Intramolecular Ring-Opening of Cyclopropanones by Enolate Anions

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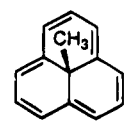
Treatment of *cis*-4a-methyldecalin-2,7-dione with 2 equiv of bromine gave *cis*-3,6(dieq)-dibromo-4a-methyldecalin-2,7-dione (**9**). Dehydrobromination of **9** with $LiBr/Li_2CO_3$ in DMF gave *cis*-6-methylbicyclo[4.4.0]deca-4,7-diene-3,9-dione (**3**). However, dehydrobromination of **9** with DBU in THF gave 1-bromo-5-methyltricyclo[4.4.0.$0^{1,7}$]decane-2,8-dione (**11**). Bromination of *cis*-1-carbomethoxy-2-hydroxy-4a-methylbicyclo[4.4.0]-1-decen-7-one (**7**), with cupric bromide in $CHCl_3$/EtOAc provided *cis*-6(eq)-bromo-1-carbomethoxy-2-hydroxy-4a-methylbicyclo[4.4.0]-1-decen-7-one (**13**), whereas bromination of **7** with 2 equiv of bromine in $CHCl_3$ provided *cis*-6(eq)-bromo-8(eq)-bromo-1-carbomethoxy-2-hydroxy-4a-methylbicyclo[4.4.0]-1-decen-7-one (**14**). Dehydrobromination of **13** with $LiBr/Li_2CO_3$ in DMF resulted in the loss of HBr with the formation of the methyl *cis*-3,4,4a,7,8,8a-hexahydro-2-hydroxy-4a-methyl-7-oxo-1-naphthoate (**16**). However, dehydrobromination of **13** with DBU in THF gave **16** (17%), 7-carbomethoxy-5-methyltricyclo[4.4.0.$0^{1,7}$]decane-2,8-dione (**17**) (41%), and 2-carbomethoxy-1-hydroxy-8-methyltetracyclo[4.4.0.$0^{1,6}$.$0^{2,4}$]decan-5-one (**18**) (40%). Dehydrobromination of the dibromo keto ester **14** gave only the tetracyclic ketol ester **20**. Bromination of keto ester **7** with NBS and triethylamine gave the two epimers of methyl *cis*-3,4,4a,5,6,7,8,8a-octahydro-1-bromo-4a-methyl-2,7-dioxo-1(2*H*)-naphthoate (**15**). Dehydrobromination of **15a/b** with a variety of bases did not give the tricyclic diketo ester **22** but instead resulted in reductive debromination to regenerate starting material **7**. The formation of **17** and **18** from **13** and of **20** from **14** are interpreted as occurring by novel intramolecular nucleophilic ring-openings of cyclopropanone–Favorskii intermediates by enolate anions.

Introduction

In connection with two ongoing projects directed towards the synthesis of 13-methylphenalene (**1**) and "truncatriene (**2**)", we needed *cis*-6-methylbicyclo[4.4.0]-deca-4,7-diene-3,9-dione (**3**) as starting material.[1,2] This paper describes the synthetically useful and mechanistically intriguing results in connection with our new synthesis of the desired diene-dione **3**, which had first been reported by Wenkert et al.[3] They obtained it by treating the chloro keto ester **4** with acid (100% yield) and through the interesting dehydrohalogenation/rearrangement of **5** with KO-t-Bu in DMSO (33% yield). Because it was difficult to obtain and separate the unstable **4** reproducibly in good yields, we undertook a detailed investigation of the reaction of **5** with KOtBu in DMSO in order to optimize the yield of **3** from this rather capricious reaction. The results of that study will be reported elsewhere.[4]

In this paper, we wish to report our somewhat unexpected results of the bromination–dehydrobromination of the known *cis*-4a-methyldecalin-2,7-dione (**6**)[3,5] and the related keto ester **7**. We expected that this sequence would not only lead to a more efficient synthesis of **3**,



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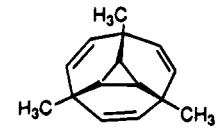

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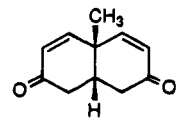

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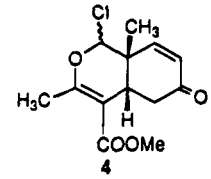

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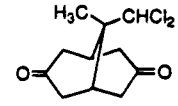

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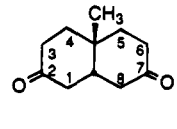
but also would provide direct access to the tricyclic diene-dione **8**, a key intermediate in our approach toward trimethyltruncatriene (**2**).



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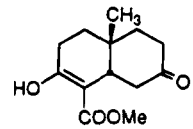

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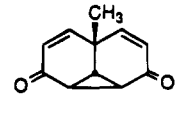

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Results and Discussion

Keto ester **7** was prepared from 4-methylanisole according to the method of Birch[6] and of Taber.[7] Hydrolysis and decarboxylation of **7** in refluxing acetic acid/20%

[⊗] Abstract published in *Advance ACS Abstracts*, January 1, 1995.

(1) Huang, W. Ph.D. Thesis, City University of New York, 1990.

(2) Karimi, S. Ph.D. Thesis, City University of New York, 1991. Presented at the 202nd American Chemical Society National Meeting, San Francisco, April 1992; Organic Poster Session no. 76.

(3) Wenkert, E.; Haviv, F.; Zeithin, E. *J. Am. Chem. Soc.* **1969**, *91*, 2291.

(4) Huang, W.; Karimi, S.; Grohmann, K. To be submitted for publication.

(5) Danishefsky, S.; Chakakamannil, S.; Uang, B. J. *J. Org. Chem.* **1982**, *47*, 2231.

(6) Birch, A. J.; Hill, J. S. *J. Chem. Soc. (C)* **1966**, 419.

(7) Taber, D. F. Ph.D. Thesis, Columbia University, 1974. We thank Professor Taber for making sections of his thesis available to us.

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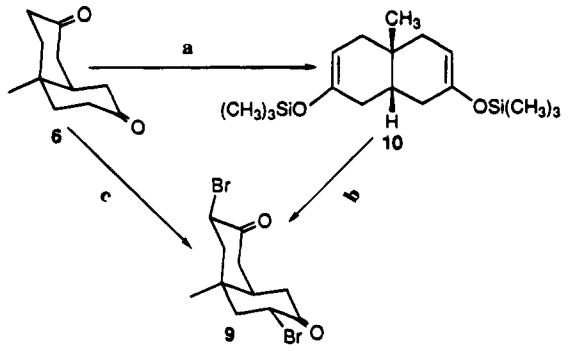
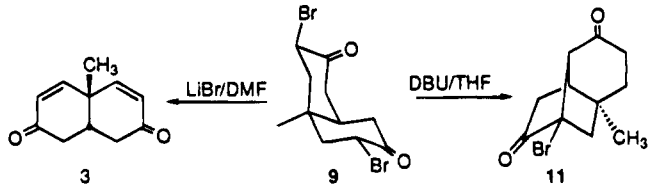
Scheme 1[a]



[a] (a) $(CH_3)_3SiCl/NEt_3/CH_3CN$; (b) NBS/THF; (c) $CuBr_2/CHCl_3$/EtOAc.

Scheme 2



phosphoric acid gave *cis*-4a-methyldecalin-2,7-dione (**6**)[3] in 70% isolated yield.

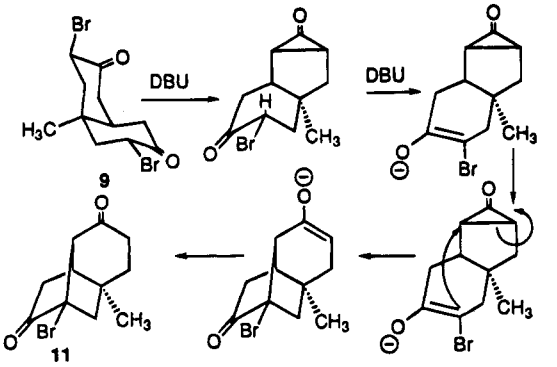
Bromination of **6** with 2 equiv of bromine in glacial acetic acid or with $CuBr_2$ in ethyl acetate/chloroform[8] gave *cis*-3,6(dieq)-dibromo-4a-methyldecalin-2,7-dione (**9**) in 65−70% yield. Alternatively, bis(trimethylsilyl) enol ether **10** was prepared from **6** by to the general procedure of Duboudin.[9] Treatment of **10** with NBS in anhydrous THF also afforded **9** (Scheme 1).

All three methods gave as the major product the same dibromide **9** with both bromine's equatorial. The stereochemistry of **9** was unambiguously established through an X-ray structure analysis.[10] The magnetically nonequivalent protons at C-3 and C-6 each appear as a set of doublets of doublets, the X-part of an ABX-system, with $J_{3(ax)-4(ax)} = J_{6(ax)-5(ax)} = 13$ Hz, and $J_{3(ax)-4(eq)} = J_{6(ax)-5(eq)} = 6.4$ Hz.[11] No bromination was observed at C-1 or C-8 of **6**.

Dehydrobromination of **9** with $LiBr/Li_2CO_3$ in DMF[12] at 120 °C yielded **3** as the only product, isolated in 45% yield (Scheme 2). On the other hand, treatment of **9** with DBU in THF gave *only* 1-bromo-5-methyltricyclo[4.4.0.0^{1,7}]-decane-2,8-dione (**11**) in 48% isolated yield. The structure of **11** was firmly established by X-ray crystallography.[10]

The easy formation of the functionalized tricyclic skeleton in **11** is of considerable interest synthetically as well as mechanistically. Several mechanistic pathways can account for the formation of **11**, but a Favorskii-like route[13,14] involving an intermediate cyclopropanone, followed by an intramolecular nucleophilic attack by a bromo enolate anion on a cyclopropanone carbon with subsequent protonation, most economically fits the experimental results (Scheme 3). However, an alternative S_N2' reaction of the bromo enolate anion with an allylic bromoenol intermediate cannot be ruled out.

Scheme 3



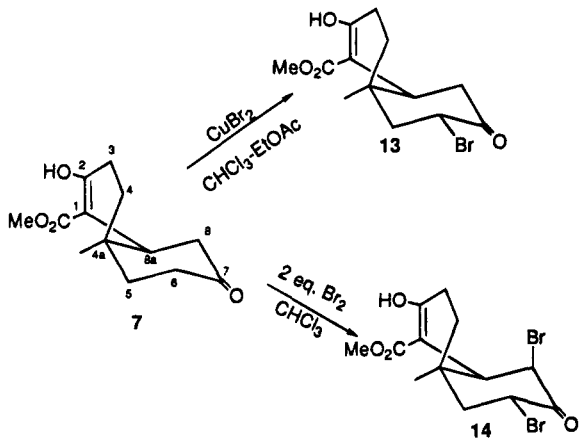
The efficient formation of the tricyclic bromo ketone **11**, a structure common to many terpenes, suggests an application of this reaction to the synthesis of sativene, from the well-known Wieland−Miescher ketone. The results of this work will be reported in a subsequent communication.[2,15]

In an effort to study the scope of this reaction and to include additional functionality, we also investigated the bromination/dehydrobromination of keto ester **7**. Bromination of **7** with cupric bromide in chloroform/ethyl acetate gave monobromide **13** in 80% yield. Treatment of **7** with 2 equiv of bromine in chloroform gave dibromide **14** in 81% yield. This same dibromide also was obtained upon further bromination of **13**. The structures of both bromides were inferred from their IR and NMR spectra. In both bromides, as well as in the starting material, the β-keto ester unit is completely enolized as indicated by one-proton singlets at $\delta = 12.4$ and 12.6. Furthermore, the IR absorption of the α-bromocyclohexanone carbonyl group in **13** appears at 1740 cm^{-1}, 18 cm^{-1} higher than the corresponding vibration in the starting material. This suggests an equatorial bromine in **13**.[16] The ^1H NMR spectrum of **13** displayed for the proton at C-6 the typical doublet of doublets, the X part of an ABX pattern, at $\delta = 4.8$.[17] In **14**, this doublet of doublets is shifted downfield by 0.73 ppm to 5.53, which suggests that an axial bromine at C-8 is causing 1,3-diaxial deshielding.

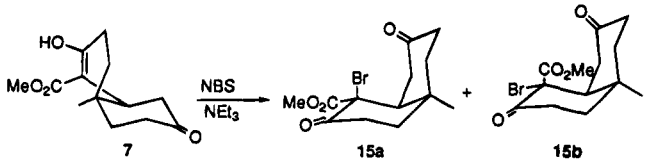
In addition, a doublet at $\delta = 4.8$ with $J_{8(eq)-8a(ax)} = 5$ Hz is observed for H_8. The exact structure and stereochemistry of each crystalline bromide was firmly established by X-ray crystallography.[10] It is noteworthy that no bromination took place at C-2 of the ester enol (Scheme 4). A similar lack of reactivity of the enol double bond has been reported for 2-carbomethoxycyclohexanone[18] and 2-carboethoxycyclopentanone.[19]

(8) King, L. C.; Ostrum, K. G. *J. Org. Chem.* **1964**, *29*, 3459.
(9) Caseau, P.; Chackalamannil, S.; Uang, B. J.; Duboudin, F. *J. Organomet. Chem.* **1980**, *201*, C9−C13.
(10) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(11) See Günther, H. *NMR-Spektroskopie*; Thieme Verlag: Stuttgart, Germany, 1973.
(12) Holysz, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 4432.
(13) For reviews of the Favorskii rearrangement see: Kende, A. *Org. React.* **1960**, *11*, 261. Chenier, C. *J. Chem. Educ.* **1978**, *55*, 286. Gutsche, C. D.; Redmore, D. In *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968; p 46. March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley: Interscience, 1985; p 971 and references therein.
(14) For a very recent discussion of the Favorskii rearrangement see: Albizati, K.; Barbee, T. R.; Guy, H.; Heeg, M. J. *J. Org. Chem.* **1991**, *56*, 6773, 6777.
(15) Karimi, S.; Todaro, L.; Grohmann, K. *J. Org. Chem.*, to be submitted.
(16) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing Corp.: New York, 1959; p 170.
(17) Bacca, N. S.; Williams, D. H. *Applications of NMR-Spectroscopy in Organic Chemistry*; Holden-Day Inc.: San Francisco, CA, 1964; p 51.

Scheme 4



Scheme 5



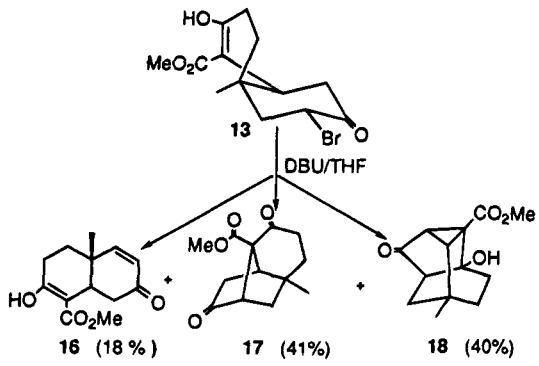
In contrast to these results, treatment of the keto ester **7** at 0 °C with 1 mol equiv of NBS or bromine in dichloromethane in the presence of an excess of triethylamine gave a mixture of two epimers **15a** and **15b** (Scheme 5). These bromo esters were separated by column chromatography and subsequent recrystallization to provide **15a** and **15b** in isolated yields of 36 and 27%, respectively. The very similar IR and ^{1}H NMR spectra of **15a** and **15b** no longer showed an enol to be present in either epimer. An X-ray structure analysis established epimer **15a** to be *cis*-1(ax)-bromo-1(eq)-carbomethoxy-4a-methyldecalin-2,7-dione.[10] The different regioselectivity of the acid-catalyzed vs the base-promoted bromination in this β-keto ester system is noteworthy and synthetically useful.

Dehydrobromination of the monobromo ester **13** with $LiBr/Li_2CO_3$ in DMF at 120 °C gave the unsaturated ester **16** in 64% isolated yield. However, dehydrobromination of **13** with DBU in THF afforded a surprising mixture of the unsaturated ester **16**, tricyclic keto ester **(17)**, and the tetracyclic keto alcohol **18** in yields of 18, 41, and 40%, respectively (Scheme 6). The compounds were separated by radial chromatography. The structures of **17** and **18** were established by X-ray crystallography.[10] The IR of **18** showed the OH band at 3540 cm^{-1} and two different C=O stretching frequencies at 1755 and 1720 cm^{-1}.

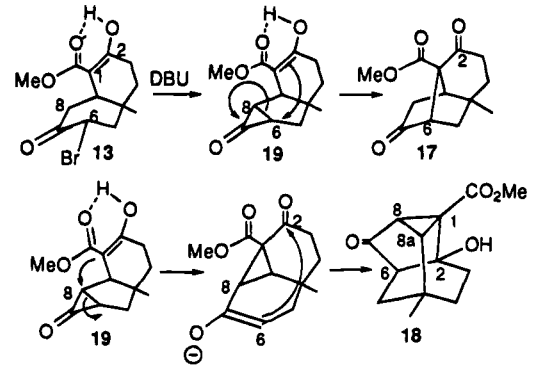
The easy formation of the highly functionalized tri- and tetracyclic esters **17** and **18** from **13** is remarkable. Both compounds can be rationalized as the result of competitive intramolecular nucleophilic attack by the keto ester enolate anion onto C-6 and C-8 of a common Favorskii intermediate **19** formed in a first step (Scheme 7).

Intramolecular nucleophilic ring-opening at C-6 of **19** followed by protonation would provide **17**, whereas nu-

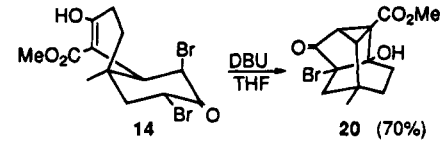
Scheme 6



Scheme 7



Scheme 8



cleophilic attack at C-8 of **19** followed by an intramolecular aldol-addition to the keto group leads to the tetracyclic ketol **18**.

The dehydrobromination of dibromo ester **14** with either DBU in THF or with $LiBr/Li_2CO_3$ in DMF gave **20** as the sole product in 70% isolated yield (Scheme 8). The IR spectrum of **20** is very similar to that of **18** with the exception that the ketone-carbonyl absorption is shifted to higher wavenumbers (1770 for **20** vs 1755 cm^{-1} for **18**). The structure of **20** was established by an X-ray analysis.[10]

The formation of **20** can be rationalized mechanistically through an intramolecular nucleophilic ring-opening of the bromocyclopropanone intermediate **21** by the keto ester enolate anion. The formation of the bromocyclopropanone **21a** (and not **21b**) appears to be the result of a preferential loss of equatorial bromide as opposed to the loss of an axial bromide (Scheme 9). It is well documented that rigid polycyclic axial α-bromo ketones do not undergo Favorskii rearrangement.[20]

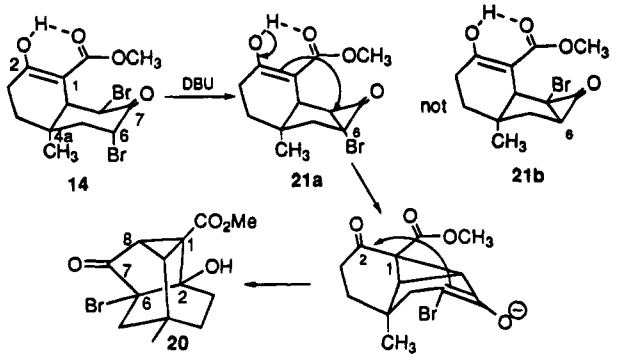
Every attempt to dehydrohalogenate *cis*-1(ax)-bromo-1-carbomethoxy-4a-methyldecalin-2,7-dione **(15a)** or its epimer **15b** under a variety of conditions did not lead to the expected tricyclic diketo ester **22**; instead, a reductive debromination to **7** was observed. This last results is somewhat surprising in view of the well-documented

(18) See *J. Am. Chem. Soc.* **1950**, *72*, 2127; **1976**, *98*, 984; *Beilstein 10*, EIV no. 1284, p 2608. Brenner, J. E. *J. Org. Chem.* **1961**, *26*, 22. Hussey J.; Pindler R. *J. Chem. Soc.* **1962**, 1517. *Indian J. Chem.* **1969**, *7*, 876.

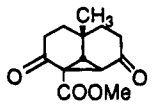
(19) *Beilstein 10*, EIV, no. 1284, p 2604. Sepatryew, C. *Z. Obsch. Chem. (Russian)* **1951**, *27*, 2214, 2217. *Liebigs Ann. Chem.* **1948**, *192*, 479. *Liebigs Ann. Chem.* **1952**, *225*, 453, 460. *Acta Chim. Scand.* **1948**, *2*, 383.

(20) Smissman, E. E.; Lemke, T. L.; Kristiansen, O. *J. Am. Chem. Soc.* **1966**, *88*, 334.

Scheme 9



facile formation of cyclopropane rings by a 1,3-dehydrohalogenation.[21]



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In conclusion, the intramolecular nucleophilic attack at the α-carbons of cyclopropanone–Favorskii intermediates by enolate anions provides a novel flexible entry to functionalized tri- and tetracyclic systems, valuable intermediates for the synthesis of many natural and unnatural products. These transformations add a new dimension to known reactions of cyclopropanones, such as carbonyl additions and (2 + 4) cycloadditions.[22]

Experimental Section

General. All air-moisture sensitive reactions were performed under a positive pressure of Ar or N_2. All solvents and reagents were distilled, dried, and/or recrystallized prior to use according to standard laboratory procedures. Melting points are uncorrected. Proton and carbon NMR spectra were measured in $CDCl_3$ on a GE/Bruker QE 300 MHz spectrometer. Analytical thin layer chromatography (TLC) was conducted on "Polygram" Sil G/UV254 plate (0.25 mm) from Macherey & Nagel. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Radial chromatography was performed on a Harrison Research Chromatotron using glass plates coated with Merck silica gel 60. Mass spectra were obtained on a Hewlet Packard 5989A GC mass spectrometer (EI). X-ray structures were determined on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation). Structures were solved by a multiple solution procedure and refined by full matrix least squares. In the final refinement, the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are $R = 0.05$ and $wR = 0.06$.

***cis*-4a-Methyl-decalin-2,7-dione (6).** A solution of **7**[6,7] (2 g, 8.4 mmol), in acetic acid (35 mL) and phosphoric acid (3.5 mL), was stirred at reflux overnight. The mixture was allowed to cool, and the acetic acid was evaporated under reduced pressure. The residue was poured into 100 mL of ice–water and neutralized with sodium bicarbonate. The solution was extracted with ether (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Crystallization of the solid residue from ether–hexane gave the diketone **6** (1.1 g, 73%): mp 91–93 °C. The compound was identical with an authentic sample.[3,5] ^1H NMR: $\delta = 2.47$ (m, 6H), 2.15 (m, 5H), 1.69 (m, 2H), 1.34 (s, 3H). ^{13}C NMR: $\delta = 209.9, 44.5, 43.7, 37.3, 34.2, 32.0, 25.7$.

***cis*-3,9-Bis[(trimethylsilyl)oxy]-6-methylbicyclo[4.4.0]-deca-3,8-diene (10).** Dione **6** (0.36 g, 2 mmol) was dissolved in dry acetonitrile (12 mL). Triethylamine (1.2 mL, 8 mmol), sodium iodide (1.2 g, 8 mmol), and trimethylsilyl chloride (1 mL, 8 mmol) were added sequentially. After 15 min at rt, the reaction mixture was heated to 70 °C for 1 h. After TLC indicated the absence of starting material, a cold aqueous saturated $NaHCO_3$ (15 mL) and ether were added (20 mL). The aqueous phase was separated and extracted with ether (2 × 20 mL). The organic layer was dried over K_2CO_3, filtered, and concentrated in vacuo to give the bis-silyl enol ether **10** (0.65 g) in quantitative yield. The product was used in the next step without purification. ^1H NMR: $\delta = 4.7$ (br s, 2H), 2.05 (m, 4H), 1.81 (m, 4H), 1.5 (d, 1H, $J = 10.9$ Hz), 0.96 (s, 3H), 0.17 (s, 9H), 0.16 (s, 9H).

***cis*-3,6(dieq)-Dibromo-4a-methyldecalin-2,7-dione (9) via the Reaction of 10 with NBS.** Recrystallized NBS ($CHCl_3$, 0.73 g, 4.1 mmol) was added to a solution of the bis-silyl enol ether **10** (0.65 g, 2 mmol) in THF (15 mL), and the reaction was stirred at rt under N_2 for 1 h. The reaction was quenched with ice–water and diluted with ether (2 × 30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography (30% ethyl acetate in hexane) gave **9** (0.49 g, 62%) as white crystals: mp 127–129 °C. ^1H NMR: $\delta = 4.9$ (dd, 1H, $J = 13$, 6 Hz), 4.75 (dd, 1H, $J = 13.6$, 6.1 Hz), 2.92 (dd, 1H, $J = 14.5$, 4.5 Hz), 2.76 (t, 1H, $J = 13.4$ Hz), 2.6 (d, 1H, $J = 10.1$ Hz), 2.51 (dd, 1H, $J = 13.9$, 6.18 Hz), 2.4 (m, 3H), 2.19 (t, 1H, $J = 13.8$), 1.45 (s, 3H). ^{13}C NMR: $\delta = 199.1, 198.8, 51.9, 51.4, 50.2, 45.5, 43.7, 42.7, 38.5, 25.8, 25.6$. X-ray structure: see ref 10.

Dione 9 from 6 with Copper Bromide/Ethyl Acetate/Chloroform. Finely ground copper(II) bromide (0.78 g, 3.5 mmol) was placed in a round bottom flask fitted with a reflux condenser. Ethyl acetate (20 mL) was added and brought to reflux. Compound **6** (0.18 g, 1 mmol) was dissolved in hot $CHCl_3$ (20 mL) and added to the flask. The resulting dark green reaction mixture was refluxed for 1 h until its color changed from green to amber. The copper(I) bromide was filtered and washed with $CHCl_3$. The organic layer was washed with aqueous $Na_2S_2O_3$, $NaHCO_3$, and ice–water (2 × 60 mL) in this order. The aqueous layers were extracted with ether (2 × 60 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **9** in quantitative yield. The crude material was digested with anhydrous ether and refrigerated overnight to yield pure dibromo diketone **9** as needles, 0.21 g (80%): mp 127–129 °C.

Dione 9 from 6 and Bromine in Acetic Acid. Compound **6** (0.9 g, 5 mmol) was added to a solution of glacial acetic acid containing 5 drops of 48% HBr. To this mixture bromine (1.6 g, 10 mmol) dissolved in glacial acetic acid (10 mL) was added dropwise over 20 min. The solution was stirred for 3 h. The reaction was quenched with ice–water (20 mL) and diluted with ether (2 × 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$ (5%), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography (30% ethyl acetate in hexane) gave **9** (1.1 g, 65%) as white crystals: mp 127–129 °C.

***cis*-6-Methylbicyclo[4.4.0]deca-4,7-diene-3,9-dione (3) from 9.** Compound **9** (0.34 g, 1 mmol) was added to a stirred suspension of dry LiBr (0.26 g, 3 mmol) and Li_2CO_3 (0.23 g, 3.1 mmol) in dry DMF (25 mL) under N_2, and the mixture was stirred at 120 °C for 1.5 h. The reaction mixture was cooled, poured onto ice–water (100 mL) neutralized with acetic acid, and extracted with ether (3 × 50 mL). The ether layer was washed with brine and dried over $MgSO_4$, and the solvent was removed on the rotary evaporator. The crude residue (0.17 g, 96%) contained mainly **3** according to TLC and NMR. Puri-

(21) (a) See Wendisch, D. Cyclopropanes. *Houben-Weyl*, Band IV, Teil 3, Georg Thieme Verlag: Stuttgart, 1971; p 89 and refs therein. (b) Grohmann, K.; Miller, L. S.; Dannenberg, J.; Todaro, L. *J. Am. Chem. Soc.* **1981**, *103*, 6249. Win, W. W.; Todaro, L.; Grohmann, K. G. *J. Org. Chem.* **1994**, *59*, 2803.

(22) See Wendisch, D. Cyclopropanes. *Houben-Weyl*, Band IV, Teil 3, Georg Thieme Verlag: Stuttgart, 1971; p 665 and refs therein. Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25.

fication by chromatography on SiO_2 and recrystallization from hexane gave pure *cis*-6-methylbicyclo[4.4.0]deca-4,7-diene-3,8-dione **3** (0.85 g, 48%, mp 76–78 °C). The compound was identical with an authentic sample.[3]

1-Bromo-5-methyltricyclo[4.4.0.0^{1,7}]decane-2,8-dione (11) from 9 and DBU in THF. To a solution of dibromide **9** (0.13 g, 0.385 mmol) in dry THF (10 mL) under N_2 was added DBU (0.15 mL) and the mixture was stirred at 50 °C overnight. The reaction was quenched with ice–water (30 mL), neutralized with 2 N HCl, and extracted with ether (2 × 20 mL). The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography (15% ethyl acetate/hexane) afforded **11** (47 mg, 48%) as white crystals, mp = 100–102 °C. ^{1}H NMR: δ = 2.82 (s, 1H), 2.66 (m, 2H), 2.48 (m, 3H), 2.26 (dd, 1H, J = 18.8, 5.2 Hz), 1.8 (m, 3H), 1.25 (s, 3H). ^{13}C NMR: δ = 205.7, 202.3, 66.6, 64.9, 46.4, 42.7, 41.2, 37.8, 37.0, 36.8, 22.8. *m/z*: 256/258 (M^+), 177 (100%) (M^+ − Br). X-ray structure: see ref 10.

***cis*-6(eq)-Bromo-1-carbomethoxy-2-hydroxy-4a-methylbicyclo[4.4.0]-1-decen-7-one (13).** Finely ground copper(II) bromide (0.45 g, 2.01 mmol) was placed in a round bottom flask fitted with a reflux condenser. Ethyl acetate (10 mL) was added and brought to reflux on a hot plate. Compound **7** (0.24 g, 1 mmol) was dissolved in hot $CHCl_3$ (10 mL) and added to the flask. The dark green reaction mixture was refluxed and stirred for 1 h until its color had changed to light amber. Copper(I) bromide was filtered off and washed with $CHCl_3$ (2 × 20 mL). The organic layer was washed with ice–water (60 mL) containing $Na_2S_2O_3$ (0.2 g) and aqueous $NaHCO_3$. The aqueous layers were extracted with ether (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **13** (0.32 g) in quantitative yield. Compound **13** was recrystallized from a CH_2Cl_2–hexane mixture forming colorless needles: mp 179–181 °C.

13. ^{1}H NMR: δ = 12.37 (s, 1H), 4.8 (dd, 1H, J = 13.6, 5.8 Hz), 3.77 (s, 3H), 2.93 (dd, 1H, J = 14.2, 4.7 Hz), 2.71 (m, 1H), 2.45 (m, 3H), 2.23 (m, 3H), 1.52 (m, 1H), 1.04 (s, 3H). ^{13}C NMR: δ = 200.3, 172.2, 171.9, 100.0, 52.8, 51.8, 51.4, 44.9, 41.8, 35.1, 26.2, 26.1, 25.1. IR (CCl_4): 1740, 1660, 1620 cm^{-1}. X-ray structure: see ref 10.

***cis*-6(eq)-Bromo-8(ax)-bromo-1-carbomethoxy-2-hydroxy-4a-methylbicyclo[4.4.0]-1-decen-7-one (14).** A solution of bromine (0.4 g, 2.5 mmol) in $CHCl_3$ (10 mL) was slowly added to β-keto ester **7** (0.24 g, 1 mmol) dissolved in $CHCl_3$ (10 mL) over a period of 15 min. The solution was stirred overnight at rt. The reaction was quenched with ice–water (30 mL) containing $NaHSO_3$ (5%), and the layers were separated. The organic layer was washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (20% ethyl acetate in hexane) gave **14** (0.32 g, 80%): mp 178–179 °C.

14. ^{1}H NMR: δ = 12.59 (s, 1H), 5.53 (dd, 1H, J = 14.3, 5.6 Hz), 4.79 (d, 1H, J = 5 Hz), 3.79 (s, 3H), 2.92 (d, 1H, J = 4.9 Hz), 2.78 (m, 1H), 2.47 (m, 3H), 2.2 (t, 1H), 1.39 (m, 1H), 1.01 (s, 3H). ^{13}C NMR: δ = 195.5, 174.9, 171.4, 96.8, 53.8, 51.9, 51.0, 47.9, 44.7, 35.2, 27.9, 27.2, 26.0. X-ray structure: see ref 10.

Bromination of 6 with NBS in the Presence of Triethylamine, 15a and 15b. NBS (7.83 g, 44 mmol), dissolved in CH_2Cl_2 (300 mL), was added dropwise to a solution of the β-keto ester **6** (4.76 g, 20 mmol) in dry CH_2Cl_2 (150 mL) and triethylamine (16.7 mL) under N_2. The solution was cooled with an ice bath. The mixture was stirred in the ice bath for 2 h. Ice–water (200 mL) containing concd HCl (11 mL) was added. The water layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with ice–water and with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography (30% EtOAc/hexane) gave **15a** (2.28 g, 36%; mp 108–110 °C after recrystallization from ether/hexane).

15a. ^{1}H NMR: δ = 3.84 (s, 3 H), 3.1 (m, 2 H), 2.57 (m, 5 H), 2.19 (dd, 2 H), 1.81 (m, 1 H), 1.62 (m, 1 H). ^{13}C NMR: δ = 208.5, 198.9, 167.7, 71.8, 54.0, 49.1, 41.3, 36.4, 35.2, 33.3, 33.1, 27.8. IR (CCl_4): 1740, 1725, 1270 cm^{-1}. X-ray structure: see ref 10. Secondly, **15b** was eluted (1.68 g, 27%, mp 115–116 °C).

15b. ^{1}H NMR: δ = 3.75 (s, 3H), 3.26 (dd, 1 H, J = 18, 3 Hz), 2.87 (dd, 1 H, J = 10, 7 Hz), 2.65 (m, 2 H), 2.47 (m, 3 H), 2.17 (m, 1 H), 1.91 (m, 2 H), 1.53 (m, 1 H), 1.25 (s, 3 H). ^{13}C NMR: δ = 206.8, 196.9, 168.6, 72.3, 54.5, 53.4, 40.2, 38.9, 36.0, 35.6, 30.1, 27.5. IR (CCl_4): 1740, 1736, 1255 cm^{-1}.

Synthesis of *cis*-1-Carbomethoxy-2-hydroxy-4a-methylbicyclo[4.4.0]deca-1,5-dien-7-one (16) by LiBr/Li_2CO_3/DMF Dehydrobromination of 13. Solid **13** (0.32 g, 1 mmol) was added to a stirred suspension of dry LiBr (0.14 g, 1.63 mmol) and Li_2CO_3 (0.18 g, 2.69 mmol) in dry DMF (10 mL) at 120 °C under N_2. Stirring was continued for 75 min at the same temperature. The reaction was cooled, poured into dilute HOAc/ice–water (50 mL), and extracted with ether (2 × 50 mL). The ether extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give **16** as the only product (0.15 g, 64% after recrystallization from hexane/ethyl acetate, mp 98–100 °C).

16. ^{1}H NMR: δ = 12.41 (s, 1H), 6.66 (d, 1H, J = 10.1 Hz), 5.93 (d, J = 10.1 Hz), 3.78 (s, 3H), 2.84 (dd, 1H, J = 13.2, 4.2 Hz), 2.72 (dd, 1H, J = 17, 4.3 Hz), 2.42 (m, 2H), 2.2 (q, 1H, J = 13.2 Hz), 1.88 (m, 1H), 1.56 (m, 1H), 1.15 (s, 3H). ^{13}C NMR: δ 195.5, 174.9, 171.4, 96.8, 53.8, 51.9, 51.0, 47.9, 44.7, 35.2, 27.8, 27.2, 26.0.

Dehydrobromination of 13 with DBU in THF, 16–18. Monobromide **13** (0.64 g, 2 mmol) was dissolved in THF (20 mL) under N_2. DBU (0.6 mL, 4 mmol) was added to this solution and the mixture was heated at 60 °C for 15 h. After being cooled, it was quenched with ice cold HCl (1 N). The mixture was diluted with ether (2 × 30 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by radial chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded **16** (0.08 g, 17%): mp 97–100 °C (hexane).

The second compound eluted from the plate was 7-carbomethoxy-5-methyltricyclo[4.4.0.0^{1,7}]decane-2,8-dione **(17)** (0.194 g, 41%, mp 107–108 °C (hexane).

17. ^{1}H NMR: δ = 3.73 (s, 3H), 2.94 (d, 1H, J = 5.4 Hz), 2.74 (m, 2H), 2.53 (m, 1H), 2.44 (d, 1H, J = 18.9 Hz), 2.05 (m, 3H), 1.81 (m, 1H), 1.44 (d, 1H, J = 14.6 Hz), 1.2 (s, 3H). ^{13}C NMR: δ = 210.1, 206.2, 169.9, 71.2, 56.3, 52.7, 49.3, 38.2, 37.6, 36.3, 35.5, 35.0, 24.0. IR (CCl_4): 1770 cm^{-1} (C=O, 2-ketone), 1750 (C=O, ester), 1720 (C=O, 8-ketone). *m/z* = 236 (M^+, 100%). X-ray structure: see supplementary material and ref 10.

The third compound eluted from the plate was 2-carbomethoxy-1-hydroxy-8-methyltetracyclo[4.4.0.0^{1,6}.0^{2,4}]decan-5-one **(18)** (0.19 g, 40%), colorless crystals, mp 104–105 °C (hexane).

18. ^{1}H NMR: δ = 3.76 (s, 3H), 2.4 (dd, 1H, J = 7.6, 1.9 Hz), 2.26 (dd, 1H, J = 7.6 2.74 Hz), 2.16 (dd, 1H, J = 7.9, 1.6 Hz), 2.08 (d, 1H, J = 10.8 Hz), 1.93 (m, 2H), 1.68 (m, 1H), 1.58 (m, 3H), 1.16 (s, 3H). ^{13}C NMR: δ = 207.9, 171.2, 74.2, 52.2, 51.1, 43.3, 40.6, 38.6, 37.3, 35.8, 29.1, 27.8, 25.5. IR (CCl_4): 3540 (OH), 1755 (C=O, ketone), 1720 (C=O, ester). *m/z* = 236 (M^+, 71%). X-ray structure: see ref 10.

6-Bromo-2-carbomethoxy-1-hydroxy-8-methyltetracyclo[4.4.0.0^{1,6}.0^{2,4}]decan-5-one (20). DBU (0.08 g, 1 mmol) was added dropwise by syringe to a solution of dibromo ketone **14** (0.2 g, 0.5 mmol) dissolved in dry THF (10 mL) under N_2. Stirring was continued overnight at 55 °C before the reaction was quenched with ice-cold HCl (10%, 50 mL). The mixture was diluted with ether (2 × 20 mL), and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give **20** (0.11 g, 70%) as pale yellow crystals. Recrystallization (hexane/ethyl acetate) afforded crystallographically pure colorless needles mp 114–116 °C.

20. ^{1}H NMR: δ = 3.81 (s, 1H), 3.75 (s, 3H), 2.56 (d, 1H, J = 7.6 Hz), 2.27 (dd, 1H, J = 7.5, 2.5 Hz), 2.11 (m, 4H), 1.81 (q, 1H, J = 2 Hz), 1.67 (m, 1H), 1.16 (s, 3H). ^{13}C NMR: δ = 199.3, 170.1, 74.2, 69.2, 52.5, 52.3, 42.5, 38.1, 37.4, 32.8, 31.7, 26.3, 24.9. IR (CCl_4): 3540 (OH), 1770 (C=O, ketone), 1720 (C=O, ester). X-ray structure: see ref 10.

Synthesis of 20 by Lithium Bromide/Lithium Carbonate/Dimethylformamide Dehydrobromination. Compound **14** (0.2 g, 0.5 mmol) was added as a solid to a stirred suspension of dry LiBr (0.14 g, 1.63 mmol) and Li_2CO_3 (0.18 g, 2.69 mmol) in dry DMF (10 mL) at 120 °C under N_2. Stirring was continued for 75 min at the same temperature. The reaction was cooled, poured into dilute HOAc/ice–water, and extracted with ether. The ether extracts were washed with brine and aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the tetracyclic compound **20** as the only product (80 mg, 50%).

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Supplementary Material Available: ^1H- and ^{13}C-NMR spectra and IR spectra of all new compounds (33 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm edition of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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