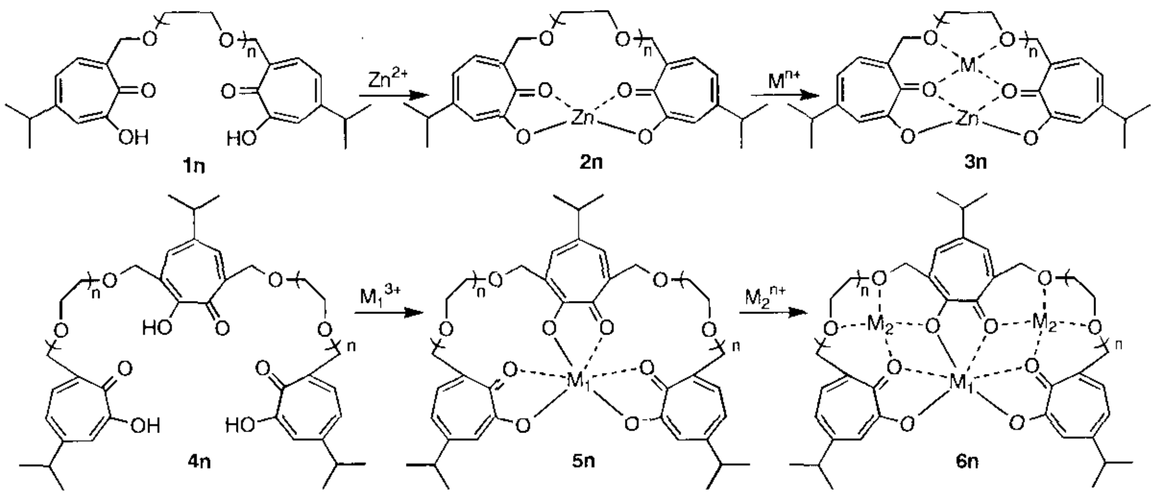
SYNTHESIS OF NEW PODAND POSSESSING THREE TROPOLONOIDS CONNECTED BY TWO OLIGOETHYLENE GLYCOL CHAINS

Tadahiro Kato,* Takehisa Kato, Takuro Kanbe, Yoshiko Tokuno, and Shigeyuki Kikumoto

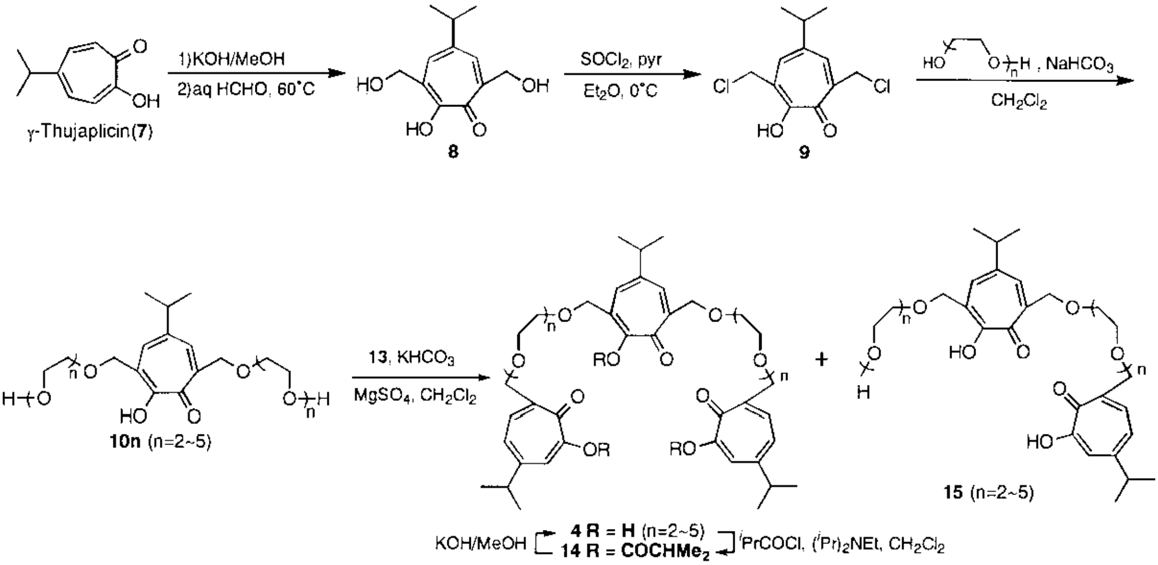
Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162-0825, Japan

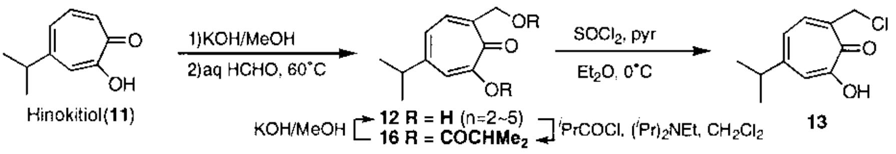
Abstract-For the purpose of exploitation of new podands possessing positive cooperativity in cation binding, three tropolonoid moieties are connected by two oligoethylene glycol chains. This note describes the preparation of diethylene to pentaethylene glycol derivatives possessing three tropolonoids (**4n**).

In our previous paper,[1] we reported the synthesis of oligoethylene glycol derivatives (**1n**) having tropolonoid moieties at both terminals in expectation of their good podand nature for the cooperative binding of two different types of metal ions.[2,3] It was found that **1n** (n = 2-5) forms the chelation with Zn^{2+} to give clathrate compound (**2n**), which binds, as expected, with an additional metal ion (M^{n+}) to form **3n**. When M^{n+} are bivalent alkaline earth metal ions, partition coefficient values are larger than those of the typical crown ethers, exhibiting a gross correlation between ionic diameters and the cavity size.[4] As an extension of our study, we are much interested in the cooperative binding properties of analogous compounds (**4n**), which are expected to bind with two additional metal ions (M_2^{n+}) to form complex (**6n**) after formation of clathrate compound (**5n**) by chelation with M_1^{3+} ion. Here we report the synthesis of **4n** (n = 2-5) to find the binding properties toward metal ions.



5-Isopropyl tropolone [2-hydroxy-5-isopropylcycloheptatrienone, γ-thujaplicin(**7**)] was selectively converted to 3,7-bischloromethyl-γ-thujaplicin (**9**) by the sequential treatments of potassium salt of **7** with 37% aq HCHO solution at 60°C to 3,7-bishydroxymethyl-γ-thujaplicin (**8**) (91%) followed by chlorination (86%) with thionyl chloride and pyridine. Introduction of two oligoethylene glycol groups at 3- and 7-methylene positions of **9** was achieved by reactions with large excess of oligoethylene glycol in the presence of NaHCO$_3$, affording bisoligoethylene glycol ether (**10n**) (n = 2-5) in 30-57% yields. The both terminal hydroxyl groups of **10n** were etherified to give the objectives **4n** (n = 2-5) in moderate yields (*ca.* 40%) when **10n** (n = 2-5) was treated with 7-chloromethylhinokitiol (**13**)[5] in the presence of NaHCO$_3$ and MgSO$_4$. The compound (**13**) was prepared from hinokitiol (**11**) through the hydroxymethyl derivative (**12**). The moderate yields of the coupling reaction is due to the imperfect etherification, giving **15n** as the identified by product.





The objectives (**4n**) (n = 2-5) were purified by converting the reaction mixture into the corresponding triisobutyrate (**14n**) followed by silica gel column chromatography and then hydrolysis with KOH. In the esterification reaction of **4n** with isobutyryl chloride, formation of isomeric esters was not observed due to the presence of 7-methyleneoxy group of hinokitiol nucleus. In fact esterifcation of 7-hydroxymethylhinokitiol (**12**) under the same conditions gave **16** selectively in 92% yield.

The metal complex formation of **4** and **15** and their positive cooperativities in cation binding will be reported near future.

EXPERIMENTALS

Unless otherwise noted, ^{1}H NMR and ^{13}C NMR spectra were recorded on solutions in $CDCl_3$ with $SiMe_4$ as an internal standard with JEOL FX-90Q spectrometer. Chemical shifts are reported in δ units, and *J* values are in Hz. The MS spectra were measured with Hitachi M-80 spectrometer. Column chromatographic purification was carried out on using Kiesel gel 60, Art 7734 (70-230 mesh) or Nacalai Tesque Cosmosil 140C-18 OPN (reverse phase). Water applied in the experiments was purified with Advantec GS-200 distillation apparatus. All the tropolonoid compounds excepting **8** (mp 117°C), **9** (decomposed), **13** (decomposed) were obtained as pale yellow oil. The usual work up involved dilution of the reaction mixture with water, extraction with ether and evaporation after washing the organic extracts with water and brine, followed by drying over Na_2SO_4.

3,7-Bischloromethyl-γ-thujaplicin (9). Potassium salt of *γ-thujaplicin* (**7**) was prepared from **7** (1.09 g, 6.62 mmol) by adding 1M KOH-MeOH (7.31 mL, 7.31 mmol) and then complete evaporation of MeOH. A mixture of the potassium salt of **7** and 37% aqueous formaldehyde (1.61 mL, 19.9 mmol) in water (10 mL) was stirred for 43 h at 60°C and poured into water, acidified with 1 M HCl and then extracted with ether. The usual work up afforded 3,7-bishydroxymethyl-γ-thujaplicin (**8**) (910 mg, 61%) after recystallization from benzene-MeOH as pale green needles, mp 116-117°C. ^{1}H NMR δ_H = 7.91 (2H, s), 4.82 (4H, s), 3.06 (1H, sept, *J*=7.0 Hz), 1.36 (6H, d, *J*=7.0 Hz). ^{13}C NMR δ_C = 167.8 (2C, s), 149.2 (s), 139.2 (2C, s), 135.4 (2C, d), 62.7 (2C, t), 40.1 (d), and 24.1 (2C, q). EIMS Found: m/z 224. Calcd for $C_{12}H_{16}O_4$: M, 224.

A mixture of bishydroxymethyl-γ-thujaplicin (**8**) (50.2 mg, 0.223 mmol), pyridine (35.2 μL, 0.435 mmol) and thionyl chloride (35.3 μL, 0.479 mmol) in anhydrous ether (5 mL) was stirred for 2 h at 0°C under argon atmosphere. The ether solution was separated and evaporated at rt to give bischloromethyl-γ-thujaplicin (**9**) (37.1 mg, 64%) as a yellow powder. ^{1}H NMR δ_H = 7.57 (2H, s), 4.79 (4H, s), 2.95 (1H, sept, *J*=7.0 Hz), 1.30 (6H, d, *J*=7.0 Hz). ^{13}C NMR δ_C = 167.7 (2C, s), 147.3 (s), 138.5 (2C, d), 132.9 (2C, s), 44.9 (2C, t), 38.7 (d), and 23.8 (2C, q). Anal. Calcd for $C_{12}H_{14}O_2Cl_2$: C, 55.19; H, 5.40. Found: C, 54.85; H, 5.10.

Oligoethylene Glycol Bisethers (10n) (n = 2-5). A mixture of 3,7-bischloromethyl-γ-thujaplicin (**9**) (553 mg, 2.12 mmol), diethylene glycol (20 mL) and anhydrous $NaHCO_3$ (373 mg, 4.45 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 21 h. The mixture was poured into 1 M HCl and extracted with CH_2Cl_2. The usual work up afforded 3,7-bis(2-hydroxyethoxymethyl)-γ-thujaplicin (**10n**) (n =2) (251 mg, 30%) after reverse phase flash chromatography with H_2O:MeCN (5:1 v/v). ^{1}H NMR δ_H = 7.70 (2H, s), 4.76 (4H, s), 3.76 (8H, m), 3.72 (4H, m), 3.68 (4H, m), 2.96 (1H, sept, *J*=7.0 Hz), and 1.28 (6H, d, *J*=7.0 Hz). ^{13}C NMR δ_C = 166.5 (2C, s), 147.8 (s), 134.6 (2C, s), 134.5 (2C, d), 72.5 (2C, t), 70.3 (4C, t), 69.8 (2C, t), 61.6 (2C, t), 38.8 (d), and 23.9 (2C, q). EIMS Found: m/z 400. Calcd for $C_{20}H_{32}O_8$: M, 400. By the similar reactions with oligoethelene glycol $[H(OCH_2CH_2)_nOH]$, **10n** (n = 3, 57%), (n = 4, 42%), and (n = 5, 43%) were prepared. **10n** (n = 3) ^{1}H NMR δ_H = 7.74 (2H, s), 4.80 (4H, s), 3.78 (12H, m), 3.73 (12H, m), 2.98 (1H, sept, *J*=7.0 Hz), and 1.30 (6H, d, *J*=7.0 Hz). ^{13}C NMR δ_C = 166.2 (2C, s), 147.5 (s), 134.5 (2C, s), 134.2 (2C, d), 72.4 (2C, t), 70.6 (2C, t), 70.2 (6C, t), 69.6 (2C, t), 61.5 (2C, t), 38.7 (d), and 23.7 (2C, q). EIMS Found:m/z 488. Calcd for $C_{24}H_{40}O_{10}$: M, 488. **10n** (n = 4) ^{1}H NMR δ_H = 7.68 (2H, s), 4.74 (4H, s), 3.71 (8H, m), 3.65 (12H, m), 3.62 (12H, m), 2.95 (1H, sept, J=7.0 Hz), and 1.28 (6H, d, J=7.0 Hz). ^{13}C NMR δ_C = 166.2 (2C, s), 147.5 (s), 134.5 (2C, s),134.1 (2C, d), 72.4 (2C, t), 70.4 (12C, t), 69.7 (2C, t), 61.4 (2C, t), 38.7 (d), and 23.8 (2C, q). EIMS Found: m/z 576. Calcd for $C_{28}H_{48}O_{12}$: M, 576. **10n** (n = 5) ^{1}H NMR δ_H = 7.70 (2H, s), 4.72 (4H, s), 3.72 (8H, m), 3.62 (32H, m), 2.96 (1H, sept, J=7.0 Hz), and 1.28 (6H, d, J=7.0 Hz). ^{13}C NMR δ_C = 166.1 (2C, s), 147.6 (s), 134.9 (2C, s), 134.1 (2C, d), 72.3 (2C, t), 70.3 (16C, t), 70.0 (2C, t), 61.3 (2C, t), 38.6 (d), and 23.7 (2C, q). EIMS Found: m/z 664. Calcd for $C_{32}H_{56}O_{14}$: M, 664.

Coupling of 10n (n = 2-5) with 7-Chloromethylhinokitiol (13). After a mixture of **10n** (n = 2) (198 mg, 0.495 mmol), anhydrous $MgSO_4$ (1.0 g), 7-chloromethylhinokitiol (**13**) (316 mg, 1.49 mmol) and $KHCO_3$ (164 mg, 1.63 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 3 days, the mixture was poured into 0.5 M HCl and extracted with CH_2Cl_2. After washing with brine and drying over Na_2SO_4, the CH_2Cl_2 solution was evaporated to give the crude product. The crude product was passed through a Cosmosil column with H_2O:MeCN (1:1 v/v) to separate the by-product (**12**) (*ca.* 30 mg) from the reaction mixture. To the crude eluants were added anhydrous $MgSO_4$ (1.0 g), 7-chloromethylhinokitiol (**13**) (316 mg, 1.49 mmol) and $KHCO_3$ (164 mg, 1.63 mmol) in CH_2Cl_2 (5 mL) and the mixture was treated similarly to give the crude product. To the resultant crude product in CH_2Cl_2 (10 mL) were added *N,N*-diisopropylethylamine (1.29 mL, 7.43 mmol) and isobutyryl chloride (0.529 mL, 4.95 mmol). After the mixture was stirred overnight at rt, excess MeOH was added and the stirring was continued for further 3 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether. The ether solution was successively washed with saturated aqueous NH_4Cl and then brine and dried over Na_2SO_4. Evaporation of the solvent and column chromatography with SiO_2 (hexane: AcOEt 3:1 v/v) afforded isobutyrate (**14n**) (n=2) in 41% yield. By the similar reactions, isobutyrates (**14n**) (n = 3, 33%), (n = 4, 37%) and (n = 5, 33%) were prepared. Isobutyrate (**14n**)(n = 2) ^{1}H NMR δ_H = 7.62 (2H, d, J=9.9 Hz), 7.50 (2H, s), 7.19 (2H, d, J=1.8 Hz), 7.00 (2H, dd, J=1.8, 9.9 Hz), 4.60 (8H, s), 3.76 (8H, m), 3.74 (8H, m), 2.90 (6H, m), 1.32 (18H, d, J=7.0 Hz), and 1.28 (18H, d, J=6.4 Hz). ^{13}C NMR δ_C = 175.1 (s), 174.4 (3C, s), 173.8 (2C, s), 165.5 (s), 157.5 (2C, s), 152.7 (2C, s), 152.2 (2C, s), 146.1 (2C, s), 143.1(s), 133.3 (2C, d), 130.7 (2C, d), 129.4 (4C, d), 70.4 (8C, t), 69.9 (4C, t), 38.9 (d), 37.8 (2C, d), 34.0 (3C, d), 23.0 (6C, q), and 18.9 (6C, q). FABMS Found: m/z 963.5126. Calcd for $C_{54}H_{74}O_{15}$ + H: M, 963.5106. **14n** (n = 3) FABMS Found: m/z 1052.5657. Calcd for $C_{58}H_{82}O_{17}$ + H, 1052.5630. **4n** (n = 4) FABMS Found: m/z 1139.6111. Calcd for $C_{62}H_{90}O_{19}$ + H: M, 1139.6154. **14n** (n = 5) FABMS Found: m/z 1227.6691. Calcd for $C_{66}H_{89}O_{23}$ + H: M, 1227.6679.

Hydrolysis of Isobutyrate (14n) (n = 2-5). After the isobutyrate (**14n**) (n = 2) (63.6 mg, 66.3 μmol) in 1 M KOH-MeOH (5 mL, 5 mmol) was stirred for 5 min at rt, the mixture was poured into 1 M HCl and extracted with AcOEt. The AcOEt solution was washed with brine and dried over Na_2SO_4. Evaporation of the volatile materials and then Cosmosil column chromatography with H_2O:MeCN (2:1 v/v) furnished pure **4n** (n = 2) (47.8 mg, 96%). By the similar treatment, the rest of the isobutyrates (**14n**) (n = 3-5) provided pure **4n** (n = 3-5) in almost quantitative yield. If necessary, the purification can be achieved by Cosmosil column chromatography with H_2O:MeCN (2:1 v/v). **4n** (n = 2) ^{1}H NMR δ_H = 7.80 (2H, d, J=9.9 Hz), 7.65 (2H, s), 7.34 (2H, d, J=1.8 Hz), 7.02 (2H, dd, J=1.8, 9.9 Hz), 4.73 (8H, s), 3.79 (16H, m), 2.88 (3H, sept, J=7.0 Hz), and 1.26 (18H, d, *J*=7.0 Hz). ^{13}C NMR (67.5 MHz) δ_C = 171.8 (2C, s), 166.2 (2C, s), 165.8 (2C, s), 158.3 (2C, s), 150.6 (s), 136.5 (2C, s), 136.3 (2C, d), 134.5 (2C, s), 134.2 (2C, d), 126.2 (2C, d), 119.5 (2C, d), 70.5 (4C, t), 70.4 (4C, t), 69.6 (4C, t), 38.5 (3C, d), and 23.3 (6C, q). FABMS Found: m/z 753.3867. Calcd for $C_{42}H_{56}O_{12}$ + H: M, 753.3850. **4n** (n = 3) ^{1}H NMR δ_H = 7.80 (2H, d, *J*=9.9 Hz), 7.74 (2H, s), 7.34 (2H, d, *J*=1.8 Hz), 7.04 (2H, dd, *J*=1.8, 9.9 Hz), 4.74 (8H, s), 3.77 (16H, m), 3.75 (8H, m), 2.89 (3H, sept, *J*=7.0 Hz), and 1.26 (18H, d, *J*=7.0 Hz). ^{13}C NMR (67.5 MHz) δ_C = 172.1 (2C, s), 166.3 (2C, s), 165.9 (2C, s), 158.5 (2C, s), 150.4 (s), 136.7 (2C, s), 136.2 (2C, d), 134.6 (2C, s), 134.3 (2C, d), 126.3 (2C, d), 119.6 (2C, d), 70.8 (4C, t), 70.6 (4C, t), 70.5 (4C, t), 69.8 (4C, t), 38.7 (3C, d), and 23.5 (6C, q). FABMS Found: m/z 841.4388. Calcd for $C_{46}H_{64}O_{14}$ + H: M, 841.4374. **4n** (n = 4) ^{1}H NMR δ_H = 7.82 (2H, d, *J*=9.9 Hz), 7.76 (2H, s), 7.38 (2H, d, *J*=1.8 Hz), 7.06 (2H, dd, *J*=1.8, 9.9 Hz), 4.76 (8H, s), 3.79 (16H, m), 3.73 (16H, m), 2.94 (3H, sept, *J*=7.0 Hz), and 1.30 (18H, d, *J*=7.0 Hz). ^{13}C NMR (67.5 MHz) δ_C = 171.8 (2C, s), 166.2 (2C, s), 165.8 (2C, s), 158.3 (2C, s), 150.4 (s), 136.5 (2C, s), 136.1 (2C, d), 134.5 (2C, s), 134.1 (2C, d), 126.2 (2C, d), 119.5 (2C, d), 70.5 (8C, t), 70.4 (8C, t), 69.6 (4C, t), 38.5 (3C, d), and 23.4 (6C, q). FABMS Found: m/z 929.4913. Calcd for $C_{50}H_{72}O_{16}$ + H: M, 929.4898. **4n** (n = 5) ^{1}H NMR δ_H = 7.79 (2H, d, *J*=9.9 Hz), 7.72 (2H, s), 7.35 (2H, d, *J*=1.8 Hz), 7.02 (2H, dd, *J*=1.8, 9.9 Hz), 4.70 (8H, s), 3.74 (20H, m), 3.68 (20H, m), 2.89 (3H, sept, *J*=7.0 Hz), and 1.26 (18H, d, *J*=7.0 Hz). ^{13}C NMR (67.5 MHz) δ_C = 171.9 (2C, s), 166.2 (2C, s), 165.8 (2C, s), 158.3 (2C, s), 150.4 (s), 136.6 (2C, s), 136.1 (2C, d), 134.5 (2C, s), 134.2 (2C, d), 126.3 (2C, d), 119.5 (2C, d), 70.5 (10C, t), 70.4 (10C, t), 69.6 (4C, t), 38.5 (3C, d), and 23.4 (6C, q). FABMS Found: m/z 1017.5414. Calcd for $C_{54}H_{80}O_{18}$ + H: M, 1017.5423.

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