

Synthesis of *cis-transoid-cis-* and *cis-cisoid-cis-*Tetracyclo[6.6.0.0^{1,11}.0^{3,7}]-tetradecan-12-ones via Novel Rearrangement

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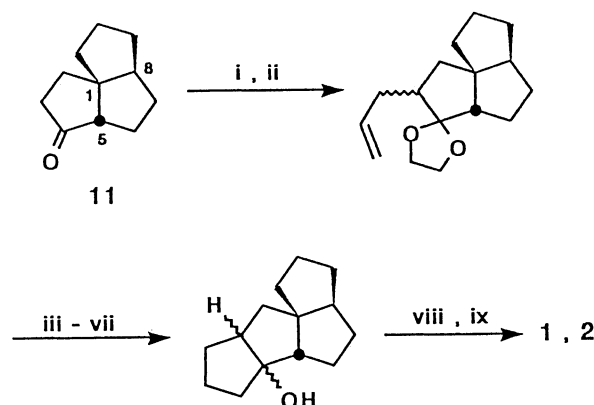
Synopsis. A new type of tetracyclic compounds, *cis-transoid-cis-* and *cis-cisoid-cis-*tetracyclo[6.6.0.0^{1,11}.0^{3,7}]-tetradecan-12-ones, having a tetraquinane framework, has been synthesized by the novel acid-catalyzed rearrangement.

Considerable attention has been paid on fused five-membered ring system (tetraquinanes) of tetracyclo[6.6.0.0^{1,11}.0^{3,7}]-tetradecane (**1** and **2**) skeleton because of its unique structure and the isolation of antibiotic diterpenes possessing this skeleton.¹⁾ Recently we have developed an efficient method for constructing the angularly fused triquinane ketones through the novel rearrangement of the fused 5-6-4 ketones and have applied it to the total syntheses of some triquinane natural products.²⁾ As further extension of our work, we disclose here the synthesis of the title compounds **3** and **4** having the tetraquinane framework by the novel rearrangement of the fused 5-5-6-4 ketones, *cis-transoid-cis-* and *cis-cisoid-cis-*tetracyclo[6.6.0.0^{1,12}.0^{2,6}]-tetradecan-11-ones (**5** and **6**).

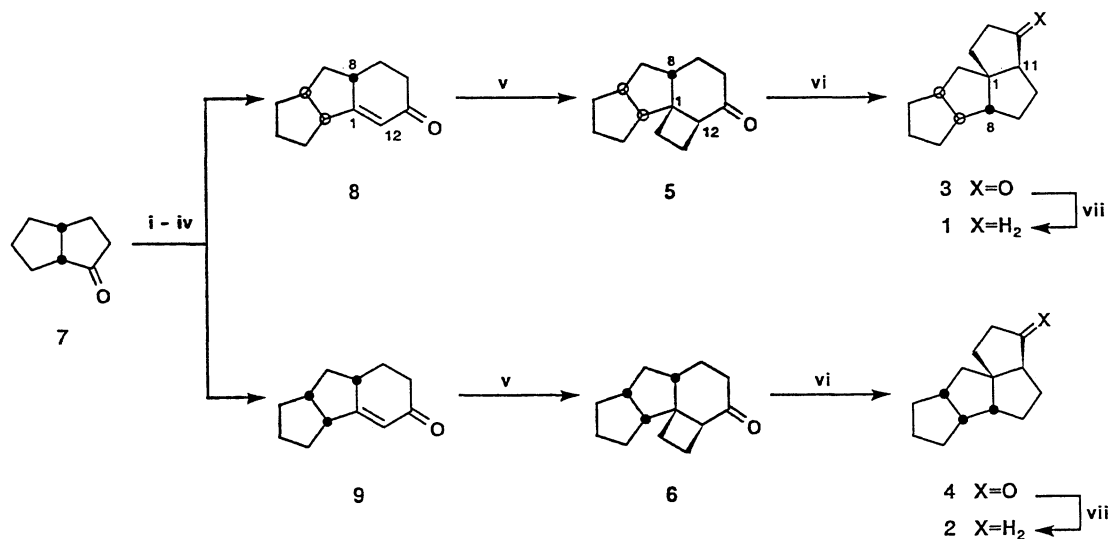
The cyclobutyl ketones **5** and **6** were prepared readily from the known diquinane ketone, bicyclo[3.3.0]-octan-2-one (**7**),³⁾ by the method described previously (Scheme 1);^{2a)} reaction of the silyl enol ether of **7** with 2-methyl-2-vinyl-1,3-dioxolane followed by hydrolysis and condensation gave two tricyclic enones **8** and **9** in 26% and 32% yields, respectively. Photocycloaddition of **9** to ethylene afforded the tetracyclic ketone **6** in 78%

yield while the same reaction of **8** was sluggish to give the ketone **5** in 26% yield. The stereochemistry of **5** and **6** was unambiguously established based on the single-crystal X-ray analysis of the *p*-bromobenzoate **10** derived from **6** by reduction and esterification (Fig. 1).

The rearrangement of **5** and **6** with AlCl₃ proceeded smoothly to give the desired tetraquinane ketones **3** and **4** in 96% and 90% yields, respectively. The tetra-



Scheme 2. i) LDA, allyl bromide, ii) TsOH·H₂O, ethylene glycol, iii) B₂H₆, NaOH, H₂O₂, iv) MsCl, Et₃N, v) LiBr, vi) NaI, vii) Mg, HgCl₂, viii) (EtO)₂POCl, TMEDA, ix) Li, EtNH₂, *t*-BuOH.



Scheme 1. i) LDA, TMSCl, ii) 2-Methyl-2-vinyl-1,3-dioxolane, TiCl₄, Ti(O*i*-Pr)₄, iii) 10% HCl, iv) KOH, v) *hν*, CH₂=CH₂, vi) AlCl₃, vii) N₂H₄, KOH.

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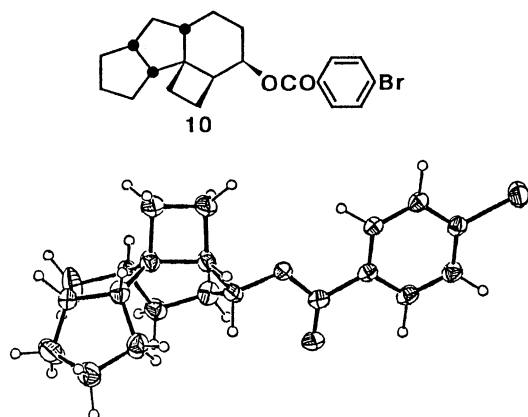


Fig. 1. Molecular structure of *p*-bromobenzoate **10**.

quinane structures were confirmed by comparison of the hydrocarbons **1** and **2** derived from **3** and **4** with the authentic samples prepared independently from tricyclo[6.3.0.0^{1,5}]undecan-4-one (**11**)^{2a} using the procedure reported previously (Scheme 2).⁴ Further application of this rearrangement to the construction of other unique carbon skeletons is in progress.

Experimental

All boiling and melting points were uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer as liquid films unless otherwise stated. ¹H NMR (90 or 400 MHz) and ¹³C NMR (22.5 or 100 MHz) spectra were obtained on a JEOL JNM-FX-90Q or a JEOL JNM-GSX-400 spectrometer in CDCl₃. Mass spectra (MS) were measured with a JEOL JMS-DX303 spectrometer. The technique of chromatography were the same as were used in the previous work.^{2a}

cis-transoid-cis and **cis-cisoid-cis-1,12-Didehydrotricyclo[6.4.0.0^{2,6}]dodecan-11-ones** (**8** and **9**). To a solution of lithium diisopropylamide (LDA) prepared from diisopropylamine (6.25 ml, 44.4 mmol) and BuLi (34.1 ml, 44.4 mmol) in hexane in dry tetrahydrofuran (THF) (30 ml) was added dropwise a solution of **7**³ (5.0 g, 40.3 mmol) in dry THF (45 ml) at -78°C during 20 min under a nitrogen atmosphere. The solution was stirred for 30 min at -78°C and then trimethylsilyl chloride (TMSCl) (11.0 ml, 86.6 mmol) was added. The mixture was warmed to room temperature. A cold NH₄Cl solution was added and the mixture was extracted with ether. The combined organic phase was washed with brine and dried over MgSO₄. Evaporation of the solvent followed by distillation of the crude product under reduced pressure gave the silyl enol ether (7.21 g, 91%): bp 69–70 $^{\circ}\text{C}/800$ Pa; IR 3030, 1640, 1250, 850 cm^{-1} . Reaction of the silyl enol ether (3.73 g, 19.1 mmol) with 2-methyl-2-vinyl-1,3-dioxolane (2.61 g, 22.9 mmol) in the presence of titanium (IV) chloride (TiCl₄) (4.18 ml, 38.1 mmol) and titanium (IV) isopropoxide (Ti(O*i*-Pr)₄) (11.4 ml, 38.1 mmol) followed by hydrolysis in 10% HCl (20 ml) and THF (20 ml) were performed as described previously^{2a} to give the recovered **7** (0.48 g) and the diketones (2.32 g, 82%) after flash chromatography (20% ether–petroleum ether): IR 1730, 1710 cm^{-1} . Reaction of the diketones (2.0 g, 10.3 mmol) with potassium hydroxide (KOH) (1.74 g, 30.9 mmol) in ethyl alcohol (17 ml) was done as described previously^{2a} to give **8** (0.64 g, 35%) and **9** (0.78 g, 43%) after column chromatography on silica gel (7% ether–petroleum ether). **8**: IR 1660, 1190, 860 cm^{-1} ; ¹H NMR δ =1.1–3.2 (m, 15H), 5.80 (s, 1H);

¹³C NMR δ =27.5 (t), 29.2 (t), 34.1 (t), 35.4 (t), 37.0 (t), 38.2 (t), 39.8 (d), 41.7 (d), 48.9 (d), 121.3 (d), 179.4 (s), 199.4 (s); MS *m/z* (%) 176 (*M*⁺, 47), 148 (100), 107 (38). Found: *m/z* 176.1201. Calcd for C₁₂H₁₆O: *M*, 176.1202. **9**: IR 1660, 1190, 860 cm^{-1} ; ¹H NMR δ =0.80 (dt, *J*=10, 12 Hz, 1H), 1.2–3.2 (m, 14H), 5.82 (s, 1H); ¹³C NMR δ =24.9 (t), 28.9 (t), 31.5 (t), 32.4 (t), 36.6 (t), 38.9 (t), 41.8 (d), 43.4 (d), 47.9 (d), 121.0 (d), 178.8 (s), 199.3 (s); MS *m/z* (%) 176 (*M*⁺, 62), 148 (100), 134 (38), 107 (44). Found: C, 81.45; H, 9.17%. Calcd for C₁₂H₁₆O: C, 81.77; H, 9.15%.

cis-transoid-cis-Tetracyclo[6.6.0.0^{1,12}.0^{2,6}]tetradecan-11-one (**5**). Irradiation of **8** (704 mg, 4.0 mmol) in dichloromethane (CH₂Cl₂) (200 ml) for 20 h was performed as described previously^{2a} to give **5** (200 mg, 26%) and the recovered **8** (30 mg) after column chromatography on alumina (4% ether–petroleum ether): IR 1700 cm^{-1} ; ¹H NMR δ =1.0–2.8 (m); ¹³C NMR δ =21.1 (t), 25.0 (t), 26.4 (t), 26.7 (t), 29.4 (t), 34.3 (t), 35.2 (t), 35.9 (t), 40.8 (d), 42.2 (d), 50.9 (d), 52.7 (d), 54.4 (s), 214.5 (s); MS *m/z* (%) 204 (*M*⁺, 45), 176 (44), 175 (42), 148 (100), 134 (35), 91 (41). Found: C, 81.98; H, 9.95%. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87%.

cis-cisoid-cis-Tetracyclo[6.6.0.0^{1,12}.0^{2,6}]tetradecan-11-one (**6**). Irradiation of **9** (2.90 g, 16.5 mmol) in CH₂Cl₂ (280 ml) for 6 h was done as described previously^{2a} to give **6** (2.57 g, 78%) and the recovered **9** (0.8 g) after column chromatography on alumina (4% ether–petroleum ether): IR 1700 cm^{-1} ; ¹H NMR δ =0.8–2.9 (m); ¹³C NMR δ =20.2 (t), 25.0 (t), 26.0 (t), 28.7 (t), 31.9 (t), 33.0 (t), 35.0 (t), 35.6 (t), 42.3 (d), 45.0 (d), 46.6 (d), 53.2 (s), 55.0 (d), 213.6 (s); MS *m/z* (%) 204 (*M*⁺, 40), 174 (64), 148 (100), 134 (43). Found: C, 81.97; H, 9.98%. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87%.

cis-transoid-cis-Tetracyclo[6.6.0.0^{1,11}.0^{3,7}]tetradecan-12-one (**3**). Reaction of **5** (100 mg, 0.49 mmol) with aluminum (III) chloride (AlCl₃) (130 mg, 0.98 mmol) in CH₂Cl₂ (5 ml) for 3.5 h was performed as described previously^{2a} to give **3** (96 mg, 96%) after flash chromatography (5% ether–petroleum ether): IR 1730 cm^{-1} ; ¹H NMR δ =1.2–2.8 (m); ¹³C NMR δ =25.4 (t), 30.2 (t), 32.1 (t), 33.5 (t), 33.5 (t), 33.7 (t), 39.7 (t), 44.2 (d), 46.9 (t), 52.8 (d), 58.9 (d), 59.3 (d), 61.0 (s), 222.9 (s); MS *m/z* (%) 204 (*M*⁺, 100), 175 (66), 147 (34), 96 (46). Found: C, 82.33; H, 9.99%. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87%.

cis-cisoid-cis-Tetracyclo[6.6.0.0^{1,11}.0^{3,7}]tetradecan-12-one (**4**). Reaction of **6** (1.71 g, 8.38 mmol) with AlCl₃ (2.24 g, 16.8 mmol) in CH₂Cl₂ (44 ml) for 3.5 h was done as described previously^{2a} to give **4** (1.54 g, 90%) after flash chromatography (5% ether–petroleum ether): IR 1730 cm^{-1} ; ¹H NMR δ =1.0–2.8 (m); ¹³C NMR δ =27.3 (t), 28.1 (t), 29.3 (t), 30.4 (t), 31.5 (t), 32.7 (t), 37.7 (t), 44.3 (t), 45.6 (d), 45.9 (d), 53.4 (d), 57.1 (d), 62.6 (s), 222.8 (s); MS *m/z* (%) 204 (*M*⁺, 100), 175 (82), 147 (58), 80 (42), 67 (41). Found: C, 82.12; H, 9.95%. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87%.

cis-transoid-cis-Tetracyclo[6.6.0.0^{1,11}.0^{3,7}]tetradecane (**1**). Wolff-Kishner reduction of **3** (75 mg, 0.37 mmol) with 80% hydrazine hydrate (0.22 ml, 3.68 mmol) and KOH (144 mg, 2.57 mmol) in diethylene glycol (2 ml) was performed as described previously^{2a} to give **1** (50 mg, 70%) after flash chromatography (petroleum ether): ¹³C NMR δ =25.9 (t), 27.3 (t), 32.4 (t), 33.3 (t), 33.7 (t), 34.8 (t), 41.2 (t), 44.4 (d), 48.1 (t), 51.1 (d), 51.9 (d), 59.2 (d), 64.0 (s); MS *m/z* (%) 190 (*M*⁺, 53), 162 (100), 147 (78), 78 (28). Found: C, 88.28; H, 11.66%. Calcd for C₁₄H₂₂: C, 88.35; H, 11.65%.

cis-cisoid-cis-Tetracyclo[6.6.0.0^{1,11}.0^{3,7}]tetradecane (**2**). Wolff-Kishner reduction of **4** (150 mg, 0.74 mmol) with 80% hydrazine hydrate (0.45 ml, 7.35 mmol) and KOH (289 mg, 5.15 mmol) in diethylene glycol (4 ml) was done as described previously^{2a} to give **2** (95 mg, 68%) after flash chromatography (petroleum ether): ¹³C NMR δ =26.0 (t), 27.6 (t), 28.8 (t), 30.0 (t), 32.1 (t), 33.5 (t), 36.1 (t), 39.9 (t), 44.0 (d), 46.0 (t),

46.7 (d), 48.9 (d), 55.6 (d), 65.3 (s); MS m/z (%) 190 (M^+ , 28), 162 (98), 161 (37), 147 (100). Found: C, 88.33; H, 11.82%. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65%.

Synthesis of Authentic Samples of 1 and 2. Authentic samples were prepared by the method similar to that reported previously.⁴⁾ To a solution of LDA (2.4 mmol) prepared as described above in dry THF (5 ml) was added a solution of tricyclo[6.3.0.0^{1,5}]undecan-4-one (**11**)^{2a)} (328 mg, 2 mmol) and hexamethylphosphoric triamide (0.38 ml, 2.2 mmol) in dry THF (5.0 ml) at -78°C under a nitrogen atmosphere. The solution was stirred at -78°C for 1 h and then allyl bromide (1.67 ml, 20 mmol) was added. The solution was stirred at -78°C for 1 h and poured into NH_4Cl solution. The mixture was extracted with ether and the combined organic phase was dried (MgSO_4). Evaporation of the solvent followed by flash chromatography (4% ether-petroleum ether) of the crude product gave the α -allyl ketones (318 mg, 90%) and the recovered **11** (41 mg): IR 3050, 1730, 1630, 900 cm^{-1} . Reaction of the ketones (318 mg, 1.57 mmol), ethylene glycol (0.44 ml, 7.87 mmol), and *p*-toluenesulfonic acid monohydrate ($\text{TsOH} \cdot \text{H}_2\text{O}$) (8 mg, 0.04 mmol) in toluene (10 ml) for 2.5 h gave the acetals: IR 3050, 1630, 900 cm^{-1} . Hydroboration of the crude acetals with diborane generated from NaBH_4 (48 mg, 1.26 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (0.17 ml, 1.57 mmol) in dry THF (7 ml) and the subsequent oxidation with 30% H_2O_2 –10% NaOH solution gave the alcohols: IR 3350 (br), 1040 cm^{-1} . Mesylation of the crude alcohols with methanesulfonyl chloride (MsCl) (0.36 ml, 4.69 mmol) and triethylamine (1.10 ml, 7.85 mmol) in dry ether (2 ml) gave the mesylates: IR 1345, 1180, 1040 cm^{-1} . Reaction of the crude mesylates with lithium bromide (410 mg, 4.72 mmol) in acetone (8 ml) gave the bromides (343 mg, 76% from **11**) after flash chromatography (8% ether-petroleum ether): IR 1730 cm^{-1} . Reaction of the above bromides (343 mg, 1.20 mmol) with sodium iodide (270 mg, 1.81 mmol) in acetone (3 ml) gave the iodides (333 mg, 83%) after flash chromatography (8% ether-petroleum ether): IR 1730 cm^{-1} . Reaction of the above iodides (333 mg, 1.00 mmol) with magnesium (49 mg, 2.01 mmol) and mercury(II) chloride (HgCl_2) (8 mg, 0.03 mmol) in dry THF (6 ml) gave the inseparable alcohols (67 mg, 32%) after flash chromatography (30% ether-petroleum ether): IR 3350 (br), 1000 cm^{-1} ; $^1\text{H NMR}$ δ =1.0–2.6 (m); MS m/z (%) 206 (M^+ , 50), 177 (72), 164 (100), 98 (82). Found: C, 81.30; H, 10.71%. Calcd for $C_{14}H_{22}\text{O}$: C, 81.50; H, 10.75%. Reaction of the above alcohols (60 mg, 0.29 mmol) with BuLi (0.39 ml, 0.58 mmol) and *N,N,N',N'*-tetramethyl-1,4-butanediamine (TMEDA) (0.26 ml, 1.74 mmol) followed by addition of diethyl phosphorochloridate ($(\text{EtO})_2\text{POCl}$) (0.05 ml, 0.32 mmol) gave the diethyl phosphates: IR 1250, 1010 cm^{-1} . Reaction of the crude phosphates with lithium (20 mg, 2.9 mmol) in dry diethylamine (EtNH_2) (13 ml) followed by addition of *t*-butyl alcohol (*t*-BuOH) (0.1 ml, 1.2 mmol) in dry THF (3 ml) gave the recovered alcohols (28 mg) (elution with 30% ether-petroleum ether) and two hydrocarbons (9 mg, 30% and 7 mg, 24%) (elution with petroleum ether) after flash chromatography, whose $^{13}\text{C NMR}$ spectra were identical with those of **1** and **2**, respectively.

cis-cisoid-cis-Tetracyclo[6.6.0.0^{1,12}.0^{2,6}]tetradecan-11-yl *p*-Bromobenzoate (10). Reduction of **6** (173 mg 0.85 mmol) with LiAlH_4 (48 mg, 1.27 mmol) in dry ether (15 ml) was performed as described previously^{2a)} to give two alcohols (130 mg, 74% and 19 mg, 11%) after flash chromatography

(30% ether-petroleum ether). **Major:** IR 3300 (br), 1060, 1020, 955, 940 cm^{-1} . **Minor:** IR 3300 (br), 1060, 950 cm^{-1} . Esterification of the major alcohol (130 mg, 0.63 mmol) with *p*-bromobenzoyl chloride (347 mg, 1.58 mmol) in pyridine (4 ml) was done as described previously^{2a)} to give **10** (192 mg, 78%) after flash chromatography (5% ether-petroleum ether): mp 85 – 86°C (recrystallized from hexane); IR (KBr) 1710, 1580, 1260, 1170, 1110, 1100, 1005, 755 cm^{-1} ; $^1\text{H NMR}$ δ =1.16 (m, 1H), 1.2–1.4 (m, 4H), 1.6–2.0 (m, 11H), 2.15 (dt, J =13.8, 9.1 Hz, 1H), 2.22 (dd, J =18.1, 9.1 Hz, 1H), 2.45 (m, 1H), 2.85 (m, 1H), 5.01 (dt, J =11.6, 5.8 Hz, 1H), 7.54 (d, J =8.5 Hz, 2H), 7.85 (d, J =8.5 Hz, 2H); $^{13}\text{C NMR}$ δ =16.4 (t), 27.2 (t), 27.2 (t), 30.3 (t), 31.5 (t), 35.5 (t), 35.8 (t), 36.5 (t), 38.9 (d), 43.3 (d), 46.0 (d), 54.1 (s), 56.7 (d), 73.6 (d), 127.7 (s), 129.9 (s), 131.0 (d, 2C), 131.6 (d, 2C), 165.4 (s); MS m/z (%) 390 (M^+ +2, trace), 388 (M^+ , trace), 188 (66), 160 (100). Found: C, 64.90; H, 6.42; Br, 20.48%. Calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2\text{Br}$: C, 64.79; H, 6.47; Br, 20.52%.

X-Ray Analysis of 10. Crystal data: $\text{C}_{21}\text{H}_{25}\text{O}_2\text{Br}$, M_r 389.31, triclinic, space group $P\bar{1}$, a =10.314(2), b =13.214(2), c =7.699(1) Å, β =95.23(2) $^\circ$, V =930.02(2) Å³, D_{calcd} =1.395 g cm^{-3} , Z =2. Diffraction intensities were measured on a Rigaku four-circle diffractometer by using Ni-filtered $\text{Cu K}\alpha$ radiation (λ =0.5617 Å) by θ - 2θ scan technique. A total of 2754 reflections was collected up to 2θ =120 $^\circ$, among which 2535 were observed reflections. The crystal structure was solved by the direct method⁵⁾ and refined by the full matrix least-squares method⁶⁾ to the R index of 0.058. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined isotropically.⁷⁾

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- 7) Tables of the bond lengths, bond angles, observed and calculated structure factors, atomic coordinates, and anisotropic thermal parameters are deposited as Document No. 8944 at the Office of the Editor of Bull. Chem. Soc. Jpn.