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Alternative Syntheses of the New D_{2d} Symmetric Tetramethyl Tricyclo-[3.3.0.0^{3,7}]octane-1,3,5,7-tetracarboxylate

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Abstract: Two alternative syntheses of the new D_{2d} symmetric tetramethyl tricyclo[3.3.0.0^{3,7}]octane-1,3,5,7-tetracarboxylate from the known dimethyl 3,7-dioxo-*cis*-bicyclo-[3.3.0]octane-1,5-dicarboxylate and 1,5-(2,2′-biphenylene)-*cis*-bicyclo[3.3.0]octane-3,7-dione are described.

Compounds containing the tricyclo[3.3.0.0^{3,7}]octane skeleton (bisnoradamantane, "natane"[1] or "stellane"[2]) are very fascinating for both synthetically and theoretically oriented organic chemists due to their intriguing physical properties and interesting reactivity.[3] For example, although stellane has an all five-membered ring structure, it contains two enantiomeric twist-boat cyclohexane unities. Altogether, stellane is an achiral compound with D_{2d} symmetry. The first synthesis of a compound with this framework was reported by Webster and Sommer in 1964,[4] and a more general approach to this skeleton was developed by Sauers in the early 1970s.[5] For more than 20 years, our research group has been engaged in a project directed to the synthesis, reactivity, and applications of these kinds of bisnoradamantane derivatives.[6−8] We have developed two general entries to this strained carbocyclic skeleton,[7] and we have generated, trapped, and dimerized several highly pyramidalized alkenes embedded into this bisnoradamantane skeleton as intermediates for more complex polycyclic structures.[8]

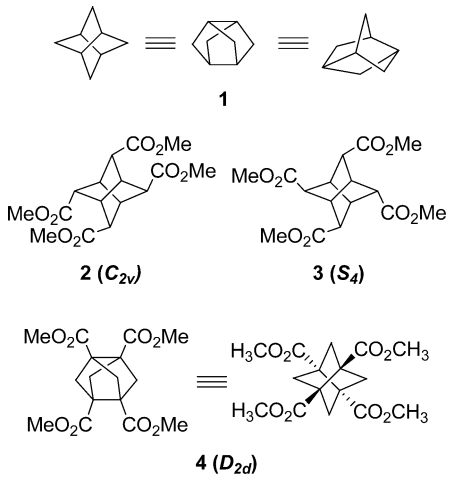

FIGURE 1. Structures of stellane, **1**, and of several derivatives thereof.

More than 20 years ago, Park and Paquette published the synthesis of two highly symmetric tetramethyl tricyclo-[3.3.0.0^{3,7}]octane-2,4,6,8-tetracarboxylates, the C_{2v}-symmetric derivative **2** and the S_4-symmetric compound **3**.[9] In this paper, we wish to report two alternative syntheses of the isomeric new tetramethyl tricyclo[3.3.0.0^{3,7}]octane-1,3,5,7-tetracarboxylate, **4**, having D_{2d} symmetry (Figure 1).

Some time ago, we described the synthesis of dimethyl tricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylate, **6a**, and its 3,7-dimethyl derivative, **6b**, by iodine oxidation of the bis-lithium enolate derived from the corresponding dimethyl *cis*-bicyclo[3.3.0]octane-3,7-dicarboxylates **5a** and **5b**, respectively.[7a] On the other hand, we have recently used the 2,2′-biphenylene subunit as two latent carboxyl

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(1) This name was first coined by Windhorst to emphasize the relationship of its four-pointed-star appearance to the NATO symbol: Windhorst, J. C. A. Ph.D. Dissertation, University of Leiden, 1975.

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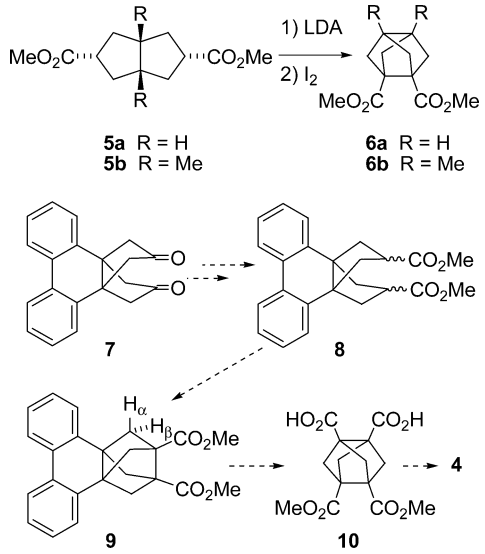
SCHEME 1. Proposed Synthesis of Tetraester 4



groups. This transformation was performed via RuO_4-promoted oxidation using a catalytic amount of $RuCl_3 \cdot H_2O$ and excess NaClO in a two-phase system ($CH_3CN-CH_2Cl_2/H_2O$).[8f] Thus, we envisaged that conversion of known diketone **7** to the tetraester **8** could be carried out via (i) homologation of **7** to diester **8**, (ii) cyclization of **8** to diester **9**, (iii) RuO_4-promoted oxidation of **9** to **10**, and (iv) esterification of **10** to afford tetraester **4** (Scheme 1).

To homologate diketone **7**,[7c] it was transformed into a mixture of the bis-vinyl iodides *syn*- and *anti*-**12** in an approximate ratio of 1:1.1 (^{1}H NMR), via the corresponding bis-hydrazone, **11**, following the Barton procedure, in 68% overall yield.[10] Then, palladium(0)-catalyzed methoxycarbonylation[11] of **12** afforded **13** in 73% yield, as a mixture of syn and anti regioisomers in an approximate ratio of 1:1.1 (^{1}H NMR), equal to the ratio of the regioisomeric starting diiodides. Catalytic hydrogenation (Pd/C) of the mixture of *syn*- and *anti*-**13** gave a mixture of *endo,endo*-, *exo,endo*-, and *exo,exo*-**8** in an approximate ratio of 73:23:4 (^{1}H NMR) in 90% yield. An analytical sample of pure *endo,endo*-**8** was obtained by crystallization from methanol. The stereochemistry of this compound was unequivocally established by X-ray diffraction analysis.[12]

To fully characterize the other two stereoisomers, we epimerized the above stereoisomeric mixture by reaction with sodium methoxide in anhydrous methanol, thus obtaining a new mixture of *endo,endo*-, *exo,endo*-, and *exo,exo*-**8** in an approximate ratio of 1:3.5:2.1 (^{1}H NMR, see the Supporting Information for details). Column chromatography of this mixture followed by crystallization of selected fractions in methanol allowed us to obtain and to fully characterize highly enriched mixtures of *exo,endo*- and *exo,exo*-**8**. The configuration of *exo,exo*-**8** was also established unequivocally by single-crystal X-ray crystallographic analysis.[12]

Reaction of a mixture of diesters **8** (obtained by crystallization from methanol of the hydrogenation mixture of **13**; approximate ratio of *endo,endo*-, *exo,endo*-, and *exo,exo*-**8**, 170:6:1 by ^{1}H NMR) with 2 equiv of LHMDS in anhydrous THF followed by reaction of the corresponding bis-enolate with 1 equiv of iodine gave **9** in 68% yield. Interestingly, the yield of **9** was lower when LDA was used as the base, as for the synthesis of **6a** and **6b**.[7a]

Oxidation of the 2,2′-biphenylene subunit of **9** to two carboxyl groups was carried out with RuO_4 by using a catalytic amount of $RuCl_3 \cdot H_2O$ and an excess of an aqueous solution of NaClO (4.25%) in a two-phase system ($CH_3CN-CH_2Cl_2/H_2O$) for ca. 4 days.[8f] In this way, diacid **10** was obtained in 68% yield of crystallized product, which was esterified with an ethereal solution of diazomethane to give the title compound **4**, in 89% yield (Scheme 2). The simplicity of the ^{1}H (2 singlets) and ^{13}C (4 signals) NMR spectra of **4** nicely prove the symmetry of the compound, whose structure was also established by X-ray diffraction analysis.[12] The seven-step reaction sequence from diketone **7** to tetraester **4** proceeds in 17% overall yield.

Also, an alternative synthesis of **4** was developed starting from the known dioxodiester **14** (Scheme 3).[6a,13] Attempts to carry out the conversion of **14** to the corresponding bis-hidrazone using either basic or acidic conditions failed, probably due to the instability of the ester groups toward hydrazine under the reaction conditions. Thus, homologation of **14** as carried out for **7** was not possible.

Alternatively, **14** was homologated via the corresponding mixture of bis-enol triflates, **15**. Reaction of **14** with KHMDS and *N*-phenyltriflimide under conditions similar to those previously used by Deslongchamps et al. in a related substrate[14] gave a mixture of *anti*- and *syn*-**15** in an approximate ratio of 10:1 (^{1}H NMR), in 88% yield.

Worthy of note, *anti*-**15** was obtained as the main product of this reaction. This result may be due to equilibration of the intermediate bis-enolates, with the *anti*-bis-enolate most likely being favored due to reduced electrostatic interactions vis-à-vis the corresponding syn compound. Palladium-mediated methoxycarbonylation of **15** yielded a mixture of *anti*-**16**, *syn*-**16**, and trimethyl *cis*-bicyclo[3.3.0]octa-2,6-diene-1,3,5-tricarboxylate (in an approximate ratio of 19:2:1, ^{1}H NMR, 78% approximate yield) which was used as such in the next step.

Catalytic hydrogenation of the above mixture produced tetraester **17** as a mixture of two stereoisomers (relative area by GC/MS 96.5/3.5, 96% yield after filtration through a short pad of Celite). Crystallization of the above mixture from diethyl ether gave pure *exo,exo*-**17**, whose stereochemistry was unequivocally established by single-crystal X-ray crystallographic analysis.[12]

Curiously, hydrogenation of diester **13** afforded a mixture of three stereoisomers in which *endo,endo*-**8** predominates. The stereoselectivity observed to accompany hydrogenation of **13** might reflect the lower steric hindrance of the flat 2,2′-biphenylene group of **13**, which

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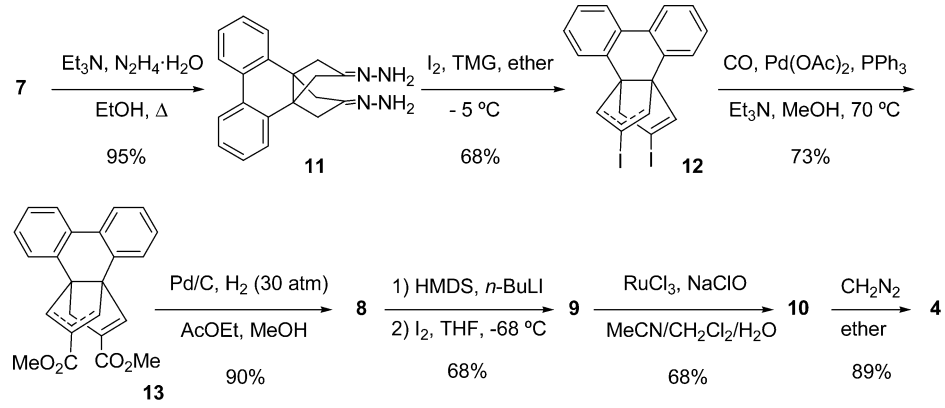
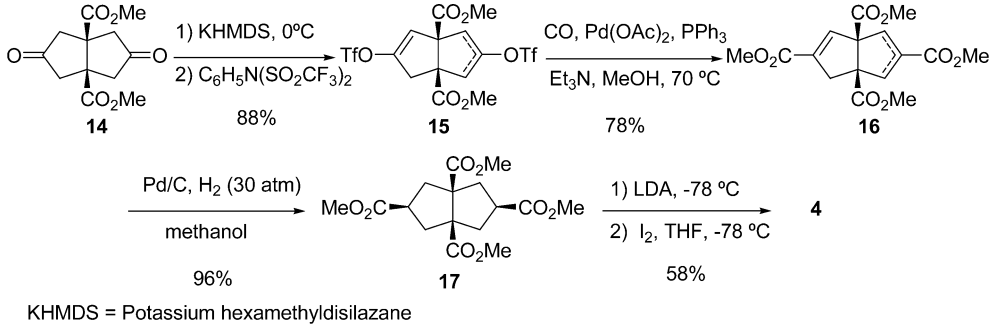
SCHEME 2. Synthesis of Tetraester 4 from Diketone 7



SCHEME 3. Synthesis of Tetraester 4 from Dioxodiester 14



favors the transfer of hydrogen by the exo faces of the carbon−carbon double bonds. Similarly, the freely rotating methoxycarbonyl groups in **16** may hinder hydrogenation from the exo faces, thus giving mainly *exo,exo*-**17**.

Reaction of diester **17** with 2.4 equiv of LDA in anhydrous THF followed by reaction of the corresponding bis-enolate with 1.2 equiv of iodine gave **4** in 58% yield. This alternative synthesis of tetraester **4** consists of only four steps from the known diketone **14** and provides **4** in 38% overall yield. Although it is three steps shorter than the previously developed approach, the low yield of the synthesis of the starting diketone **14** (16% yield) from dimethyl 3-oxoglutarate and disodium dihydroxytartrate[13] (which no longer is available commercially) together with the high cost of *N*-phenyltriflimide render the first approach more practical for the synthesis of tetraester **4**.

In conclusion, two alternative syntheses of the new D_{2d} symmetric tetraester **4** have been developed. Although longer, the approach starting from phenanthrenequinone seems to be more practical than that starting from **14**. Work is underway to use the novel bisnoradamantane derivatives herein described in the synthesis of more complex polycyclic compounds.

Experimental Section

General Methods.[12] **Dimethyl 3,7-(2,2′-Biphenylene)-tricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylate (9).** A solution of LHMDS was prepared by reacting a solution of HMDS (0.7 mL, 3.19 mmol) in anhyd THF (3.5 mL) with *n*-butyllithium (1.2 mL, 2.5 M in hexanes, 3.0 mmol) at −68 °C (inside temperature) under argon for 1 h. Then, a solution of a stereoisomeric mixture of diesters **8** (ratio of *endo,endo*-, *endo,exo*-, and *exo,exo*-**8** = 170:6:1), obtained by crystallization of the mixture from the hydrogenation of **13** (0.5 g, 1.33 mmol) in anhyd THF (3.5 mL), was added dropwise keeping the temperature at −68 °C. Stirring was continued for 1 h at this temperature, and then a solution of iodine (0.34 g, 1.33 mmol) in anhyd THF (8 mL) was added dropwise. The mixture was maintained 1 h at −68 °C and then allowed to warm to room temperature over 15 h. The mixture was acidified with HCl (10% aqueous solution) until pH 2 and the THF was removed in vacuo. The remaining aqueous phase was extracted with diethyl ether (4 × 15 mL), and the combined organic extracts were washed with $Na_2S_2O_3$ (10% aqueous solution, 3 × 15 mL) and brine (2 × 15 mL), dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure to furnish a pale brown solid (0.5 g). Column chromatography of this residue (silica gel, 12 g, hexanes/ethyl acetate, 9/1) gave diester **9** (0.34 g, 68% yield). The analytical sample of **9** was obtained by crystallization from ethyl acetate/hexanes: mp 180−181 °C; IR (KBr) 1728 cm^{-1}; ^{1}H NMR δ 2.14 [d, J = 7.3 Hz, 4 H, 2(4,6,8)-H$_\alpha$], 2.56 [d, J = 7.3 Hz, 4 H, 2(4,6,8)-H$_\beta$], 3.70 (s, 6 H, CH_3O), 7.20−7.26 [complex signal, 6 H, 3′(3″)-H, 4′(4″)-H and 5′(5″)-H], 7.93−7.96 [m, 2 H, 6′(6″)-H]; ^{13}C NMR (100.6 MHz) δ 49.1 [C, C3(7)], 51.9 (CH_3, CH_3O), 56.2 [C, C1(5)], 58.4 [CH_2, C2(4,6,8)], 123.2 [CH, C6′(6″)], 126.8 (CH) and 127.0 (CH) [C3′-(3″) and C5′(5″)], 128.1 [CH, C4′(4″)], 131.1 [C, C1′(1″)], 136.3 [C, C2′(2″)], 172.6 (C, CO_2CH_3); GC/MS (rt 36.90 min), *m*/*z* 375 (20), 374 (M$^{\bullet+}$, 76), 342 [(M − MeOH)$^{\bullet+}$, 42], 314 [(M − HCO_2-Me)$^{\bullet+}$, 69], 286 (53), 283 [(M − HCO_2Me − MeO)$^+$, 56], 255 [(M − HCO_2Me − CO_2Me)$^+$, 99], 254 (50), 229 (44), 228 (47), 215 [(M − HCO_2Me − $C_3H_4CO_2$Me)$^+$, 100). Anal. Calcd for $C_{24}H_{22}O_4$ (374.44): C, 76.99; H, 5.92. Found: C, 76.98; H, 6.05.

3,7-Bis(methoxycarbonyl)tricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylic Acid (10). To a solution of **9** (0.5 g, 1.34 mmol) in CH_2Cl_2 (10 mL), acetonitrile (10 mL), and H_2O (20 mL) was added $RuCl_3$·H_2O (17 mg, 0.08 mmol), and then aqueous NaOCl (175 mL, 4.25% aqueous solution, approximately 100 mmol) was

added dropwise. The flask was stoppered, and the mixture was vigorously stirred at room temperature for 100 h. The organic layer was separated, and the aqueous phase was washed with CH_2Cl_2 (4 × 20 mL), cooled (ice bath), made acidic (pH ≈ 2−3) with 2 N HCl (10 mL), and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give pure **10** as a white solid (0.28 g, 68% yield). An analytical sample of **10** was obtained by crystallization from ethyl acetate/hexanes: mp 238−239 °C; IR (KBr) 3750−2800 (max at 3166), 1738, 1687 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 2.23 [broad s, 8 H, 2(4,6,8)-H], 3.68 (s, 6 H, CH_3O), 4.89 (broad s, 2 H, CO_2H); ^{13}C NMR (CD_3OD) δ 52.6 (CH_3, CH_3O), 53.3 [CH_2, C2(4,6,8)], 58.9 (C) and 59.0 (C), [C1-(5) and C3(7)], 173.0 (C) and 174.4 (C), (CO_2H and CO_2CH_3); GC/MS (rt 15.74 min) *m*/*z* 295 [$(M - OH)^+$, 4], 281 [$(M - CH_3O)^+$, 15], 234 [$(M - HCO_2CH_3 - H_2O)^{\bullet+}$, 56], 195 (32), 190 (44), 163 (48), 162 (42), 131 (41), 119 (44), 103 (90), 91 (40), 77 (79), 65 (47), 59 [$(CO_2CH_3)^+$, 100]. Anal. Calcd for $C_{14}H_{16}O_8$ (312.28): C, 53.85; H, 5.16. Anal. Calcd for $C_{14}H_{16}O_8 \cdot 0.75H_2O$ (325.79): C, 51.61; H, 5.41. Found: C, 51.31; H, 5.02.

Tetramethyl Tricyclo[3.3.0.0^{3,7}]octane-1,3,5,7-tetracarboxylate (4): (a) From Diacid 10. Excess of an ethereal solution of diazomethane was added to **10** (25 mg, 0.1 mmol). The resulting solution was filtered, glacial acetic acid was added to destroy the excess of diazomethane, and the volatile materials were eliminated at reduced pressure to give pure **4** (24 mg, 89% yield).

(b) From Tetraester 17. A solution of LDA was prepared by treating a solution of anhydrous diisopropylamine (1.58 mL, 11.2 mmol) in anhydrous THF (12.2 mL) with *n*-butyllithium (4.5 mL, 2.5 M in hexanes, 11.2 mmol) at −78 °C (bath temperature) under argon for 1 h. Then, a solution of **17** (1.6 g, 4.68 mmol) in anhydrous THF (28 mL) was added dropwise keeping the temperature at −78 °C. Stirring was continued for 1 h at this temperature, and then a solution of iodine (1.42 g, 5.62 mmol) in anhydrous THF (33 mL) was added dropwise. The mixture was maintained 1 h at −78 °C, and then it was allowed to warm to room temperature overnight. The mixture was acidified with HCl (10% aqueous solution) until pH 2, and the THF was removed in vacuo. The remaining aqueous phase was extracted with ethyl acetate (4 × 70 mL), and the combined organic extracts were washed with $Na_2S_2O_3$ (10% aqueous solution, 3 × 70 mL) and brine (2 × 70 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to dryness to furnish a yellow solid (1.81 g), that was triturated with diethyl ether to furnish pure **4** as a white solid (0.92 g, 58% yield): mp 223−225 °C; IR (KBr) 1732 cm^{-1}; ^1H NMR (300 MHz) δ 2.27 (s, 8 H, CH_2), 3.71 (s, 12 H, CH_3O); ^{13}C NMR δ 52.1 [CH_3, 1(3,5,7)-CO_2CH_3], 52.2 [CH_2, C2(4,6,8)], 57.4 [C, C1(3,5,7)], 171.1 [C, 1(3,5,7)-CO_2CH_3]; GC/MS (rt 27.18 min) *m*/*z* 340 ($M^{\bullet+}$, 0.1), 309 [$(M - CH_3O)^+$, 30], 280 [$(M - HCO_2CH_3)^{\bullet+}$, 14], 248 [$(M - HCO_2CH_3 - CH_3OH)^{\bullet+}$, 100], 241 (67), 221 (41), 220 [$(M - 2HCO_2CH_3)^{\bullet+}$, 31], 216 (32), 209 (91), 189 [$(M - 2HCO_2CH_3 - CH_3O)^+$, 80], 177 (41), 161 [$(M - 2HCO_2CH_3 - CO_2CH_3)^+$, 55], 59 [$(CO_2CH_3)^+$, 85]. Anal. Calcd for $C_{16}H_{20}O_8$ (340.33): C, 56.47; H, 5.92. Found: C, 56.12; H, 6.17.

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Supporting Information Available: Experimental procedures and characterization data for compounds **8**, **11**−**13**, and **15**−**17**, including copies of the NMR spectra. Crystallographic information files (CIF) of **4**, *exo*,*exo*-**8**, *endo*,*endo*-**8**, and *exo*,*exo*-**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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