g, 2 mmol) in boiling anhydrous ether (20 mL). The mixture was heated to reflux for 16 h and then cooled to 20 °C, and the precipitated product was collected by filtration, dried, and crystallized from acetonitrile to give 475 mg (39%) of **21**, mp 215–217 °C dec. On being allowed to stand, the mother reaction solution deposited another 40 mg of **21**.

Anal. Calcd for $C_{34}H_{37}N_5O_6$: C, 66.76; H, 6.10; N, 11.45. Found: C, 66.61; H, 6.09; N, 11.50.

2-Amino-8-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (23). Compound **21** (475 mg, 0.84 mmol) was dissolved in dimethylformamide (15 mL) containing 1.5 mL of 1 N NaOH. After being stirred at room temperature for 6 h, the reaction solution was made neutral with the addition of 1 N HCl and then evaporated to dryness. The residue was stirred with water, and the solid material was collected by filtration. Crystallization of this material from methanol afforded 400 mg (91%) of **23**, mp 245–247 °C dec.

Anal. Calcd for $C_{32}H_{31}N_5O_5$: C, 67.95; H, 5.52; N, 12.38. Found: C, 67.86; H, 5.53; N, 12.27.

2-Amino-4-oxo-3*H*-8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (24). A mixture of acetyl chloride (0.5 mL) and *n*-butyl alcohol (10 mL) was stirred at room temperature for 1 h. To this was added compound **23** (500 mg, 0.88 mmol), and the suspension was stirred at room temperature for another hour. The precipitate formed was collected by filtration, washed immediately with anhydrous ether, and then added to methanol (5 mL). The magnetically stirred mixture was carefully neutralized with 5 M KOH/MeOH. After evaporation of the methanol, the solid residue was purified by silica gel column chromatography with ethyl acetate/acetone/methanol/water (6:1:1:1). Fractions containing **24** were evaporated in vacuo. the solid residue was redissolved in hot methanol, filtered through a 0.5-μm filter and evaporated to dryness to give analytically pure **24** (133 mg, 53%): mp >250 °C; UV λ_{max} (pH 7) 263 nm (ε 9150); λ_{min} (pH 7) 232 nm (ε 2910); λ_{max} (pH 0) 246 nm (ε 8450); λ_{min} (pH 0) 231 nm (ε 5760); λ_{max} (pH 14) 264 nm (ε 9840); λ_{min} (pH 14) 234 nm (ε 2570).

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.87; H, 5.02; N, 23.25. Found: C, 40.27; H, 4.62; N, 23.12.

Acknowledgment. We wish to thank Mr. Marvin Olsen for the ^1H NMR spectra.

Registry No. **1**, 54346-27-9; **2**, 54346-29-1; **3**, 55458-17-8; **4**, 55522-55-9; **5**, 71774-62-4; **6**, 1820-80-0; **7**, 34682-99-0; **8**, 54346-18-8; **10**, 71774-63-5; **11**, 71774-64-6; **12**, 62946-44-5; **13α**, 60526-02-5; **14**, 71774-65-7; **15α**, 71774-66-8; **15β**, 71774-67-9; **16**, 62156-20-1; **17**, 62156-19-8; **18**, 71774-68-0; **19**, 71774-69-1; **20**, 71774-70-4; **21**, 71774-71-5; **22**, 71774-72-6; **23**, 71774-73-7; **24**, 71774-74-8; **27**, 62156-06-3; **28**, 62156-21-2; **29**, 62156-08-5; hydroxylamine hydrochloride, 5470-11-1; *N*-carbethoxythiourea, 3673-38-9; carbethoxy isothiocyanate, 16182-04-0; 2-[((dimethylamino)methylene)amino]-3-methyl-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine, 71774-75-9; dimethylformamide dimethyl acetal, 4637-24-5; 2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-D-ribofuranosylacetonitrile, 56703-40-3; dimethylformamide, 68-12-2; bis(dimethylamino)-*tert*-butoxymethane, 5815-08-7; hydrazine, 302-01-2.

(±)-Carpesiolin: Total Synthesis and Structural Determination

Piet Kok,[1b] Pierre J. De Clercq,[1a] and Maurits E. Vandewalle*

State University of Ghent, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan, 271 (S.4), B-9000 Gent, Belgium

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The total synthesis of the helenanolide (±)-carpesiolin starting from the key trans-fused hydroazulenic ketone **1** is described. Salient features of the sequence involve the introduction of the α configuration at C-10 via catalytic hydrogenation (**9**), the stereoselective reduction of cycloheptenone **14**, obtained from **9** in five steps, to yield exclusively the α-oriented allylic alcohol **16** and its conversion into lactone **19** via stereodirected epoxidation, regioselective epoxide ring opening by dilithioacetate, and selective ring closure to the C-7, C-8 oriented γ-lactone. **19** is further transformed into the title compound. This total synthesis also enables the full structural determination of (±)-carpesiolin as **6**.

In connection with our continuing efforts directed toward pseudoguaianolides we have reported the short and efficient synthesis of ketone **1** (50% overall yield, 6 steps) from 2-methylcyclopentenone,[2,3] its conversion into several ambrosanolides, characterized by a β-oriented C-10 methyl group (damsin (**2**),[3] neoambrosin, parthenin (**3**) and hymenin),[4] and recently its transformation into intermediate **4**,[5] possessing the α orientation for the methyl group at C-10, which is a characteristic feature of the helenanolides.[6] In this paper we describe the conversion of **1** into (±)-carpesiolin, an antibacterial helenanolide recently isolated from *Carpesium abrotanoides* L by Maruyama and Omura;[7] its structure was tentatively assigned as **5** on spectroscopic and biogenetic grounds. Our synthesis of the title compound not only unequivocally establishes the relative stereochemistry of carpesiolin as depicted in **6** but also clearly demonstrates the general potentiality of our approach[8] based on ketone **1** for the synthesis of both ambrosanolides[9] and helenanolides.[10]

In view of the systematic structural features displayed

(1) (a) Bevoegdverklaard Navorser of the NFWO. (b) Bursary of the IWONL.
(2) D. Termont, P. De Clercq, D. De Keukeleire, and M. Vandewalle, *Synthesis*, 46 (1977).
(3) P. De Clercq and M. Vandewalle, *J. Org. Chem.*, **42**, 3447 (1977).
(4) P. Kok, P. De Clercq, and M. Vandewalle, *Bull. Soc. Chim. Belg.*, **87**, 615 (1978).
(5) P. Kok, P. De Clercq, M. Vandewalle, J. P. Declercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.*, 2063 (1979).
(6) (a) W. Herz, *Nobel Symp. 25*, 153 (1974); (b) H. Yoshioka, T. J. Mabry, and B. N. Timmerman, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, Japan, 1973; J. Romo and H. R. de Vivar, *Fortschr. Chem. Org. Naturst.*, **25**, 90 (1976).
(7) M. Maruyama and S. Omura, *Phytochemistry*, **16**, 782 (1977).
(8) M. Vandewalle, P. De Clercq, M. Demuynck, P. Kok, G. Rozing, and F. Scott, *Excerpta Med., Sect. 1*, 130 (1979).
(9) For other syntheses of ambrosanolides, see R. A. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976); P. A. Grieco, Y. Ohfune, and G. Majetich, *ibid.*, **99**, 7393 (1977); J. A. Marshall and R. H. Gillison, *ibid.*, **98**, 4312 (1976); M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and K. Ilirotsu, *ibid.*, **100**, 5565 (1978); P. A. Grieco, T. Oguri, S. Burke, E. Rodriguez, G. T. DeTitta, and S. Fortier, *J. Org. Chem.*, **43**, 4552 (1978); P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *J. Am. Chem. Soc.*, **101**, 2196 (1979).
(10) For the first synthesis of an helenanolide, see Y. Ohfune, P. A. Grieco, C.-L. J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, **100**, 5946 (1978).

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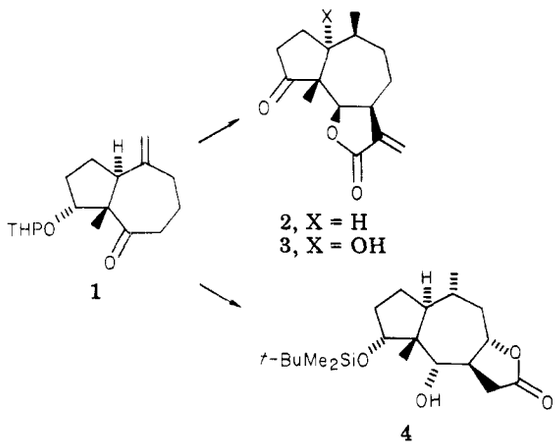
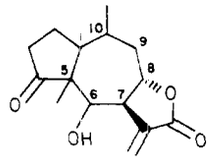


1 4

by the pseudoguaianolides,[6b] we assumed the structure of carpesiolin to be either **6** or **7**: indeed, whereas most natural products possess a trans-fused hydroazulene skeleton, a 7,8-trans-fused α-methylene γ-lactone is only encountered in helenanolides, thus suggesting relative configurations at C-1, C-5, C-7, C-8, and C-10 as shown in



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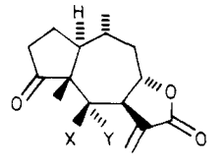
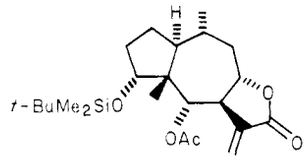


6, X = H; Y = OH
7, X = OH; Y = H

6 and **7**. With lactone **4** being available, both compounds can in principle be synthesized and thus this matter settled. Unfortunately, we failed[11] to effect the hydrolysis of the *tert*-butyldimethylsilyl ether in **8**, readily available

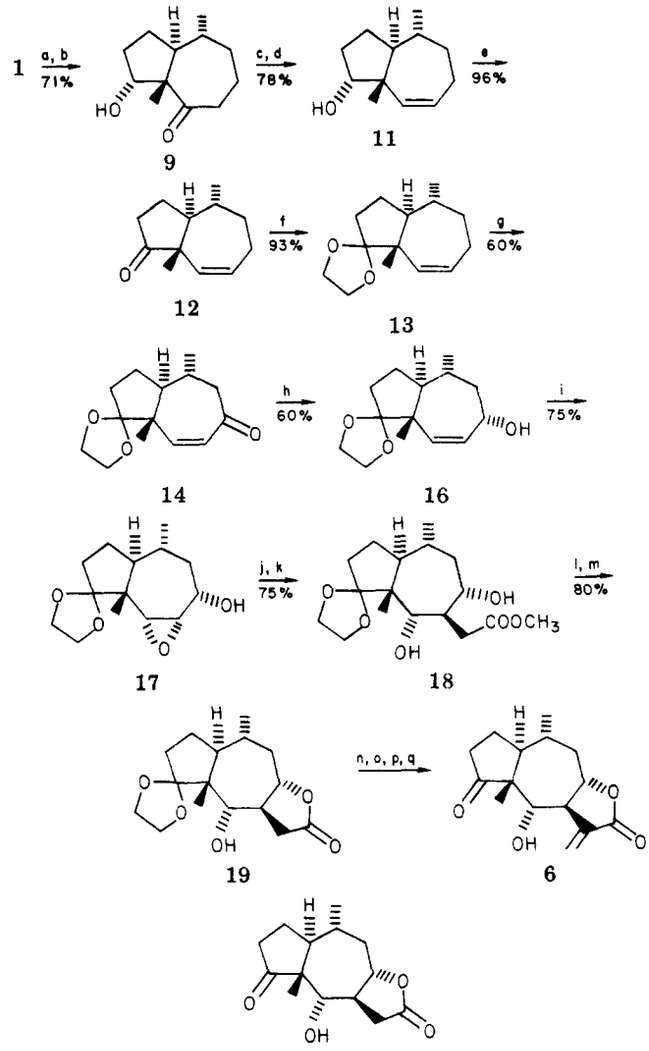


8

from **4**,[12] and were thus forced to consider an alternative strategy, based on an appropriate choice of the functionality at C-4 at an early stage of our synthesis.

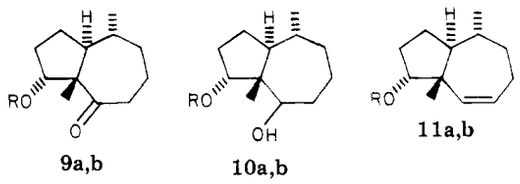
The successful route to (±)-carpesiolin (**6**) is illustrated in Chart I. The introduction of the requisite α stereochemistry at C-10 was readily accomplished by hydrolysis of intermediate **1** (83%), followed by catalytic hydrogenation[13] (87%) to ketone **9**. The presence of a homoallylic α-methylene γ-lactone in carpesiolin necessitates the functionalization of C-6, C-7, and C-8. Because of the failure[14] of the Bamford–Stevens reaction on **9a**, we were,

Chart I



a, $TsOC_5H_5NH$ (0.1 equiv), EtOH, 55–60 °C, 6 h; b, H_2, Pd-C (10%), MeOH; c, $TsNHNH_2$, EtOH, 90 °C, 4 h; d, MeLi, ether, 25 °C, 4 h; e, $CrO_3 \cdot py_2$, CH_2Cl_2, 25 °C, 15 min; f, $(CH_2OH)_2$, PhH, 22 h; g, CrO_3, 3,5-dimethylpyrazole (15 equiv), CH_2Cl_2, −15 °C, 7 h; h, DIBAH (1.0 M, hexane), PhH, 0 °C, 90 min; i, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C, 3 h; j, CH_2COOLi_2 (15 equiv), DME, 60 °C, 24 h; k, CH_2N_2; l, KOH, MeOH, 1 h, 70 °C; m, C_6H_5N, Ac_2O, CH_2Cl_2; n, LDA (15 equiv), $CH_2{=}NMe_2I$ (20 equiv), HMPA-THF; o, MeI, dioxane, 90 °C, 24 h; p, $NaHCO_3$, EtOAc; q, TsOH, benzene, 25 °C, 24 h

at the origin, forced to use a five-step sequence for the introduction of the 6,7 double bond in the hydroazulene skeleton (**9** → **11**): reduction of the tetrahydropyranyl ether derivative **9a** with lithium aluminum hydride (LAH) to the alcohol **10a**, elimination of the corresponding mesylate (mesyl chloride, pyridine) in hot pyridine, and final hydrolysis of **11a** (pyridinium *p*-toluenesulfonate, ethanol, 55 °C, 5 h) gave the alcohol **11** in 30% overall yield. A



9a,b **10a,b** **11a,b**

a, R = THP; b, R = *t*-$BuMe_2Si$

(11) No fluoride ion was employed for this cleavage. It is, however, worth mentioning that the hydrolysis of the silyl ether **4** proceeds very smoothly (trifluoroacetic acid, chloroform) to the corresponding diol (mp 127–128 °C); for the X-ray diffraction analysis of the latter compound, see J. P. Declercq, G. Germain, M. Van Meerssche, P. Kok, P. De Clercq, and M. Vandewalle, submitted for publication in *Acta Crystallogr.*

(12) The acetate **8** was obtained from **4** by a classical α-methylenation procedure (vide infra), followed by treatment with acetic anhydride and 4-(dimethylamino)pyridine.

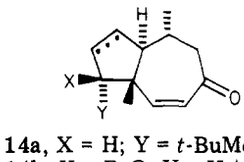
(13) Depending on the run, 10–25% of the C-10 isomer is formed and separated by column chromatography; see G. P. Rozing, P. De Clercq, and M. Vandewalle, *Synthesis*. 225 (1978).

(14) Treatment of **9a** with *p*-toluenesulfonylhydrazide (60% water–methanol, 60 °C, 2 h) gave exclusively the alcohol **9**.

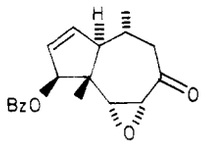
better alternative was provided with the synthesis of **11b** which eventually led to intermediate **4**: protection of the hydroxyl group in **9** (*tert*-butyldimethylsilyl chloride, imidazole, 25 °C, 24 h, 88%), reduction with diisobutylaluminum hydride (DIBAH, 1 M solution in hexane, benzene, 0 °C, 3 h, 60–72%) to the alcohol **10b**, and treatment with thionyl chloride in pyridine (0 °C, 45 min, 55%) yielded olefin **11b**.

However, due to the aforementioned difficulties[11] encountered in the removal of the silyl ether in **8**, we decided to oxidize the hydroxyl group at C-4 at an early stage (**11** → **12**). Much to our surprise we were gratified to find that the Bamford–Stevens sequence (Chart I) could be performed directly on **9**, giving the desired alcohol **11** in 78% overall yield, thus enabling minimal use of protective groups. Collins reagent was found superior to Jones oxidation for the conversion of **11** into ketone **12** (96%). The acetal **13** obtained in 93% yield after prolonged reaction times[15] (22 h) was directly oxidized to the corresponding enone **14** by using chromic anhydride–3,5-dimethylpyrazole complex (15.0 equiv)[16] in 60% yield.

The reduction of enone **14** with diisobutylaluminum hydride gave after column chromatographic purification one epimeric alcohol (NMR analysis).[15] One need not debate the structure of this alcohol for the matter was unambiguously proven through a single X-ray diffraction analysis of a subsequent product **20**, showing it to possess the α stereochemistry (**16**). The stereoselectivity displayed in this reduction calls, however, for comment: indeed, whereas it has already been observed that similar enones did yield the α-hydroxyl group upon reduction (e.g., **14a** with DIBAH,[5,8] 90%; **14b** with LAH[17]), it was found by Grieco[10] that the corresponding epoxy ketone **15** gave exclusively in near-quantitative yield the β-oriented alcohol upon reduction with sodium borohydride in ethanol. These results suggest a profound difference in conformational behavior of the enones (**14**, **14a**, and **14b**) compared to the keto epoxide **15**. In connection with conformational studies in the hydroazulene field[18] it can be shown that the torsional constraints imposed in the seven-membered ring by the trans fusion of the cyclopentane at C-1,C-5 and by the presence of a double bond (**14**) or an epoxide (**15**) are preferentially accommodated by a twisted-boat conformation (TB) in the case of **14** with a small endocyclic torsion angle at C-7,C-8 (30°),[19] allowing to some extent π overlap in the conjugated system, and a chair conformation (C) in the case of **15**. Inspection of Dreiding molecular models indicates that in the TB form of **14** attack should occur from the β face due to steric hindrance of H-1 and the C-10 methyl group, whereas in the C form of **15** the β face is severely hindered by H-10 and the methyl group at C-5, thus provoking the α approach of the reducing agent. In both cases the experimental results are in accord with the expectations.



14a, X = H; Y = *t*-BuMe$_2$SiO
14b, X = BzO; Y = H ($\Delta^{2,3}$)



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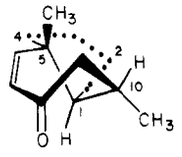
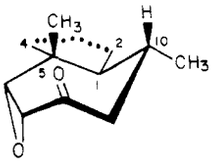


TB



C

Epoxide **17**, obtained by Henbest[20]-type oxidation from the allylic alcohol **16**, has the correct stereochemistry for the introduction of the β-oriented alkyl side chain at C-7; treatment with 15 equiv of dilithioacetate[21] in dimethoxyethane at 60 °C for 24 h, followed by treatment with diazomethane, yielded the ester **18** (mp 161–163 °C) possessing the all-trans configuration at C-6,C-7,C-8. A two-step sequence was advantageously used for the conversion of **18** into lactone **19**: saponification of the ester **18**, directly followed by treatment with acetic anhydride–pyridine, gave the alcohol **19** (mp 119–121 °C) in 80% yield;[22] under these circumstances no corresponding acetate could be detected.[23]

At this stage we resorted to a single-crystal X-ray diffraction analysis of intermediate **20**[22] (mp 171–172 °C) in order to determine unambiguously its stereochemistry, thus establishing the correctness of our various configurational assumptions.[24] The introduction of the methylene moiety on the γ-lactone was accomplished by using a three-step sequence[25] involving reaction of the dianion of hydroxy lactone **19** with Eschenmoser's dimethylmethyleneammonium iodide[26] in tetrahydrofuran–hexamethylphosphoramide and quaternization of the resulting amine followed by elimination; acid hydrolysis eventually afforded (±)-carpesiolin (**6**) in 17% overall yield after column chromatographic purification on silica gel. The spectral properties and TLC behavior of the synthetic material showed it to be identical with an authentic sample of natural carpesiolin.[27] Whereas the present synthesis thus establishes unequivocally the relative stereochemistry of carpesiolin as depicted in **6**, the absolute configuration of the natural product as shown in this enantiomer is assumed on biogenetic grounds.[28]

Experimental Section

IR spectra were recorded on a Perkin-Elmer 337 spectrometer

(15) Acetal **13** was contaminated with starting enone **12** (~10%); removal of this byproduct occurred at a later stage (**14** → **16**) which resulted in a lower yield of **16** (60%).
(16) W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 2057 (1978).
(17) P. A. Grieco, *Excerpta Med., Sect. 1*, 121 (1979).
(18) P. De Clercq, work in progress.
(19) The TB form of **14** possesses a pseudotwofold axis passing through atom C-10 and the midpoint of the bond from C-6 to C-7: this particular cycloheptene conformation has already been encountered (X-ray analysis) in cycloheptenone derivatives; see, e.g., J. L. Atwood, M. D. Williams, R. H. Garner, and E. J. Cone, *Acta Crystallogr., Sect. B*, **30**, 2066 (1974); A. T. McPhail and K. D. Onan, *J. Chem. Soc., Perkin Trans. 2*, 332 (1976). For conformational diagrams of cycloheptene conformations, see, e.g., O. Ermer and S. Lifson, *J. Am. Chem. Soc.*, **95**, 4121 (1973).
(20) H. B. Henbest and R. A. Wilson, *J. Chem. Soc.*, 1958 (1957).
(21) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972); cf. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. Etheredge, *J. Am. Chem. Soc.*, **99**, 6066 (1977).
(22) The alternative method for lactonization using TsOH in dry benzene yielded deketalized lactone **20**.
(23) We had observed that the reaction of **19** with acetic anhydride–pyridine (80 °C) proceeded very slowly (10% conversion after 2 h); see also ref 12.
(24) We thank Professor M. Van Meerssche, Dr. J. P. Declercq and Dr. G. Germain of the University of Louvain-La-Neuve (Laboratoire de chimie physique et de cristallographie, B-1348 Louvain-la-Neuve, Belgium) for these measurements.
(25) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).
(26) J. Schreiber, M. Haag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **10**, 330 (1971).
(27) We thank Dr. Masao Maruyama for kindly sending a sample of natural carpesiolin and NMR spectra of carpesiolin and its acetate.
(28) J. B. Hendrickson, *Tetrahedron*, 7, 82 (1959).

and ^1H NMR spectra on Varian EM-390 and HR-300 spectrometers ($CDCl_3$) with Me_4Si as internal standard (room temperature). Mass spectra were obtained from an AEI MS-50 mass spectrometer. Melting points are uncorrected. Stereochemical designations of substituents in bicyclic compounds are indicated by *c* (cis) and *t* (trans) relative to a reference substituent (*r*).

***t*-5,*c*-10-Dimethyl-*c*-4-hydroxy-*r*-1*H*-bicyclo[5.3.0]decan-6-one (9).** A solution of 9.89 g (35.6 mmol) of 1[2,3] and 0.89 g (3.56 mmol) of pyridinium *p*-toluenesulfonate in 284 mL of dry ethanol was heated at 55–60 °C for 6 h. The solvent was removed in vacuo, hot isooctane was added, and the solids were filtered off. The hydroxy ketone crystallized out upon cooling, and concentration of the mother liquor yielded another crop (yield 5.73 g, 83%; mp 66–68 °C). A 4-g (20.6 mmol) sample of the product and palladium on charcoal (10%) in 200 mL of dry methanol was hydrogenated at room temperature under atmospheric pressure for 4 h. The reaction mixture was filtered on Celite and concentrated in vacuo. Column chromatographic purification (silica gel, dichloromethane–diethyl ether, 20:1) yielded 3.5 g (87%)[13] of product **9**: IR (neat) 3400, 1690 cm^{-1}; NMR (90 MHz) δ 4.06 (m, 1 H), 1.02 (s, 3 H), 0.96 (d, 3 H); MS *m/z* 196 (M^+).

***t*-5,*c*-10-Dimethyl-*c*-4-hydroxy-*r*-1*H*-bicyclo[5.3.0]dec-6-ene (11).** A solution of 5.16 g (26.3 mmol) of the ketone **9** and 5.38 g (28.9 mmol) of *p*-toluenesulfonylhydrazide in 41 mL of dry ethanol was heated at reflux for 4 h. After concentration in vacuo, the solid was taken up in 100 mL of dry ether; to the stirred suspension was added dropwise 60 mL (4 equiv) of a 1.75 M solution of methyllithium in ether at 20–25 °C. After the mixture was stirred for 4 h, water was added and the product isolated with ether. Workup and column chromatography on silica gel with isooctane–ethyl acetate (9:1) yielded 3.67 g (78%) of **11** (light yellow oil): IR (neat) 3400, 1650, 1455, 1370, 1030 cm^{-1}; NMR (90 MHz) δ 5.5–6.0 (m, 2 H), 3.75 (d, J = 4.8 Hz, 1 H), 0.96 (d, 3 H), 0.88 (s, 3 H); MS *m/z* (rel intensity) 180 (M^+, 7), 162 (24), 93 (100). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.58; H, 11.23.

***t*-5,*c*-10-Dimethyl-*r*-1*H*-bicyclo[5.3.0]dec-6-en-4-one (12).** A solution of 1.525 g (8.48 mmol) of alcohol **11** in 19 mL of dichloromethane was added at 20 °C to a suspension of 13.12 g (50.83 mmol) of Collins reagent in 114 mL of dichloromethane. The mixture was stirred for 15 min and then directly purified on 115 g of Florisil with dichloromethane as eluent, yielding 1.45 g (96%) of ketone **12**: IR (neat) 1735, 1645, 1460, 1160, 735 cm^{-1}; NMR (90 MHz) δ 5.4–6 (m, 2 H), 1.01 (s, 3 H).

Ethylene Ketal of *t*-5,*c*-10-Dimethyl-*r*-1*H*-bicyclo[5.3.0]dec-6-en-4-one (13). A solution of 582 mg (3.27 mmol) of ketone **12**, 5 mg of *p*-toluenesulfonic acid, and 1.5 mL of ethylene glycol in 30 mL of benzene was heated at reflux for 22 h with a Dean–Stark water separator. The solution was cooled, solid potassium carbonate was added, and the mixture was filtered and concentrated in vacuo. Purification by column chromatography on silica gel using isooctane–ether (20:1) yielded 676 mg (93%) of ketal **13**: IR (neat) 1455, 1155, 1050, 730 cm^{-1}; NMR (90 MHz) δ ~5.65 (m, 2 H), 3.92 (m, 4 H), 1.04 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H).

4-Ethylene Ketal of *t*-5,*c*-10-Dimethyl-*r*-1*H*-bicyclo[5.3.0]dec-6-ene-4,8-dione (14). To a suspension of 7.49 g (74.9 mmol) of chromium trioxide in 40 mL of dichloromethane was added, at −20 °C, 7.20 g (74.9 mmol) of 3,5-dimethylpyrazole. After the mixture was stirred for 20 min, a solution of 1.11 g (4.99 mmol) of the alkene **13** in 7 mL of dichloromethane was added and the mixture stirred at −10 °C for 7 h. The reaction mixture was quenched with 32 mL of 5 N sodium hydroxide and extracted after 30 min with ether. Usual workup and purification by column chromatography on silica gel using 25% ethyl acetate–isooctane yielded 707 mg (61%) of ketone **14**: IR (neat) 1675 cm^{-1}; UV (MeOH) λ_{max} 230 nm; NMR (90 MHz) δ 6.38 and 5.96 (AB quartet, J = 12 Hz, 2 H), 3.96 (m, 4 H), 1.14 (s, 3 H), 1.02 (d, J = 6.0 Hz, 3 H); MS *m/z* (rel intensity) 99 (100), 55 (12).

Ethylene Ketal of *t*-5,*c*-10-Dimethyl-8-*c*-hydroxy-*r*-1*H*-bicyclo[5.3.0]dec-6-en-4-one (16). To a solution of 170 mg (0.72 mmol) of enone **14** in 8 mL of benzene at 0 °C was added 1.17 equiv of diisobutylaluminum hydride (1 M solution in hexane, 0.84 mL). After 15 min, 5 mL of methanol was added and the reaction mixture stirred for 90 min at room temperature. Filtration, concentration in vacuo, and purification by column chromatography on silica gel using 20% ethyl acetate–isooctane yielded 102 mg (60%) of the allylic alcohol **16**: IR (neat) 3400, 1460, 1180, 1160, 1130, 1060, 1025, 740, 700 cm^{-1}; NMR (90 MHz) δ 5.68 (br s, 2 H), 4.48 (m, 1 H), 3.94 (m, 4 H), 0.98 (s, 3 H); MS *m/z* (rel intensity) 238 (M^+, 2), 119 (20), 99 (100), 93 (14), 91 (15), 55 (18).

Ethylene Ketal of *t*-5,*c*-10-Dimethyl-*c*-6,7-epoxy-8-*c*-hydroxy-*r*-1*H*-bicyclo[5.3.0]decan-4-one (17). To a solution of 484 mg (2.03 mmol) of allylic alcohol **16** in 24 mL of dry dichloromethane at 0 °C was added 454 mg (2.63 mmol) of *m*-chloroperbenzoic acid and the mixture stirred for 3 h. A 30-mL sample of dichloromethane was added and the organic phase washed with 5% sodium sulfite, sodium bicarbonate, and brine. Usual workup and purification by column chromatography on silica gel using 70% ethyl acetate–isooctane yielded 387 mg (75%) of epoxide **17**: IR (KBr) 3200, 1165, 1065, 1050, 1020, 915 cm^{-1}; NMR (360 MHz) δ 4.09 (m, 2 H), 3.95 (m, 3 H), 3.22 (d, J = 5.2 Hz, 1 H), 2.99 (d, J = 5.2 Hz, 1 H), 0.91 (s, 3 H), 0.88 (d, J = 6.4 Hz, 3 H); MS *m/z* (rel intensity) 171 (28), 110 (20), 99 (21), 70 (24), 54 (26), 53 (21), 42 (100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.33; H, 8.67.

Ethylene Ketal of Methyl (*t*-5,*c*-10-Dimethyl-*c*-6,*c*-8-dihydroxy-4-oxo-*r*-1*H*-bicyclo[5.3.0]dec-7-*t*-yl)acetate (18). To a solution of 4.73 mL (33.74 mmol) of diisopropylamine in 30 mL of dimethoxyethane, at −42 °C, was added 23.7 mL (33.2 mmol) of a 1.4 M solution of *n*-butyllithium in hexane during 10 min. After 15 min, 0.95 mL (16.6 mmol) of acetic acid in 4 mL of dimethoxyethane was added, and the mixture was warmed up to 43 °C and stirred for 90 min. To a solution of 281 mg (1.11 mmol) of the epoxide **17** in 7 mL of dimethoxyethane was then added with a syringe the suspension as described above and the reaction stirred at 60 °C for 24 h. After the mixture was cooled to −10 °C, 25 mL of water was added. The water layer was acidified to pH 3 and extracted with ethyl acetate. The organic phase was dried on magnesium sulfate and then treated with an excess of diazomethane in ether. The mixture was concentrated in vacuo to two-thirds of its volume and then washed with brine. Usual workup and purification by column chromatography on silica gel using 70% ethyl acetate–isooctane yielded 271 mg (75%) of the methyl ester **18**: mp 161–163 °C; IR (KBr) 3440, 1740, 1155, 1000 cm^{-1}; NMR (360 MHz) δ 4.13 (s, 1 H), 3.86–4.02 (m, 4 H), 3.77 (m, 1 H), 3.70 (s, 3 H), 3.69 (s, 1 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.86 (s, 3 H); MS *m/z* (rel intensity) 235 (2), 141 (22), 99 (100), 97 (27), 87 (16), 86 (17). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 61.86; H, 8.60.

Ethylene Ketal of (*t*-5,*c*-10-Dimethyl-*c*-6-hydroxy-4-oxo-*r*-1*H*-bicyclo[5.3.0]dec-7-*t*-yl)acetic Acid γ-Lactone (19). A solution of 60 mg (0.183 mmol) of the ester **18** and 38 mg of potassium hydroxide in 1 mL of methanol was heated at reflux for 1 h. The methanol was evaporated in vacuo, the residue acidified with 1 N hydrochloric acid to pH 3, and the water layer extracted with dichloromethane. After the extract was dried on magnesium sulfate, 0.5 mL of pyridine and 0.25 mL of acetic anhydride were added, and the mixture was stirred for 30 min. Concentration in vacuo and purification of the residue by column chromatography using 30% ethyl acetate–isooctane yielded 43 mg (80%) of lactone **19**: IR (KBr) 3500, 1770, 1270, 1230, 1220, 1180, 1110, 1070, 1060, 1045, 1020, 970, 925 cm^{-1}; NMR (360 MHz) δ 4.23 (ddd, J = 3.8, 10.0, and 11.8 Hz, 1 H), ~3.97 (m, 4 H), 3.54 (d, J = 10.0 Hz), 1.01 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H); MS *m/z* (rel intensity) 296 (M^+, 1), 141 (19), 99 (100), 44 (51). Anal. Calcd for $C_{16}H_{24}O_4$: C, 64.84; H, 8.16. Found: C, 64.56; H, 7.93.

(±)-Carpesiolin (6). To a solution of 0.72 mL (5.17 mmol) of diisopropylamine in 18 mL of tetrahydrofuran, at −78 °C, was added 3.27 mL (5.17 mmol) of a 1.58 M solution of *n*-butyllithium in hexane during 10 min. After 15 min a solution of 102 mg (0.345 mmol) of lactone **19** in 7 mL of tetrahydrofuran and 1.2 mL (6.89 mmol) of hexamethylphosphoric triamide was added dropwise over a period of 1 h. The solution was stirred for 15 min at −78 °C and for 15 min at −42 °C and was then added through a syringe to 1.275 g (6.89 mmol) of the Eschenmoser reagent[26] in 4 mL of tetrahydrofuran. The reaction mixture was stirred for 45 min at −42 °C and for 30 min at room temperature and was then acidified with 5% hydrochloric acid to pH 2 and made alkaline with potassium carbonate. Water was added (6 mL) and the product extracted with ethyl acetate. The organic phase was dried

over sodium sulfate and concentrated in vacuo. The residue was taken up in 15 mL of dioxane, 27 mL of methyl iodide was added, and the mixture was heated at reflux for 24 h. The solvents were evaporated in vacuo; the residue was washed with 16 mL of ether (8×) and then taken up in 8 mL of a 8% sodium bicarbonate solution and 72 mL of ethyl acetate. The suspension was stirred for 30 min, the organic phase was separated, and a new portion of 45 mL of ethyl acetate was added to the water layer. After the mixture was stirred for 30 min, the combined ethyl acetate solutions were dried on magnesium sulfate and the solvent was removed in vacuo. The residue was taken up in 1 mL of benzene containing 2 mg of *p*-toluenesulfonic acid and 5 μL of water. The mixture was stirred for 24 h at room temperature. Purification by column chromatography on silica gel using 30% acetone–isooctane yielded 15 mg (17%) of (±)-carpesiolin (**6**), which was recrystallized from chloroform–hexane: mp 145–148 °C (sublimes); IR (KBr) 3500, 1765, 1730, 1270, 1130, 1100, 1070, 980, 955 cm^{-1}; NMR δ 6.23 (d, J = 4.5 Hz, 1 H), 6.01 (d, J = 3.2 Hz, 1 H), 4.39 (ddd, J = 2.8, 10.0, and 12.0 Hz, 1 H), 4.02 (br d, J = 8.8 Hz, 1 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.04 (s, 3 H); MS m/z (rel intensity) 264 (M^+, 1), 246 (22), 189 (22), 147 (22), 119 (20), 105 (24), 97 (100), 95 (20), 91 (22), 79 (28), 77 (24), 69 (20), 67 (26), 55 (38), 44 (22), 43 (30), 41 (58), 39 (24), 32 (24).

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Ring Size Effect on the Photoreaction of [*n*.3.2]Propellanones Involving a Cyclobutanone Ring

Yoshihiro Fukuda,* Toshihiko Negoro, Yoshito Tobe, Koji Kimura, and Yoshinobu Odaira

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

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In the photoreactions in methanol of [*n*.3.2]propellanones **1–4** and [*n*.3.2]propellanediones **5–8** involving a cyclobutanone ring, cycloelimination products show increasing predominance over ring-expansion products with increasing third-ring size. In addition, in the case of **5–8**, the yield of the syn-form acetals **16a–19a** was slightly more than the yield of the anti-form acetals **16b–19b**, and the syn/anti ratio increases by degrees as the third ring changes from a five- to an eight-membered ring. These ring size effects are discussed.

Recently, the chemistry of propellanes has attracted much attention, especially in view of structure–reactivity relationships,[1] and we have been deeply interested in these relationships on [*n*.3.2]propellane derivatives.[2] In this ring system, the bicyclo[3.2.0]heptane moiety has a rigid boat geometry independent of the conformational flexibility of the third alicyclic ring. Therefore, the tricyclo[*n*.3.2.0] ring system serves as a good model for examination of the steric effect of the third alicyclic ring. We have previously reported on the remarkable effect of the ring size on the stereoselectivity in the hydride reduction of [*n*.3.2]propellanones[2g] and also on the chromic acid oxidation of [*n*.3.2]propellanols[2h] and have pointed out that the ring size effect is attributable to the steric effect associated with the conformational flexibility of the third alicyclic ring.

In order to explain the size effect of another alicyclic ring on the photochemical behavior of the cyclobutanone moiety incorporated into a propellane system, we have now selected as suitable model compounds [*n*.3.2]propellanones **1–4** or [*n*.3.2]propellanediones **5–8** involving a cyclobutanone, a cyclopentane, or a cyclopentanone ring and a five- to eight-membered alicyclic ring.

As is well-known,[3] three major processes in the photochemical behavior of cyclobutanones are (i) ring expansion (formation of an oxacarbene), (ii) cycloelimination (formation of an olefin and ketene), and (iii) decarbonylation. Therefore, our attention has been focused on the steric effect of the third alicyclic ring on these major processes in the photoreaction of [*n*.3.2]propellanones.

[*n*.3.2]Propellanones involving a cyclobutanone ring were synthesized as shown in Scheme I. On irradiation of the bicyclic enones **20–23** with a large excess of vinyl acetate[4] in ether at −70 °C, the respective cycloadducts were afforded in good yields. These cycloadducts were converted in moderate yields to cyclobutanols by tosylhydrazone reduction or Wolff–Kishner reduction. Finally, Jones oxidation of the cyclobutanols produced the desired cyclobutanones **1–4** in fair yields.

When 10^{-2} M solutions of [*n*.3.2]propellanones **1–4** in methanol were irradiated in Pyrex tubes at 20 °C with a

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