New Synthesis of Troponoid Compounds via the Iron Carbonyl Promoted Cyclocoupling between Polybromo Ketones and 1,3-Dienes[1,2]

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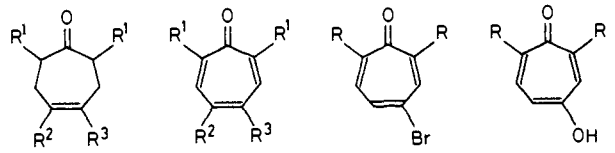
Abstract: Synthetic applications of the iron carbonyl promoted 3 + 4 cyclocoupling between polybromo ketones and 1,3-dienes are described. 4-Cycloheptenones derived from secondary dibromo ketones and open-chain 1,3-dienes are readily converted to alkylated tropones and γ-tropolones through a bromination-dehydrobromination procedure. Cyclopropanation of the 4-cycloheptenones followed by the bromination and dehydrobromination leads to 4,5-homotropones, which in H_2SO_4 exist as hydroxyhomotropylium ions. 8-Oxabicyclo[3.2.1]oct-6-en-3-ones, produced by the reaction of dibromo ketones and furan, also serve as a precursor of troponoid compounds. 2,7-Nonamethylenetropone has been prepared from the adduct of 2,12-dibromocyclododecanone and furan. The cyclocoupling reaction between tetrabromoacetone or 1,1,3-tribromo-4-methylpentan-2-one and furan derivatives has been utilized for the synthesis of naturally occurring nezukone and α- and β-thujaplicins.

Since the first discovery of troponoid compounds in natural plant tissues, a wide variety of synthetic approaches for these new nonbenzenoid aromatic compounds have been done so far.[3-10] None of the procedures, however, are generally applicable for synthesizing appropriately substituted troponoids, because specific introduction of substituents at desired positions is not easy to achieve. We now present a new efficient synthesis of troponoids based on the iron carbonyl promoted 3 + 4 → 7 cyclocoupling between polybromo ketones and 1,3-dienes.[1] This method is widely useful for obtaining various alkylated tropones, tropolones, 4,5-homotropones, and bridged tropones. The synthetic utility of these new procedures has been further demonstrated by the synthesis of naturally occurring troponoids such as nezukone and α- and β-thujaplicins.

Results and Discussion

Synthesis of Troponoids from 4-Cycloheptenone Derivatives. One of the new procedures starts from the 2,7-dialkylated 4-cycloheptenones.[1] The easiness of the conversion is attributable to the presence of a double bond at the C_4–C_5 position in the starting ketones **1–6** (Table I). Thus, by the simple



1–6 8–13 14, R = CH_3 15, R = $CH(CH_3)_2$ 16, R = CH_3 17, R = $CH(CH_3)_2$

bromination-dehydrobromination procedures, we obtained various troponoid compounds via the 4-cycloheptenones as key intermediates.

A. Alkylated Tropones. Treatment of 2,7-dimethyl-4-cycloheptenone (**1**) with 2 equiv of pyrrolidone hydrotribromide (PHT) gave mainly 2,4,5-tribromo-2,7-dimethylcycloheptanone (**7**), which was subjected to dehydrobromination with LiCl in DMF at 140 °C to afford the previously reported 2,7-dimethyltropone (**8**) in 64% overall yield. Similarly new troponoids **9–13** were synthesized starting from 4-cycloheptenones **2–6**, as shown in Table I. Structures of the products were immediately established by comparing their NMR, IR, UV, and mass spectra with those reported for this class of compounds.[7,11,12]

B. γ-Tropolones. Although numerous procedures have been developed for the synthesis of γ-tropolones,[13-18] none of the existing procedures is suitable for general preparative purposes. The new method described below provides 2,7-dialkyl-γ-tropolones selectively and in good yields. Bromination of **1** with 5.5 equiv of pyridinium bromide perbromide in acetic acid yielded 2,7-dimethyl-2,4,5,7-tetrabromocycloheptanone, which without separation was treated with LiCl in DMF, giving 4-bromo-2,7-dimethyltropone (**14**) in 85% yield. Prominent UV absorptions due to the tropone chromophore occurred at 239 nm (log ε 4.45), 330 (3.92), and 345 (3.83). The red shift caused by halogen atom on the tropone nucleus is well known.[19] Hydrolysis of **14** was effected in a mixture of 48% HBr–H_2O–acetic acid in a sealed tube, affording 2,7-dimethyl-γ-tropolone (**16**) in 55% overall yield based on **1**. 2,7-Diisopropyl-γ-tropolone (**17**) was obtained in 46% overall yield by the same procedure. Compounds **16** and **17** in 0.1 N NaOH showed UV maxima in the region of 238–241 nm (log ε 4.3) and 368–371 (4.3); a distinct red shift was observed for the intense absorptions compared to those of the parent compound (227 nm (log ε 4.27) and 359 (4.27)).[16] The assignments in ^1H NMR spectra were made on the basis of the chemical shifts and splitting patterns (see Experimental Section). The calculated electron densities on the ring carbons of γ-tropolone[20] predict that absorptions due to ring protons appear in the order of H_5, H_3, and H_6 from the high field, in accord with the present structural assignment. Thus, the possible tautomeric structures, 3,5-dialkyl-γ-tropolones, were ruled out. The preference of the structures **16** and **17** over 3,5-dialkyl-γ-tropolones can be explained by both electronic and steric factors. Introduction of two alkyl groups to the electron-deficient C_2 and C_7 positions of γ-tropolone stabilizes the aromatic system to a greater extent than the alternative substitution at the electron-rich ring carbons C_3 and C_5. In addition, steric re-

Scheme I

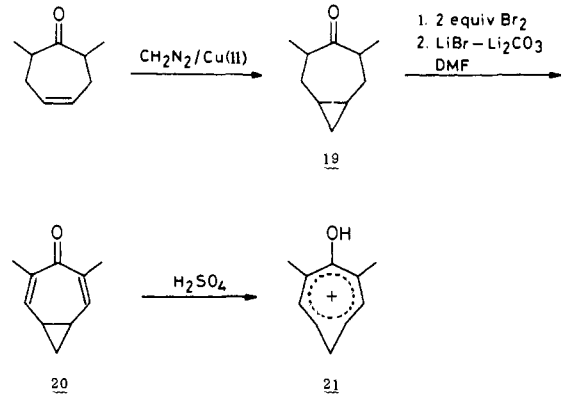


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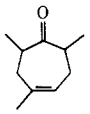
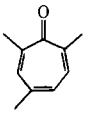
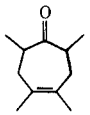
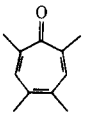
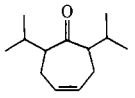
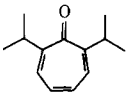
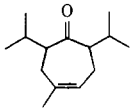
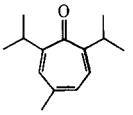
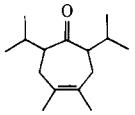
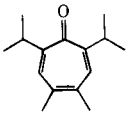
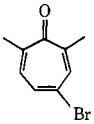
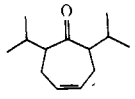
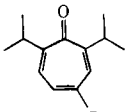
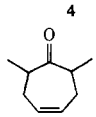
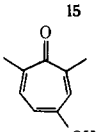
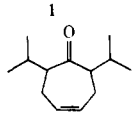
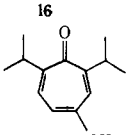
Table I. Synthesis of Troponoid Compounds

4-Cycloheptenone	Product	Yield,[a] %	Mp, °C	UV, nm (log ε)[b]	IR,[c] cm^{-1}
 1	 8	64, 42[d]	Oil	234 (4.40), 241 (4.33), 325 (3.84), 336 (3.77)	1558
 2	 9	46	Oil	237 (4.19), 333 (3.89), 342 (3.86)	1559
 3	 10	66	88–89	239 (4.25), 339 (3.76), 346 (3.76)	1553
 4	 11	63	Oil	238 (4.24), 243 (4.20), 325 (3.65), 340 (3.55)	1571
 5	 12	50	Oil	238 (4.31), 328 (3.80)[e]	1572
 6	 13	53	47–48	240 (4.32), 334 (3.86)[e]	1563
 1	 14	85	Oil	239 (4.45), 330 (3.92), 345 (3.83)	1570
 4	 15	83	Oil	239 (4.30), 319 (3.85)[e]	1576
 1	 16	55	168–170	238 (4.34), 368 (4.28)[f]	1466[g]
 4	 17	46	160–161	241 (4.31), 371 (4.29)[f]	1457[g]

[a] Isolated yield based on the 4-cycloheptenone unless otherwise specified. [b] Taken in H_2O unless otherwise stated. [c] Recorded in $CHCl_3$ except where otherwise indicated. Only the strongest band in the 1700–1400-cm^{-1} region is reported. [d] 2,4-Dimethyl-8-oxabicyclo[3.2.1]octan-3-one was used as the starting material. [e] In methanol. [f] In 0.1 NaOH. [g] As Nujol mull.

pulsion between the carbonyl oxygen and two alkyl substituents in **16** or **17** is smaller than that between the hydroxyl group and alkyl substituents in 3,5-dialkyl derivatives.

C. 4,5-Homotropones and Hydroxyhomotropylium Ions. The first preparation of 4,5-homotropone (**18**)[21,22] has demonstrated high stability of this unique molecule, regardless of the *cis*-divinylcyclopropane structure which usually suffers facile Cope rearrangement. We developed a new, convenient route to the 2,7-dialkyl-4,5-homotropones starting from 4-cycloheptenones as illustrated in Scheme I. When gaseous diazomethane diluted with nitrogen was introduced into a solution of 2,7-dimethyl-4-cycloheptenone (**1**) in a mixture of benzene and hexane at −5 to −10 °C in the presence of a catalytic amount of bis(*N*-α-phenylethylsalicylaldiminato)copper(II),[23] **19** was obtained in 90% yield. Bromination of **19** was done by addition of bromine into a mixture of **19** and sodium acetate in chloroform. The resulting dibromo derivatives were further subjected to dehydrobromination with a mixture of LiBr and Li_2CO_3 in DMF, giving the desired 4,5-homotropone **20.** The overall yield based on **19** was 33%. All physical properties ex-

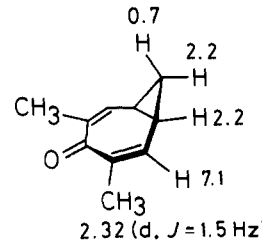


Figure 1. NMR of **20** in CCl_4, δ from Me_4Si as the external standard.

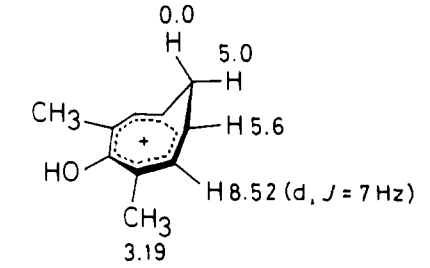
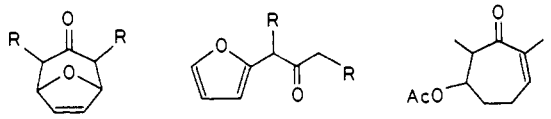


Figure 2. NMR of **21** in 96% H_2SO_4, δ from Me_4Si as the external standard.

hibited by **20** (see Experimental Section) are characteristic of a cross-conjugated dienone structure, suggesting that the extent of the cyclic conjugation through cyclopropane ring is relatively small as was shown in the parent compound **18.** Thus the stability of 4,5-homotropone is not affected by introducing alkyl groups at the C_2 and C_7 positions; **20** remained unchanged upon heating at 100 °C. As expected, protonation on the carbonyl oxygen resulted in the formation of an aromatic structure. The NMR data of **20** and its protonated species **21** are compared in Figures 1 and 2. Apparently, the homotropone **20** in 96% H_2SO_4 exists as the hydroxyhomotropylium ion **21.** In going from **20** to **21,** the multiplet due to an endo proton of the cyclopropane methylene shifted to a somewhat higher field (δ 0.7 → 0.0), while that of the exo one shifted greatly to a lower field (δ 2.2 → 5.0).[24] The large chemical shift difference between these methylene protons of **21** compared with that of the parent dienone **20** (5.0 vs. 1.5 ppm) shows evidence for the presence of an induced diamagnetic ring current in **21.** The present method is useful for preparing other 2,7-dialkyl-4,5-homotropones starting from 4-cycloheptenones.

Synthesis of Troponoids from 8-Oxabicyclo[3.2.1]oct-6-en-3-ones. In the preceding paper we reported that the reactive species derived from the reaction of α,α'-dibromo ketones and iron carbonyls can be trapped with furan to give 8-oxabicyclo[3.2.1]oct-6-en-3-one (**22**) in high yields. The adducts also can be converted to troponoid compounds.

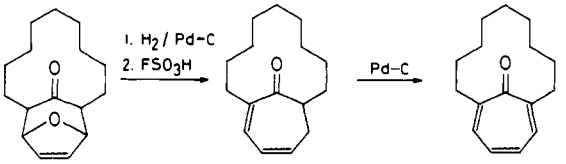
A. Alkylated Tropones and γ-Tropolones. Attempts to cleave the ether linkage of **22** resulted in the recovery of the starting materials or formation of the rearranged product **23.** There-



fore, the cyclic keto ether **22** (R = CH_3) was first hydrogenated over 5% Pd/C. Ether cleavage of the corresponding saturated compound **24** was then effected by treatment with boron trifluoride etherate in acetic anhydride, leading to enone acetate **25** in 49% yield. Allylic bromination of **25** with 1.3 equiv of *N*-bromosuccinimide (NBS) in CCl_4 in the presence of a catalytic amount of benzoyl peroxide afforded a stereoisomeric mixture of monobrominated products, 6-acetoxy-4-bromo-2,7-dimethylcyclohept-2-en-1-one in 94% yield. Exposure of the resulting bromide to a mixture of LiCl and Li_2CO_3 in DMF gave 2,7-dimethyltropone (**8**) in 92% yield.

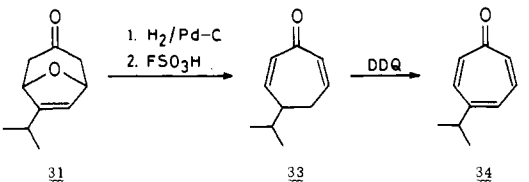
2,7-Dimethyl-γ-tropolone (**16**) can be derived from the enone acetate **25** via the bromotropone **14** which can easily be obtained by bromination of **25** with 2.5 equiv of NBS and subsequent dehydrohalogenation with LiCl–Li_2CO_3 in DMF in 41% yield. Although the overall yields were not as high as those obtained with 4-cycloheptenone (**1**), the present procedure has synthetic convenience, because the starting bicyclic ketone **22** can be prepared in very high yield.[1]

B. 2,7-Bridged Tropones. We prepared 2,7-nonamethylenetropone (**29**)[25] from the readily available bicyclic ketone **26.**[1] Catalytic hydrogenation of the keto ether **26** over 5% Pd-C gave the saturated derivative (**27**) in quantitative yield. Ether cleavage of **27** was first attained with boron trifluoride etherate,[2b] but later we found that fluorosulfuric acid is more effective for this purpose. Thus, treatment of **27** with fluorosulfuric acid at room temperature gave the linearly conjugated dienone **28** in 60% yield. Upon treatment of **28** with 10% Pd/C in benzene at 130 °C the bridged tropone **29** was produced in 51% yield.



Synthesis of Naturally Occurring Troponoids. Since thujaplicins were found in essential oils of certain plants[26,27] these troponoid compounds contributed much to elucidate the chemistry of nonbenzenoid aromatic systems.[3] Their antibacterial and antifungal activities were well known and various synthetic approaches have been done.[28-31] We developed a new synthetic procedure leading to this interesting class of compounds.

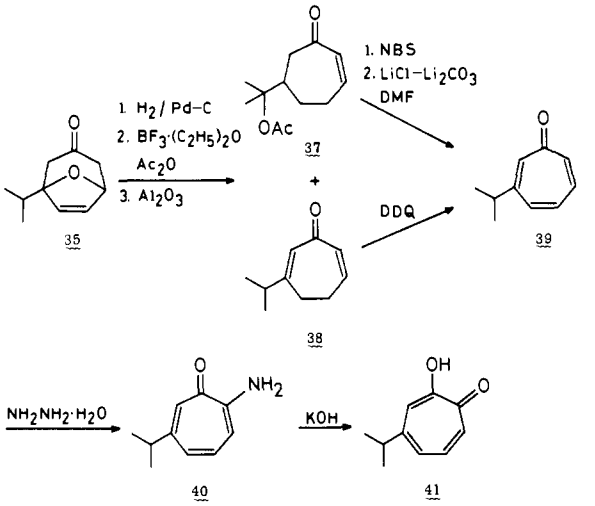
A. Nezukone. The naturally occurring tropone **34**[32] is easily accessible by the present method starting from **31** which was prepared by the reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone (**30**) and 3-isopropylfuran followed by treatment of the adducts with Zn–Cu couple. Hydrogenation of **31,** followed by treatment with fluorosulfuric acid, gave the cross-conjugated dienone **33** in 59% yield. The dienone **33** was then dehydrogenated with



2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to give nezukone (**34**) in 54% yield. The structure of **34** was confirmed by comparison of the semicarbazone with a sample derived from the natural product.

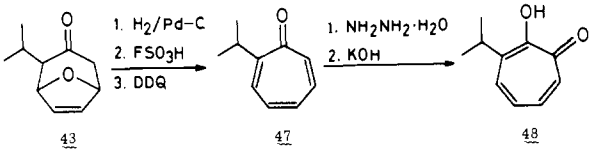
B. β-Thujaplicin (Hinokitiol). Synthesis of β-thujaplicin (**41**) starts from the bicyclic ketone **35** obtained by the iron carbonyl promoted cyclocoupling reaction of tetrabromoacetone (**30**) and 2-isopropylfuran (Scheme II). Hydrogenation of **35** over Pd/C gave 1-isopropyl-8-oxabicyclo[3.2.1]octan-3-one (**36**) in 96% yield. Sequential treatment of **36** with boron trifluoride etherate in acetic anhydride and then with basic alumina gave the acetoxy enone **37** and the dienone **38** in 33 and 25% yields, respectively, accompanied by the production of 6-isopropylidenecyclohept-2-enone (9%). The acetoxy enone **37** was converted to the tropone **39**[34] in 77% yield by bromination with NBS followed by dehydrobromination with LiCl–Li_2CO_3 in DMF. The cross-conjugated dienone **38** could also be con-

Scheme II



verted to the tropone **39** in 80% yield by simple heating with DDQ and a catalytic amount of *p*-toluenesulfonic acid in benzene. The tropone **39** thus obtained was treated with hydrazine hydrate to give 2-amino-6-isopropyltropone (**40**) in quantitative yield. Subsequent hydrolysis in 2 N alcoholic KOH yielded the desired β-thujaplicin (**41**) quantitatively. The spectral properties of **41** were identical with those of the authentic sample.[29,33]

C. α-Thujaplicin. α-Thujaplicin (**48**) can easily be prepared starting from **43** obtained from 1,1,3-tribromo-4-methylpentan-2-one (**42**) and furan. Hydrogenation of **43** over 10% Pd/C afforded the saturated ketone **44** in 96% yield. Cleavage of the ether linkage of **44** with fluorosulfuric acid gave 2-isopropyl-6-hydroxycyclohept-2-enone (**45**, 57% yield) and a small amount of 2-isopropylcyclohepta-2,6-dienone (**46**, 11%). Conversion of **45** and **46** to 2-isopropyltropone (**47**)[34] was ef-



fected in good yield by heating a mixture of **45** and **46** with DDQ in the presence of *p*-toluenesulfonic acid (55% overall yield from **44**). The tropone **47** can be converted to α-thujaplicin (**48**) by the known procedure.[29,34]

Conclusion

We have demonstrated synthetic utility of the iron carbonyl promoted cyclocoupling between polybromo ketones and 1,3-dienes. We feel that the present results display the general utility of the new method and suggest wide applicability to the synthesis of both natural and artificial troponoid compounds.

Experimental Section

General. All melting and boiling points are uncorrected. Infrared spectra (IR) were obtained from samples as CCl_4 solutions unless otherwise stated and were recorded on a JASCO Model DS-402G spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in CCl_4 unless otherwise indicated at 60 MHz on a JEOL C-60H spectrometer or at 100 MHz on a Varian HA-100D instrument. The chemical shifts were presented in parts per million (δ) downfield from internal tetramethylsilane. Low-resolution mass spectra were taken at an ionization voltage of 70 eV on a Hitachi RMU-6C spectrometer. Ultraviolet (UV) spectra were measured on a Perkin-Elmer Model 202 spectrophotometer or a Hitachi Model 323 instrument. Gas–liquid partition chromatography (GLC) analyses were performed on Yanagimoto Model G-8 and Hitachi Model 063 gas chromatographs equipped with a flame ionization detector using a 3 mm × 2 m column packed with 5% Apiezon grease L on 60–80 mesh Diasolid M. Preparative scale GLC was carried out on Varian Model 1700 thermal conductivity instrument equipped with a 3/8 in. × 7 ft column packed with 10% Apiezon grease L on 60–80 mesh Neopak 1A. Analytical thin layer chromatography (TLC) was done on E. Merck Kieselgel GF_{254} precoated plates (0.25-mm layers). Preparative TLC separation was performed with 20 × 20 cm glass plates coated with a 1.0-mm layer of E. Merck Kieselgel PF_{254}. The position of compounds is shown by R_f values. Silicic acid powders (E. Merck Kieselgel 60, 70–230 mesh) were used for column chromatography. Exact mass spectra were taken in a laboratory of Professor A. Tatematsu, Department of Pharmaceutical Science, Meijo University. Elemental analyses were performed at the Microanalytical Center of Kyoto University. All new compounds gave satisfactory elemental analyses or molecular ion peaks in exact mass spectra.

Materials and Solvents. The ketones **1–6, 22** (R = CH_3), and **26** were prepared from the corresponding α,α′-dibromo ketones and open-chain 1,3-dienes or furan.[1] PHT,[35] pyridinium bromide perbromide,[36] α,α,α′,α′-tetrabromoacetone (**30**),[37] and Zn–Cu couple[38] were prepared according to the literature procedures and dried over P_2O_5. $Fe_2(CO)_9$ was prepared by the procedure of King[39] and stored over KOH. LiCl and Li_2CO_3 were dried at 100 °C for 12 h under reduced pressure (0.05 mm). NBS was recrystallized from water and dried in vacuo over P_2O_5. FSO_3H was obtained from Aldrich Chemical Co. and distilled in vacuo before use. Reagent grade ether and THF were distilled from $LiAlH_4$ immediately before use. DMF and boron trifluoride etherate were distilled over CaH_2. All other solvents and reagents were reagent grade and liquid materials were distilled before use.

Synthesis of 2,7-Dialkyltropones from 2,7-Dialkyl-4-cycloheptenones. 2,7-Dimethyltropone (8). This experiment is illustrative for the conversion of 2,7-dialkyl-4-cycloheptenones to 2,7-dialkyltropones. A mixture of 2,7-dimethyl-4-cycloheptenone (**1**, 46.0 mg, 0.333 mmol) and PHT (604 mg, 1.21 mmol) in THF (4 mL) was stirred in the dark at 25 °C for 10 h. The solvent was evaporated and to the residue was added water (5 mL). The mixture was extracted with $CHCl_3$ (5 mL × 5) and the combined extracts were washed twice with water (10 mL). The organic layer was dried and concentrated to give a yellow oil (115 mg), which consisted mainly of 2,4,5-tribromo-2,7-dimethylcycloheptanone (**7**): NMR δ 1.23 (d, J = 7 Hz, $CHCH_3$), 2.07 (s, $CBrCH_3$), 1.7–2.9 (m, $CHCH_3$ and CH_2), 3.0–4.0 (m, CH_2), 4.2–4.8 (m, 2 $CHBr$). A mixture of the bromination products (115 mg) and LiCl (200 mg, 4.72 mmol) in DMF (2 mL) was heated at 140 °C for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (50 mL × 6). The combined organic layers were washed with brine and then dried. Evaporation of the solvent followed by purification by preparative TLC (1:1 benzene–hexane, two developments, and 1:10 ether–benzene, R_f 0.44) gave **8** (28.5 mg, 64%). IR and UV spectra were identical with those reported.[7] NMR ($CDCl_3$) δ 2.32 (s, 2 CH_3), 6.7–7.5 (A_2B_2, ring protons); mass spectrum m/e 134 (M^+), 106, 91 (base peak).

2,4,7-Trimethyltropone (9). Bromination of 2,4,7-trimethyl-4-cycloheptenone (**2**, 46.4 mg, 0.305 mmol) with PHT (925 mg, 1.86 mmol) was carried out in THF (3 mL) at 25 °C for 12 h and workup gave a yellow oil (105 mg). The product was mixed with LiCl (200 mg, 4.82 mmol) in DMF (2 mL) and heated at 140 °C for 1 h. Purification of the crude product by TLC (1:1 benzene–hexane, two developments, and 1:10 ether–benzene) afforded **9** (20.7 mg, 46%, R_f 0.34): IR ($CHCl_3$) 3007 (m), 2952 (w), 2920 (m), 1684 (w), 1624 (w), 1604 (w), 1559 (s), 1518 (m), 1460 (w), 1425 (w), 1370 (m), 1234 (w), 1160 (m), 1034 (w), 1005 (w), 839 cm^{-1} (m); NMR ($CDCl_3$) δ 2.29 (br s, 3 CH_3), 6.6–6.9 (m, H_5), 7.1–7.3 (m, H_3 and H_6); mass spectrum m/e 148 (M^+), 120, 105 (base peak); exact mass spectrum m/e 148.0893 (calcd for $C_{10}H_{12}O$, 148.0888).

2,4,5,7-Tetramethyltropone (10). A mixture of 2,4,5,7-tetramethyl-4-cycloheptenone (**3**, 41.5 mg, 0.244 mmol) and THP (554 mg, 1.11 mmol) in THF (3 mL) was stirred at 25 °C for 15 h. Workup gave a bromination product (85 mg). Dehydrobromination was done by heating the bromination product with a mixture of LiCl (200 mg, 4.70 mmol) and DMF (2 mL) at 140 °C for 1 h. A pure sample of **10** (26.9 mg, 66%), mp 88–89 °C (from petroleum ether), was obtained after purification by TLC (1:1 benzene–hexane, two developments, and 1:10 ether–benzene, R_f 0.22): IR ($CHCl_3$) 3005 (m), 1688 (m), 1612 (w), 1553 (s), 1500 (m), 1450 (m), 1428 (m), 1373 (m), 1308 (w), 1164 (m), 1095 (w), 1031 (w), 907 (w), 830 cm^{-1} (w); NMR ($CDCl_3$) δ 2.28 (br s, 4 CH_3), 7.30 (br s, H_3 and H_6); mass spectrum

m/e 162 (M^+), 134, 119 (base peak); exact mass spectrum *m/e* 162.1042 (calcd for $C_{11}H_{14}O$, 162.1045).

2,7-Diisopropyltropone (11). A mixture of 2,7-diisopropyl-4-cycloheptenone (**4**, 13.5 mg, 0.067 mmol) and PHT (150 mg, 0.302 mmol) in THF (2 mL) was stirred at 25 °C for 15 h. The reaction mixture was worked up as usual. Heating the mixture (at least three components) with LiCl (50 mg, 1.18 mmol) in DMF (1 mL) at 150 °C for 1 h afforded after workup and separation by preparative TLC (1:1 benzene–hexane, three developments) **11** (8.4 mg, 63%, R_f 0.39): IR ($CHCl_3$) 3014 (w), 2970 (s), 2936 (w), 2376 (w), 1678 (w), 1626 (w), 1602 (w), 1571 (s), 1513 (w), 1464 (m), 1394 (m), 1376 (m), 1360 (m), 1318 (w), 1280 (w), 1103 (w), 1046 (m), 976 (w), 936 cm^{-1} (w); NMR ($CDCl_3$) δ 1.19 (d, J = 7.0 Hz, 2 $CH(CH_3)_2$), 3.1–3.8 (m, 2 $CH(CH_3)_2$), 6.7–7.3 (A_2B_2, ring protons); mass spectrum *m/e* 190 (M^+), 175, 147 (base peak); exact mass spectrum *m/e* 190.1375 (calcd for $C_{13}H_{18}O$, 190.1358).

2,7-Diisopropyl-4-methyltropone (12). Reaction of 2,7-diisopropyl-4-methyl-4-cycloheptenone (**5**, 44.4 mg, 0.216 mmol) and PHT (424 mg, 0.852 mmol) in THF (2 mL) at 25 °C for 15 h followed by usual workup gave a yellow oil (133 mg). TLC analysis (1:1 benzene–hexane) indicated that three products (R_f 0.48, 0.27, and 0.21) were formed. The crude products, without purification, were heated with LiCl (220 mg, 5.18 mmol) in DMF (2 mL) at 140 °C for 75 min. The reaction mixture was worked up and subjected to TLC (1:1 benzene–hexane, two developments, and 1:10 ether–benzene) giving **12** (21.9 mg, 50%, R_f 0.63): IR ($CHCl_3$) 3007 (m), 2962 (s), 2927 (m), 2865 (m), 1690 (w), 1627 (w), 1572 (s), 1516 (s), 1464 (m), 1396 (m), 1376 (m), 1362 (w), 1317 (w), 1260 (w), 1098 (w), 1053 (m), 1002 (w), 913 (w), 837 cm^{-1} (m); NMR ($CDCl_3$) δ 1.20 and 1.21 (two d, J = 7.0 Hz, $CH(CH_3)_2$), 2.36 (s, $=CCH_3$), 3.2–3.9 (m, 2 $CH(CH_3)_2$), 6.6–7.0 (m, H_5), 7.0–7.2 (m, H_3 and H_6); mass spectrum *m/e* 204 (M^+), 189, 161 (base peak); exact mass spectrum *m/e* 204.1497 (calcd for $C_{14}H_{20}O$, 204.1514).

2,7-Diisopropyl-4,5-dimethyltropone (13). A mixture of 2,7-diisopropyl-4,5-dimethyl-4-cycloheptenone (**6**, 48.0 mg, 0.216 mmol) and PHT (653 mg, 1.31 mmol) in THF (4 mL) was stirred at 25 °C. After 15 h, the reaction mixture was worked up to give a crude bromination product (215 mg). Four components were detected by TLC analysis (benzene, R_f 0.61, 0.51, 0.30, and 0.16). The crude product was heated with LiCl (200 mg, 4.70 mmol) and DMF (3 mL) at 130 °C for 1 h and then at 145 °C for 20 min. Workup followed by preparative TLC (1:1 benzene–hexane, three developments) afforded **13** (24.9 mg, 53%, R_f 0.32): mp 47–48 °C (from petroleum ether); IR ($CHCl_3$) 3010 (m), 2966 (s), 2931 (w), 2865 (w), 1683 (w), 1620 (w), 1563 (s), 1495 (m), 1465 (s), 1409 (m), 1383 (w), 1362 (w), 1325 (w), 1233 (w), 1165 (w), 1110 (w), 1058 (w), 1010 (w), 908 cm^{-1} (w); NMR ($CDCl_3$) δ 1.19 (d, J = 7.0 Hz, 2 $CH(CH_3)_2$), 2.27 (s, 2 $=CCH_3$), 3.1–3.8 (m, 2 $CH(CH_3)_2$), 7.00 (s, H_3 and H_6); mass spectrum *m/e* 218 (M^+), 203, 175 (base peak); exact mass spectrum *m/e* 218.1551 (calcd for $C_{15}H_{22}O$, 218.1671).

2,7-Dimethyl-γ-tropolone (16). A solution of **1** (46.4 mg, 0.336 mmol) and pyridinium bromide perbromide (590 mg, 1.84 mmol) in acetic acid (2 mL) was allowed to stand at 30 °C for 12 h. Aqueous workup gave crude bromination product (170 mg). TLC analysis (1:1 benzene–hexane) showed that three products (R_f 0.48 (major), 0.35, and 0.15) were formed. The crude bromides were treated with LiCl (150 mg, 3.54 mmol) in DMF (2 mL) at 130 °C for 1 h. Usual workup followed by TLC separation (1:1 benzene–hexane, two developments, and benzene) afforded a pure sample of 4-bromo-2,7-dimethyltropone (**14**, 61.0 mg, 85%, R_f 0.56): IR ($CHCl_3$) 2955 (m), 1605 (w), 1570 (s), 1508 (w), 1420 (w), 1370 (m), 1168 (m), 1150 (w), 1070 (w), 1042 (w), 1030 (w), 970 (m), 892 (w), 868 (w), 842 cm^{-1} (m); NMR ($CDCl_3$) δ 2.28 (br s, 2 CH_3), 6.9–7.1 (m, H_3 and H_6), 7.3–7.5 (m, H_5); mass spectrum *m/e* 214, 212 (1:1 ratio, base peak, M^+), 186, 184, 171, 169; UV (H_2O) λ_{max} 239 nm (log ϵ 4.45), 330 (3.92), 345 (3.83). Anal. (C_9H_9OBr) C, H. A mixture of **14** (27.5 mg, 0.129 mmol), 48% HBr (1.5 mL), water (2.0 mL), and acetic acid (1.5 mL) in a sealed tube was heated at 130 °C for 8 h. After the reaction mixture was concentrated, the residue was dissolved in CH_3OH (3 mL) containing sodium acetate (200 mg, 2.44 mmol). The solvent was evaporated and the resulting solid was extracted with ether (10 mL × 6). Evaporation of the solvent followed by TLC purification (1:1 ether–benzene, three developments) gave **16** (12.5 mg, 55% based on **1**, R_f 0.15): mp 168–170 °C (from ethyl acetate); IR (Nujol mull) 2924 (s), 2862 (m), 2680 (w), 2560 (w), 1625 (w), 1596 (w), 1466 (s), 1363 (s), 1294 (m), 1235 (m), 1185 (m), 1153 (m), 1054 (w), 1025 (m), 837 (m), 757 (w), 746 (w), 736 cm^{-1} (w); NMR (Me_2SO-d_6) δ 2.03 (s, CH_3), 2.13 (s, CH_3), 6.66 (dd, $J_{3,5}$ = 2.5, $J_{5,6}$ = 10.5 Hz, H_5), 7.62 (d, J = 2.5 Hz, H_3), 7.63 (d, J = 10.5 Hz, H_6); mass spectrum *m/e* 150 (M^+), 122, 107 (base peak); exact mass spectrum *m/e* 150.0685 (calcd for $C_9H_{10}O_2$, 150.0681).

2,7-Diisopropyl-γ-tropolone (17). Bromination of **4** (76.0 mg, 0.392 mmol) with pyridinium bromide perbromide (1.26 g, 3.95 mmol) in acetic acid (3 mL) followed by workup gave the crude tetrabromide (260 mg) (R_f 0.65, benzene). The crude bromide was heated in a mixture of LiCl (300 mg, 7.05 mmol) and DMF (3 mL) at 130–140 °C for 1.5 h. Workup followed by TLC purification (benzene) of the crude product gave pure 4-bromo-2,7-diisopropyltropone (**15**, 89 mg, 83%, R_f 0.45): IR ($CHCl_3$) 2965 (s), 2870 (w), 1615 (w), 1576 (s), 1505 (w), 1466 (m), 1394 (m), 1378 (m), 1246 (w), 1096 (w), 1063 (w), 1011 (w), 985 (w), 935 (w), 860 (w), 848 cm^{-1} (w); NMR δ 1.16 (d, J = 7.0 Hz, $CH(CH_3)_2$), 1.20 (d, J = 7.0 Hz, $CH(CH_3)_2$), 3.0–3.7 (m, 2 $CH(CH_3)_2$), 6.8–7.0 (m, H_3 and H_6), 7.0–7.1 (m, H_5); mass spectrum *m/e* 270, 268 (1:1 ratio, M^+); UV (CH_3OH) λ_{max} 239 nm (log ϵ 4.30), 319 (3.85). Anal. ($C_{13}H_{17}OBr$) C, H. Hydrolysis of **15** (44.0 mg, 0.161 mmol) in a mixture of 48% HBr (4.5 mL), water (6.0 mL), and acetic acid (4.5 mL) was carried out at 130 °C for 10 h. Workup followed by preparative TLC (benzene) gave **17** (18.8 mg, 46% based on **4**), mp 130–135 °C. A pure sample of **17** was obtained by recrystallization from ethyl acetate: mp 160–161 °C; IR (Nujol mull) 2960 (s), 2925 (s), 2855 (s), 2740 (w), 2690 (w), 2570 (w), 1628 (w), 1606 (w), 1457 (s), 1390 (m), 1374 (m), 1279 (m), 1230 (m), 1199 (m), 1164 (w), 1101 (w), 1050 (m), 962 (w), 932 (w), 871 (w), 846 (m), 825 (w), 800 (w), 740 (w), 720 cm^{-1} (w); NMR (Me_2SO-d_6) δ 1.08 (d, J = 7.0 Hz, $CH(CH_3)_2$), 1.11 (d, J = 7.0 Hz, $CH(CH_3)_2$), 3.0–3.6 (m, 2 $CH(CH_3)_2$), 6.41 (dd, $J_{3,5}$ = 2.0, $J_{5,6}$ = 10.0 Hz, H_5), 7.05 (d, J = 2.0 Hz, H_3), 7.12 (d, J = 10.0 Hz, H_6); mass spectrum *m/e* 206 (M^+) (base peak), 191, 163; exact mass spectrum *m/e* 206.1317 (calcd for $C_{13}H_{18}O_2$, 206.1307).

3,5-Dimethylbicyclo[5.1.0]octan-4-one (19). Gaseous diazomethane diluted with N_2 was bubbled into a solution of **1** (388 mg, 2.80 mmol) and bis(*N*-α-phenylethylsalicylaldiminato)copper(II) (100 mg, 0.195 mmol) in a 1:1 mixture of benzene and hexane (5.0 mL) at −10 to 0 °C. The introduction of diazomethane was continued until more than 95% of **1** was consumed. The solvent was evaporated and the residual oil was purified by preparative TLC (silica gel, benzene, R_f 0.21) to give **19** (383 mg, 90%). GLC analysis indicated that **19** was a mixture of at least two stereoisomers. The spectral properties of the mixture follow: IR 1702, 1692 (C=O), 3040, 1025 cm^{-1} (cyclopropane); NMR δ −0.1 to 1.2 (m, cyclopropane ring protons), 1.01 (d, J = 7.0 Hz, CH_3), 1.05 (d, J = 7.0 Hz, CH_3), 1.23 (d, J = 7.0 Hz, CH_3), 1.8–2.2 (m, 2 CH_2), 2.2–2.9 (m, 2 CHCO); mass spectrum *m/e* 152 (M^+). Anal. ($C_{10}H_{16}O$) C, H. The products were used for further reaction without separation.

2,7-Dimethyl-4,5-homotropone (20). To a mixture of **19** (103 mg, 0.679 mmol) and anhydrous sodium acetate (223 mg, 2.72 mmol) in freshly distilled $CHCl_3$ (5.6 mL) was added a solution of Br_2 (185 mg, 1.66 mmol) in the same solvent (1.0 mL) and the mixture was stirred at room temperature for 2 h. Br_2 (94 mg, 0.59 mmol) was added renewedly and the mixture was allowed to stand at room temperature for an additional 8 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2. Evaporation gave 2,7-dibromo-2,7-dimethylbicyclo[5.1.0]octan-4-one as a pale yellow oil (275 mg) which was subjected to further reaction without purification. A mixture of the bromination product (275 mg), LiBr (590 mg, 6.79 mmol), and Li_2CO_3 (500 mg, 6.79 mmol) in dry DMF (10 mL) was kept at 150 °C for 5 h. Usual workup gave a yellow oil (ca. 1 g), which was dissolved in a mixture of 1:1 ethyl acetate–hexane (5 mL) and the solution was washed with water (2 mL × 3) to remove DMF. Evaporation of the solvent gave a yellow oil (103 mg) which was purified by TLC (1:1 ether–hexane, two developments) to afford **20** (33 mg, 33%, R_f 0.60) as colorless crystals, mp 34–35 °C (from petroleum ether), accompanied by 2,5-dimethylbicyclo[5.1.0]oct-2-en-4-one (16.0 mg, 16%). **20**: IR 2955 (m), 2920 (m), 1645 (w), 1615 (s), 1455 (m), 1430 (w), 1400 (m), 1375 (m), 1355 (w), 1245 (w), 1163 (w), 1118 (w), 1030 (m), 1023 (m), 953 (w), 903 (w), 893 (w), 855 cm^{-1} (m); UV (C_2H_5OH) λ_{max} 216 nm (log ϵ 3.77), 281 (3.74); mass spectrum *m/e* 148 (M^+), 133, 119, 105 (base peak). Anal. ($C_{10}H_{12}O$) C, H. The NMR data of **20** is shown in Figure 1. The structure of 2,5-dimethylbicyclo[5.1.0]-oct-2-en-3-one was tentatively determined based on its spectral properties: IR (film) 1655, 1455, 1373, 1015 cm^{-1}; NMR δ 0.0–1.5

(m, cyclopropane ring protons), 1.01 (d, J = 8.0 Hz, CH_3), 1.74 (br s, $=CCH_3$), 1.7–2.2 (m, CH_2), 2.2–2.8 (m, $CHCH_3$), 6.0–6.3 (m, $=CH$); mass spectrum m/e 150 (M^+).

2,7-Dimethylhydroxyhomotropylium Cation (21). A solution of **20** (11.0 mg) in CCl_4 (0.1 mL) was placed in an NMR tube and cooled to −10 °C. To this was added 96% H_2SO_4 (0.4 mL) and the mixture was shaken vigorously for a few minutes. Carbon tetrachloride was then removed under reduced pressure and the resulting solution of **21** was subjected to NMR analysis at room temperature. A sample for UV measurement was prepared by extracting a solution of **20** in CH_2Cl_2 with the known amount of 96% H_2SO_4 as described above. UV (H_2SO_4) λ_{max} 207 nm (log ϵ 4.08), 250 (4.25), 328 (3.67).

Conversion of 8-Oxabicyclo[3.2.1]oct-6-en-3-ones to Troponoids. 2,4-Dimethyl-8-oxabicyclo[3.2.1]octan-3-one (24). A solution of 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**22**, R = CH_3) (1.01 g, 6.64 mmol, a 1:1 mixture of cis and trans isomers) in C_2H_5OH (11 mL) was stirred in the presence of 10% Pd/C (ca. 200 mg) under an atmospheric pressure of H_2 for 60 h. The crude product (1.01 g) was purified by column chromatography (1:10 ether–benzene) to give a 1:1 mixture of cis and trans isomers of **24** (954 mg, 94%) as a pale yellow oil. The spectral properties of the mixture follow: IR 1707 (C=O), 1147, 1087, 1038 cm^{-1}; NMR δ 0.89 (d, J = 7.0 Hz, CH_3(eq)), 1.24 (d, J = 7.0 Hz, CH_3(ax)), 1.6–1.7 (m, C_6 and C_7 methylene), 1.8–2.3 (m, COCH(eq)), 2.4–2.9 (m, COCH(ax)), 4.0–4.5 (m, OCH); mass spectrum m/e 154 (M^+), 98, 86. Anal. ($C_9H_{14}O_2$) C, H.

6-Acetoxy-2,7-dimethylcyclohept-2-enone (25). To a solution of **24** (106 mg, 0.69 mmol) in dry acetic anhydride (0.75 mL) was added a solution of boron trifluoride etherate (56.3 mg, 0.397 mmol) in the same solvent (0.75 mL) and the mixture was stirred at 30 °C for 24 h under N_2. The excess acetic anhydride and boron trifluoride etherate were removed in vacuo and the resulting residue was purified by TLC (1:10 acetone–hexane, two developments) to give the starting keto ether **24** (15.3 mg, R_f 0.44), **25** (65.7 mg, 49%, R_f 0.40), and an unidentified compound (22.0 mg, R_f 0.33). **25**: IR 1736, 1235 (ester), 1676 cm^{-1} (enone); NMR δ 1.07 (d, J = 7.0 Hz, $COCHCH_3$), 1.8–1.9 (m, $=CCH_3$), 1.99 (s, $COCH_3$), 2.1–2.6 (m, 2 CH_2), 2.6–3.2 (m, $COCHCH_3$), 4.9–5.4 (m, $CHOCOCH_3$), 6.3–6.7 (m, $=CH$); mass spectrum m/e 154 (M^+), 136, 108; UV (C_2H_5OH) λ_{max} 240 nm (log ϵ 3.85). Anal. ($C_{11}H_{16}O_3$) C, H.

2,7-Dimethyltropone (8) from 25. A mixture of **25** (27.7 mg, 0.141 mmol), NBS (35.6 mg, 0.20 mmol), benzoyl peroxide (3 mg), and CCl_4 (0.2 mL) was heated at 85 °C for 15 min under N_2. Solid material was filtered off and the filtrate was concentrated to give a yellow oil (34 mg). TLC purification (1:10 ether–hexane, three developments) gave 6-acetoxy-4-bromo-2,7-dimethylcyclohept-2-enone as a mixture of three stereoisomers (total yield 34 mg, 94%, R_f 0.40, 0.29, and 0.19). The main product (R_f 0.29) exhibited the following spectral properties: IR 1743, 1226 (ester), 1687 cm^{-1} (enone); NMR δ 1.15 (d, J = 6.0 Hz, $COCHCH_3$), 1.8–1.9 (m, $=CCH_3$), 2.05 (s, $OCOCH_3$), 2.2–3.1 (m, $CHCH_3$), 2.50 (dd, J = 3.5 and 5.0 Hz, CH_2), 4.5–5.2 (m, CHBr and $CHOCOCH_3$), 6.4–6.6 (m, $=CH$); mass spectrum m/e 276, 274 (1:1 ratio) (M^+). The stereoisomeric mixture (28.0 mg, 0.108 mmol) was mixed with LiCl (44.8 mg, 1.08 mmol) and Li_2CO_3 (5.3 mg, 0.06 mmol) in dry DMF (1 mL) and heated at 140 °C for 1 h. After usual workup a yellow-brown oil (19.2 mg) was obtained. Purification by TLC (1:10 ether–hexane, three developments) gave a pure sample of **8** (13.3 mg, 92%) as a colorless oil. The IR and NMR spectra of **8** were superimposable on those of an authentic sample.[7]

4-Bromo-2,7-dimethyltropone (14) from 25. The enone acetate **25** (26.6 mg, 0.136 mmol) was brominated by heating with NBS (60.5 mg, 0.340 mmol) and benzoyl peroxide (3 mg) in CCl_4 (0.3 mL) at 80–90 °C for 15 min under N_2. The solid material was removed by filtration and the filtrate was concentrated to give a brown oil. Preparative TLC (1:10 ether–hexane) gave a mixture containing at least five compounds (63.2 mg, R_f 0.43, 0.38, 0.33, 0.27, and 0.20). This was subjected to further reaction without separation. The bromination products were dissolved in dry DMF (1 mL) and heated with LiCl (51 mg, 1.3 mmol) and Li_2CO_3 (6.2 mg, 0.07 mmol) at 140 °C for 2 h. The reaction mixture was worked up as usual to give a brown oil. Purification by TLC (1:10 ether–hexane, three developments) gave **14** (11.8 mg, 41%, R_f 0.33) and **8** (4.8 mg, 26%, R_f 0.24). The IR and NMR spectra of these products were identical with those of authentic samples prepared starting from **1**.

***trans*-17-Oxatricyclo[9.4.1.1^{12,15}]heptadecan-16-one (27).** A solution of *trans*-17-oxatricyclo[9.4.1.1^{12,15}]heptadec-13-en-16-one (**26**) (661 mg, 2.67 mmol) in C_2H_5OH (10 mL) was stirred in the presence of 5% Pd/C (ca. 30 mg) under H_2 atmosphere for 48 h. After removal of the catalyst by filtration the filtrate was concentrated in vacuo to give **27** (670 mg, 100%) as a colorless solid: IR 1708 (C=O), 1062 cm^{-1} (C–O–C); NMR δ 0.9–1.6 (m, 7 CH_2), 1.6–1.9 (m, 3 CH_2), 1.9–2.2 (m, CH_2 and COCH(eq)), 3.19 (dd, J = 4.5 and 10.5 Hz, COCH(ax)), 4.30 (m, 2 OCH); mass spectrum m/e 250 (M^+), 232, 221. Anal. ($C_{16}H_{26}O_2$) C, H.

Bicyclo[9.4.1]heptadeca-1(15),13-dien-16-one (28). To the tricyclic ketone **27** (50.0 mg, 0.20 mmol) was added FSO_3H (2.2 mL). The solution was stirred at room temperature for 4.5 h. The reaction mixture was added dropwise to a mixture of solid $NaHCO_3$ and CH_2Cl_2 (30 mL) at −10 to 0 °C. Solid material was removed by filtration and the filtrate was washed successively with saturated $NaHCO_3$ solution (1 mL) and saturated KNO_3 solution. Concentration of the organic layer gave a crude product (48.6 mg). Preparative TLC (1:10 ethyl acetate–hexane, two developments) afforded a pure sample of **28** (27.5 mg, 59.5%). Its IR and NMR spectra were identical with the reported ones.[25]

2,7-Nonamethylenetropone (29). A mixture of **28** (30.7 mg, 0.132 mmol), 10% Pd/C (213 mg), and benzene (2 mL) was heated at 130 °C for 13.5 h in a sealed tube. After workup the crude product (29 mg) was purified by preparative TLC (1:5 ethyl acetate–hexane) to give **29** (15.5 mg, 51%). The IR, NMR, and mass spectra of **29** were identical with those of an authentic sample.[25]

Synthesis of Natural Troponoids. Preparation of 3-Isopropylfuran. 3-Isopropylfuran was obtained by the application of the procedure reported for the synthesis of 2-isopropylfuran.[40] A 1.50 M solution of CH_3MgI in ether (120 mL, 0.18 mol) was added dropwise to ethyl 3-furoate (10.5 g, 74.0 mmol) in the same solvent (38 mL) at room temperature. After workup and distillation 3-isopropenylfuran was obtained in 42% (3.30 g) yield: bp 42–44 °C (36 mm); NMR δ 1.95 (d, J = 2.0 Hz, CH_3), 4.86 (m, a proton of $=CH_2$ cis to CH_3), 5.16 (s, a proton of $=CH_2$ trans to CH_3), 6.46 (AB, J = 2.0 Hz, OCH=CH), 7.23 (AB, J = 2.0 Hz, OCH=CH), 7.32 (s, OCH); mass spectrum m/e 108 (M^+). Hydrogenation of 3-isopropenylfuran (3.25 g, 30.0 mmol) was performed in a mixture of pentane (30 mL) and ether (20 mL) in the presence of 10% Pd/C (200 mg) under H_2 for 105 min. Workup followed by short-path distillation gave a 4:1 mixture of 3-isopropylfuran and 3-isopropyltetrahydrofuran (3.54 g).

6-Isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (31). To a mixture of tetrabromoacetone (**30**, 7.50 g, 20.0 mmol) and $Fe_2(CO)_9$ (5.50 g, 15.0 mmol) was added a solution of 3-isopropylfuran (0.880 g, 8.00 mmol, contaminated with 3-isopropyltetrahydrofuran (0.22 g)) in benzene (20 mL) and the mixture was stirred at 60 °C for 2.5 h. The reaction mixture was cooled to room temperature and to this were added Zn–Cu couple (10.0 g, 0.15 g-atom), NH_4Cl-saturated CH_3OH (15 mL), and benzene (40 mL). The mixture was vigorously stirred for 20 min and then a saturated aqueous solution of ethylenediaminetetraacetic acid disodium salt (250 mL) and CH_2Cl_2 (100 mL) were added to quench the reaction. Solid material was removed by filtration through a Celite 545 pad. Concentration of the CH_2Cl_2 layer gave an oil (2.40 g). Purification by column chromatography (silica gel, 50 g) eluted with 1:10 ether–benzene afforded **31** (0.945 g, 71%): IR 1718 cm^{-1} (C=O); NMR δ 1.10 (d, J = 6.5 Hz, $CH(CH_3)_2$), 2.19 (dd, J = 6.0 and 16.0 Hz, C_4 methylene), 2.1–2.3 (m, $CH(CH_3)_2$), 2.68 (ddd, J = 1.5, 4.5, and 17.0 Hz, C_2 methylene), 4.83 (m, 2 OCH), 5.73 (dd, J = 1.5 and 1.5 Hz, =CH); mass spectrum m/e 166 (M^+), 151, 123. Anal. ($C_{10}H_{14}O_2$) C, H.

6-Isopropyl-8-oxabicyclo[3.2.1]octan-3-one (32). The olefinic keto ether **31** (550 mg, 3.30 mmol) in CH_3OH (5.6 mL) saturated with Na_2CO_3 was stirred overnight in the presence of 10% Pd/C (102 mg) under H_2 atmosphere. Workup and distillation of the crude product (478 mg) in vacuo gave **32** (425 mg, 77%), bp 108–130 °C (bath temperature, 0.6 mm), which crystallized: mp 22–25 °C; IR 1720 cm^{-1} (C=O); NMR δ 0.92, 0.95 (two d, J = 6.5 Hz, $CH(CH_3)_2$), 1.0–2.8 (m, 3 CH_2, CH_2, and $CHCH(CH_3)_2$), 4.40, 4.60 (two m, OCH); mass spectrum m/e 168 (M^+). Anal. ($C_{10}H_{16}O_2$) C, H.

Nezukone (34). A solution of **32** (20.0 mg, 0.120 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise to stirred FSO_3H (0.8 mL) at room temperature and the mixture was further stirred at this temperature for 13 min. This solution was diluted with CH_2Cl_2 (2 mL) and cooled to 0 °C. Then solid $NaHCO_3$ (3 g) was added in 1-g portions and the mixture was stirred at room temperature for 2 h. Solid material was removed by filtration and the filtrate was concentrated in vacuo to give

a yellow oil (20.0 mg), which was purified by column chromatography (silica gel, 2 g, 1:10 acetone–hexane) yielding **33** (10.7 mg, 59%). Structural assignment of this unstable dienone was done based on its spectral properties: IR 1650 (C=O), 1615 cm^{-1} (C=C); NMR δ 0.98 (d, J = 7.0 Hz, $CH(CH_3)_2$), 1.90 (m, $CH(CH_3)_2$), 2.45 (m, $CHCH_2$), 5.58 (d, J = 12.0 Hz, 2 COCH=), 6.46 (br d, J = 12.0 Hz, 2 COCH=C*H*); mass spectrum *m/e* 150 (M^+), 135, 107; UV (C_2H_5OH) λ_{max} 237 nm (log ϵ 3.72).

A solution of **33** (22.0 mg, 0.15 mmol), 2,3-dichloro-5,6-dicyanoquinone (DDQ, 37.0 in benzene (1.5 mL) mg, 0.16 mmol), and a catalytic amount of *p*-toluenesulfonic acid was stirred in a sealed tube at 100 °C for 30 min under argon. After removal of the solid material by filtration the filtrate was concentrated to give an oil (36.0 mg), which was dissolved in benzene (2 mL). The solution was washed successively with saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL). The organic layer was dried and concentrated in vacuo to afford a residue (16.2 mg). Distillation under reduced pressure gave **34** (10.8 mg, 54%) as a pale yellow oil. An analytical sample of **34** was obtained by TLC (1:10 ether–benzene, R_f 0.19) followed by distillation. IR, NMR, UV, and mass spectra of **34** were identical in all respects with those of natural nezukone. The semicarbazone of **34** melted at 170–173 °C. Upon mixing with the semicarbazone derived from natural nezukone, no depression of melting point was observed.

1-Isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (35). A mixture of **30** (40.0 g, 107 mmol), $Fe_2(CO)_9$ (27.3 g, 75.0 mmol), and 2-isopropylfuran (5.50 g, 50.0 mmol) in benzene (100 mL) was stirred at 60 °C for 2 h. Workup as described in the preparation of **31** followed by treatment with Zn–Cu couple (70 g, 1.07 g-atoms) in 95% CH_3OH (300 mL) at room temperature for 30 h gave a brown oil (4.4 g). After purification with a short alumina column, **35** (3.09 g, 47% yield based on 2-isopropylfuran), mp 35–37 °C, was obtained. An analytical sample was prepared by preparative GLC: IR 1713 cm^{-1} (C=O); NMR δ 0.95 (d, J = 6.5 Hz, $CH(CH_3)_2$), 1.5–2.8 (m, 2 CH_2 and $CH(CH_3)_2$), 4.8–5.1 (m, OCH), 5.9–6.3 (m, 2 =CH); mass spectrum *m/e* 166 (M^+), 151, 123 Anal. ($C_{10}H_{14}O_2$) C, H.

1-Isopropyl-8-oxabicyclo[3.2.1]octan-3-one (36). The cycloadduct **35** (520 mg, 3.13 mmol) was stirred in C_2H_5OH (6.6 mL) containing 10% Pd/C (89 mg) and $NaHCO_3$ (316 mg, 3.76 mmol) under atmospheric pressure of H_2 at room temperature for 15 h. After usual workup **36** (505 mg, 96%) was obtained as a pale yellow oil which was suitable for the next reaction without further purification. An analytical sample was obtained by preparative GLC: IR 1715 cm^{-1} (C=O); NMR δ 0.92 and 0.97 (d, J = 6.5 Hz, $CH(CH_3)_2$), 1.5–2.8 (m, 4 CH_2 and $CH(CH_3)_2$), 4.5–4.8 (m, OCH). Anal. ($C_{10}H_{16}O_2$) C, H.

3-Isopropyltropone (39). The ether linkage of **36** was cleaved as follows. To a solution of **36** (100 mg, 0.60 mmol) in acetic anhydride (2.0 mL) kept at −20 °C was added boron trifluoride etherate (10 drops) with stirring. The reaction mixture was allowed to come slowly to −10 °C and stirred at this temperature for an additional 3 h, and to this mixture was added saturated $NaHCO_3$ solution (5 mL). Extractive workup of the aqueous solution with ethyl acetate gave a crude oil (130 mg), which was again dissolved in ethyl acetate (3.0 mL) and stirred with basic alumina (4.0 g) at room temperature overnight. The oily product was subjected to preparative TLC (1:20:20 ether–acetone–hexane) to give 6-isopropylidenecyclohept-2-enone (10 mg, 9%), 6-(α-acetoxyisopropyl)cyclohept-2-enone (**37**, 41 mg, 33%), and a 2:1 mixture (38 mg) of 3-isopropylcyclohepta-2,6-dienone (**38**, 25%) and unreacted **36**. **37**: IR 1732 (ester carbonyl), 1667 cm^{-1} (enone carbonyl); NMR δ 1.43 (s, $C(CH_3)_2$), 1.93 (s, $COCH_3$), 1.8–2.2 (m, C_5 methylene), 2.2–2.7 (m, =CCH_2, $COCH_2$, and CH), 5.87 (d, J = 12.0 Hz, COC*H*=CH), 6.48 (dt, J = 12.0 and 5.0 Hz, COCH=C*H*); mass spectrum *m/e* 210 (M^+), 150; UV (C_2H_5OH) λ_{max} 226 nm (log ϵ 3.79). Anal. ($C_{12}H_{18}O_3$) C, H. The dienone **38** was separated from slightly less polar **35** by repeated column chromatography (1:20:20 ether–acetone–hexane). The dienone **38** thus obtained is unstable at room temperature and structure determination was done based on spectral data: IR 1646 (C=O), 1612 cm^{-1} (C=C); NMR δ 1.14 (d, J = 7.0 Hz, $CH(CH_3)_2$), 2.2–2.8 (m, 2 CH_2, and $CH(CH_3)_2$), 5.89 (br s, COC*H*=CCH), 5.96 (br d, J = 13.0 Hz, COC*H*=CH), 6.50 (m, COCH=C*H*); mass spectrum *m/e* 150 (M^+). Structural assignment of 6-isopropylidenecyclohept-2-enone was tentatively done based on its spectral properties: IR 1670 cm^{-1} (C=O); NMR δ 1.68 and 1.75 (two s, $C(CH_3)_2$), 2.4–2.7 (m, 2 CH_2), 3.27 (m, $COCH_2$), 5.85 (d, J = 12.0 Hz, COC*H*=CH), 6.2–6.8 (m, COCH=C*H*); mass spectrum *m/e* 152 (M^+).

The acetoxy enone **37** was readily converted to **39.** A mixture of **37** (60 mg, 0.29 mmol), NBS (55 mg, 0.29 mmol), and azobisisobutyronitrile (15 mg) in CCl_4 (1.0 mL) was stirred at 80 °C for 1 h under N_2. After removal of insoluble succinimide by filtration, the filtrate was evaporated to leave an oil. Preparative TLC (1:10 ether–benzene) yielded crude 6-(α-acetoxyisopropyl)-4-bromocyclohept-2-enone as a semisolid (82 mg, 98%). The bromide (60 mg, 0.21 mmol), without further purification, was dissolved in DMF (1.5 mL), mixed with dry LiCl (40 mg) and Li_2CO_3 (40 mg), and heated at 130–140 °C for 1 h. Extractive workup and preparative TLC (1:2:20 ether–acetone–hexane) of the resulting oil gave **39** (24.4 mg, 77%, R_f 0.35) as a pale yellow oil: IR 1637, 1586 cm^{-1} (tropone ring); NMR δ 1.23 (d, J = 6.5 Hz, $CH(CH_3)_2$), 2.70 (seven lines, J = 6.5 Hz, $CH(CH_3)_2$), 6.75 (m, aromatic protons); mass spectrum *m/e* 148 (M^+), 120, 105; UV (C_2H_5OH) λ_{max} 236 nm (log ϵ 4.23), 303 (3.67). An analytical sample was obtained by bulb-to-bulb distillation, bp 110–120 °C (bath temperature) (3 mm). Anal. ($C_{10}H_{12}O$) C, H.

The tropone **39** was also prepared from **38.** A mixture of **38** (15 mg, 0.10 mmol), DDQ (34 mg, 0.15 mmol), and a catalytic amount of *p*-toluenesulfonic acid in dry benzene (1 mL) was heated in a sealed tube at 100 °C for 3 h. TLC separation of the mixture (1:4:20 ether–acetone–hexane, three developments) gave pure tropone **39** (12 mg, 80%).

β-Thujaplicin (Hinokitiol) (41). To a solution of **39** (11 mg, 0.074 mmol) in C_2H_5OH (0.5 mL) was added 100% hydrazine hydrate (7 drops) at room temperature. The reaction mixture was allowed to stand at room temperature for 15 min and concentrated in vacuo. The resulting oil was dissolved in ether and passed through a short silica gel column to yield after concentration 2-amino-6-isopropyltropone (**40**, 12 mg, 100%) as a pale yellow oil: IR 1594 cm^{-1}; NMR δ 1.24 (d, J = 6.5 Hz, $CH(CH_3)_2$), 2.76 (seven lines, J = 6.5 Hz, $CH(CH_3)_2$), 6.30 (br s, NH_2), and 6.3–7.0 (m, aromatic protons); mass spectrum *m/e* 163 (M^+), 120. The amino tropone **40** (11 mg, 0.068 mmol) was heated with 2 N KOH in 50% aqueous ethanol at 100 °C for 20 h. The mixture was cooled, acidified (pH 1) by the addition of 6 N HCl, and extracted with 1:1 ether–benzene. The organic layer was dried and concentrated to leave **41** (11 mg, 100%). The IR, NMR, UV, and mass spectra were superimposable on those of the authentic sample.

2-Isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (43). A mixture of 1,1,3-tribromo-4-methylpentan-2-one (**42**, 1.68 g, 5.00 mmol), $Fe_2(CO)_9$ (2.20 g, 6.04 mmol), and furan (15 mL) was heated at reflux for 16 h and worked up in a usual manner to give a dark oil (1.38 g). Treatment of this oil with Zn–Cu couple (3.6 g, 55.0 mg-atoms) in CH_3OH (15 mL) saturated with NH_4Cl at room temperature for 1.5 h followed by preparative TLC (1:10 ethyl acetate–hexane) afforded **43** (290 mg, 35%), which has an α-isopropyl group: IR 1720 cm^{-1} (C=O); NMR δ 0.90 and 1.05 (two d, J = 6.5 Hz, $CH(CH_3)_2$), 1.5–2.9 (m, CH_2, CHCO, and $CH(CH_3)_2$), 4.95 (m, 2 OCH), 6.17 (s, 2 =CH); mass spectrum *m/e* 166 (M^+). Anal. ($C_{10}H_{14}O_2$) C, H.

2-Isopropyl-8-oxabicyclo[3.2.1]octan-3-one (44). Catalytic hydrogenation of **43** (133 mg, 0.80 mmol) was carried out in C_2H_5OH (0.8 mL) over 10% Pd/C (13.5 mg) under atmospheric pressure of H_2. After workup the oily residue was distilled at ca. 100 °C (0.05 mm) to afford **44** (128 mg, 96%): IR 1710 cm^{-1} (C=O); NMR δ 0.88 and 1.00 (d, J = 6.5 Hz, $CH(CH_3)_2$), 1.5–3.0 (m, 3 CH_2 and $CHCH(CH_3)_2$), 4.6 (m, 2 OCH); mass spectrum *m/e* 168 (M^+). Its semicarbazone melted at 203–205 °C. Anal. ($C_{11}H_{19}N_3O_2$) C, H, N.

2-Isopropyltropone (47). A solution of **44** (150 mg, 0.89 mmol) in CH_2Cl_2 (2.4 mL) was added dropwise to stirred FSO_3H (600 mg, 6.00 mmol) at 0 °C over a period of 4 min and the resulting heterogeneous mixture was stirred at room temperature for 1 h. The mixture was diluted with cold ether (10 mL) and poured into a stirred slurry of $NaHCO_3$ (4.0 g, 47.6 mmol) in ether (16 mL) at 0 °C during 5 min. Stirring was continued for 3 h at room temperature. Inorganic salts were removed by filtration and the filtrate was concentrated to give a yellow oil (127 mg). Separation by preparative TLC (1:1 ethyl acetate–hexane) afforded 2-isopropyl-6-hydroxycyclohept-2-enone (**45**, 85 mg, 57%, R_f 0.14, 1:3 ethyl acetate–hexane) as the major product: IR 3640, 3340 (OH), 1670 cm^{-1} (C=O); NMR δ 0.99 (d, J = 7.0 Hz, $CH(CH_3)_2$), 1.5–2.0 (m, =$CHCH_2CH_2$), 2.0–2.7 (m, $COCH_2$ and OH), 2.76 (m, $CH(CH_3)_2$ and =$CHCH_2$), 4.20 (five lines, J = 6.0 Hz, CHOH), 6.38 (t, J = 6.0 Hz, =CH); mass spectrum *m/e* 168

(M^+); UV (C_2H_5OH) λ_{max} 238 nm (log ϵ 3.88). Anal. ($C_{10}H_{16}O_2$) C, H. The minor product was tentatively assigned as 2-isopropylcyclohepta-2,6-dienone (**46**, 15 mg, 11%, R_f 0.59, 1:3 ethyl acetate–hexane): IR 1650 (C=O), 1620 cm^{-1} (C=C); NMR δ 0.99 (d, J = 7.0 Hz, $CH(CH_3)_2$), 2.38 (m, $2CH_2$), 2.92 (seven lines, J = 7.0 Hz, $CH(CH_3)_2$), 5.8–6.4 (m, 3 =CH); mass spectrum *m/e* 150 (M^+); UV (C_2H_5OH) λ_{max} 237 nm (log ϵ 3.78).

For obtaining **47**, the reaction mixture was subjected to further reaction without separating **45** and **46**. Thus, the mixture of **45** and **46** (75 mg, obtained from **44** (80 mg, 0.48 mmol)), DDQ (238 mg, 1.05 mmol), *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol), and benzene (6 mL) in a sealed tube was stirred at 160 °C for 1.5 h. After removal of black precipitates by filtration, the filtrate was concentrated to leave a dark brown oil (230 mg). Purification by TLC (1:1 acetone–hexane) afforded **47** (39 mg, 55% based on **44**, R_f 0.5) as a pale yellow oil. IR, NMR, UV, and mass spectra were identical with those of an authentic sample.[34]

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