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Chirality pairing recognition, a unique reaction forming spiral alkaloids from amino acids stereoselectively in one-pot

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Abstract: A novel chirality pairing recognition was found between D- and L-amino acid derivatives. Novel spiral alkaloids formed in the recognition reaction. Possible mechanism was proposed for the stereoselective and chemoselective reactions.

Keywords: chirality pairing recognition reaction, spiral alkaloid, amino acid derivatives

Introduction

Sexual selectivity and recognition are the important characteristics of life in evolutions in nature since "sex" means re-combination between two "sexual units", and "recognition" means one unit can select the most suitable one for its re-productions, which looks like a male needs a female in a family. Although "molecular sex" was first used in nucleic acids hybridize studies[1], and "molecular recognition" has been widely used in chiral compound separations, which via space match each other, however, they are physical behaviors.[2] In this report, we show the first chemical behavior example of chirality pairing recognition reaction or molecular sex recognition reactions where D-(+)-amino acid derivative could selectively react with the corresponding L-(–)-amino acid analog to form single product combined by D- and L-amino derivative (D-L) instead of mixtures of D-D and L-L products. Novel spiral alkaloid with unique sketch formed in the one-pot reactions.

Results and Discussion

Our initial attempt at synthesizing chiral compound **3** by reacting an oxalaldehyde with a tryptophan methyl ester (**1**) in CH_2Cl_2 did not yield the desired product [3] (Fig. 1). The major compound (60% yield) obtained had neither the quaternary C-4'a at 108.3 ppm nor C-9'a at 130.8 ppm, but had one new quaternary ^{13}C at 64.7 and one new tertiary ^{13}C at 88.3 ppm. This indicated that one C=C of the second indole moiety became a C-C bond. A new condensation reaction happened in the procedure after normal Pictet-Spengler reaction in the first condensations.[4] H-H COSY, HMBC and HSQC experimental results exhibited that its planar structure as **4**. The key NOE between the H-3/H-9' and H-1/H-1' in ROESY experiments suggested that the major product have the **4a** stereochemistry. Moreover, the experimental high resolution MS data (459.2022, $[M + H]^+$) agrees well with the calculated M^+ of 458.1954 (Fig. 1). Similarly, the minor product had the structure of **4b** from *cis*-**2**.

We also used amines (**5**, **6**, **9** and **10**) and esters (**7** and **8**) in the study. When **5** was used as the starting material, compound **11** were obtained with about 47% yield. Similarly, **12** from **6**, **13** from **7**, **14** from **8** and **15** from **9** were obtained, respectively. The results are summarized below. It was found that the presence of a strong electron-withdrawing group of –OH on the indole ring of **10** inhibited the reaction to **16**, while the presence of CH_3 on **9** promoted the reaction to **15**.

A mechanism for the transformation is proposed (Fig. 2) whereby after the second Schiff base (**17**) is formed, N-2' can chelate with an H^+ to form the first five-membered ring (C-1'–C-4'a formation, **18**), then the positive charge can transfer to C-9'a. N-2 in **19** immediately connected to C-9'a after loss of a H^+ via a concerned procedure.[5] The key requirement in the cycloaddition reactions is that a proton must be present on the indole *N* atom. Thus, if this proton was replaced by a methyl group as in **20** and **21**, the condensation cannot take place. This prediction is recorded when **20** or **21** was used in the condensations.

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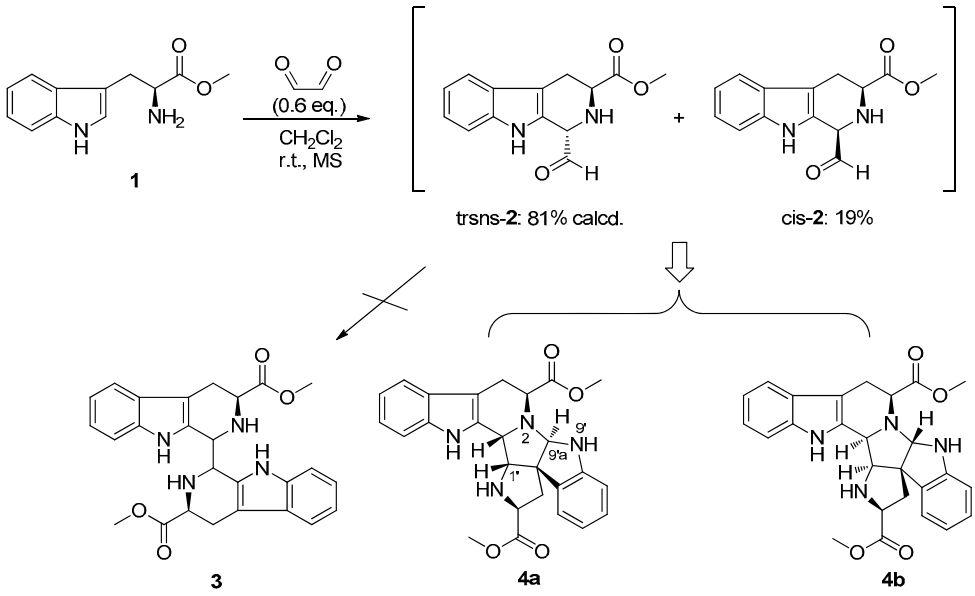
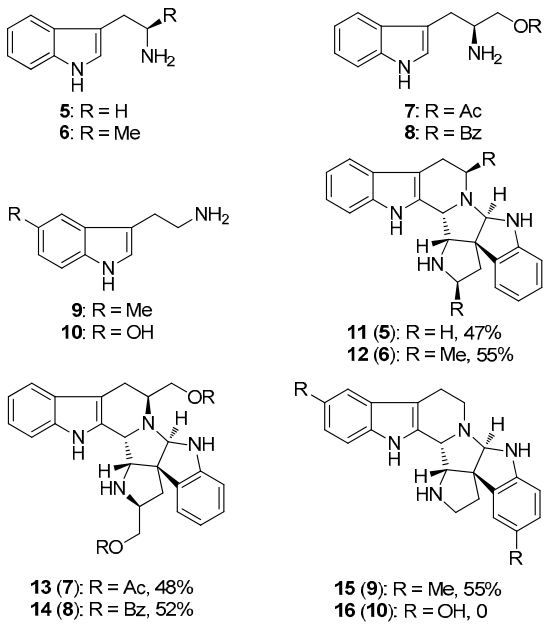


Fig. 1. Possible structures in the new condensation reactions

The unexpected molecular chirality pairing recognition was observed when a (D)-amino acid derivative was mixed with an equal molar of the corresponding (L)-amino acid derivative. For example, D-(+)-**1** reacted with L-(–)-**1**, only one major product formed. This product can be separated as two compounds using chiral column. Their ^{1}H and ^{13}C NMR were the same, and the determined optical rotation for **22** was +187.3, while the ent-**22** had –189.2 in chloroform. It exhibited that the separated two products were the enantiomers. Its planar structure was well established as **22** using ^{13}C NMR and HMBC spectra (see Electronic Supplementary Material for more details). Its relative configuration was identified using ROESY experiments. The key interactions between the H-3 and H-9'a, and H-1'and H-3' showed it having the relative configuration of **22**. Further absolute configuration determination was performed by comparing their optical rotation and circular dichroism to those obtained via quantum theory. Other pairs of substrates, D-(+)-**8** and L-(–)-**8**, D-(+)-**7** and L-(–)-**7**, D-(+)-**6** and L-(–)-**6**, were used in the reactions, only one major L-D product formed, there was no D-D, or L-L products in the reactions. In the L-D products, each pair of them was separated into two enantiomers. Their optical rotations for the enantiomers of **23**, **24** and **25** were +150.3, +127.2 and +166.7. The recorded optical rotations for ent-**23**, ent-**24** and ent-**25** were –148.5, –130.2 and –170.3, respectively. The results are summarized in Table 1.

Furthermore, as shown in Fig. 3 below, the TLC spots and HPLC retention times of the different products are examined. Clearly the differences among the D-D and D-L products are obvious. For example, the R_f value of the D-D product **4a** from D-(+)-**1** was about 0.8, while that of D-L product derived from D-(+)-**1** and L-(–)-**1** was about 0.45. The minor product obtained in the same reaction **4b** had about 0.30 of R_f value. When the three compounds were mixed at c point, the three compounds were well separated, and they exhibited the same R_f values as the standard point in the left ($1^{\#}$). The different R_f values between the D-D products **13** (derived from D-(+)-**7** ($2^{\#}$)) and D-L products **23** (derived from D-(+)-**7** and L-(–)-**7**)) were also obvious. Similarly, the D-D product **14** from D-(+)-**8** had different R_f value from that of **24**, which was derived from D-(+)-**8** and L-(–)-**8**. The R_f values of **12** (D-D product from D-(+)-**6**) was the same as that of **25** which derived from D-(+)-**6** and L-(–)-**6** in TLC experiments. It looks like that this does not agree with the obtained results. However, they had different retention time (RT) in HPLC using chiral column ($4^{\#}$). For example, the D-D product **12** had about 17.3 minute, L-L product had very close RT of 17.52 minutes. But the D-L product **25** (include its ent-**25**, L-D product) had 13.7 or 16.1 minute. The experiments confirmed the products formed in the reactions of the D- and L-amino acid analogue mixtures are different from the use of D- or L-amino acid analogue.



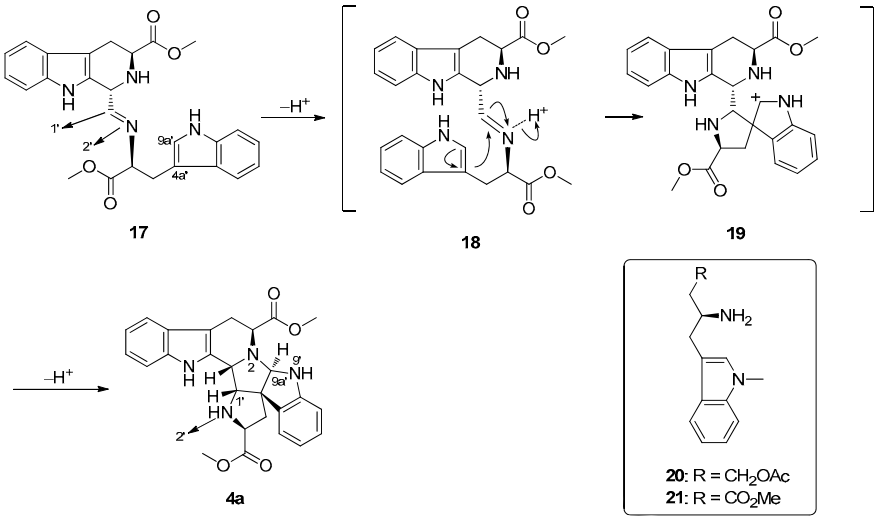


Fig. 2. Proposed mechanisms for formation of **4** from intermediate **17**

This special reaction should belong to chirality recognition reaction. However, it may be called as chirality pairing recognition reaction, or molecular sex recognition reaction if D-(+)- or L-(–)-amino acid derivatives are considered as opposite sex pairs. Then their corresponding reaction products as enantiomer mixtures could be expected as natural behavior, which tends to occur in nature. This behavior looks like the sex selectivity of livings.

The discoveries of different chirality selectivities may disclose some secrets during life evolution. For example, if L-amino acids formed with a little more excessive quantity than D-amino acids due to some reasons in oceanic era, the excessive quantity of L-amino acids may be involved in life formation, then the left equal mole of L- and D-amino acids may take similar chirality pairing recognition reactions, because it is easy to form CHO-CHO and other simple organic

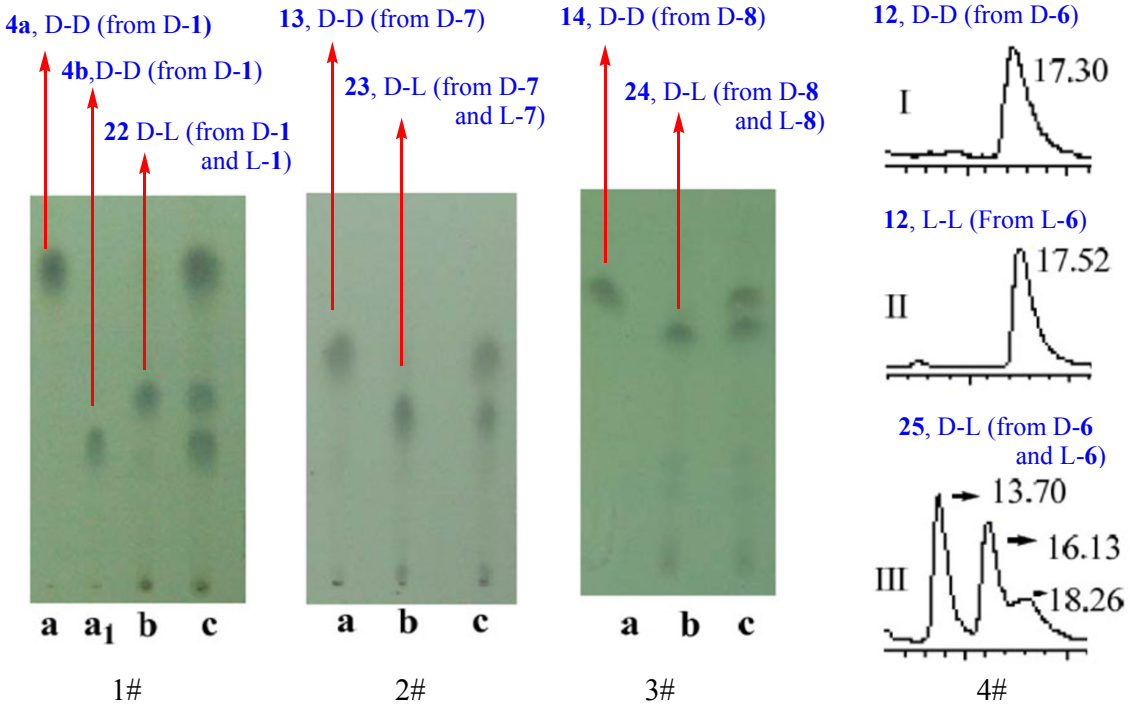
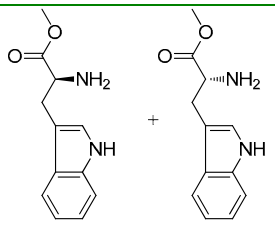
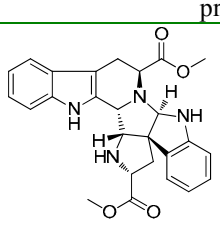
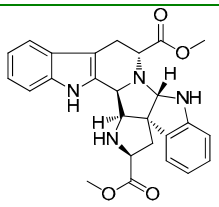
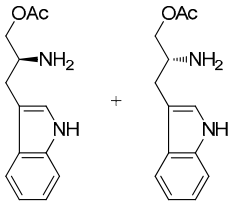
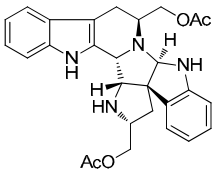
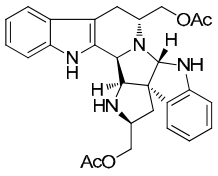
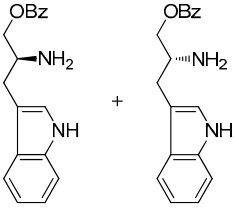
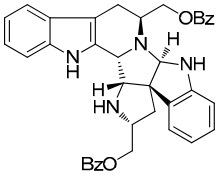
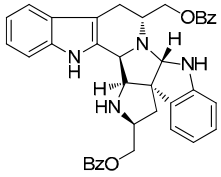
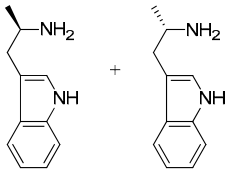
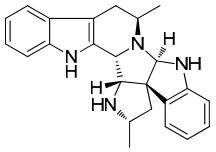
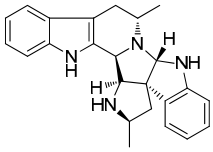


Fig. 3. TLC analyses (1# to 3#), spot **a**: pure major product (D-D, or L-L) from D- or L-amino acid derivatives; $\mathbf{a_1}$: pure minor product; **b**: products in solution of D- and L-amino acid derivatives; **c**: mixed **a** (and $\mathbf{a_1}$ in 2#) and **b** (ethyl acetate:petrol ether = 1:1)**.** Mixtures of ethyl acetate/petrol ether with 1.5/1 were used in 1# and 1/1 in 2#. $CHCl_3$ and methanol (60:1) was used in 3#. In 4#, case I is the retention time (RT, minute) of reaction product of D-methyltrypotamine in HPLC using chiral column; case II is the RT for retention time for reaction product of L-methyltrypotamine. Case III is the RT for mixture of D- and L-methyltrypotamine products, and their RTs in HPLC are different from those in cases I and II (their R_f values in TLC are the same under lab conditions).

Table 1. Chirality pairing recognition reactions in presence of CHOCHO

substrates	products	
 1#: D-(+)-**1** + L- (–)-**1**, rt	 **22**, 50% L-D product	 ent-**22**, 50% D-L product
 2#: D-(+)-**7** + L- (–)-**7**, rt	 **23**, 50% L-D product	 ent-**23**, 50% D-L product
 3#: D-(+)-**8** + L- (–)-**8**, rt	 **24**, 50% L-D product	 ent-**24**, 50% D-L product
 4#: D-(+)-**6** + L- (–)-**6**, 3-5 °C	 **25**, 50% L-D product	 ent-**25**, 50% D-L product

compounds in oceanic era, the tiny acid under neutral conditions can accelerate the reactions. It may be a starting point of a new chemistry: evolution chemistry. Thus, it is possible to construct chirality pairing recognition or molecular sex recognition reaction which can be included in the range of evolution chemistry.

Experimental Section

General Experimental Procedures. Tryptophan methyl ester solution (1.0 mmol in 20 mL CH_2Cl_2) was cooled using ice-bath. The aldehyde (CHOCHO, 0.6 mmol) was then injected into the solution. Suitable molecular sieve was added to remove the water formed in Pictet-Spengler reaction. About 20 h later, 0.01 eq. of TFA was added into the solution for further cycloaddition. This procedure lasted over 40 h. Then the molecular sieve was filtered and the solution was removed under reduced pressure. The mixture was purified using chromatography column by silica gel. Ethyl acetate and petroleum ether mixture was used in the isolation. One major product **4a** was obtained (60%), and the minor product (23%) was obtained. Total yield is 83%. Other products can be obtained under the similar procedure when starting materials changed to the corresponding compounds.

4a. ESIMS, *m/z* 459 $[M + H]^+$. HRMS *m/z* calcd for $C_{26}H_{27}N_4O_4$ $[M + H]^+$ 459.2032, found 459.2022. $[\alpha]_D^{25}$ +156.3 (*c* 0.16, $CHCl_3$). IR (KBr): 3379, 2949, 1736, 1608, 1486, 1466, 1452, 13371, 1199, 1022, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (1H, br. s, N*H*-2'), 2.38 (1H, dd, *J* = 13.2, 9.0 Hz, H-4'), 2.50 (1H, dd, *J* = 13.2, 6.8 Hz, H-4'), 3.04 (1H, ddd, *J* = 15.7, 3.3, 1.6 Hz, H-4), 3.25 (1H, ddd, *J* = 15.6, 6.7, 1.6 Hz, H-4), 3.64 (3H, s, COOC*H*$_3$-3'), 3.70 (3H, s, COOC*H*$_3$-3), 3.90 (1H, dd, *J* = 9.0, 6.8 Hz, H-3'), 4.10 (1H, d, *J* = 5.5 Hz, H-1'), 4.27 (1H, dd, *J* = 6.6, 3.4 Hz, H-3), 4.58 (1H, br. s, N*H*-9'), 4.63 (1H, d, *J* = 5.5 Hz, H-1), 4.97 (1H, s, H-9'a), 6.63 (1H, d, *J* = 7.5 Hz, H-8'), 6.77 (1H, td, *J* = 7.5, 0.7 Hz, H-6'), 7.06–7.12 (4H, m, H-5', 6, 7', 7), 7.29 (1H, d, *J* = 6.8 Hz, H-8), 7.46 (1H, d, *J* = 7.6 Hz, H-5), 8.32 (1H, br. s, N*H*-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (C-4), 43.3 (C-4'), 52.0 (O*C*H$_3$-3'), 52.2 (O*C*H$_3$-3), 56.5 (C-3), 57.1 (C-1), 61.0 (C-3'), 64.7 (C-4'a), 72.2 (C-1'), 88.3 (C-9'a), 108.3 (C-4a), 109.5 (C-8'), 111.2 (C-8), 118.0 (C-5), 119.1 (C-6'), 119.4 (C-6), 121.8 (C-7), 123.3 (C-7'), 126.8 (C-5a), 128.5 (C-5'), 130.1 (C-5'a), 130.8 (C-9a), 136.5 (C-8a), 150.4 (C-8'a), 174.6 (*C*O-3'), 174.7 (*C*O-3).

4b. ESIMS, *m/z* 459 $[M + H]^+$. HRMS *m/z* calcd for $C_{26}H_{27}N_4O_4$ $[M + H]^+$ 459.2032, found 459.2046. $[\alpha]_D^{25}$ –146.7 (*c* 0.15, $CHCl_3$). IR (KBr): 3382, 2950, 2925, 1737, 1608, 1486, 1467, 1451, 1331, 1260, 1172, 1023, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (1H, dd, *J* = 13.2, 7.7 Hz, H-4'), 2.20 (1H, br. s, N*H*-2'), 2.64 (1H, dd, *J* = 13.2, 7.5 Hz, H-4'), 3.07 (1H, dd , *J* = 13.2, 4.6 Hz, H-4), 3.23 (1H, dd, *J* = 13.2, 11.2 Hz, H-4), 3.66 (3H, s, COOC*H*$_3$-3'), 3.86 (3H, s, COOC*H*$_3$-3), 3.92 (1H, dd, *J* = 11.2, 4.6 Hz, H-3), 4.07 (1H, dd, *J* = 7.7, 7.5 Hz, H-3'), 4.32 (1H, d, *J* = 4.5 Hz, H-1), 4.43 (1H, br. s, N*H*-9'), 5.24 (1H, d, *J* = 4.5, 3.0 Hz, H-1'), 5.24 (1H, d, *J* = 3.0 Hz, H-9'a), 6.62 (1H, d, *J* = 7.5 Hz, H-8'), 6.79 (1H, dd, *J* = 7.0, 6.8 Hz, H-6'), 7.06 (1H, m, H-6), 7.07 (1H, m, H-7), 7.08 (1H, m, H-7'), 7.09 (1H, m, H-5'), 7.23 (1H, d, *J* = 7.7 Hz, H-8), 7.47(1H, m, H-5), 8.85 (1H, br. s, N*H*-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9 (C-4), 43.7 (C-4'), 52.2 (O*C*H$_3$-3'), 52.4 (O*C*H$_3$-3), 58.1(C-3), 59.3 (C-1), 63.1 (C-3'), 63.8 (C-4'a), 72.6 (C-1'), 85.3 (C-9'a), 108.9 (C-4a), 109 (C-8'), 111.4 (C-8), 117.9 (C-5), 119.2 (C-6'), 119.4 (C-6), 121.7 (C-7), 122.7 (C-7'), 126.7 (C-5a), 128.5 (C-5'), 130.8 (C-9a), 131.5 (C-5'a), 136.6 (C-8a), 150.4 (C-8'a), 172.5 (*C*O-3'), 172.8 (*C*O-3).

11. ESIMS, *m/z* 343 $[M + H]^+$. HRMS *m/z* calcd for $C_{22}H_{23}N_4$ $[M + H]^+$ 343.1922, found 343.1930. $[\alpha]_D^{25}$ +42.6 (*c* 0.24, $CHCl_3$). IR (KBr): 3382, 2920, 1672, 1609, 1486, 1468, 1337, 1178, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.02–2.08 (1H, m, H-4'α), 2.27–2.34 (1H, m, H-4'β), 2.77–2.83 (1H, m, H-4β), 2.91–3.01 (4H, m, H-3α, 3', 4α), 3.27–3.33 (1H, m, H-3β), 3.86 (1H, d, *J* = 5.2 Hz, H-1'), 4.26 (1H, d, *J* = 5.1 Hz, H-1), 4.99 (1H, s, H-9'a), 6.56 (1H, d, *J* = 7.7 Hz, H-8'), 6.71 (1H, t, *J* = 7.3 Hz, H-6'), 6.99–7.07 (4H, m, H-6, 7, 5', 7'), 7.29 (1H, d, *J* = 7.8 Hz, H-8), 7.45 (1H, d, *J* = 7.6 Hz, H-5), 9.08 (1H, s, N*H*-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 41.3, 43.5, 49.0, 58.0, 64.0, 72.9, 87.6, 109.4, 110.2, 111.4, 117.9, 119.2, 119.3, 121.5, 122.9, 127.1, 128.2, 131.7, 132.0, 136.5, 150.5.

12. ESIMS, *m/z* 371 $[M + H]^+$. HRMS *m/z* calcd for $C_{24}H_{27}N_4$ $[M + H]^+$ 371.2235, found 371.2233. $[\alpha]_D^{25}$ –269.8 (*c* 0.22, $CHCl_3$). IR (KBr): 3428, 2918, 1608, 1470, 1336, 1188, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, d, *J* = 6.2 Hz, C*H*$_3$-3), 1.44 (3H, d, *J* = 6.2 Hz, C*H*$_3$-3'), 1.62 (1H, dd, *J* = 13.2, 11.2 Hz, H-4'α), 2.59–2.65 (2H, m, H-4α, 4'β), 2.90 (1H, ddd, *J* = 14.9, 4.0, 1.3 Hz, H-4β), 3.20–3.24 (1H, m, H-3), 3.42–3.47 (1H, m, H-3'), 3.83 (1H, d, *J* = 5.1 Hz, H-1'), 4.00 (1H, d, *J* = 3.4 Hz, N*H*-9'), 4.30 (1H, d, *J* =5.0 Hz, H-1), 5.24 (1H, d, *J* = 3.4 Hz, H-9'a), 6.65 (1H, d, *J* = 7.7 Hz, H-8'), 6.84 (1H, t, *J* = 7.3 Hz, H-6'), 7.05-7.12 (4H, m, H-6, 7, 5', 7'), 7.20 (1H, m, H-8), 7.44 (1H, m, H-5), 9.10 (1H, br. s, N*H*-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 20.5, 31.2, 49.8, 51.2, 57.6, 58.4, 64.1, 75.2, 86.7, 109.1, 110.2, 111.4, 117.7, 119.1, 119.2, 121.4, 122.7, 126.7, 128.1, 131.2, 132.6, 136.5, 150.4.

13. ESIMS, *m/z* 487 $[M + H]^+$. HRMS *m/z* calcd for $C_{28}H_{31}N_4O_4$ $[M + H]^+$ 487.2345, found 487.2339. $[\alpha]_D^{25}$ +115.2 (*c* 0.83, $CHCl_3$). IR (KBr): 3394, 2924, 1736, 1608, 1465, 1237, 1035, 741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.91 (1H, dd, *J* = 12.8, 10.7 Hz, H-4'α), 2.03 (3H, s, H-OC*H*$_3$), 2.04 (3H, s, H-OC*H*$_3$), 2.20 (1H, dd, *J* = 15.7, 5.5 Hz, H-4'β), 2.87 (1H, d, *J* = 15.3 Hz, H-4β), 3.05 (1H, dd, *J* = 15.2, 7.1 Hz, H-4α), 3.22 1H, (m, H-3'), 3.72 (1H, m, H-3), 3.84 (1H, dd, *J* = 13.0, 10.8 Hz, H-3-*CH*$_2$(α)OAc), 3.96 (1H, dd, *J* = 15.2, 6.5 Hz, H-3'-*CH*$_2$(α)OAc), 4.04 (2H, m, H-1', 3'-*CH*$_2$(β)OAc), 4.45 (1H, d, *J* = 5.3 Hz, H-1), 4.60 (1H, dd, *J* = 10.6, 4.4 Hz, H-3-*CH*$_2$(β)OAc), 4.95 (1H, s, H-9'a), 6.64 (1H, d, *J* = 7.7 Hz, H-8'), 6.80 (1H, t, *J* = 7.8 Hz, H-6'), 7.08–7.20 (4H, m, H-6, 7, 5', 7'), 7.31 (1H, d, *J* = 8.0 Hz, H-8), 7.52 (1H, d, *J* = 7.8 Hz, H-5), 8.47 (1H, s, N*H*-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 22.3, 42.4, 51.3, 55.5, 58.2, 64.2, 64.5, 66.7, 71.6, 86.3, 108.8, 109.6, 111.1, 118.0, 119.1, 119.4, 121.9, 122.9, 127.5, 128.3, 130.5, 131.6, 136.7, 150.3, 170.9, 171.3.

14. ESIMS, *m/z* 611 $[M + H]^+$. HRMS *m/z* calcd for $C_{38}H_{35}N_4O_4$ $[M + H]^+$ 611.2658, found 611.2653. $[\alpha]_D^{25}$ –166.7 (*c* 0.3, $CHCl_3$). IR (KBr): 3384, 2919, 1719, 1605, 1466, 1272, 1112, 747, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.93 (1H, dd, *J* = 13.3, 10.5 Hz, H-4'α), 2.55 (1H, dd, *J* = 13.3, 6.3 Hz, H-4'β), 2.80 (1H, dd, *J* = 12.9, 8.7 Hz, H-4β), 3.00 (1H, dd, *J* = 15.1, 3.6 Hz, H-4α), 3.57 (1H, m, H-3'), 3.71 (1H, m, H-3), 3.78 (1H, d, *J* = 5.0 Hz, H-1'), 4.31–4.38 (3H, m, H-3-*CH*$_2$(a)Obz, H-3'-*CH*$_2$OBz), 4.69 (2H, m, H-1, H-3-*CH*$_2$(b)OBz), 5.33 (1H, s, H-9'a), 6.47 (1H, d, *J* = 7.7 Hz, H-8'), 6.79 (1H, t, *J* = 7.4 Hz, H-6'), 7.03–7.07 (4H, m, H-6, 7, 5', 7'), 7.13 (1H, d, *J* = 7.4 Hz, H-8), 7.37 (2H, t, *J* = 7.7 Hz, H-Bz), 7.49–7.63 (5H, m, H-5, H-Bz), 7.90 (2H, d, *J* = 7.3 Hz, H-Bz), 8.08 (2H, d, *J* = 7.3 Hz, H-Bz), 8.72 (1H, s, *N*H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 45.2, 53.5, 58.2, 61.2, 64.2, 64.9, 67.9, 74.5, 87.1, 108.9, 109.0, 111.2, 117.8, 119.1, 119.3, 121.6, 122.7, 126.8, 128.2, 128.3, 128.8, 129.4, 129.5, 129.6, 129.8, 131.2, 132.5, 133.1, 133.5, 136.6, 150.3, 166.1, 166.2.

15. ESIMS, *m/z* 371 $[M + H]^+$. HRMS *m/z* calcd for $C_{24}H_{27}N_4$ $[M + H]^+$ 371.2235, found 371.2234. $[\alpha]_D^{25}$ +120 (*c* 0.13, $CHCl_3$). IR (KBr): 3387, 2914, 1661, 1621, 1498, 1202, 1142, 803, 732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.18 (1H, m, H-4'α), 2.28 (3H, s, C*H*$_3$), 2.40 (3H, s, C*H*$_3$), 2.45 (1H, m, H-4β), 2.74 (2H, m, H-4), 2.92–3.23 (4H, m, H-3, 3'), 4.04 (1H, br. s, *N*H-9'), 4.18 (1H, s, H-1'), 4.22 (1H, s, H-1), 5.05 (1H, s, H-9'a), 6.51 (1H, d, *J* = 8.7 Hz, H-8'), 6.93–7.18 (5H, m, H-Ar), 9.86 (1H, s, *N*H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.6, 21.8, 37.5, 43.3, 47.1, 56.5, 63.2, 70.5, 88.2, 109.8, 111.3, 111.6, 117.9, 123.8, 124.1, 127.1, 127.4, 128.6, 128.8, 129.5, 130.1, 135.3, 148.7.

22. Racemic mixture was resolved by HPLC on a Chiralcell-OD-H column (250 × 10 mm, *n*-hexane/*i*-PrOH = 85/15). $[\alpha]_D^{25}$ +187.3 (*c* 0.12, $CHCl_3$). ESIMS, *m/z* 459 $[M + H]^+$. HRMS *m/z* calcd for $C_{26}H_{27}N_4O_4$, $[M + H]^+$ 459.2032, found 459.2026. ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (1H, dd, *J* = 13.5, 7.7 Hz, H-4'α), 2.68 (1H, dd, *J* = 13.5, 7.7 Hz, H-4'β), 3.07 (1H, d, *J* = 15.7 Hz, H-4β), 3.32 (1H, dd, *J* = 15.6, 7.1 Hz, H-4α), 3.64 (3H, s, COOC*H*$_3$-3), 3.66 (3H, s, COOC*H*$_3$-3'), 3.84 (1H, d, *J* = 4.5 Hz, H-1'), 4.00 (1H, t, *J* = 7.8 Hz, H-3'), 4.28 (1H, d, *J* = 6.7 Hz, H-3), 4.50 (1H, br. s, N*H*-9'), 4.70 (1H, d, *J* = 3.7 Hz, H-1), 5.06 (1H, s, H-9'a), 6.60 (1H, d, *J* = 7.8 Hz, H-8'), 6.80 (1H, t, *J* = 7.4 Hz, H-6'), 7.08–7.12 (4H, m, H-6, 7, 5', 7'), 7.21 (1H, d, *J* = 7.9 Hz, H-8), 7.48 (1H, d, *J* = 7.0 Hz, H-5), 8.48 (1H, s, N*H*-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 44.3, 51.9, 52.2, 55.2, 56.2, 62.4, 64.4, 74.1, 88.2, 108.3, 109.5, 111.2, 117.9, 119.1, 119.3, 121.7, 122.8, 126.9, 128.5, 130.4, 131.0, 136.6, 150.7, 173.0, 174.8. The ent-**22**

had the –189.2 of optical rotation values in chloroform.

23. Racemic mixture was resolved by HPLC on a Chiralcell-OD-H column (250 × 10 mm, *n*-hexane/*i*-PrOH = 87/17). $[\alpha]_D^{25}$ +150.3 (*c* 0.45, $CHCl_3$). ESIMS, *m/z* 487 $[M + H]^+$. HRMS *m/z* calcd for $C_{28}H_{31}N_4O_4$, $[M + H]^+$ 487.2345, found 487.2364. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (1H, dd, *J* = 12.9, 10.6 Hz, H-4'α), 1.95 (3H, s, OCOCH_3-3'), 2.07 (3H, s, OCOCH_3-3), 2.35 (1H, dd, *J* = 16.5, 8.0 Hz, H-4'β), 2.90 (1H, d, *J* = 15.6 Hz, H-4β), 3.08 (1H, dd, *J* = 15.7, 7.5 Hz, H-4α), 3.73 (2H, m, H-3, 3'), 3.88 (2H, m, H-1', CH_2(α)OAc-3), 4.03 (2H, m, CH_2OAc-3'), 4.45 (1H, d, *J* = 5.2 Hz, H-1), 4.52 (1H, br. s, N*H*-9'), 4.72 (1H, dd, *J* = 10.7, 3.7 Hz, CH_2(β)OAc-3), 5.09 (1H, s, H-9'a), 6.63 (1H, d, *J* = 7.8 Hz, H-8'), 6.78 (1H, t, *J* = 7.4 Hz, H-6'), 7.06–7.12 (4H, m, H-6, 7, 5', 7'), 7.24 (1H, d, *J* = 6.7 Hz, H-8), 7.51 (1H, d, *J* = 6.7 Hz, H-5), 8.78 (1H, s, N*H*-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.0, 23.3, 44.4, 52.0, 53.8, 60.8, 63.7, 64.4, 66.0, 74.4, 88.0, 108.2, 109.4, 111.3, 117.9, 119.1, 119.2, 121.7, 122.7, 127.4, 128.2, 130.6, 132.9, 136.6, 150.1, 170.9, 171.3. The ent-**23** had the –148.5 of optical rotation values in chloroform.

24. Racemic mixture was resolved by HPLC on a Chiral-cell-OD-H column (250 × 10 mm, *n*-hexane/*i*-PrOH = 85/15). $[\alpha]_D^{25}$ +127.6 (*c* 0.47, $CHCl_3$). ESIMS, *m/z* 611 $[M + H]^+$. HRMS *m/z* calcd for $C_{38}H_{35}N_4O_4$, $[M + H]^+$ 611.2658, found 611.2650. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (1 H, dd, *J* = 12.9, 10.5 Hz, H-4'α), 2.44 (1H, dd, *J* = 13.1, 6.3 Hz, H-4'β), 3.02 (1H, d, *J* = 15.5 Hz, H-4β), 3.16 (1H, dd, *J* = 16.1, 7.0 Hz, H-4α), 3.84 (1H, m, H-3'), 3.92 (2H, m, H-3, 1'), 4.14 (1H, dd, *J* = 10.5, 8.7 Hz, CH_2(a)OBz-3), 4.27 (1H, dd, *J* = 14.5, 3.9 Hz, CH_2(a)OBz-3'), 4.44 (1H, dd, *J* = 14.5, 7.0 Hz, CH_2(b)OBz-3'), 4.54 (1H, d, H-1), 4.58 (1H, br. s, N*H*-9'), 5.01 (1H, dd, *J* = 13.5, 4.5 Hz, CH_2(b)OBz-3), 5.20 (1H, s, H-9'a), 6.58 (1H, d, *J* = 7.8 Hz, H-8'), 6.79 (1H, t, *J* = 8.7 Hz, H-6'), 7.07-7.15 (4H, m, H-6, 7, 5', 7'), 7.28 (1H, m, H-8), 7.39 (2H, t, *J* = 7.7 Hz, H-Bz), 7.44 (2H, t, *J* = 7.7 Hz, H-Bz), 7.51–7.59 (3H, m, H-5, H-Bz), 7.93 (2H, d, *J* = 7.5 Hz, H-Bz), 7.98 (2H, d, *J* = 7.5 Hz, H-Bz), 8.86 (1H, s, N*H*-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 44.5, 52.2, 53.9, 60.9, 64.0, 65.0, 65.6, 74.5, 88.4, 108.4, 109.5, 111.3, 117.9, 119.1, 119.2, 121.8, 122.7, 127.4, 128.2, 128.3, 128.4, 129.5, 129.6, 129.8, 130.1, 130.6, 130.9, 132.8, 133.1, 136.7, 150.2, 166.2, 166.8. The ent-**24** had the –130.2 of optical rotation values in chloroform.

25. Racemic mixture was separated by HPLC on a Chiral-cell-OD-H column (250 × 10 mm, *n*-hexane/*i*-PrOH = 92/8). $[\alpha]_D^{25}$ +166.7 (*c* 0.12, $CHCl_3$). ESIMS, *m/z* 371 $[M + H]^+$. HRMS *m/z* calcd for $C_{24}H_{27}N_4$, $[M + H]^+$ 371.2235, found 371.2238. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.13 (3H, d, *J* = 6.3 Hz, CH_3-3), 1.25 (3H, d, *J* = 6.6 Hz, CH_3-3'), 1.43 (1H, dd, *J* = 12.6, 10.8 Hz, H-4'α), 2.44 (1H, dd, *J* = 13.6, 5.6 Hz, H-4'β), 2.59 (1H, d, *J* = 15.5 Hz, H-4α,), 3.16 (1H, dd, *J* = 15.0, 5.9 Hz, H-4β), 3.46 (1H, m, H-3'), 3.76 (1H, m, H-3), 3.82 (1H, d, *J* = 5.7 Hz, H-1'), 4.07 (1H, br. s, N*H*-9'), 4.43 (1H, d, *J* = 5.6 Hz, H-1), 5.07 (1H, s, H-9'a), 6.59 (1H, d, *J* = 7.7 Hz, H-8'), 6.76 (1H, t, *J* = 7.5 Hz, H-6'), 7.04–7.11 (4H, m, H-6, 7, 5', 7'), 7.18 (1H, dd, *J* = 6.1, 2.8 Hz, H-8), 7.48 (1H, dd, *J* = 6.4, 2.6 Hz, H-5), 8.93 (1H, br. s, N*H*-9). ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.8, 19.6, 28.7, 48.5, 51.3, 52.5, 58.3, 64.7, 74.9, 88.9, 108.9, 109.1, 111.2, 117.8, 118.9, 119.0, 121.4, 122.7, 127.7, 127.9, 130.9, 133.5, 136.6, 150.3. The ent-**25** had the –170.3 of optical rotation values in chloroform..

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s13659-012-0003-6 and is accessible for authorized users.

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[5] (a) Intermediate **2** reacted with **1** formed only (*E*)-imines since the calculated energy of formation of the (*Z*)-imine is 5.1 kcal/mol higher than that for the (*E*)-imine in CH_2Cl_2. Two products were isolated in ratios of 2:1 to 3:1 after subsequent reactions with *trans*-**2** and *cis*-**2** (theoretically 4:1 at the B3LYP/6-31G(d) level), respectively. (b) Nyerges, M.; Rudas, M.; Bitter, I.; Toke, L. *Tetrahedron* **1997**, *53*, 3269–3280. (c) Gomez-Monterrey, I. M.; Campiglia, P., Bertamino, A.; Aquino, C.; Mazzoni, O.; Diurno, M. V.; Iacovino, R.; Saviano, M.; Sala, M.; Novellino, E.; Grieco, P. *Eur. J. Org. Chem*. **2008**, 1983–1992. (d) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc*. **2006**,*128*, 14772–14773.