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OPTICALLY ACTIVE TROPOCORONANDS HAVING AMINO ACID RESIDUES IN LINKER CHAINS: SYNTHESES, METAL COORDINATION PROPERTIES, AND THEIR ABILITIES AS AN ASYMMETRIC CATALYST

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Abstract – Optically active tropocoronands (**7**) having L-amino acid moieties were synthesized by stepwise and one-pot reactions of tropolone derivatives with amino acid linker chains. The coordination styles of their Ni(II) and Pd(II) complexes and the abilities as an asymmetric catalyst were investigated.

INTRODUCTION

Tropocoronands (TCs), which are non-benzenoid macrocycles containing two aminotroponimine[1] units bridged by polymethylene, amine, ether or thioether chains, were reported by T. Nozoe and S. J. Lippard's groups.[2] Those macrocyclic ligands have metal coordinating ability and their metal complexes have been employed in transition metal chemistry[2a-c,3] and as models for bioactive molecules.[4] TCs having higher functional groups in linker chains are interesting molecules for physical, structural, metal complexing and chemical fields. As a part of our study for such TCs, the introduction of hydroxy group(s) on the linker chains was already reported.[5] Optically active ligand-metal complexes are expected to be asymmetric catalysts and models for enzymetical metal-proteins,[6] therefore, our next interest is focused on the chemistry of chiral TCs. However, the investigation of optically active TCs is few[7] because of their synthetic intricacy.

Here we describe a detailed synthetic study of a novel family of chiral TCs (**7**) that contain L-amino acid residues in linker chains. The characteristic coordination properties for Ni(II) and Pd(II) ions and a part of their asymmetric catalytic abilities are also reported.

RESULTS AND DISCUSSION

While many chiral sources, *e. g.*, optically active diamines, diols, carboxylic acids, sulfoxides, binaphthyl compounds and so on, can be considered when chiral ligands are constructed, we took up L-amino acids which are widely existed in nature and easy to obtain at relatively low cost. With the efficient metal coordination at both aminotroponimine and amino acid moieties in mind, amino acid

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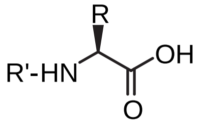
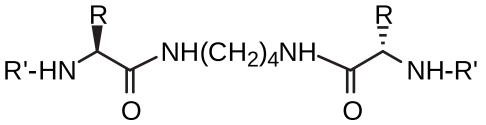
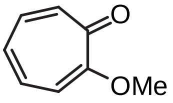
This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

residues were located at adjacent positions of seven membered ring moieties in the designed chiral TCs (**7**). As for the introducing L-amino acids, neutral ones such as alanine (Ala), valine (Val) and phenylalanine (Phe) were selected in order to avoid the synthetic difficulty.


1a: R = Me, R' = H
1b: R = *i*-Pr, R' = H
1c: R = CH_2Ph, R' = H
2: R' = Cbz


3: R' = Cbz
4: R' = H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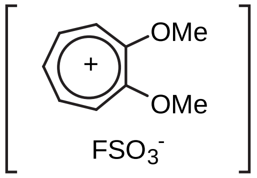
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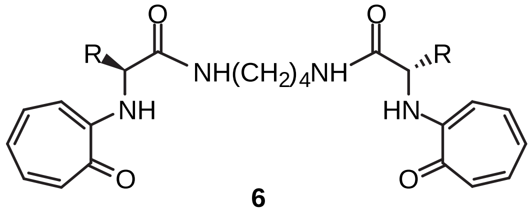
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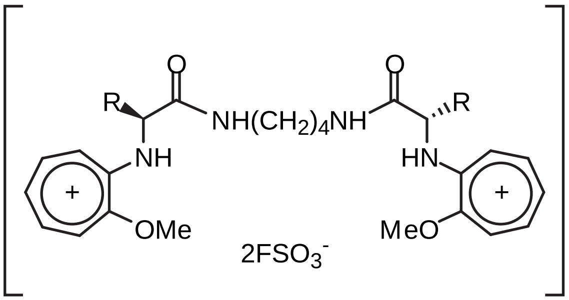
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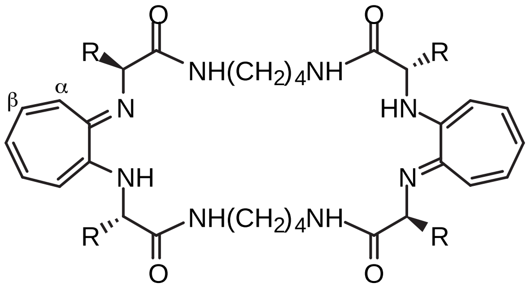
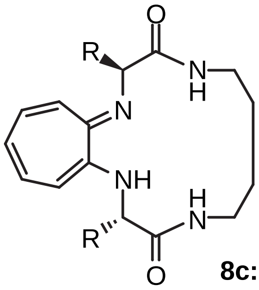

7a: R = Me
7b: R = *i*-Pr
7c: R = CH_2Ph


8c: R = CH_2Ph

First of all, we tried the stepwise synthesis of the target TCs (**7**), that is, connecting two seven membered ring moieties with an amino acid linker chain and further ring closure by another linker one. Despite the multi-step reactions, this method is appropriate to prevent the oligomerization. Treatment of *N*-benzyloxycarbonyl (Cbz)-amino acids (**2**), derived from L-amino acids (**1a**: L-Ala, **1b**: L-Val, **1c**: L-Phe) and Cbz-Cl, with 0.5 mol equiv. of 1,4-diaminobutane in the presence of DCC afforded coupling products (**3**). After deprotection of the Cbz groups by hydrogenation, resulting linker chains (**4**) were reacted with 2.4 mol equiv. of tropolone methyl ether (**5**) in ethanol under refluxing conditions to give bis(aminotropone)s (**6a**–**6c**) as yellow or pale yellow solids in 66, 70 and 36 % yields, respectively (mp 66–68 °C for **6a**, 67–69 °C for **6b**, 84–87 °C for **6c**). Compound (**6a** or **6b**) was treated with methyl fluorosulfonate (FSO_3Me) in CH_2Cl_2 at room temperature to form reactive tropyrium ion (**6a'** or **6b'**), which directly reacted with **4a** or **4b** in the presence of triethylamine in methanol for 72 h at room temperature (for **6a'**) or for 22 h at 64 °C (for **6b'**) to afford desired TC (**7a**: yield 19 %, mp 265 °C (decomp), **7b**: 10 %, 230–232 °C) as yellow solid. Phe-TC (**7c**) could not be obtained owing to a failure of formation of the corresponding tropyrium ion (**6c'**). FAB-MS spectra of synthetic TCs gave molecular ion peaks (MH^+: **7a**; *m/z* 633, **7b**; *m/z* 745.5) and the IR spectra showed the absorption maxima for NH stretching vibration of aminotroponimine moieties (ν_{NH}: **7a**; 3306 cm^{-1}, **7b**; 3292 cm^{-1}) and for C=O stretching one of amides ($\nu_{C=O}$: **7a**; 1647 cm^{-1}, **7b**; 1651 cm^{-1}). The ^{1}HNMR spectrum of **7a** showed relevant protons for the moieties of alanine, butanediamine and aminotroponimine. At seven membered ring moieties, only three kinds of protons (δ: 6.27 for H^γ, 6.34 for H^α, 6.86 for H^β) were observed. This is a characteristic pattern of aminotroponimine-compounds arising from the fast equilibrium by the hydrogen bonding between adjacent NH and C=N groups. The similar ^{1}HNMR spectrum for **7b** was observed. Together with the results of elemental analysis, those spectral data supported the proposed structures.

Secondarily, we attempted the one-pot synthesis of TC (**7**). A convenient and useful one-pot synthesis of TCs by the reaction of benzo[*b*]cyclohepta[*e*][1,4]oxazine with various diamines was reported.[2d,e] However, this method could not be adapted to the amino acid linker chains (**4**) by reason of the steric hindrance of themselves and/or resulting reaction intermediates. More reactive troponoids such dimethoxytropyrium ion (**5’**) should be needed to accomplish the synthesis. In practice, the reaction of **5’**, derived from **5** with FSO_3Me, with 1.0 mol equiv. of linker chain (**4c**) in methanol at room temperature for 7 h gave expected Phe-TC (**7c**) in 10 % yield together with its half compound (**8c**, half-Phe-TC) in 2 % yield. Both **7c** and **8c** were yellow compounds (yellow solid, mp: 241–243 °C for **7c**, yellow fine needles, mp: 258–260 °C for **8c**) and showed molecular ion peaks in FAB-MS spectra (MH^+: **7c**; *m/z* 937.5, **8c**; *m/z* 469). Their IR and ^{1}H NMR spectral and analytical data are consistent with the proposed structures. The ^{1}H NMR signals of methylene protons of **8c** were split and found at upfield by 1.20 ppm and downfield by 0.24 ppm from those of **7c** (δ 1.05 ppm, br, 8H). Anisotropic effects from its benzene rings might be exerted by the reason of strained and fixed conformation of **8c**. Ala-TC (**7a**) and Val-TC (**7b**) were also synthesized by the same manner (yield: **7a**; 20 %, **7b**; 7 %). In these cases, corresponding half-TCs could not be obtained.

Since synthetic TCs (**7**) have a large cavity enough to fit two metal cations and include two different kinds of coordination sites, that is, aminotroponimine and amide (O- and/or N- coordination) moieties, their coordinate behaviors in the presence of transition metal ions are of particular interest. It was reported that mono Ni(Ⅱ) complexes of propane- and butane-bridged TCs, which have only four coordination points (four nitrogen atoms) at aminotroponimine moieties, showed near planner structures (S = 0, low-spin complexes), whereas those of pentane- and the longer chain-bridged ones showed distorted tetrahedral structures (S = 1, high-spin complexes).[2b] The synthetic amino acid-TCs (**7**) have eight or more coordination points, and therefore the different coordination styles for Ni(Ⅱ) ion are expected. To elucidate the coordination properties, we investigated by use of UV-VIS, MS, ^{1}HNMR and IR spectral data of **7a** in the presence of Ni(Ⅱ) ion. From UV-VIS spectra of **7a** with $Ni(OAc)_2$, the complexation of **7a** and Ni(Ⅱ) ion was recognized (Figure 1). Increasing peaks at the region of 490 to 550 nm were assigned as the result of ligand-metal charge transfer transitions. Determination of the complexing composition was achieved by Job’s method.[8] As shown in Figure 2, the maximal or minimal values were observed at the molar fractions of $Ni(OAc)_2$ of 0.6 to 0.7. These results indicate the formation of **7a**·Ni_2 complex. FAB-MS spectrum of **7a** with 2.0 mol equiv. of $Ni(OAc)_2$ gave the molecular ion peak of dinuclear complex (MH$^+$: *m/z* 745, M = **7a**–4+2Ni) and its isotopic peaks. The composition was finally established by elemental analysis of precipitates from the solution of **7a** and 2.0 mol equiv. of Ni(OAc)$_2$ in CH_2Cl_2-MeOH (Anal. Calcd for $C_{34}H_{44}N_8O_4Ni_2 \cdot CH_3OH$: C, 54.02; H, 6.22; N, 14.40. Found: C, 53.96; H, 5.85; N, 14.18). Although ^{1}HNMR spectrum of **7a** with 1.0 mol equiv. of Ni(OAc)$_2$ was complicated by existence of plural compounds, the spectrum with 2.0 mol equiv. of Ni(Ⅱ) ion was simplified and gave peaks of the dinuclear complex (Figure 3). All the latter peaks were shown at the region of 0 to 10 ppm, indicating the planar coordination for Ni(Ⅱ) ion (S = 0, low-spin complex). Five kinds of the peaks at aminotroponimine moieties and the split peaks at methyl groups suggested that each of two Ni(Ⅱ) ions was coordinated with a same asymmetrical style.

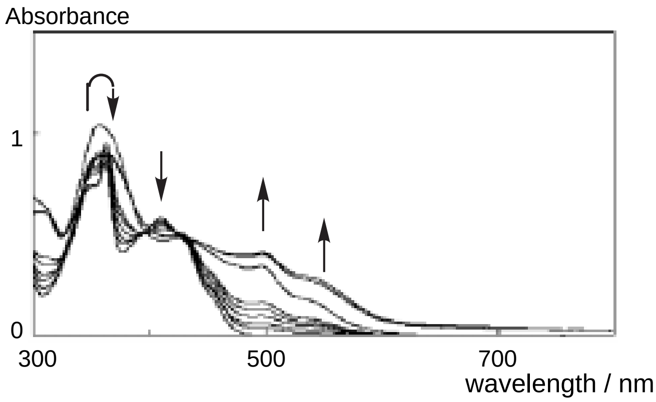


Figure 1 UV-VIS spectra of **7a** with Ni(OAc)$_2$ (0–10 mol equiv.) in CH_2Cl_2-MeOH (1 : 1, 4.0 x 10^{-5} M for **7a**)

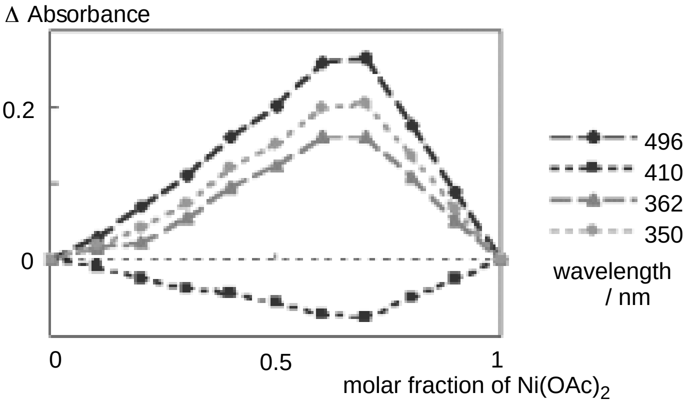


Figure 2 Job-plots of **7a** with Ni(OAc)$_2$ by use of the UV-VIS spectral data

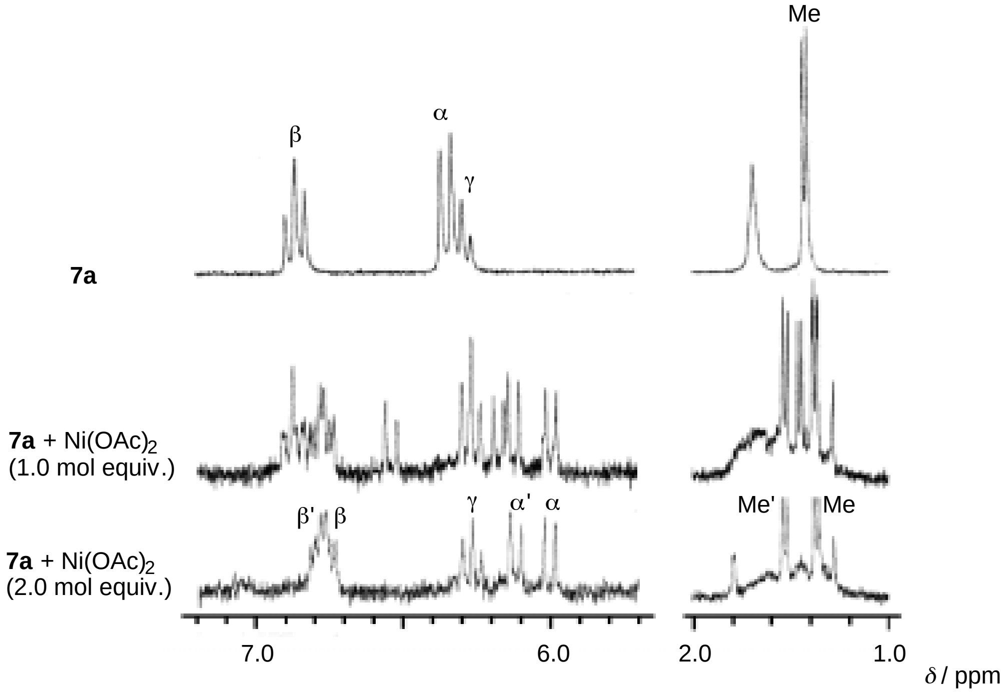
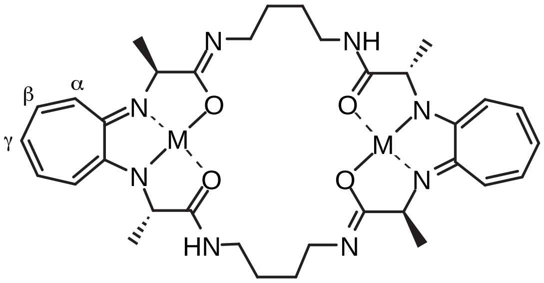


Figure 3 ^{1}HNMR spectra of **7a** in the presence of Ni(OAc)$_2$ (0–2 mol equiv.)

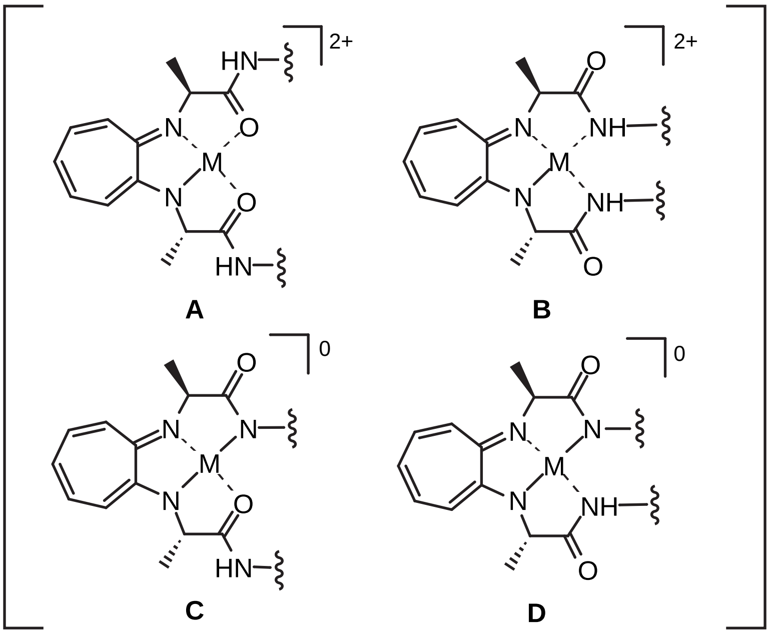
To elucidate this asymmetrical style, IR spectrum of **7a** with 2.0 mol equiv. of Ni(Ⅱ) ion was measured. The wavenumber of the absorption maxima are generally shifted down by complexation with metal ions. Indeed, only one down-shifted IR peak for C=O stretching vibration of amides, coordinated with the O atoms, was observed at 1575 cm^{-1} (*cf.* $\nu_{C=O}$: **7a**; 1647 cm^{-1}). Further characteristic peaks were shown at 1230 and 1260 cm^{-1}. The latter could be assigned as a peak for C–N stretching of amides (*cf.* ν_{C-N}: **7a**; 1256 cm^{-1}), whereas the former did not correspond to any peaks of **7a**. This might be assigned for Ni-coordinated C–O stretching vibration of iminated amide moieties.

Considering the above instrumental data, the **7a**-Ni complex should have the style of dinuclear, planar and [N$^{\text{aminotroponimine}}$, N$^{\text{aminotroponimine}}$, O$^{\text{amide}}$, O$^{\text{amide}}$] coordination as depicted in **9a**. Although other coordination styles such as **A**–**D** are also supposed, **A** and **B** are dicationic complexing ions and their structures are denied by the FAB-MS spectral data. As for **C**, two different kinds of IR peaks for C=O stretching of amides must be observed. Amide-O atoms of **D** have nothing to coordinate to Ni(Ⅱ) ion, and therefore the observed down-shifted IR peak for C=O$^{\text{amide}}$ stretching is in conflict. The X-Ray analysis is needed to estimate the structure, however, we have not obtained its single crystal yet.

In the case of **7a** with Pd(Ⅱ) ion, the similar instrumental data were obtained, suggesting that **7a**-Pd complex should have the same style of Ni-complex as depicted in **10a**. The use of Zn ion, instead of Ni and Pd ions, showed the existence of Zn(Ⅱ) dinuclear complex from the Job's plot and FAB-MS spectral data (MH$^+$: *m/z* 757, M = **7a**–4+2Zn). However, more detailed coordination style could not be elucidated because of their complicated ^{1}HNMR and IR spectral data arising from coexistence of another composed complexes such as **7a**·Zn, (**7a**)$_2$·Zn and (**7a**)$_4$·Zn, which were suggested by the Job's plot.



9a: M = Ni (Ⅱ)
10a: M = Pd (Ⅱ)



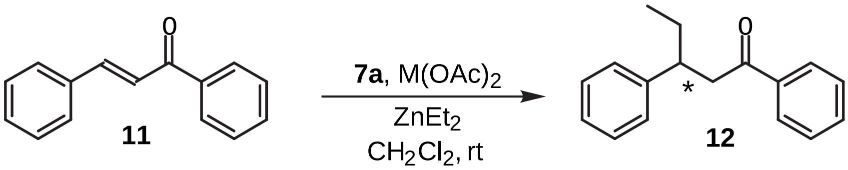
A **B**

C **D**

Searching for the abilities of chiral TCs (**7**) as an asymmetric catalyst, we attempted asymmetric conjugate addition of ZnEt$_2$ to chalcone (**11**) with chiral [N, O] ligand-metal complexes.[9] In the presence of Ni(Ⅱ) and Pd(Ⅱ) dinuclear complexes prepared from 1.0 mol % of **7a** and 2.0 mol % of M(OAc)$_2$

(M = Ni and Pd) the reactions were accelerated, but unfortunately, the values of enantiomer excess of the obtained **12** were not high (entries 1 and 2). The use of $Zn(OAc)_2$ instead of Ni and $Pd(OAc)_2$ resulted in moderate enantioselectivity of **12** with the opposite configuration (entry 3). To our surprise, the similar result in entry 3 was revealed even in the absence of metal ion (entry 4), suggesting that the same key intermediate, which may be a complex of **7a** and $ZnEt_2$, is existed in these reactions. While the asymmetric reaction has not been optimized yet, it appears that amino acid-TCs have some potential as an asymmetric catalyst.

Table 1. Conjugate addition of $ZnEt_2$ to chalcone (**11**) in the presence of TC (**7a**) or its metal complexes



entry	M	**11** / **7a** / $M(OAc)_2$ / $ZnEt_2$ (mol equiv.)	time / h	**12** / %	% e.e. (*config.*)
1	Ni	1 / 0.01 / 0.02 / 2	24	64	8 (*S*)
2	Pd	1 / 0.01 / 0.02 / 2	24	40	7 (*S*)
3	Zn	1 / 0.01 / 0.02 / 2	24	27	30 (*R*)
4	-	1 / 0.01 / - / 2	24	21	30 (*R*)
5	-	1 / - / - / 2	48	35	-

In summary, we have established the synthesis of amino acid-TCs (**7**), a new family of optically active non-benzenoid macrocyclic ligands, by the stepwise and one-pot reactions of troponoids with amino acid linker chains. The coordination properties of **7a** for Ni(II) and Pd(II) ions and their asymmetric catalytic abilities in conjugated addition have also been investigated as a part of clarification of their characteristics. Further works aimed at the coordination properties of **7** and **8c** for the other metal ions and at their wider application and development toward asymmetric reactions are in progress.

EXPERIMENTAL

Mps were determined with a Mitamura air-bath apparatus and are uncorrected. ^1H and ^{13}C NMR spectra ($SiMe_4$ as the internal standard) were obtained with Bruker AC-200 and / or AC-300 spectrometers. IR spectra were obtained with a Perkin Elmer System 2000 FT instrument and electronic spectra (UV-VIS) with a JASCO V-560 spectrophotometer. MS spectra were obtained with JEOL JMS-DX 303 spectrometers. Unless otherwise stated the spectra were taken in the following solvents / media: IR, KBr; UV-VIS, CH_2Cl_2-MeOH; ^{1}HNMR (200 and 300 MHz), $CDCl_3$, MeOH-d_4 and/or DMSO-d_6; MS spectra were taken at 70 eV by electron impact (EI) and fast atom bombardment (FAB) method. The progress of reactions was followed by TLC method using Merck Silica gel $60F_{254}$.

Typical experimental procedure for the synthesis of amino acid linker chains (4a–4c): To a suspended solution of L-amino acids (**1**, 5.27 g for **1b**, 45.0 mmol) and 5.72 g (54.0 mmol) of Na_2CO_3 in 150 mL of H_2O, 9.21 g (54.0 mmol) of Cbz-Cl was added at 0 °C. The reaction mixture was stirred at rt for 24 h and quenched with 2 N aq. HCl. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by SiO_2 column chromatography (eluted by CH_2Cl_2 : AcOEt = 10 : 1) to give Cbz-amino acids (**2**). The obtained **2** (6.78 g for **2b**, 27.0 mmol) was dissolved in CH_2Cl_2 (100 mL) and then 5.57 g (27.0 mmol) of DCC was added at 0 °C. To this solution, 1.19 g (1.36 mL, 13.5 mmol) of 1,4-diaminobutane was added dropwise and the reaction mixture was stirred at rt for 14 h. Resulting precipitates were filtered and recrystallized from CH_2Cl_2-MeOH to give coupling products (**3**). A suspended solution of **3** (1.16 g for **3b**, 2.10 mmol) and 11.6 mg (1.0 weight %) of 10% Pd-C in alcohol (60 mL, EtOH for **3a**, MeOH for **3b** and **3c**) was stirred at rt for 7 h under H_2. After filtration, the solvent was removed under reduced pressure to give linker chains (**4**). The obtained **4** was used without further purification. **2a**: yield 98 %; colorless solid, mp 80–81 °C from AcOEt; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.47 (3H, d, J = 7.3 Hz), 4.43 (1H, m), 5.13 (2H, s), 5.25 (1H, br, NH), 7.34 (5H, m); HRMS (EI(+)) Calcd for $C_{11}H_{13}NO_4$: 223.0845, Found: 223.0843. **2b**: yield 90 %; colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.91 (3H, d, J = 7.0 Hz), 0.98 (3H, d, J = 6.6 Hz), 2.21 (1H, m), 4.35 (1H, dd, J = 8.9, 4.8 Hz), 5.11 (2H, s), 5.47 (1H, d, J = 8.9 Hz, NH), 7.36 (5H, m); HRMS (EI(+)) Calcd for $C_{13}H_{17}NO_4$: 251.1158, Found: 251.1155. **2c**: yield 86 %; pale yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 3.09 (1H, dd, J = 14.0, 6.2 Hz), 3.20 (1H, dd, J = 14.0, 5.5 Hz), 4.70 (1H, m), 5.09 (2H, s), 5.22 (1H, d, J = 8.1 Hz, NH), 7.25 (5H, m), 7.32 (5H, m); HRMS (EI(+)) Calcd for $C_{17}H_{17}NO_4$: 299.1158, Found: 299.1155. **3a**: yield 22 %; colorless solid, mp 179–180 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, DMSO-d_6, δ 2.50) δ 1.18 (6H, d, J = 7.0 Hz), 1.36 (4H, m), 3.03 (4H, m), 3.98 (2H, m), 5.00 (4H, m), 7.35 (12H, m, including NH), 7.82 (2H, br, NH); IR (KBr, cm^{-1}) ν 3304, 2968, 1694, 1652; MS (FAB(+), NBA, %) m/z 499 (MH$^+$, 15). Anal. Calcd for $C_{26}H_{34}N_4O_6$: C, 62.63; H, 6.87; N, 11.24. Found: C, 62.44; H, 6.90; N, 11.09. **3b**: yield 71 %; colorless solid, mp 239–240 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, DMSO-d_6, δ 2.50) δ 0.83 (12H, d, J = 6.6 Hz), 1.38 (4H, m), 1.90 (2H, m), 3.04 (4H, m), 3.77 (2H, dd, J = 8.5, 6.9 Hz), 5.02 (4H, s), 7.21 (2H, d, J = 8.5 Hz, NH), 7.35 (10H, m), 7.90 (2H, m, NH); IR (KBr, cm^{-1}) ν 3298, 2959, 1691, 1652; MS (FAB(+), NBA, %) m/z 555 (MH$^+$, 21). Anal. Calcd for $C_{30}H_{42}N_4O_6$: C, 64.96; H, 7.63; N, 10.10. Found: C, 65.01; H, 7.60; N, 10.08. **3c**: yield 70 %; colorless solid, mp 219–220 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, DMSO-d_6, δ 2.50) δ 1.32 (4H, m), 2.75 (2H, m), 2.94 (2H, m), 3.02 (4H, m), 4.19 (2H, m), 4.93 (4H, m), 7.22 (10H, m), 7.30 (10H, m), 7.46 (2H, d, J = 8.8 Hz, NH), 7.96 (2H, m, NH); IR (KBr, cm^{-1}) ν 3304, 2960, 1694, 1652; MS (FAB(+), NBA, %) m/z 651 (MH$^+$, 14). Anal. Calcd for $C_{38}H_{42}N_4O_6$: C, 70.13; H, 6.51; N, 8.61. Found: C, 70.27; H, 6.51; N, 8.59. **4a**: yield quant.; colorless solid, mp 81–84 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (6H, d, J = 7.0 Hz), 1.58 (4H, m), 3.26 (2H, m), 3.49 (4H, m), 7.38 (2H, br, NH); IR (KBr, cm^{-1}) ν 3362, 3292, 2957, 1634; Anal. Calcd for $C_{10}H_{22}N_4O_2$: C, 52.15; H, 9.63; N, 24.33. Found: C, 52.32; H, 9.74; N, 24.17. **4b**: yield quant.; colorless solid, mp 92–93 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 0.81 (6H, d, J = 6.8 Hz), 0.98 (6H, d, J = 7.3 Hz), 1.55 (4H, m), 2.28 (2H, m), 3.22 (2H, d, J = 3.4 Hz), 3.28 (4H, m), 7.38 (2H, br, NH); IR (KBr, cm^{-1}) ν 3356, 3288, 2959, 1636; Anal. Calcd for $C_{14}H_{30}N_4O_2$: C, 58.71; H, 10.56; N, 19.56. Found: C, 58.59; H, 10.68; N, 19.50. **4c**: yield quant.; colorless solid, mp 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.42 (4H, br), 2.70 (4H, m), 3.25 (4H, m), 3.60 (2H, dd, J = 9.2, 4.0 Hz), 7.28 (10H, m); IR (KBr, cm^{-1}) ν 3364, 3292, 2941, 1635; Anal. Calcd for $C_{22}H_{30}N_4O_2$: C, 69.08; H, 7.91; N, 14.65. Found: C, 69.10; H, 7.89; N, 14.65.

Typical experimental procedure for the stepwise synthesis of TCs (7a and 7b): To a boiling solution of **4** (232 mg for **4a**, 1.01 mmol) in 2.5 mL of dry EtOH, 329 mg (2.42 mmol) of tropolone methyl ether (**5**) and 0.700 mL (5.05 mmol) of triethylamine in dry EtOH (2.5 mL) were added under N_2. The reaction mixture was boiled for 25 h and the solvent was removed *in vacuo*. The residue was purified by SiO_2 column chromatography (eluted by AcOEt) to give bis(aminotropone)s (**6**). The obtained **6** (133 mg for **6a**, 0.30 mmol) was dissolved in dry CH_2Cl_2 (1.15 mL) and then 0.142 mL (1.80 mmol) of FSO_3Me was added at rt. After formation of tropyrium ions (**6’**) (stirring for about 2 h), the solvent was exchanged to dry MeOH (40 mL) under N_2. To this solution, side chains (**4**, 86.4 mg for **4a**, 0.38 mmol) and triethylamine (0.208 mL, 1.50 mmol) in dry MeOH (20 mL) were added and the reaction mixture was stirred for 72 h at rt (for **6a’**) or for 22 h at 64 °C (for **6b’**). After evaporation of the solvent, the residue was purified by aluminum oxide column chromatography (eluted by CH_2Cl_2 : AcOEt = 1 : 1) and then recrystallized from CH_2Cl_2-MeOH to give the desired TCs (**7a** and **7b**). **6a**: yield 66 %; yellow solid, mp 66–68 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.35 (4H, m), 1.63 (6H, d, J = 7.4 Hz), 3.14 (4H, m), 4.02 (2H, m), 6.43 (2H, d, J = 10.3 Hz), 6.51 (2H, t like, J = 6 Hz, NH), 6.78 (2H, dd, J = 11.8, 9.6 Hz), 7.19 (2H, d, J = 11.0 Hz), 7.30 (2H, dd, J = 11.8, 10.3 Hz), 7.33 (2H, dd, J = 11.0, 9.6 Hz); IR (KBr, cm^{-1}) ν 3289, 2933, 1668, 1601; MS (FAB(+), NBA, %) *m/z* 439 (MH$^+$, 68); Anal. Calcd for $C_{24}H_{30}N_4O_4$: C, 65.73; H, 6.90; N, 12.78. Found: C, 65.49; H, 7.05; N, 12.48. **6b**: yield 70 %; yellow solid, mp 67–69 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.06 (6H, d, J = 7.0 Hz), 1.08 (6H, d, J = 7.0 Hz), 1.34 (4H, m), 2.45 (2H, m), 3.16 (4H, m), 3.78 (2H, m), 6.32 (2H, br, NH), 6.46 (2H, d, J = 10.3 Hz), 6.77 (2H, m), 7.21 (2H, d, J = 11.0 Hz), 7.30 (2H, m), 7.37 (2H, m); IR (KBr, cm^{-1}) ν 3293, 2963, 1655, 1594; MS (FAB(+), NBA, %) *m/z* 495 (MH$^+$, 16); Anal. Calcd for $C_{28}H_{38}N_4O_4\cdot1/2H_2O$: C, 66.77; H, 7.81; N, 11.12. Found: C, 66.75; H, 7.77; N, 10.92. **6c**: yield 36 %; pale yellow solid, mp 84–87 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.29 (4H, br), 3.13 (4H, m), 3.27 (4H, m), 4.20 (2H, m), 6.41 (2H, d, J = 10.3 Hz), 6.67 (2H, t like, J = 10 Hz), 6.82 (2H, t like, J = 6 Hz, NH), 6.96 (2H, d, J = 11.4 Hz), 7.15 (4H, m), 7.24 (10H, m), 7.43 (2H, d like, J = 6 Hz, NH); IR (KBr, cm^{-1}) ν 3293, 2926, 1655, 1593; MS (FAB(+), NBA, %) *m/z* 591 (MH$^+$, 100); Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.20; H, 6.48; N, 9.48. Found: C, 72.99; H, 6.58; N, 9.28. **7a**: yield 19 %; yellow solid, mp 265 °C (decomp) from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, $CDCl_3$/MeOH-d_4 = 1, TMS) δ 1.42 (12H, d, J = 6.6 Hz), 1.69 (8H, br), 3.30 (4H, m), 3.42 (4H, m), 4.20 (4H, q, J = 6.6 Hz), 6.27 (2H, t, J = 9.6 Hz), 6.34 (4H, d, J = 11.4 Hz), 6.86 (4H, t like, J = 10 Hz); IR (KBr, cm^{-1}) ν 3306, 2934, 1647, 1256; MS (FAB(+), NBA, %) *m/z* 633 (MH$^+$, 34); Anal. Calcd for $C_{34}H_{48}N_8O_4\cdot H_2O$: C, 62.75; H, 7.74; N, 17.22. Found: C, 63.02; H, 7.58; N, 17.32; $[\alpha]^{28}_D$ –161° (c 1.00, CH_2Cl_2/MeOH = 1). **7b**: yield 10 %; yellow solid, mp 230–232 °C from CH_2Cl_2-MeOH; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.93 (12H, d, J = 6.6 Hz), 1.03 (12H, d, J = 7.0 Hz), 1.58 (8H, br), 2.40 (4H, m), 2.89 (4H, m), 3.71 (4H, m), 4.11 (4H, d, J = 4.1 Hz), 6.33 (2H, t, J = 9.2 Hz), 6.40 (4H, d, J = 11.0 Hz), 6.63 (4H, m, NH), 6.81

(4H, t like, *J* = 10 Hz); IR (KBr, cm^{-1}) ν 3292, 2929, 1651, 1260; MS (FAB(+), NBA, %) *m/z* 745.5 (MH^+, 45); Anal. Calcd for $C_{42}H_{64}N_8O_4$: C, 67.71; H, 8.66; N, 15.04. Found: C, 67.46; H, 8.81; N, 14.87; $[\alpha]^{28}_D$ +36.0° (c 1.00, CH_2Cl_2). **7c**: not obtained owing to a failure of formation of the corresponding tropyrium ion (**6c'**).

Typical experimental procedure for the one-pot synthesis of TCs (7a–7c) and half-TC (8c): To a solution of tropolone methyl ether (**5**, 620 mg, 4.55 mmol) in dry CH_2Cl_2 (0.5 mL) was added 1.10 mL (14.0 mmol) of FSO_3Me at rt. After formation of the tropyrium ion (**5'**) (stirring for 0.5 h), the solvent was exchanged to dry MeOH (50 mL) under N_2. To this solution, 1.72 g of side chain (**4c**, 4.50 mmol) and 2.50 mL (18.0 mmol) of triethylamine in dry MeOH (400 mL) were added dropwise for 2 h and the reaction mixture was stirred for 7 h at rt. After filtration of precipitated half-TC (**8c**), the solvent was removed *in vacuo* and the residue was purified by aluminum oxide column chromatography (eluted by CH_2Cl_2 : AcOEt = 1 : 1) and then recrystallized from CH_2Cl_2-MeOH to give TC (**7c**). **7a**: yiled 20 %. **7b**: yiled 7 %. **7c**: yield 10 %; yellow solid, mp 241–243 °C from CH_2Cl_2-MeOH; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.05 (8H, br), 3.00 (4H, m), 3.13 (8H, m), 3.27 (4H, m), 4.38 (4H, m), 6.21 (2H, t, *J* = 9.2 Hz), 6.25 (4H, d, *J* = 10.7 Hz), 6.69 (4H, t like, *J* = 10 Hz), 7.11 (8H, m), 7.18 (12H, m); IR (KBr, cm^{-1}) ν 3299, 2926, 1648, 1265; MS (FAB(+), NBA, %) *m/z* 937.5 (MH^+, 21); Anal. Calcd for $C_{58}H_{64}N_8O_4\cdot 1/2CH_3OH$: C, 73.71; H, 6.98; N, 11.76. Found: C, 73.81; H, 6.86; N, 11.85, $[\alpha]^{29}_D$ –617° (c 1.00, CH_2Cl_2/MeOH = 1). **8c**: yield 2 %; yellow fine needles, mp 258–260 °C from CH_2Cl_2-MeOH; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ -0.15 (2H, m), 1.29 (2H, m), 2.56 (2H, m), 3.01 (2H, m), 3.17 (2H, dd, *J* = 13.1, 5.0 Hz), 3.40 (2H, dd, *J* = 13.1, 3.5 Hz), 4.59 (2H, m), 5.74 (2H, br, NH), 6.50 (1H, t, *J* = 9.4 Hz), 6.59 (2H, d, *J* = 11.0 Hz), 6.87 (4H, m), 6.02 (2H, t like, *J* = 10 Hz), 7.09 (6H, m); IR (KBr, cm^{-1}) ν 3278, 2962, 1655, 1272; MS (FAB(+), NBA, %) *m/z* 469 (MH^+, 100); Anal. Calcd for $C_{29}H_{32}N_4O_2$: C, 74.33; H, 6.88; N, 11.96. Found: C, 74.10; H, 6.92; N, 11.77, $[\alpha]^{26}_D$–601° (c 0.25, CH_2Cl_2/MeOH = 1).

Typical instrumental measurement for Ala-TC (7a) in the presence of Ni(Ⅱ) or Pd(Ⅱ) ion: To a solution of **7a** in $CDCl_3$-MeOH-d_4 (1 : 1, 1.0 x 10^{-3} M) was added 1.0 mol equiv. of $Ni(OAc)_2$ or $Pd(OAc)_2$ and the mixture was stood for 24 h, then its ^{1}HNMR spectrum was measured. To this sample solution was added 1.0 mol equiv. of $Ni(OAc)_2$ or $Pd(OAc)_2$ further and it was measured after 24 h. UV-VIS and FAB-MS spectra were measured by the same manner. The samples for IR spectra and elemental analysis were precipitated with hexane from the solution of **7a** and 2.0 mol equiv. of $Ni(OAc)_2$ or $Pd(OAc)_2$ in CH_2Cl_2-MeOH.

Typical experimental procedure for the conjugate addition of $ZnEt_2$ to chalcone (11) in the presence of TC (7a) or its metal complexes: A solution of 1.0 mol % of **7a** and 2.0 mol % of $M(OAc)_2$ in 2.0 mL of CH_2Cl_2-MeOH (1 : 1) was stirred at rt for 3 h and the solvent was exchanged to dry CH_2Cl_2 (5.0 mL) under N_2. To this solution, chalcone (**11**, 104 mg, 0.50 mmol) was added and then 1.00 mL (1.00 mmol) of $ZnEt_2$ (1.0 M in hexane) was added dropwise. The reaction mixture was stirred at rt for 24 h and quenched with 2 N aq. HCl. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by SiO_2 column chromatography (eluted by hexane : AcOEt = 25 : 1) to give conjugate adduct (**12**). The configuration and enantiomer excess (% e.e.) of **12** were determined by the specific rotations.[10]

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