Technische Hochschule in Darmstadt, Prof. David Dolphin of the University of British Columbia, and Prof. C. K. Chang of Michigan State. Prof. Clifford Leznoff of York University suggested the collaboration with Dr. Cerny. In our own Department, discussion with Prof. Norman Rose led to the addition of oxalic acid as a reagent. Dr. Niels Andersen analyzed the AB patterns in the proton NMR providing the data for Table II. J. Wan provided spectral data on Ag(2). Dr. Edmond Green gave additional help. The research was partly supported by a grant from Abbott Research, inc., of Bothell, WA. The mass spectrometer experiments were conducted at the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant CHE-8620177).

**Registry No.** I, TFPP derivative, 119998-79-7; IIA, 119998-81-1; IIB, 119998-82-2; IID, 119998-80-0; TFPD, 25440-14-6.

# Novel Rearrangement of 5,6-Disubstituted Bicyclo[4.2.0]octan-2-ones with $AlCl_3$. Application to Total Synthesis of (±)-5-Oxosilphiperfol-6-ene and (±)-Silphiperfol-6-ene

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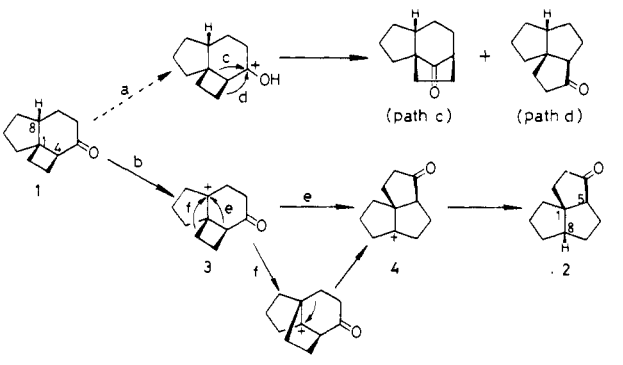
**Abstract:** The acid-catalyzed rearrangement of bi- and tricyclic cyclobutyl ketones **8–20** having a bicyclo[4.2.0]octan-2-one moiety with $AlCl_3$ was studied to elucidate the scope and limitations of the novel rearrangement by which the tricyclic ketone **1** gave the angularly fused triquinane ketone **2**. 5- or 6-methylbicyclo[4.2.0]octan-2-ones (**8** and **9**) did not rearrange. 5,6-Disubstituted bicyclo[4.2.0]octanones **10–18** without methyl substituent at C(1) rearranged smoothly via the new-type pathways to give diquinane derivatives **23–32**. Ketones **19** and **20** having a C(1) methyl group of the bicyclo[4.2.0] unit rearranged through the Cargill-type pathway to give bicyclo[3.2.1]octan-8-one derivatives **33** and **35** and the diquinane ketone **34**. Tetracyclic ketone **21** and bicyclo[5.2.0]nonan-2-one derivative **22** also rearranged via the new-type pathway to give the tetraquinane ketone **36** and homotriquinane **37**. A plausible reaction mechanism for the novel rearrangement is proposed which involves the fission of the central cyclobutane bond to generate the homoallylcarbinyl cation **43** (path g) as the primary process followed by the 1,2-hydride shift (path h) and the subsequent transannular cyclization (path i) of the cation **44** to the product. With this rearrangement as the key step, the facile total syntheses of the angularly fused triquinane natural products (±)-5-oxosilphiperfol-6-ene (**5**) and (±)-silphiperfol-6-ene (**6**) were performed.

The acid-catalyzed rearrangement of cyclobutyl ketones involved in polycyclic ring systems such as [*m.n.*2]propellanes is well-known as the Cargill reaction[1] and has been used in natural product syntheses.[2] Recently we have found that (1*S**,4*S**,8*R**)-tricyclo[6.3.0.0$^{1,4}$]undecan-5-one (**1**) rearranges under action of Lewis acid through a new pathway (path b) to give angularly fused triquinane **2** with high selectivity and proposed the mechanism via the cations **3** and **4** which is entirely different from the Cargill pathway (path a) (Scheme I).[3] This novel rearrangement is noteworthy not only from the viewpoint of the novelty in the reaction path, but also in view of the product whose skeleton is in common with angularly fused triquinane-type natural products.[4] In this connection, we wish to describe here the scope and limitations of the new-type rearrangement for various types of bicyclo[4.2.0]octan-2-one and bicyclo[5.2.0]nonan-2-one derivatives **8–22** catalyzed by Lewis acid ($AlCl_3$), a new proposal for the reaction mechanism which involves the homoallylcarbinyl cation **43**, and its application to the total syntheses of the angularly fused triquinane natural products (±)-5-oxosilphiperfol-6-ene (**5**)[5,6] and (±)-silphiperfol-6-ene (**6**)[7,8] in order to exemplify the utility of the rearrangement.

**Scheme I**



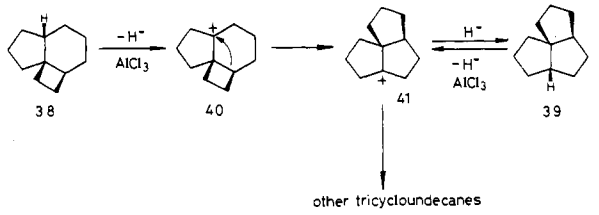

Previously, we tentatively assigned the stereochemistry of **1** to be 1*S**,4*S**,8*S** based on the well-known Wiesner's empirical

† Osaka University.
‡ Miyazaki University.

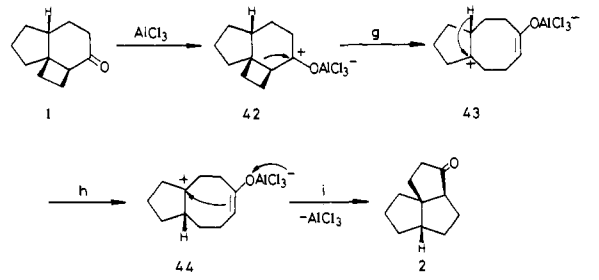
(1) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106.
(2) For a recent review, see: Wong, N. C.; Lau, K. L.; Tam, K.-F. *Top. Curr. Chem.* **1986**, *133*, 83.
(3) Ue, M.; Tsukahara, H.; Kobiro, K.; Kakiuchi, K.; Tobe, Y.; Odaira, Y. *Tetrahedron Lett.* **1987**, *28*, 3979.

0002-7863/89/1511-3707$01.50/0 

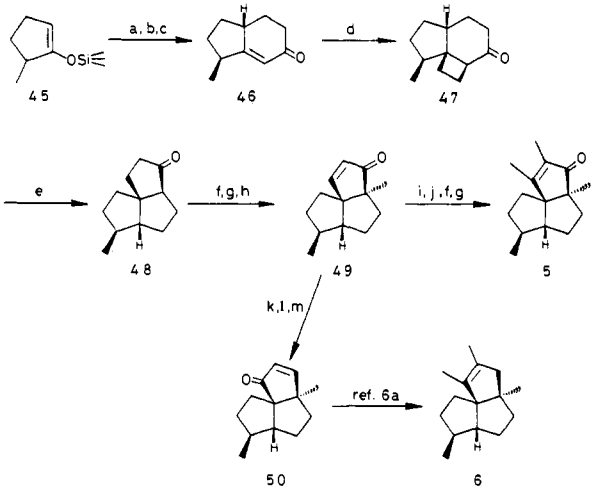
**Scheme II**




**Scheme III**

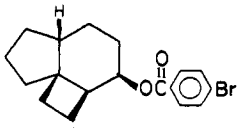



**Scheme IV**[a]




[a] (a) 2-Methyl-2-vinyl-1,3-dioxolane, $TiCl_4$, $Ti(Oi\text{-}Pr)_4$, $CH_2Cl_2$, −78 °C; (b) 10% HCl, THF, room temperature; (c) KOH, EtOH, room temperature; (d) $h\nu$, $CH_2{=}CH_2$, $CH_2Cl_2$, −78 °C; (e) $AlCl_3$, $CH_2Cl_2$, room temperature; (f) $Me_3PhNBr_3$, THF, 0 °C; (g) LiBr, $Li_2CO_3$, DMF, 110 °C; (h) LDA, HMPA, −78 °C, then MeI, −78 °C; (i) $Me_2CuLi$, $Et_2O$, 0 °C to room temperature; (j) LDA, HMPA, −78 °C, then MeI, −78 to −30 °C; (k) 30% $H_2O_2$, 25% NaOH, MeOH, 0 °C; (l) $N_2H_4{\cdot}H_2O$, AcOH, 0 °C to room temperature; (m) pyridinium dichromate, $CH_2Cl_2$, room temperature.

rule.[9,10] In order to ascertain the structure of **1**, single-crystal X-ray analysis of *p*-bromobenzoate **7** derived from **1** by reduction




**7**

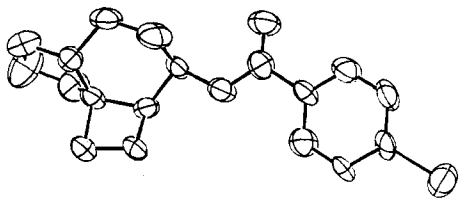


**Figure 1.** Molecular structure of *p*-bromobenzoate **7**.

followed by esterification was carried out and it was revealed that **1** has 1*S**,4*S**,8*R** stereochemistry (Figure 1).

First, the rearrangement behavior of ketones **8–22** with $AlCl_3$ was studied and the results are summarized in Table I together with that of **1**.[12] In the cases of ketones **10–14** and **20**, where the same rearranged product could be derived by both the new-type and the Cargill rearrangements, the actual pathway was determined through the experiments using the monodeuterated ketones labeled at the α-position of the carbonyl group in the same manner as described previously.[3]

The results from Table I are summarized as follows: Reactions of bicyclo[4.2.0]octan-2-ones **8** and **9** without the substituent at C(5) or C(6), respectively, gave no rearranged products. In the cases of ketones **1** and **10–18** having alkyl substituents at C(5) and C(6) positions while without methyl group at C(1) of the bicyclo[4.2.0] unit the new-type rearrangement took place easily to give di- or triquinane-type compounds **2** and **23–32** in excellent yields. However, the ketone **20** with the methyl group at C(1) and **19**, which has the same skeleton as **1** but has also the C(1) methyl, gave products **33–35** through the Cargill pathway. The methyl substituents at C(4) (entry 11), C(7), and C(8) (entries 9, 10) of the bicyclo[4.2.0] unit and at C(9) of the tricyclo-[6.3.0.$0^{1,4}$] skeleton (entry 12) have no effect on the novel rearrangement. Consequently, it is deduced that the requirement for the novel rearrangement is not only to have the alkyl substituents at C(5) and C(6) of the bicyclo[4.2.0]octan-2-one moiety but also not to have the C(1) methyl. The tetracyclic ketone **21** and the higher homologue **22** of **1** having a bicyclo[5.2.0]nonanone unit, which satisfy the above requirement, also gave the tetraquinane derivative **36** and the angularly fused ketone **37** through the new-type pathway as expected.

The above results suggest that the carbocations with positive charge at C(5) and C(6) are involved as intermediates in the novel rearrangement. The previous mechanism (Scheme I) for the formation of **2** was in accord with the above substituent effect, the deuterium labeling experiment, and the following experiments. Reaction of the hydrocarbon **38**, derived by Wolff–Kishner reduction of **1**, with $AlCl_3$ under conditions similar to that of **1**, gave tricyclo[6.3.0.$0^{1,5}$]undecane (**39**) as well as many tricycloundecane isomers at the initial stage of the reaction. Taking into account the greater facility of generation of a tertiary cyclobutylcarbinyl cation rather than a secondary one, it would be reasonable to explain the course of this hydrocarbon rearrangement by generation of the carbocation **40** corresponding to **3** at the first step followed by 1,2-alkyl shift of the central cyclobutane bond[13] to

(4) For a recent review, see: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

(5) Isolation: Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 1399.

(6) (a) Formal total synthesis: Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690. (b) First total synthesis: Demuth, M.; Hinsken, W. *Helv. Chim. Acta* **1988**, *71*, 569.

(7) Isolation: Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.

(8) Syntheses: ref. 6a. Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1985**, *26*, 5987. Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106.

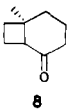
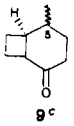
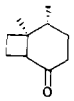
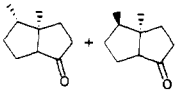
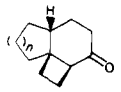
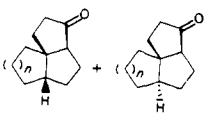
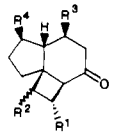
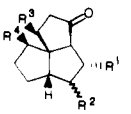
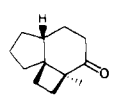
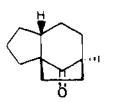
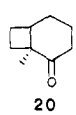
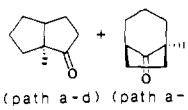
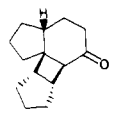
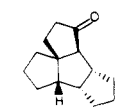
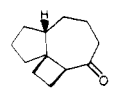
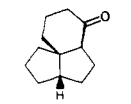
(9) (a) Marini-Bettolo, G.; Sahoo, S. P.; Pouton, G. A.; Tsai, T. Y. R.; Wiesner, K. *Tetrahedron* **1980**, *36*, 719. (b) Blount, J. F.; Gray, G. D.; Atwal, K. S.; Tsai, T. Y. R.; Wiesner, K. *Tetrahedron Lett.* **1980**, *21*, 4413 and references cited therein.

(10) Our initial assignment was supported from the fact that reduction of bicyclo[4.3.0]non-1-en-3-one (**51**) $Li/NH_3$ gave trans- and cis-fused hydrindanones in a ratio of 85:15[11] and that the head to head photoadduct (ca. 95% preference to the head to tail isomer) of the above enone to allene was transformed to the corresponding ethylene adduct **1** by (i) protection of the carbonyl group as 1,3-dioxolane, (ii) ozonolysis, (iii) Wolff–Kishner reduction, and (iv) deprotection. Details are described in the supplemental material.

(11) Cane, D. *Org. React.* (*N.Y.*) **1976**, *23*, 33.

(12) The assignment of the structures of the rearranged products **23–37** as well as the starting ketones is described in detail in the supplemental material.

**Table I.** Reaction of Bi- and Tricyclic Ketones **1** and **8–22** with $AlCl_3$[a]

| entry | reactant | rctn time, h | product, yield |
|---|---|---|---|
| 1 |  **8** | 120 | *b* |
| 2 |  **9**[c] | 48 | *d* |
| 3 |  **10** | 0.5 |  **23** 68% **24** 25% |
| 4 |  **11** | 7 | **23** 60% **24** 33% |
| |  | |  |
| 5 | **1**: $n$ = 1 (cis)[e] | 0.5 | **2** 94% |
| 6 | **12**: $n$ = 2 (cis)[e] | 1 | **25** 75% **26** 9% |
| 7 | **13**: $n$ = 2 (trans)[e] | 1 | **25** 27% **26** 67% |
| 8 | **14**: $n$ = 3 (cis)[e] | 0.5 | **27** 84% **28** 11% |
| |  | |  |
| 9 | **15**: $R^1 = CH_3$, $R^2 = \beta\text{-}CH_3$, $R^3 = R^4 = H$ | 6 | **29** 72% |
| 10 | **16**: $R^1 = CH_3$, $R^2 = \alpha\text{-}CH_3$, $R^3 = R^4 = H$ | 4.5 | **30** 76% |
| 11 | **17**: $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$ | 1.5 | **31** 80% |
| 12 | **18**: $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$ | 4 | **32** 98% |
| 13 |  **19** | 0.1 |  **33** 86% (path a-c) |
| 14 |  **20** | 0.3 |  (path a-d) **34** 51% (path a-c) **35** 28% |
| 15 |  **21** | 2 |  **36** 81% |
| 16 |  **22** | 1 |  **37** 95% |

[a] Reactant (100 mg) and 2 equiv of $AlCl_3$ in $CH_2Cl_2$ at room temperature. [b] Only tarry material was obtained and no rearranged product was detected. [c] An 8.2:1 mixture of 5$\alpha$- and 5$\beta$-methyl epimers. [d] Reactant recovered (68%). [e] The cis/trans stereochemistry denotes the stereochemical relationship between 5-6-, 6-6-, and 6-7-membered-ring systems.

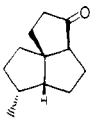
yield the carbocation **41** corresponding to **4** as shown in Scheme II.

The mechanism for the hydrocarbon rearrangement in Scheme II involves the hydride abstraction by the Lewis acid at the first step. In the case of ketone substrates, however, the Lewis acid will coordinate to carbonyl group to give the zwitterionic species such as **42**. Hydride abstraction from such species seems unlikely in view of the repulsion of positive charge at C(5) and C(8). Accordingly, we now propose an alternative but more plausible reaction mechanism which is shown in Scheme III. Namely, coordination of the carbonyl group to the Lewis acid to generate **42** followed by cleavage the central cyclobutane bond to yield the homoallylcarbinyl cation **43** (path g). A 1,2-hydride shift (path h) affords the carbocation **44**, which collapses to give the product **2** (path i). While acid promoted transannular reactions such as path i are well-known,[14] the ring opening of the cyclobutylcarbinyl to the homoallylcarbinyl cation as in path g has been observed only in highly strained systems.[15]

Next, in order to demonstrate the utility of this novel rearrangement, the total syntheses of (±)-5-oxosilphiperfol-6-ene (**5**) and (±)-silphiperfol-6-ene (**6**) were carried out (Scheme IV). Toward this end, we prepared the bicyclic enone **46** in 44% overall yield by alkylation[16] of the silyl enol ether **45**[17] with 2-methyl-2-vinyl-1,3-dioxolane[18] followed by hydrolysis and condensation.[19] Photocycloaddition of **46** to ethylene gave the tricyclic ketone **47** in 73% yield.[20] As expected, the novel rearrangement of **47** with $AlCl_3$ proceeded smoothly to give the desired angular ketone **48** in 93% yield.[21]

With the ketone **48** in hand, introduction of another three methyl groups and the $\alpha,\beta$-unsaturated carbonyl functionality for the synthesis of (±)-**5** was undertaken. $\alpha$-Bromination followed by dehydrobromination and $\alpha'$-methylation gave the enone **49**[23] in 76% overall yield. Reaction of **49** with the organocopper reagent, $\alpha$-methylation, and introduction of the double bond as

(13) The fact that the rearrangement of **18** gave **32** having the methyl group at C(11) but not at C(9) indicates that the novel rearrangement involves the migration of the central bond (path e) but not the peripheral bond (path f). Through the latter, the ketone i having the methyl group at C(9) would be obtained.



i

(14) For example, see: Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron Lett.* **1985**, *26*, 5277. Mehta, G.; Rao, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 8015 and references cited therein.

(15) McDonald, R. N.; Davis, G. E. *J. Am. Chem. Soc.* **1972**, *94*, 5078. Tobe, Y.; Ohtani, M.; Kakiuchi, K.; Odaira, Y. *J. Org. Chem.* **1983**, *48*, 5114 and references cited therein.

(16) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779.

(17) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(18) Hahn, E. F. *J. Org. Chem.* **1973**, *38*, 2092.

(19) The epimer **55** with the $\alpha$-methyl group at C(9) was also obtained in 22% overall yield as the minor product.

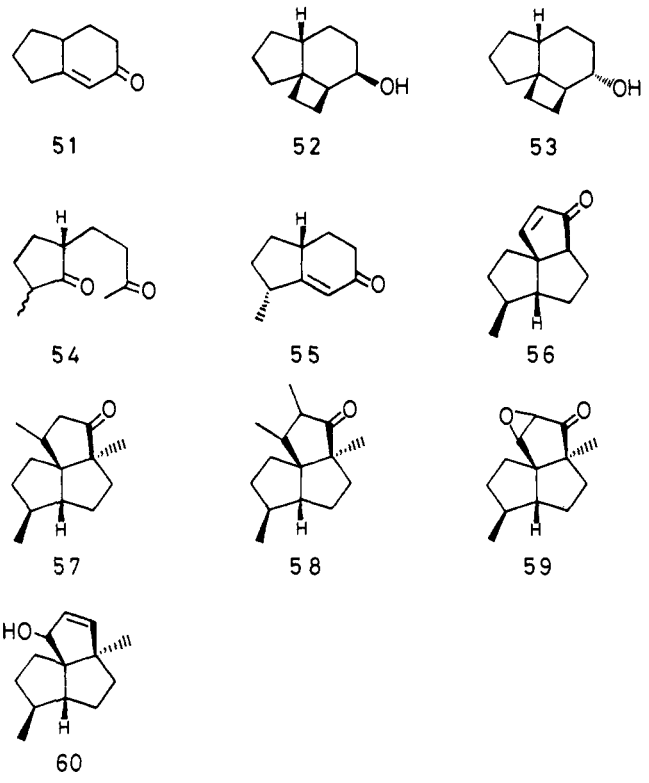
(20) For the assignment of the stereochemistry of the new stereogenic centers of **47**, see the supplemental material.

(21) The position of the C(9) methyl group on the triquinane framework was determined by the identity of the hydrocarbon obtained by Wolff–Kishner reduction of **48** with the authentic sample which was prepared from **2** by Wittig methylenation followed by hydrogenation as the major component (6:4 ratio) (see the supplemental material). The stereochemistry of the methyl group of **48** was confirmed by comparison of the observed chemical shifts of the $^{13}C$ NMR spectra with those of calculated ones based on the data of various angular-type compounds,[22] and finally by transformation to 5-oxo-silphiperfol-6-ene (**5**).

(22) For example, see: Kakiuchi, K.; Kumanoya, S.; Ue, M.; Tobe, Y.; Odaira, Y. *Chem. Lett.* **1985**, 989. Observed values ($\delta$) (parentheses show the calculated ones and positions) for **48** are as follows: 222.4 (222.3, C(4)), 60.2 (60.6, C(8)), 59.6 (60.3, C(5)), 58.7 (59.5, C(1)), 42.9 (42.8, C(9)), 39.6 (40.5, C(11)), 39.0 (39.7, C(3)), 35.3 (36.0, C(2) or (10)), 35.0 (36.0, C(10) or (2)), 31.4 (31.6, C(7)), 29.8 (29.8, C(6)), 19.6 (20.1, Me).

(23) This enone has been also prepared by Paquette[6a] and Demuth.[6b]

**Chart I**




described above gave (±)-**5** in 63% overall yield. The spectral properties (IR, $^1H$ and $^{13}C$ NMR) of the synthetic **5** were consistent with those of the natural product, (−)-5-oxosilphiperfol-6-ene (**5**), provided generously by Prof. Bohlmann.

Epoxidation of the enone **49** followed by Wharton reaction[24] and the subsequent oxidation with pyridinium dichromate[25] gave the known precursor **50**[6a] of silphiperfol-6-ene (**6**) in 51% overall yield, whose spectra were consistent with those of (+)-**50**, sent kindly by Prof. Paquette. Accordingly, the formal total synthesis of (±)-**6** was accomplished. Further application of this rearrangement to other classes of natural products is in progress.

## Experimental Section

IR spectra were recorded as liquid films unless otherwise stated. $^1H$ NMR (90 MHz) and $^{13}C$ NMR (22.5 MHz) spectra were obtained in $CDCl_3$ unless otherwise stated. For $^1H$ NMR (100 MHz) and $^{13}C$ NMR (15 MHz) $CCl_4$ and $CDCl_3$, respectively, were used unless otherwise stated. Analytical gas–liquid chromatography (GLC) was carried out with a 10% FFAP column or a 30% SE-30 column. Products were isolated by extraction of the aqueous solution with several portions of the solvent indicated. The combined organic extracts were worked up without washing (A) or were washed with (B) saturated brine, (C) sodium hydrogen carbonate ($NaHCO_3$) solution and saturated brine, or (D) 5% HCl, $NaHCO_3$ solution, and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and the organic solvent was removed in vacuo. Column chromatography was performed with Wako C-200 silica gel or Wako alumina (200 mesh) which effected equilibration to more stable cis 6–4 ring system of photocycloadducts, and flash chromatography was carried out with Merck silica gel 60 (No. 7729) and with ether–petroleum ether as the eluent (only the volume percent of ether in petroleum ether was indicated hereafter). Yields were calculated on the basis of the consumed starting materials (Chart I).

**(1*S**,4*S**,8*R**)-Tricyclo[6.3.0.0$^{1,4}$]undecan-5-one (1).** Irradiation of 7.85 g (57.7 mmol) of the enone **51**[26] with ethylene for 9 h as described previously[27] gave 8.22 g (98% yield, elution with 3% ether) of **1** and 0.94 g (15% ether) of recovered **51** after column chromatography: IR 1700 $cm^{-1}$; MS *m/e* 164 ($M^+$, 13), 108 (100), 79 (62); $^1H$ NMR (100 MHz) δ 1.2–2.4 (m, 15 H), 2.59 (t, *J* = 7 Hz, 1 H); $^{13}C$ NMR (15 MHz) δ 214.2 (s), 51.4 (s), 49.6 (d), 42.6 (d), 39.3 (t), 37.0 (t), 32.7 (t), 30.0 (t), 28.1 (t), 23.2 (t), 21.2 (t). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.45; H, 10.07.

**(1*S**,4*S**,5*R**,8*R**)-Tricyclo[6.3.0.0$^{1,4}$]undecan-5-yl *p*-Bromobenzoate (7).** To a stirred suspension of 0.55 g (14.4 mmol) of lithium aluminum hydride ($LiAlH_4$) in 100 mL of dry ether was added dropwise a solution of 4.70 g (28.6 mmol) of **1** in 120 mL of dry ether at 0 °C. The mixture was stirred at room temperature for 1.5 h and water was carefully added to the cooled mixture and then 5% HCl was added. The product was isolated by ether extraction (C), and column chromatography (20% ether) of the crude material gave 4.07 g (86% yield) and 0.44 g (9% yield) of **(1*S**,4*S**,5*R**,8*R**)-** and **(1*S**,4*S**,5*S**,8*R**)-tricyclo[6.3.0.0$^{1,4}$]undecan-5-ols (52 and 53)**, respectively. These results were described in a preliminary report.[28]

**52**: IR 3500–3050, 1040, 1010 $cm^{-1}$; MS *m/e* 166 ($M^+$, trace), 138 (100), 109 (64), 96 (76), 95 (66), 80 (57); $^1H$ NMR (100 MHz) δ 0.8–2.1 (m, 16 H), 2.56 (m, 1 H), 3.54 (m, 1 H). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.25; H, 11.27.

**53**: IR 3500–3050, 1040, 1010, 980, 930 $cm^{-1}$; MS *m/e* 166 ($M^+$, trace), 138 (98), 122 (89), 119 (91), 109 (93), 96 (100), 95 (86), 96 (60), 81 (60), 80 (79), 79 (92), 67 (67), 41 (59); $^1H$ NMR (100 MHz) δ 0.8–2.3 (m, 17 H), 3.84 (m, 1 H). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.27; H, 10.99.

To a solution of 175 mg (1.05 mmol) of **52** in 5 mL of pyridine was added a small portion of 579 mg (5.64 mmol) of *p*-bromobenzoyl chloride at room temperature. The mixture was stirred at room temperature for 18 h and water was added. The product was isolated by ether extraction (D), and flash chromatography (5% ether) of the crude material followed by recrystallization from petroleum ether gave 317 mg (87% yield) of **7** as white columns: mp 106–107 °C; IR (KBr) 1710, 1580, 1280, 1120, 1005, 755 $cm^{-1}$; MS *m/e* 350 ($M^+ + 2$, trace), 348 ($M^+$, trace), 185 (54), 183 (85), 148 (78), 120 (100); $^1H$ NMR (100 MHz, $CDCl_3$) δ 0.8–2.2 (m, 15 H), 2.83 (dt, *J* = 10, 7 Hz, 1 H), 5.01 (dt, *J* = 10, 6Hz, 1 H), 7.59 (d, *J* = 9 Hz, 2 H), 7.87 (d, *J* = 9 Hz, 2 H); $^{13}C$ NMR δ 165.4 (s), 131.6 (d, 2 C), 131.0 (d, 2 C), 129.9 (s), 127.7 (s), 72.7 (d), 50.5 (s), 43.1 (d), 39.8 (d), 37.4 (t), 34.2 (t), 30.7 (t), 29.3 (t), 26.9 (t), 23.2 (t), 16.6 (t). Anal. Calcd for $C_{18}H_{21}O_2Br$: C, 61.90; H, 6.06; Br, 22.88. Found: C, 61.97; H, 6.03; Br, 22.82.

**General Procedure of Reactions of Ketones 1 and 8–22 with $AlCl_3$.** A solution of 100 mg of the ketone and 2 equiv of aluminum(III) chloride ($AlCl_3$) in 5 mL of methylene chloride ($CH_2Cl_2$) was stirred at room temperature. The progress of the reaction was monitored by GLC or IR. Water was added to the cooled mixture. The product was isolated by ether extraction (C) and the crude material was purified by flash chromatography (5–10% ether). The yields are summarized in Table I.

**(1*R**,5*S**,8*S**)-Tricyclo[6.3.0.0$^{1,5}$]undecan-4-one (2).** The $^{13}C$ NMR data of **2** were consistent with those reported in the literature.[29]

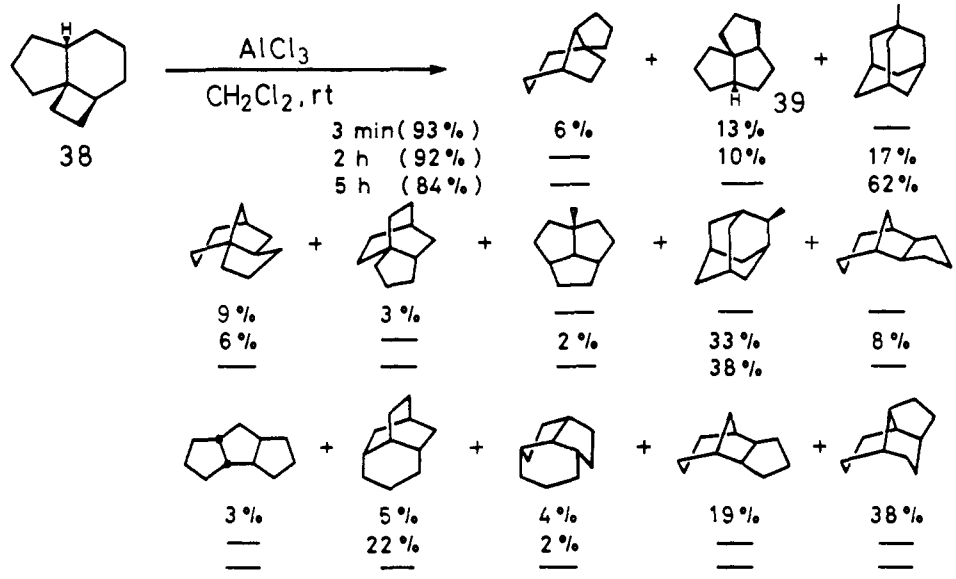
**(1*S**,4*S**,8*S**)-Tricyclo[6.3.0.0$^{1,4}$]undecane (38).** A solution of 2.00 g (12.2 mmol) of **1**, 0.86 g (12.2 mmol) of potassium hydroxide (KOH), and 0.62 mL (12.2 mmol) of 80% hydrazine hydrate ($N_2H_4 \cdot H_2O$) in 50 mL of diethylene glycol was refluxed at ca. 150 °C for 3 h. Excess hydrazine and water were distilled off and the solution was heated at 210 °C for 4 h. The cooled solution was neutralized with 10% HCl. The product was isolated by ether extraction (B), and flash chromatography (petroleum ether) of the crude material gave 1.60 g (87% yield) of **38**: IR ($CCl_4$) 2930, 2850, 1440 $cm^{-1}$; MS *m/e* 150 ($M^+$, 3), 122 (100), 80 (58); $^1H$ NMR δ 0.7–2.0 (m, 17 H), 2.2–2.4 (m, 1 H); $^{13}C$ NMR δ 47.8 (s), 43.2 (d), 37.9 (d), 37.6 (t), 34.2 (t), 31.6 (t), 30.3 (t), 26.3 (t), 23.0 (t), 21.4 (t), 20.6 (t). Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.78; H, 12.01.

**Rearrangement of 38 with $AlCl_3$.** Reactions of 500 mg (3.33 mmol) and 200 mg (1.33 mmol) of **38** for 3 min, 2 h, and 5 h with $AlCl_3$ under conditions similar to that of **1** gave 464 mg (93% yield), 460 mg (92% yield), and 167 mg (84% yield) of tricycloundecanes involving **tricyclo[6.3.0.0$^{1,5}$]undecane (39)** as shown below after flash chromatography (petroleum ether), respectively. The product distributions are also shown in Chart II. The hydrocarbons were identified by comparison of $^{13}C$ NMR spectra with those reported in the literature as described previously.[30]

**(6*R**,9*S**)-9-Methylbicyclo[4.3.0]non-1-en-3-one (46).** To 175 mL of dry $CH_2Cl_2$ was added 6.58 mL (60.2 mmol) of freshly distilled titanium(IV) chloride ($TiCl_4$) and then 17.7 mL (60.2 mmol) of freshly distilled titanium(IV) isopropoxide ($Ti(O\text{-}i\text{-}Pr)_4$) at −78 °C under a nitrogen atmosphere. To the solution was added dropwise a solution of 3.60

(24) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3016.
(25) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(26) Aumiller, J. C.; White, J. A. *J. Org. Chem.* **1976**, *41*, 2955.
(27) Kakiuchi, K.; Tsugaru, T.; Tobe, Y.; Odaira, Y. *J. Org. Chem.* **1981**, *48*, 4204.
(28) Ue, M.; Nagashima, T.; Kinugawa, M.; Kakiuchi, K.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *Chem. Lett.* **1988**, 1521.
(29) Mehta, G.; Rao, K. S. *Tetrahedron Lett.* **1984**, *25*, 3481.
(30) Kakiuchi, K.; Ue, M.; Wakaki, I.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Org. Chem.* **1986**, *51*, 281. Kakiuchi, K.; Ue, M.; Kumanoya, S.; Takeuchi, H.; Tobe, Y.; Odaira, Y. *Chem. Lett.* **1986**, 1479.

**Chart II**




g (48.3 mmol) of 2-methyl-2-vinyl-1,3-dioxolane[18] and 5.10 g (30.1 mmol) of **45**[17] in 180 mL of dry $CH_2Cl_2$ at −78 °C during 30 min.[16] The solution was stirred at −78 °C for 1 h and water was added. The product was isolated by ether extraction (B) and the crude material was dissolved in 20 mL of 10% HCl and 20 mL of tetrahydrofuran (THF). The solution was stirred at room temperature for 30 min and water was added. The product was isolated by ether extraction (B), and flash chromatograpy (15% ether) of the crude material gave 3.56 g (77% yield) of **2-(3′-oxobutyl)-5-methylcyclopentanones 54** in an approximate 2:1 ratio, which were not separated and were analyzed as a mixture: IR 1730, 1720, 1360, 1160 $cm^{-1}$; MS *m/e* 168 ($M^+$, 38), 111 (74), 98 (50), 43 (100); $^1H$ NMR δ 0.9–1.1 (m, 3 H), 1.2–2.2 (m, 11 H containing s at 2.08), 2.50 (t, *J* = 7.2 Hz, 2 H); $^{13}C$ NMR δ 221.3 (s), 207.5 (s), 47.2 (d), 43.6 (d), 40.5 (t), 29.3 (t), 29.2 (q), 27.2 (t), 23.9 (t), 13.9 (q) for the major isomer and 221.6 (s), 207.5 (s), 46.3 (d), 42.2 (d), 40.7 (t), 29.3 (q), 28.4 (t), 26.3 (t), 23.9 (t), 14.6 (q) for the minor isomer. Anal. Calcd for $C_{10}H_{16}O$: C, 71.39; H, 9.59. Found: C, 71.01; H, 9.65.

To a solution of 3.91 g (70.0 mmol) of KOH in 35 mL of ethyl alcohol (EtOH) was added a solution of 3.50 g (20.8 mmol) of the above diketones **54** in 12 mL of EtOH at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 2 h and acetic acid and then water were added. The product was isolated by ether extraction (B), and column chromatography (12% ether) of the crude material gave 1.77 g (57% yield) of **46** and 0.90 g (29% yield) of the epimeric enone **55**.

**46**: IR 3020, 1660 $cm^{-1}$; MS *m/e* 150 ($M^+$, 64), 122 (100); $^1H$ NMR δ 1.15 (d, *J* = 7.1 Hz, 3 H), 1.3–2.8 (m, 10 H), 5.84 (t, *J* = 2.1 Hz, 1 H); $^{13}C$ NMR δ 198.4 (s), 178.7 (s), 120.7 (d), 42.1 (d), 38.2 (d), 36.7 (t), 32.8 (t), 31.4 (t), 29.0 (t), 18.7 (q).

**55**: IR 3020, 1660 $cm^{-1}$; MS *m/e* 150 ($M^+$, 47), 122 (100); $^1H$ NMR δ 1.08 (d, *J* = 7.2 Hz, 3 H), 1.3–2.8 (m, 10 H), 5.81 (t, *J* = 2.1 Hz, 1 H); $^{13}C$ NMR δ 197.7 (s), 178.3 (s), 119.8 (d), 41.6 (d), 37.0 (d), 36.7 (t), 31.6 (t), 29.4 (t), 28.6 (t), 17.6 (q).

**(1*R**,4*S**,8*R**,11*S**)-11-Methyltricyclo[6.3.0.0$^{1,4}$]undecan-5-one (47).** Irradiation of 1.09 g (7.28 mmol) of **46** with ethylene for 11 h as described above gave 0.75 g (73% yield, elution with 3% ether) of **47** and 0.24 g (15% ether eluent) of recovered **46** after column chromatography: IR 1700 $cm^{-1}$; MS *m/e* 178 ($M^+$, 37), 150 (60), 122 (100), 108 (54), 93 (46); $^1H$ NMR δ 0.93 (d, *J* = 6.4 Hz, 3 H), 1.1–2.8 (m, 15 H); $^{13}C$ NMR δ 213.0 (s), 53.7 (s), 47.7 (d), 42.4 (d), 40.0 (d), 36.9 (t), 31.3 (t), 28.7 (t), 27.5 (t), 25.1 (t), 20.9 (t), 14.0 (q). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.73; H, 10.25.

**(1*R**,5*S**,8*R**,9*S**)-9-Methyltricyclo[6.3.0.0$^{1,5}$]undecan-4-one (48).** Reaction of 608 mg (3.41 mmol) of **47** with $AlCl_3$ for 30 min as described above gave 566 mg (93% yield) of **48** after column chromatography (3% ether): IR 1730 $cm^{-1}$; MS *m/e* 178 ($M^+$, 74), 149 (91), 123 (77), 121 (74), 96 (69), 94 (77), 93 (83), 80 (86), 79 (100); $^1H$ NMR δ 0.98 (d, *J* = 5.0 Hz, 3 H), 1.1–2.5 (m, 15 H); $^{13}C$ NMR δ 222.4 (s), 60.2 (d), 59.6 (d), 58.7 (s), 42.9 (d), 39.6 (t), 39.0 (t), 35.3 (t), 35.0 (t), 31.4 (t), 29.8 (t), 19.6 (q). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.60; H, 10.19.

**(1*R**,5*S**,8*R**,9*S**)-5,9-Dimethyltricyclo[6.3.0.0$^{1,5}$]undec-2-en-4-one (49).** To a solution of 288 mg (1.62 mmol) of **48** in 7 mL of dry THF was added 639 mg (1.70 mmol) of trimethylphenylammonium tribromide ($Me_3PhNBr_3$) in one portion at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and poured into a mixture of 8 mL of $NaHCO_3$ solution, 8 mL of 1 M sodium thiosulfate ($Na_2S_2O_3$) solution, and 8 mL of brine. The product was isolated be ether extraction (B) and the crude material was roughly separated by flash chromatography (7% ether). A mixture of the above bromides, 2.07 g (23.8 mmol) of lithium bromide (LiBr), and 1.77 g (23.8 mmol) of lithium carbonate ($Li_2CO_3$) in 12 mL of freshly distilled dimethylformamide (DMF) was stirred at ca. 110 °C (bath temperature) for 2 h under a nitrogen atmosphere. The mixture was poured into a mixture of 30 mL of $NaHCO_3$ solution, 15 mL of 1 M $Na_2S_2O_3$ solution, and 30 mL of brine. The product was isolated by ether extraction (B), and flash chromatography (7% ether) of the crude material gave 48 mg of recovered **41** and 210 mg (88% yield) of **(1*R**,5*S**,8*R**,9*S**)-9-methyltricyclo[6.3.0.0$^{1,5}$]undec-2-en-4-one (56)**: IR 1700, 1350 $cm^{-1}$; MS *m/e* 176 ($M^+$, 50), 121 (100); $^1H$ NMR δ 0.99 (d, *J* = 6.6 Hz, 3 H), 1.2–2.4 (m, 11 H), 5.96 (d, *J* = 6.3 Hz, 1 H), 7.47 (d, *J* = 6.3 Hz, 1 H); $^{13}C$ NMR δ 217.7 (s), 170.5 (d), 130.6 (d), 64.3 (s), 58.5 (d), 56.9 (d), 39.4 (d), 35.6 (t), 35.2 (t), 27.7 (t), 27.5 (t), 19.3 (q). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.51; H, 9.19.

To a solution of lithium diisopropylamide (LDA) prepared from 0.41 mL (2.90 mmol) of diisopropylamine and 2.90 mL (2.90 mmol) of 1 N BuLi in hexane in 12 mL of dry THF was added dropwise a solution of 405 mg (2.29 mmol) of **56** and 0.41 mL (2.29 mmol) of hexamethylphosphoramide (HMPA) in 5 mL of dry THF at −78 °C for 5 min under a nitrogen atmosphere. The solution was stirred for 30 min and 1.45 mL (22.9 mmol) of methyl iodide (MeI) was added. The solution was stirred at −78 °C for 2 h and poured into $NaHCO_3$ solution. The product was isolated by ether extraction (B), and flash chromatography (10% ether) of the crude material gave 371 mg (85% yield) of **49**, whose spectroscopic data (IR, $^1H$ and $^{13}C$ NMR) were identical with those reported by the Paquette[6a] and Demuth[6b] groups.

**(±)-5-Oxosilphiperfol-6-ene (5).** To a solution of 900 mg (4.73 mmol) of copper(I) iodide in 2 mL of dry ether was added 8.70 mL (8.70 mmol) of 1 N methyllithium in ether via a syringe at room temperature under a nitrogen atmosphere. The clear solution was cooled at 0 °C and a solution of 153 mg (0.81 mmol) of **49** in 3 mL of dry ether was added via a syringe. The solution was stirred at 0 °C for 30 min and then at room temperature for 2 h. Ammonium chloride ($NH_4Cl$) solution was carefully added to the cooled solution. The product was isolated by ether extraction (B), and flash chromatography (10% ether) of the crude material gave 161 mg (98% yield) of the trimethylated ketone **57** as a single product after flash chromatography (10% ether): IR 1730, 1370 $cm^{-1}$; MS *m/e* 206 ($M^+$, 63), 164 (78), 136 (91), 135 (100), 122 (54), 121 (89), 107 (69), 41 (66); $^1H$ NMR δ 0.96 (d, *J* = 6.4 Hz, 3 H), 0.98 (d, *J* = 6.2 Hz, 3 H), 1.01 (s, 3 H), 1.1–2.6 (m, 13 H); $^{13}C$ NMR δ 225.8 (s), 64.0 (s), 63.4 (d), 57.7 (s), 46.6 (t), 43.5 (d), 40.5 (t), 38.5 (d), 35.3 (t), 30.2 (t), 29.1 (t), 20.0 (q), 19.6 (q), 18.4 (q). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.26; H, 10.83.

α-Methylation of 161 mg (0.79 mmol) of **57** was carried out as described above. In this case, after addition of methyl iodide, the solution was stirred at −30 °C for 4 h to give 55 mg of recovered **57** and 88 mg (74% yield) of the tetramethylated ketone **58** after flash chromatography (2% ether): IR 1730, 1370 $cm^{-1}$; MS *m/e* 220 ($M^+$, 82), 136 (100), 135

(57), 121 (65); $^1$H NMR $\delta$ 0.9-1.1 (m, 12 H containing s at 1.08), 1.2-2.1 (m, 12 H).

$\alpha$-Bromination of 85 mg (0.39 mmol) of **58** and the subsequent dehydrobromination as described above gave 73 mg (86% yield) of (±)-**5** after flash chromatography (10% ether) whose spectral data (IR, $^1$H and $^{13}$C NMR) were identical with those of the natural product.[5]

**(1*R**,5*R**,8*R**,9*S**)-5,9-Dimethyltricyclo[6.3.0.0$^{1,5}$]undec-3-en-2-one (50).** To a solution of 189 mg (1.00 mmol) of **49** in 1.8 mL of methyl alcohol (MeOH) was added 0.7 mL (6.90 mmol) of 30% hydrogen peroxide ($H_2O_2$) at 0 °C. The solution was stirred at 0 °C for 10 min and 0.35 mL (2.10 mmol) of 25% sodium hydroxide (NaOH) solution was added. The solution was stirred at 0 °C for 30 min and ice-water was added. The product was isolated by ether extraction (B), and flash chromatography (10% ether) of the crude material gave 6 mg of recovered **49** and 180 mg (91% yield) of the epoxy ketone **59** as a single product: IR 1730, 1370, 850 cm$^{-1}$; MS *m/e* 206 (M$^+$, 18), 149 (100); $^1$H NMR $\delta$ 1.01 (d, $J$ = 5.1 Hz, 3 H), 1.03 (s, 3 H), 1.2-2.2 (m, 10 H), 3.42 (d, $J$ = 2.3 Hz, 1 H), 3.66 (d, $J$ = 2.3 Hz, 1 H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.95; H, 8.96.

To a solution of 119 mg (0.58 mmol) of **59** in 0.5 mL of MeOH was added 0.10 mL (1.82 mmol) of 80% $N_2H_4{\cdot}H_2O$ via a syringe at 0 °C under a nitrogen atmosphere. The solution was stirred at 0 °C for 5 min and 7.14 $\mu$L (0.13 mmol) of acetic acid was added dropwise via a syringe.[24] The solution was stirred at 0 °C for 10 min and then at room temperature for 4 h and brine was added. The product was isolated by ether extraction (B), and flash chromatography of the crude material gave 79 mg (10% ether eluent) of recovered **59** of 21 mg (57% yield, elution with 15% ether) of the allyl alcohol **60**: IR 3500-3050, 3020, 1600, 1010, 940, 780 cm$^{-1}$; MS *m/e* 192 (M$^+$, 100), 177 (52), 150 (49), 148 (40), 135 (39), 109 (53), 108 (51), 107 (51), 97 (89), 81 (48); $^1$H NMR $\delta$ 0.8-2.2 (m, 17 H containing d at 0.97, $J$ = 4.9 Hz, and s at 1.02), 4.23 (bd s, 1 H), 5.73 (d, $J$ = 5.7 Hz, 1 H), 5.85 (dd, $J$ = 5.7, 2.3 Hz, 1 H).

A mixture of 37 mg (0.19 mmol) of **60** and 112 mg (0.29 mmol) of pyridinium dichromate[25] in 2 mL of $CH_2Cl_2$ was stirred at room temperature for 3 h. Flash chromatography (10% ether) of the mixture gave 33 mg (97% yield) of **50**, whose spectral data (IR, $^1$H and $^{13}$C NMR) were identical with those of (+)-**50**, provided by Prof. Paquette.[6a]

**Acknowledgment.** We thank Professor M. Fetizon and Dr. J. Boivin of Ecole Polytechnique for valuable suggestions about the rearrangement pathways and Professors F. Bohlmann of Technical University Berlin and L. A. Paquette of The Ohio State University for generous supplies of copies of the original IR and $^1$H NMR spectra of (-)-**5** and (+)-**50**, respectively.

**Supplementary Material Available:** Details of preparation of cyclobutyl ketones **8-22** and structure determination of the starting and rearranged ketones, Experimental Section except for that described in the text, Tables II-VII listing final atomic parameters, final anisotropic thermal parameters, bond length, and bond angles of **7**, and a figure of **7** (45 pages). Ordering information is given on any current masthead page.

# Nucleophile-Selective Iodocyclizations: Butyrolactone versus Tetrahydrofuran Formation

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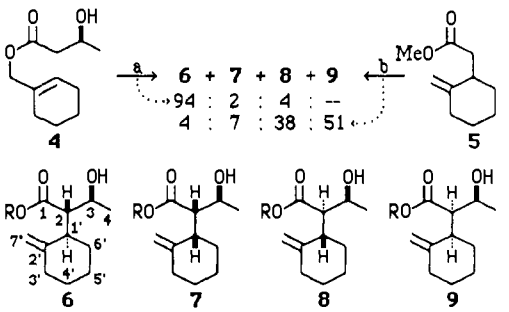
**Abstract:** Nucleophile selectivity in the electrophilic cyclization of substrates like **3** has been investigated in the context of efficient chemo- and stereoselective functionalization of 3-hydroxy-2-(2-methylenecyclohexan-1-yl)butyric acids (cf., **6-9**) via iodocyclization. In addition, composite nucleophile selectivities for this diastereomeric series were used to probe the reliability of ground-state conformational analysis as an indicator of relative reactivities for the various conformations of **3**. The results provide unambiguous evidence for $C_{1'}$,$C_2$,$C_3$ stereocontrol in these kinetic iodocyclizations.

The electrophilic cyclization reaction[2] is a multipurpose transformation, which continues to receive methodological[3] and synthetic[4] attention, particularly in regard to the stereocontrolled elaboration of highly functionalized heterocycles. We recently reported[5] the efficient and highly stereoselective functionalization of heptadienoate **1** via its iodolactonization (Figure 1). Indeed, of the four possible iodolactonization products of **1**, **2** was formed almost exclusively, the result of 147:1 group (i.e., olefin) and 30:1 face selectivities. It was noted that this impressive kinetic preference, the consequence of a transition-state bias capable of differentiating the two diastereotopic olefins, is mirrored in the

**Scheme I**




[a](i) 2 equiv of LDA, THF, -78 °C. (ii) -78 °C → 50 °C. (iii) $H_3O^+$. (iv) $CH_2N_2$, ether. [b](i) LDA, THF, -78 °C. (ii) $CH_3CHO$. (iii) $H_3O^+$.

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