 76 | 19:35:46 | **3c** 0 |

[a] Reaction was carried out using 1.0 mmol of **1**, 5.0 mmol of MsOH, 5.0 mmol of zinc powder, and 10 mL of solvent.
[b] Isolated yields.
[c] Determined by $^1$H NMR spectra (Ref. 6).

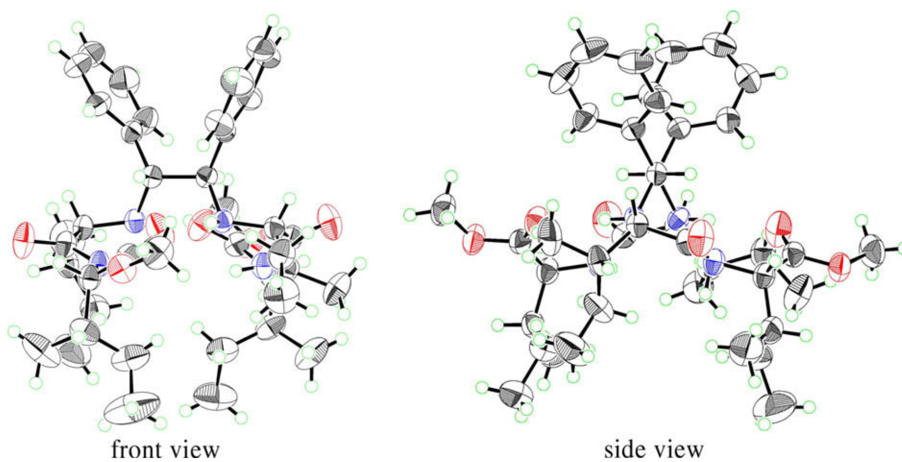
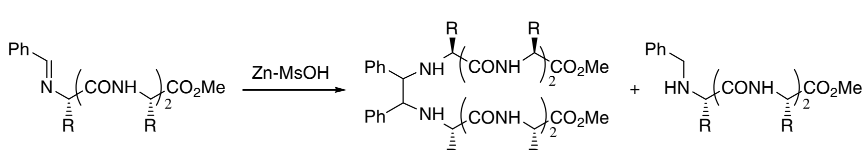



**Figure 2.** X-ray crystal structure (ortep) of ***(R,R)*-2b**.

In summary, the reduction of the aromatic imines prepared from dipeptide methyl esters of (*S*)-valine and (*S*)-isoleucine with Zn–MsOH in THF at −50 °C efficiently gave the corresponding *R*,*R*-dimers in high stereoselectivities: 95% and 99%, respectively. To obtain the high yield and stereoselectivity of the *R*,*R*-dimers, it is important to keep the reaction temperature at −50 °C during the reaction. The reduction of the imine derived from tripeptide methyl ester of (*S*)-valine with Zn–MsOH in THF at −30 °C also effectively gave the corresponding *R*,*R*-dimer in high stereoselectivity (94%). This reaction provides a practical method for the

**Table 3**
Reductive coupling of **4** to **5**[a]




**4a** (R = *i*-Pr)
**4b** (R = *sec*-Bu)
**5a**
**5b**
**6a**
**6b**

| Run | R | Solvent | Temp (°C) | Time (h) | % Yield[b] of **5** | *R*,*R*:*R*,*S*:*S*,*S*[c] in **5** | % Yield[b] of **6** |
|---|---|---|---|---|---|---|---|
| 1 | *i*-Pr | THF | −20 | 48 | **5a** 84 | 87:9:4 | **6a** 5 |
| 2 | *i*-Pr | THF | −30 | 72 | **5a** 91 | 94:5:1 | **6a** 0 |
| 3 | *i*-Pr | DMF | 0 | 24 | **5a** 75 | 21:48:31 | **6a** 0 |
| 4 | *sec*-Bu | THF | −20 | 48 | **5b** 75 | 76:15:9 | **6b** 5 |
| 5 | *sec*-Bu | THF | −30 | 72 | **5b** 82 | 80:18:2 | **6b** 0 |
| 6 | *sec*-Bu | DMF | 0 | 24 | **5b** 61 | 16:48:36 | **6b** 0 |

[a] Reaction was carried out using 1.0 mmol of **4**, 5.0 mmol of MsOH, 5.0 mmol of zinc powder, and 10 mL of solvent.
[b] Isolated yields.
[c] Determined by $^1$H NMR spectra (Ref. 6).

synthesis of $C_2$-symmetric 1,2-diamines promising as new chiral ligands and catalysts from α-amino acids. The investigation of the scope and limitation for this reaction is in progress.

## References and notes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2. (a) Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315–1318; (b) Annunziata, R.; Benaglia, B.; Caporale, M.; Raimondi, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2727–2734; (c) Liu, X.; Liu, Y.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43*, 6787–6789.
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5. Typical procedure for the reduction of aromatic imines (Table 1, run 6) is as follows. To a solution of **1a** (318 mg, 1 mmol) in THF (10 mL) were added MsOH (0.48 g, 5 mmol) and zinc powder (0.325 g, 5 mmol) at −50 °C under nitrogen, and the suspension was stirred for 48 h at this temperature. After addition of saturated aqueous $NaHCO_3$ (20 mL), the solution was filtered off. The filtrate was extracted with ethyl acetate three times, and the organic layer was dried over $MgSO_4$ and concentrated. The product **2a** (288 mg, 90% yield) was isolated by column chromatography on silica gel (hexanes–ethyl acetate). The diastereomeric ratio of **2a** was determined to be 95:3:2 by $^1$H NMR analysis.[6] Of the three isomers of dimer **2a**, the major isomer could be separated by column chromatography on silica gel (hexanes–ethyl acetate) from the other two isomers. The major isomer of **2a** could be crystallized from hexanes–ethyl acetate (2:1) and its stereoconfiguration was confirmed to be *R*,*R* by X-ray crystallography.[7] The $^1$H and $^{13}$C NMR spectra of the mixture of the other two isomers showed that major isomer was $C_1$-symmetric (*R*,*S*) and minor one was $C_2$-symmetric (*S*,*S*).
   **(*R*,*R*)-2a**: White solid. Mp 156–157 °C (recryst. from hexanes–ethyl acetate, 2:1). $[\alpha]_D^{22}$ −77.4 (*c* 1.10, $CHCl_3$). IR (KBr) 3345, 3320, 1730, 1678, 1507, 1497, 773, 702 cm$^{-1}$. $^1$H NMR ($CDCl_3$) δ 0.82 (d, 6H, *J* = 6.9 Hz), 0.87 (d, 6H, *J* = 6.9 Hz), 0.95 (d, 6H, *J* = 6.9 Hz), 1.02 (d, 6H, *J* = 6.9 Hz), 1.89–2.00 (m, 2H), 2.28–2.38 (m, 2H), 2.76 (d, 2H, *J* = 5.0 Hz), 3.08–3.15 (m, 2H), 3.65 (br d, 2H, *J* = 7.8 Hz), 3.87 (s, 6H), 4.89 (dd, 2H, *J* = 4.6, 10.0 Hz), 6.89–7.10 (m, 10H), 8.59, (br d, 2H, *J* = 10.0 Hz). $^{13}$C NMR ($CDCl_3$) δ 17.6 (q), 17.9 (q), 19.28 (q), 19.34 (q), 30.8 (d), 31.0 (d), 52.1 (q), 55.8 (d), 65.7 (d), 66.8 (d), 126.5 (d), 127.5 (d), 140.9 (s), 173.9 (s), 174.2 (s).
   **(*R*,*R*)-2b**: White solid. Mp 161–163 °C (recryst. from hexanes–ethyl acetate, 2:1). $[\alpha]_D^{21}$ −62.6 (*c* 1.01, $CHCl_3$). IR (KBr) 3345, 3331, 1724, 1678, 1506, 1495, 887, 856, 777, 768, 702, 658 cm$^{-1}$. $^1$H NMR ($CDCl_3$) δ 0.70 (t, 6H, *J* = 7.3 Hz), 0.78 (d, 6H, *J* = 7.3 Hz), 0.94 (d, 6H, *J* = 7.3 Hz), 0.99 (d, 6H, *J* = 6.4 Hz), 1.04–1.14 (m, 2H), 1.17–1.28 (m, 2H), 1.41–1.52 (m, 4H), 1.60–1.69 (m, 2H), 2.00–2.09 (m, 2H), 2.81 (d, 2H, *J* = 5.0 Hz), 3.03–3.11 (m, 2H), 3.63 (br d, 2H, *J* = 8.3 Hz), 3.86 (s, 6H), 4.88 (dd, 2H, *J* = 5.0, 10.5 Hz), 6.89–7.10 (m, 10H), 8.61 (d, 2H, *J* = 10.5 Hz). $^{13}$C NMR ($CDCl_3$) δ 11.2 (d), 11.3 (d), 15.6 (d), 15.7 (d), 24.9 (t), 25.2 (t), 37.68 (d), 37.72 (d), 52.1 (q), 55.7 (d), 65.0 (d), 67.0 (d), 126.6 (d), 127.7 (d), 141.1 (s), 174.1 (s), 174.3 (s).
   **(*R*,*R*)-2c**: Colorless paste. $[\alpha]_D^{22}$ −38.7 (*c* 0.98, $CHCl_3$). $^1$H NMR ($CDCl_3$) δ 0.29 (d, 3H, *J* = 6.4 Hz), 0.77 (d, 3H, *J* = 6.4 Hz), 0.97 (d, 3H, *J* = 6.4 Hz), 1.30–1.79 (m, 6H), 2.77–2.85 (m, 1H), 3.08 (dd, 1H, *J* = 2.7, 10.9 Hz), 3.72–3.76 (m, 1H), 3.83 (s, 3H), 4.87–4.93 (m, 1H), 7.01–7.14 (m, 5H), 9.07 (d, 1H, *J* = 10.1 Hz). $^{13}$C NMR ($CDCl_3$) δ 19.8 (q), 21.3 (q), 23.0 (q), 23.4 (q), 24.2 (d), 25.0 (d), 41.7 (t), 42.6 (t), 49.6 (d), 52.3 (q), 58.2 (d), 66.6 (d), 126.9 (d), 128.0 (d), 140.6 (s), 175.2 (s), 175.7 (s).
   **(*R*,*R*)-5a**: White solid. Mp >300 °C (recryst. from MeOH). $[\alpha]_D^{21}$ −110 (*c* 1.02, $CHCl_3$). IR (KBr) 3293, 1749, 1647, 1559, 1522, 1508, 773, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$) δ 0.88 (d, 3H, *J* = 6.9 Hz), 0.94 (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.8 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 1.05 (d, 3H, *J* = 6.6 Hz), 1.06 (d, 3H, *J* = 6.7 Hz), 1.92–2.02 (m, 1H), 2.13–2.23 (m, 1H), 2.25–2.35 (m, 1H), 2.74 (d, 1H, *J* = 4.9 Hz), 3.30–3.40 (m, 1H), 3.76 (s, 3H), 4.41 (dd, 1H, *J* = 8.7, 9.8 Hz), 4.72 (dd, 1H, *J* = 4.6, 8.7 Hz), 6.66 (d, 1H, *J* = 8.70 Hz), 6.77–7.08 (m, 5H), 8.70 (d, 1H, *J* = 9.8 Hz). $^{13}$C NMR ($CDCl_3$) δ 17.7 (q), 18.5 (q), 18.7 (q), 19.3 (q), 19.4 (q), 19.6 (q), 31.08 (d), 31.10 (d), 31.2 (d), 51.9 (q), 57.5 (d), 58.3 (d), 66.3 (d), 67.3 (d), 126.5 (d), 127.6 (d), 141.4 (s), 172.0 (s), 172.7 (s), 174.8 (s).
   **(*R*,*R*)-5b**: White solid. Mp 294–296 °C (recryst. from hexanes–ethyl acetate, 2:1). $[\alpha]_D^{21}$ −84.0 (*c* 0.86, $CHCl_3$). IR (KBr) 3293, 1749, 1647, 1518, 773, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$) δ 0.71 (t, 6H, *J* = 7.6 Hz), 0.84 (d, 6H, *J* = 7.1 Hz), 0.93 (t, 6H, *J* = 7.5 Hz), 0.96 (t, 6H, *J* = 7.6 Hz), 1.01 (d, 6H, *J* = 6.8 Hz), 1.03 (d, 6H, *J* = 6.9 Hz), 1.17–1.35 (m, 6H), 1.44–1.56 (m, 4H), 1.62–1.72 (m, 4H), 1.94–2.10 (m, 4H), 2.79 (d, 2H, *J* = 5.2 Hz), 3.27–3.38 (m, 2H), 3.78 (s, 6H), 4.33 (t, 2H, *J* = 9.5 Hz), 4.80 (dd, 2H, *J* = 4.5, 8.8 Hz), 6.52 (d, 2H, *J* = 8.8 Hz), 6.80–7.09 (m, 10H), 8.71 (d, 2H, *J* = 10.1 Hz). $^{13}$C NMR ($CDCl_3$) δ 10.8 (q), 11.3 (q), 11.7 (q), 15.4 (q), 15.9 (q), 16.0 (q), 25.0 (t), 25.20 (t), 25.24 (t), 36.9 (d), 37.7 (d), 37.8 (d), 51.8 (q), 56.6 (d), 57.4 (d), 65.4 (d), 67.3 (d), 126.5(d), 127.6 (d), 141.3 (s), 171.9 (s), 172.6 (s), 174.8 (s).
6. The chemical shifts (δ) of methyne protons adjacent to the ester carbonyl group in **2** and **5** were as follows: **(*R*,*R*)-2a** 4.89; **(*R*,*S*)-2a** 4.28 and 4.49; **(*S*,*S*)-2a** 4.36; **(*R*,*R*)-2b** 4.88; **(*R*,*S*)-2b** 4.30 and 4.50; **(*S*,*S*)-2b** 4.38; **(*R*,*R*)-2c** 4.90; **(*R*,*S*)-2c** 4.27 and 4.42; **(*S*,*S*)-2c** 4.40; **(*R*,*R*)-5a** 4.72; **(*R*,*S*)-5a** 4.41 and 4.54; **(*S*,*S*)-5a** 4.47; **(*R*,*R*)-5b** 4.80; **(*R*,*S*)-5b** 4.45 and 4.57; **(*S*,*S*)-5b** 4.51.
7. All measurements of X-ray crystallographic analysis were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the YADOKARI-XG software package. Crystal data are as follows: CCDC 699821 and 699822 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
   **(*R*,*R*)-2a** (CCDC 699821): $C_{36}H_{54}N_4O_6$, FW = 638.83, mp 156–157 °C, orthorhombic, $P2_12_12_1$ (no. 19), colorless block, $a$ = 11.853(6) Å, $b$ = 11.992(5) Å, $c$ = 26.363(10) Å, $V$ = 3747(3) Å$^3$, $T$ = 223 K, $Z$ = 4, $D_{calcd}$ = 1.132 g/cm$^3$, $\mu$ = 0.77 cm$^{-1}$, GOF = 0.93.
   **(*R*,*R*)-2b** (CCDC 699822): $C_{40}H_{62}N_4O_6$, FW = 694.94, mp 161–163 °C, orthorhombic, $P2_12_12_1$ (no. 19), colorless block, $a$ = 12.1564(9) Å, $b$ = 12.4135(12) Å, $c$ = 27.409(2) Å, $V$ = 4136.1(6) Å$^3$, $T$ = 298 K, $Z$ = 4, $D_{calcd}$ = 1.116 g/cm$^3$, $\mu$ = 0.75 cm$^{-1}$, GOF = 1.015.