1,1-dimethylethoxy)carbonyl deriv.), 99766-18-4; (±)-**9**, 69349-93-5; (±)-**10** (isomer 1), 99766-12-8; (±)-**10** (isomer 2), 99766-20-8; (±)-**12** (1-(trichloro-1,1-dimethylethoxy)carbonyl deriv.), 99766-19-5; (±)-**13**, 99783-13-8; (±)-**14**, 99766-13-9; $Pd(diphos)_2$, 31277-98-2; $ClCOCH_2SO_2C_6H_4Me$-*p*, 997766-14-0; $ClCO_2C(Me_2)CCl_3$, 66270-36-8; tryptamine, 61-54-1; (±)-3-[2-(3-indolyl)ethyl]-4-chloro-8-(phenylthio)-*cis*-3-azoniabicyclo[4.4.0]-3,7-decadiene phosphorodichloridate, 99766-17-3.

# Identification of New Constituents of Quince Fruit Flavor (*Cydonia oblonga* Mill. = *C. vulgaris* Pers.)[1]

Masakazu Ishihara,* Tomoyuki Tsuneya, Haruyasu Shiota, and Minoru Shiga

*Division of Flavor Research, Shiono Koryo Kaisha Ltd., Yodogawa-ku, Osaka 532, Japan*

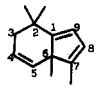
Kazumi Nakatsu

*Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Uegahara, Nishinomiya, Hyogo 662, Japan*

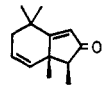
*Received August 5, 1985*

As a flavor of quince fruit, four new bicyclo[4.3.0]nonanes, 2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,7,9(1)-triene (**1**), (+)-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one (**2**), (−)-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-ol (**3**), and (−)-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,9(1)-diene-7,8-diol (**4**), have been identified. Racemic compounds **1**–**4** have been synthesized from 4-oxoisophorone by direct and regioselective reduction to 4-hydroxy-2,6,6-trimethyl-2-cyclohexen-1-one followed by ketal Claisen rearrangement. 3,4-Didehydro-β-ionol (**5**) has also been found to be one of the constituents of quince fruit oil.

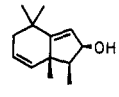
In previous papers,[2-4] we reported the occurrence of 62 compounds as the volatile components in quince fruit (*Cydonia oblonga* Mill. = *C. vulgaris* Pers.). Among them, (2*R*,4*S*)-(+)- and (2*R*,4*R*)-(−)-2,7-dimethyl-5(*E*),7-octadien-4-olides and *cis*- and *trans*-3-methyl-5-(3-methyl-1-(*E*),3-butadien-1-yl)tetrahydrofurans, which have a characteristic sweet odor and are regarded as the important contributors of quince fruit flavor, were isolated and identified. Extending our study on the structural elucidation of the volatile components, we have found four new bicyclo[4.3.0]nonanes (**1**, **2**, **3**, and **4**) and 3,4-didehydro-β-ionol (**5**). In this report, we describe the isolation, structural elucidation, and synthesis of these compounds.



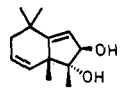
1



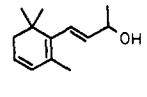
2



3



4

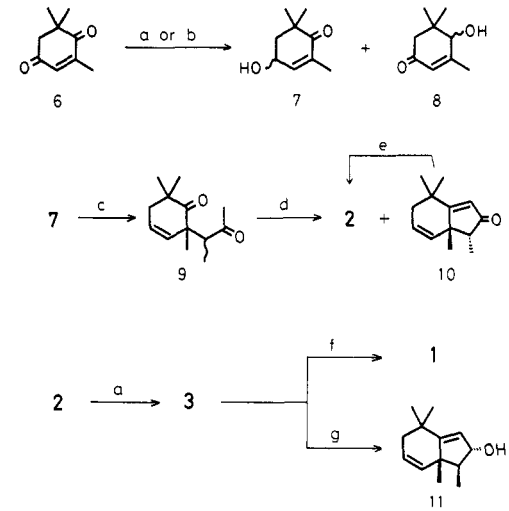


5

## Results and Discussion

**Isolation and Structural Elucidation.** Workup of the oil was described in the foregoing paper,[4] each compound was isolated in a pure state for instrumental analysis by repeated silica gel column chromatography followed by preparative GC or preparative HPLC. In the previous paper,[4] we discussed structures of hydrocarbon **1** and alcohol **3** on the basis of spectral data, although the exact position of a double bond on the cyclohexene ring was not clear at that time. In the present work, this problem was solved by detailed analysis of the $^1H$ NMR spectral data and synthesis of these compounds.

Scheme I[a]



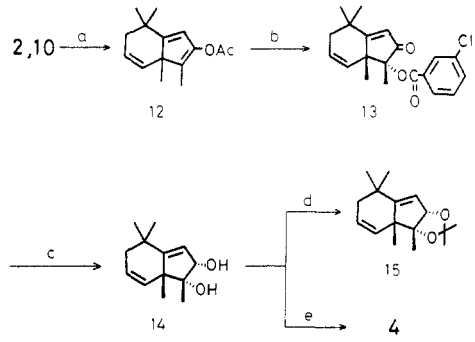

[a] (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$/MeOH. (b) $NaBH_4$/MeOH. (c) $CH_3C(OEt)_2CH_2CH_3$, $H^+$. (d) 0.5 N KOH/aqueous EtOH, reflux. (e) (1) LDA/THF, −78 °C; (2) $H^+$. (f) $POCl_3$/pyridine. (g) (1) $(=NCO_2Et)_2$, $Ph_3P$, $PhCO_2H$/THF; (2) 10% KOH/aqueous MeOH.

High-resolution mass spectroscopy (HRMS) revealed that the ketone **2**, $[\alpha]_D^{26}$ +11° (c 0.2, MeOH), has the molecular formula $C_{13}H_{18}O$. The α,β-unsaturated cyclopentenone skeleton was confirmed by IR bands at 1710 and 1605 $cm^{-1}$. When one of the *gem*-dimethyl's signals at δ 1.33 in the $^1H$ NMR spectrum (360 MHz) was irra-

(1) A part of this work was presented at the 9th International Congress of Essential Oils, Singapore, March 1983.
(2) Tsuneya, T.; Ishihara, M.; Shiota, H.; Shiga, M. *Agric. Biol. Chem.* **1980**, *44*, 957.
(3) Ishihara, M.; Tsuneya, T.; Shiota, H.; Shiga, M.; Yokoyama, Y. *Agric. Biol. Chem.* **1983**, *47*, 2121.
(4) Tsuneya, T.; Ishihara, M.; Shiota, H.; Shiga, M. *Agric. Biol. Chem.* **1983**, *47*, 2495.

0022-3263/86/1951-0491$01.50/0 

Scheme II[a]




[a] (a) $CH_2$=C(OAc)$CH_3$, $H^+$, reflux. (b) MCPBA/$CH_2Cl_2$. (c) $LiAlH_4/Et_2O$. (d) Acetone, $H^+$. (e) (1) (=$NCO_2Et)_2$, $Ph_3P$, $PhCO_2H$/THF; (2) 10% KOH/aqueous MeOH.

diated, the broad double triplet at $\delta$ 2.08 ($H_{ax}$–C(3)) was sharpened, suggesting the existence of W-type long-range coupling. Two allylic long-range couplings between each 3-H and 5-H clearly revealed the existence of methylene protons adjacent to a double bond. These long-range couplings were also observed in **3** and **4**.

The diol **4**, $[\alpha]_D^{26}$ –6° (*c* 0.35, MeOH), was characterized as $C_{13}H_{20}O_2$ by HRMS. The IR spectrum showed a hydroxyl absorption at 3420 $cm^{-1}$, and the $^1H$ NMR spectrum exhibited four methyls at $\delta$ 1.20 (s), 1.21 (s), 1.27 (s), and 1.32 (s). Two hydroxyl protons appeared at $\delta$ 1.60 and 1.70; one of them was predictably attached to C-7 because the methyl signal at C-7 at $\delta$ 1.32 was a singlet.

3,4-Didehydro-$\beta$-ionol (**5**) was identified by comparing its MS spectral data and retention time on GC with those of the synthesized sample because it was too unstable to isolate by preparative GC. This compound has recently been reported as a constituent of *Lycium Chinese* M.[5]

**Synthesis of Racemic Compounds 1–5.** The synthesis of the racemates of compounds **1–3** is outlined in Scheme I. Although 4-hydroxy-2,6,6-trimethyl-2-cyclohexen-1-one (**7**) was previously prepared from 4-oxoisophorone (**6**)[6] by a multistep sequence,[7] we have found a direct preparation of **7** by the simple and regioselective reduction of **6**. Compound **6** was reduced with a quarter of the molar quantity of sodium borohydride ($NaBH_4$) in the presence of cerium(III) chloride in methanol at –5 to 0 °C to afford a 92:8 mixture of **7** and 4-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (**8**)[8] in 84% yield, whereas in the absence of cerium salt **8** was obtained as a major product (**7**:**8** = 2:98). The ketal Claisen rearrangement[9] of **7** with 2,2-diethoxybutane gave the diketone **9** as a nearly 1:1 mixture of diastereoisomers in 76.5% yield. This mixture was refluxed with 0.5 N potassium hydroxide (KOH) in aqueous ethanol to afford **2** and **10** as a 1:1 mixture in 95.7% yield, which was separable by passage through a silica gel column. Pure **10** was epimerized by treatment with lithium diisopropylamide in THF at –78 °C to afford **2** as the sole product.[10] The Luche reduction[11] of **2** gave

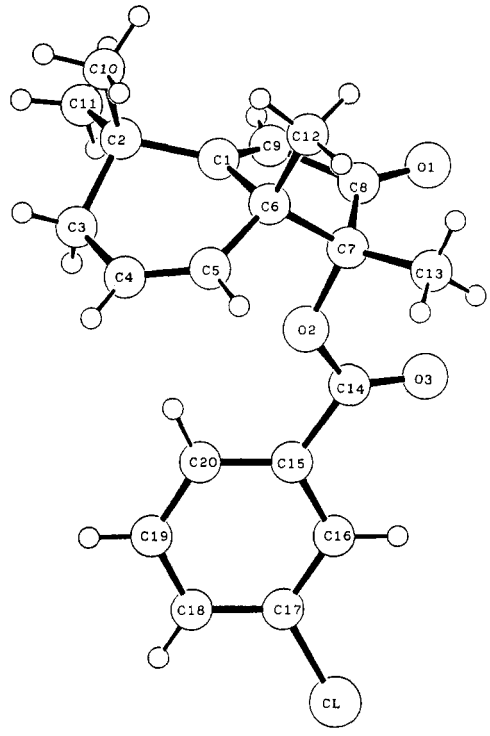



**Figure 1.** Molecular structure of **13**.

the alcohol **3** in 97% yield. The assignment of the stereochemistry of **3** was confirmed by $^1H$ NMR comparison of two methine protons at C-7 and C-8 with those of its isomer **11**, which was obtained in 74% yield by treatment of **3** with Mitsunobu's reagent.[12] In **3**, two methine protons at C-7 and C-8 appear at $\delta$ 1.62 and 4.41, while in **11** the corresponding protons are at $\delta$ 1.67 and 4.31, respectively. In **11**, the syn hydroxyl deshields the methine at C-7 and the syn methyl shields the methine at C-8.[13] These observations lead us to assume that the hydroxyl group of **3** is $\beta$ oriented. Dehydration of **3** with phosphoryl chloride in pyridine provided hydrocarbon **1** in 22.4% yield. Analytical data (IR, $^1H$ NMR, MS, and GC retention time) of the synthesized **1**, **2**, and **3** were identical with those of natural samples.

The diol **4** and its C-8 epimer **14** were prepared from a mixture of **2** and **10** (Scheme II). Oxidation of enol acetate **12**, obtained by acid-catalyzed acetoxylation of **2** and **10** with *m*-chloroperbenzoic acid in dichloromethane, gave the keto ester **13** as sole product in 66% yield.[14] In the NOE experiment of **13**, the olefinic proton at C-5 exhibits 15% and 6.7% of NOE with methyls at C-6 and C-7, respectively, suggesting that two vicinal dimethyls are situated in a cis configuration. An X-ray structure analysis of **13** confirmed the above assignment. Figure 1 shows the molecular structure with the atomic labeling. The torsion angle for the C12–C6–C7–C13 is 41°, indicating the cis configuration.

Lithium aluminum hydride reduction of **13** gave 7$\alpha$,8$\alpha$-diol **14** in 73% yield. The cis vicinal diol of **14** was confirmed by transformation of **14** to the corresponding acetonide **15**.[15] Inversion of the hydroxyl group on C-8

(5) Sannai, A.; Fujimori, T.; Kato, K. The 25th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Yamaguchi, October 1981, Abstr. no. AI-15.

(6) 4-Oxoisophorone is readily available by direct oxidation of isophorone: (a) Hosokawa, T.; Inui, S.; Murahashi, S. *Chem. Lett.* **1983**, 1081. (b) Freer, V. J.; Yates, P. *Chem. Lett.* **1984**, 2031.

(7) Widmer, E.; Zell, R.; Lukac, T.; Caadei, M.; Schonhdzer, P.; Broger, E. A. *Helv. Chim. Acta* **1981**, *64*, 2405.

(8) Isler, O.; Lindlar, H.; Montavon, M.; Ruegg, R.; Saucy, G.; Zeller, P. *Helv. Chim. Acta* **1956**, *39*, 2041.

(9) Daub, G. W.; Sanchez, M. G.; Cromer, R. A.; Gibson, L. L. *J. Org. Chem.* **1982**, *47*, 743.

(10) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733.

(11) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(12) (a) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. (b) Bose, A. K.; Lal, B.; Hoffman W. A., III; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.

(13) Pothberg, I.; Sundoro, B.; Balanikas, G.; Kirsch, S. *J. Org. Chem.* **1983**, *48*, 4345.

(14) Williamson, K. L.; Coburn, J. I.; Herr, M. F. *J. Org. Chem.* **1967**, *32*, 3934.

of **14** was achieved by Mitsunobu's method to give **4** (52%). Analytical data (IR, $^1$H NMR, MS, and GC retention time) of the synthesized **4** were identical with those of natural **4**.

3,4-Didehydro-β-ionol (**5**) was prepared by a well-known method,[16] and its MS spectral data and GC retention time were identical with those of the natural compound. Additionally, hydrocarbon **1** was obtained by refluxing **5** in 5% aqueous citric acid in 80% yield. This result suggests the existence of **5** as a precursor of the newly isolated bicyclo compounds in nature. These compounds have a hydroxyl or carbonyl group at C-8 which constitutes a unique structure among the previously isolated series of ionone homologues.[17]

## Experimental Section

All boiling points and melting points are uncorrected. The IR spectra were obtained on a JASCO IRA-1 type spectrometer. The $^1$H NMR spectra were measured on a Hitachi R-24B (60-MHz), JEOL FX-100 (100-MHz), or a Nicolet NT-360 (360-MHz) spectrometer. Samples were dissolved in $CDCl_3$, and the chemical shift values (δ) are expressed in ppm downfield from the internal standard $Me_4Si$. Gas chromatography was performed on a Hewlett Packard 5840A gas chromatograph instrument equipped with FID and a 0.28 mm (i.d.) × 40 m glass capillary column coated with SF-96. The column temperature was programmed from 70 to 220 °C at 3 °C/min, and nitrogen was used as carrier gas. GC–MS spectra were taken on a Hitachi M-80A combined GC–MS instrument or a Hitachi M-52 GC–MS instrument equipped with the same glass capillary column described above. High-resolution mass spectra were measured on a Hitachi M-80A instrument. The preparative GC was performed on a Varian Aerograph 2700 with TCD and a 4 mm (i.d.) × 4 m glass column coated with 20% PEG 20M. The preparative HPLC was carried out with a Water's limited HPLC instrument with UV and RI detectors. A column of μ-Porasil and hexane as the eluting solvent were used. The optical rotations were measured in methanol on a Perkin-Elmer Model 141 polarimeter.

**Isolation.** The essential oil (0.93 g), obtained by steam distillation of the commercially available fresh quince fruit, was chromatographed on silica gel. Elution with hexane, a hexane–ether mixture, ether, and methanol gave ten fractions: fraction I (hexane, 148 mg), II (hexane, 24 mg), III (hexane–ether, 98:2, 2 mg), IV (95:5, 89 mg), V (92.5:7.5, 12 mg), VI (9:1, 54 mg), VII (8:2, 114 mg), VIII (7:3, 114 mg), IX (ether, 149 mg), and X (methanol, 127 mg). The hydrocarbon **1** was contained in fraction I. Ketone **2** was in fractions V and VI. Alcohol **3** and 3,4-didehydro-β-ionol were in fractions VI and VII. The diol **4** was in fractions IX and X.

**2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,7,9(1)-triene (1).** The title compound **1** (5.8% of the oil) was isolated by preparative HPLC: IR (neat) 3050, 3020, 1640, 1610, 1380, 1360, 820, 720 cm$^{-1}$; $^1$H NMR (100 MHz) δ 1.15 (s, 3 H, $CH_3$), 1.26 (s, 6 H, $CH_3$), 1.84 (s, 3 H, $CH_3$), 1.97–2.32 (m, 2 H, $CH_2$), 5.60–6.09 (m, 4 H, CH=); MS, *m/z* (relative intensity) 174 ($M^+$, 30), 159 (100), 144 (14), 131 (12), 105 (10); GC retention time 33.47 min; HRMS calcd for $C_{13}H_{18}$ $M^+$ *m/z* 174.1408, found $M^+$ *m/z* 174.1435.

**(+)-2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one (2).** The title compound **2** (0.28% of the oil) was isolated by rechromatography on silica gel followed by preparative GC: $[\alpha]_D^{26}$ +11° (*c* 0.2, MeOH); IR (neat) 3030, 1710, 1605, 1370, 1260, 1185, 998, 865, 810, 720 cm$^{-1}$; $^1$H NMR (360 MHz) δ 1.10 (d, *J* = 7 Hz, 3 H, $CH_3$), 1.17 (s, 3 H, $CH_3$), 1.25 (s, 3 H, $CH_3$), 1.33 (s, 3 H, $CH_3$), 2.08 (dt, *J* = 2.5 and 17 Hz, 1 H, 3-$H_{ax}$), 2.16 (ddd, *J* = 1.3, 5, and 17 Hz, 1 H, 3-$H_{eq}$), 2.77 (q, *J* = 7 Hz, 1 H, CH), 5.62 (ddd, *J* = 2.5, 5, and 10 Hz, 1 H, CH=), 5.71 (dddd, *J* = 0.5, 1.3, 2.5, and 10 Hz, 1 H, CH=), 5.88 (d, *J* = 0.5 Hz, 1 H, CH=); MS, *m/z* (relative intensity) 190 ($M^+$, 64), 175 (100), 162 (10), 147 (64), 134 (18), 119 (36), 105 (24), 91 (16), 67 (10); GC retention time 43.12 min; HRMS calcd for $C_{13}H_{18}O$ $M^+$ *m/z* 190.1356, found $M^+$ *m/z* 190.1315.

**(−)-2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-ol (3).** The title compound **3** (3.09% of the oil) was isolated by the same method as compound **2**: $[\alpha]_D^{26}$ −40° (*c* 0.67, MeOH); IR (neat) 3330, 3050, 3020, 1650, 1060, 1020, 1010, 805, 720 cm$^{-1}$; $^1$H NMR (360 MHz) δ 1.00 (s, 3 H, $CH_3$), 1.06 (d, *J* = 7 Hz, 3 H, $CH_3$), 1.12 (s, 3 H, $CH_3$), 1.14 (s, 3 H, $CH_3$), 1.62 (dq, *J* = 7 and 8 Hz, 1 H, CH), 1.80 (br s, 1 H, OH), 1.90 (ddd, *J* = 1.3, 4.6, and 17 Hz, 1 H, 3-$H_{ax}$), 1.96 (dt, *J* = 2.7 and 17 Hz, 1 H, 3-$H_{eq}$), 4.41 (dd, *J* = 1.2 and 8 Hz, 1 H, CH), 5.37 (br t, *J* = 1.2 Hz, 1 H, CH=), 5.47 (ddd, *J* = 2.7, 4.6, and 10 Hz, 1 H, CH=), 5.55 (dddd, *J* = 0.5, 1.3, 2.7, and 10 Hz, 1 H, CH=); MS, *m/z* (relative intensity) 192 ($M^+$, 9), 177 (30), 174 (19), 159 (100), 144 (19), 136 (24), 121 (59), 119 (46), 107 (29), 105 (33), 93 (20), 91 (18), 71 (20), 69 (12), 43 (12); GC retention time 42.36 min; HR MS calcd for $C_{13}H_{20}O$ $M^+$ *m/z* 192.1513, found $M^+$ *m/z* 192.1483.

**(−)-2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,9(1)-diene-7,8-diol (4).** The title compound **4** (0.98% of the oil) was isolated by the same method as compound **2**: $[\alpha]_D^{26}$ −6° (*c* 0.35, MeOH); IR (neat) 3420, 3050, 3020, 1650, 1045, 1030, 1010, 960, 725 cm$^{-1}$; $^1$H NMR (360 MHz) δ 1.20 (s, 3 H, $CH_3$), 1.21 (s, 3 H, $CH_3$), 1.27 (s, 3 H, $CH_3$), 1.32 (s, 3 H, $CH_3$), 1.60 (br s, 1 H, OH), 1.70 (br s, 1 H, OH), 1.93 (dt, *J* = 2.6 and 17 Hz, 1 H, 3-$H_{ax}$), 2.03 (dd, *J* = 5.7 and 17 Hz, 1 H, 3-$H_{eq}$), 4.15 (d, *J* = 3.2 Hz, 1 H, CH), 5.57 (ddt, *J* = 1, 2.6, and 10 Hz, 1 H, CH=), 5.65 (d, *J* = 3.2 Hz, 1 H, CH=), 5.85 (ddd, *J* = 2.6, 5.7, and 10 Hz, 1 H, CH=); MS, *m/z* (relative intensity) 208 ($M^+$, 1), 193 (1), 190 (9), 175 (35), 157 (12), 147 (24), 135 (100), 119 (36), 107 (28), 105 (17), 93 (19), 43 (58); GC retention time 49.47 min; HRMS calcd for $C_{13}H_{20}O_2$ $M^+$ *m/z* 208.1462, found $M^+$ *m/z* 208.1487.

**3,4-Didehydro-β-ionol (5).** The title compound **5** (3.61% of the oil) was too unstable to isolate in a pure state by preparative GC, so IR and $^1$H NMR spectra could not be obtained: MS, *m/z* (relative intensity) 192($M^+$, 14), 177 (5), 174 (9), 159 (28), 121 (30), 119 (100), 43 (26); GC retention time 43.39 min; HRMS calcd for $C_{13}H_{20}O$ $M^+$ *m/z* 192.1513, found $M^+$ *m/z* 192.1478.

**4-Hydroxy-2,6,6-trimethyl-2-cyclohexen-1-one (7) and 4-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (8).** To a mixture of 4-oxoisophorone (**6**) (50 g, 0.33 mol) and $CeCl_3 \cdot 7H_2O$ (45 g, 0.12 mol) in methanol (150 mL) was added a solution of $NaBH_4$ (3.3 g, 0.09 mol) in alkaline methanol (100 mL) at −5 to 0 °C in the period of 20 min. The reaction mixture was stirred at the same temperature for 30 min and was poured into a cold 20% $NH_4Cl$ aqueous solution, and the organic substances were extracted 3 times with ether. The ether layer was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). After removal of the solvent, the residue was distilled to give **7** (39 g, 77%, bp 109–111 °C/4 mmHg, lit.[7] bp 91–94 °C/0.003 torr) and **8** (3.4 g, 7%, bp 123–127 °C/4 mmHg, lit.[8] bp 105–110 °C/0.1 mmHg).

To a mixture of **6** (1.5 g, 10 mmol) in methanol (10 mL) was added a solution of $NaBH_4$ (100 mg, 2.6 mmol) in alkaline methanol (10 mL) at −10 °C, and the reaction mixture was stirred at −10 °C for 1.2 h. After the workup described above, the residue was chromatographed on silica gel (ether–hexane, 3:7) to give **7** (16 mg, 1%) and **8** (1.23 g, 81%).

**2-(2-Oxobut-3-yl)-2,6,6-trimethyl-3-cyclohexen-1-one (9).** A solution of **7** (17 g, 0.11 mol), 2,2-diethoxybutane (52 g, 0.36 mol), and propionic acid (1.1 g, 0.015 mol) was refluxed for 24 h. The ethanol formed was occasionally removed by distillation from the reaction flask, at the end of the reaction, the mixture was heated to 200 °C, cooled, and then poured into a saturated $NaHCO_3$, and the organic substances were extracted with ether. The ether layer was washed twice with brine and dried ($MgSO_4$). The residue was distilled to give 17.5 g (76.5%) of **9** as a nearly 1:1 mixture of diastereoisomers. Column chromatography on silica gel (ether–hexane, 1:9) enables purification of the substance for instrumental analysis, bp 103–105 °C/4 mmHg. One isomer eluted first: IR (neat) 3020, 1700 cm$^{-1}$; $^1$H NMR (60 MHz) δ 1.05 (d, *J* = 7 Hz, 3 H, $CH_3$), 1.13 (s, 6 H, $CH_3$), 1.16 (s, 3 H, $CH_3$), 2.13 (s, 3 H, $CH_3$), 2.05 (d, *J* = 16 Hz, 1 H, $H_{ax}$–C(5)), 2.39 (dd, *J* = 1.5 and 16 Hz, 1 H, $H_{eq}$–C(5)), 3.08 (q, *J* = 7 Hz, 1 H, CH), 5.56–6.00 (m, 2 H, CH=); MS, *m/z* (relative intensity) 208 ($M^+$,

(15) Sakan, T.; Abe, K. *Tetrahedron Lett.* **1968**, 2471.

(16) Mousseron-Canet, M.; Mousseron, M.; Legendre, P. *Bull. Soc. Chim. Fr.* **1964**, 50.

(17) To our knowledge, 7-hydroxy-2,2,6,7-tetramethylbicyclo[4.3.0]-non-9(1)-en-8-one, which has been identified as a burley tobacco constituent, is the only example of this type of compound ever reported: (a) Demole, E.; Berthet, D. *Helv. Chim. Acta* **1972**, *55*, 1866. (b) Roberts, D. L.; Rhode, W. A. *Tob. Int.* **1972**, *16*, 107.

5), 165 (14), 152 (15), 137 (54), 109 (27), 95 (100), 70 (21), 43 (30); HRMS calcd for $C_{13}H_{20}O_2$ $M^+$ $m/z$ 208.1462, found $M^+$ $m/z$ 208.1468. The other isomer: IR (neat) 3030, 1700 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 1.13 (s, 3 H, $CH_3$), 1.15 (s, 6 H, $CH_3$), 1.24 (d, $J$ = 7 Hz, 3 H, $CH_3$), 2.04 (s, 3 H, $CH_3$), 2.08 (dd, $J$ = 5.2 and 16 Hz, 1 H, $H_{ax}$–C(5)), 2.67 (dt, $J$ = 2.4 and 16 Hz, 1 H, $H_{eq}$–C(5)), 3.22 (q, $J$ = 7 Hz, 1 H, CH), 5.46 (dd, $J$ = 2.4 and 10 Hz, 1 H, CH=), 5.82 (ddd, $J$ = 2.4, 5.2, and 10 Hz, 1 H, CH=); MS, $m/z$ (relative intensity) 208 ($M^+$, 2), 165 (7), 152 (8), 137 (47), 109 (26), 95 (100), 70 (25), 43 (44); HRMS calcd for $C_{13}H_{20}O_2$ $M^+$ $m/z$ 208.1462, found $M^+$ $m/z$ 208.1469.

**2,2,6β,7β-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one (2) and 2,2,6β,7α-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one (10).** A mixture of **9** (13.7 g, 66 mmol) and 0.5 N potassium hydroxide in 90% aqueous ethanol (100 mL) was refluxed for 1 h and then was poured into cold water (200 mL), and the organic substances were extracted 3 times with ether. The ether layer was washed with brine and dried ($MgSO_4$). The residue was distilled to give 12.0 g (95.7%) of **2** and **10** (52:48 ratio on GC) as a colorless oil. Column chromatography on silica gel (ether–hexane, 1:9) gave pure **2** and **10**. Analytical data (IR, $^1H$ NMR, MS, and GC retention time) of **2** were identical with those of a natural sample: bp 105–107 °C/4 mmHg; HRMS calcd for $C_{13}H_{18}O$ $M^+$ $m/z$ 190.1356, found $M^+$ $m/z$ 190.1300. Spectral data of **10**: IR (neat) 1705, 1602 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 0.96 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.25 (s, 3 H, $CH_3$), 1.31 (s, 3 H, $CH_3$), 1.34 (s, 3 H, $CH_3$), 2.09 (m, 2 H, $CH_2$), 2.23 (q, $J$ = 7 Hz, 1 H, CH), 5.57 (m, 2 H, CH=), 5.69 (s, 1 H, CH=); MS, $m/z$ (relative intensity) 190 ($M^+$, 75), 175 (100), 147 (72), 134 (25), 119 (49), 105 (26); HRMS calcd for $C_{13}H_{18}O$ $M^+$ $m/z$ 190.1356, found $M^+$ $m/z$ 190.1308.

**Conversion of 10 into 2.** Lithium diisopropylamide (2 mmol) was prepared from diisopropylamine (300 mg, 3 mmol) and $n$-butyllithium (15% hexane solution, 1 mL, 2 mmol) in THF (2 mL) at −78 °C under argon atmosphere. To this mixture was added a solution of **10** (190 mg, 1 mmol) in THF (1 mL) at the same temperature. After 20 min of stirring, a saturated $NH_4Cl$ (0.5 mL) was added at −40 °C. The mixture was poured into a cold dilute HCl and extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was evaporated to give 190 mg (100%) of **2** as a colorless oil.

**2,2,6β,7β-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8β-ol (3).** To a mixture of **2** (520 mg, 2.7 mmol) and $CeCl_3 \cdot 7H_2O$ (1.0 g, 2.6 mmol) in methanol (10 mL) was added a solution of $NaBH_4$ (100 mg, 2.6 mmol) in alkaline methanol (5 mL) at 0 °C in the period of 5 min. The reaction mixture was stirred at room temperature for 30 min to afford, after extractive workup and chromatography on silica gel (ether–hexane, 1:9), 510 mg (97%) of **3** as a colorless oil. Analytical data (IR, $^1H$ NMR, MS, and GC retention time) were identical with those of a natural sample: HRMS calcd for $C_{13}H_{20}O$ $M^+$ $m/z$ 192.1513, found $M^+$ $m/z$ 192.1510.

**2,2,6β,7β-Tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8α-ol (11).** To a mixture of **3** (430 mg, 2.2 mmol), triphenylphosphine (630 mg, 2.4 mmol), and benzoic acid (295 mg, 2.4 mmol) in THF (8 mL) was added dropwise a solution of diethyl azodicarboxylate (420 mg, 2.4 mmol) in THF (2 mL). The mixture was stirred at room temperature for 9 h. The residue after evaporation of THF was directly chromatographed on silica gel (ether–hexane, 1:9) to give 520 mg (79%) of the benzoate, which was hydrolyzed with 8% KOH in aqueous methanol to afford 97 mg (94%) of **11** as a colorless oil after chromatography on silica gel (ether–hexane, 1:9): IR (neat) 3360, 1643, 1040 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 1.02 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.14 (s, 6 H, $CH_3$), 1.16 (s, 3 H, $CH_3$), 1.57 (br s, 1 H, OH), 1.67 (dq, $J$ = 3.2 and 7 Hz, 1 H, CH), 1.91 (m, 2 H, $CH_2$), 4.31 (dd, $J$ = 3.2 and 6 Hz, 1 H, CH), 5.24–5.83 (m, 3 H, CH=); MS, $m/z$ (relative intensity) 192 ($M^+$, 26), 177 (100), 159 (73), 136 (77), 121 (67), 119 (56), 107 (27), 105 (21), 43 (22); HRMS calcd for $C_{13}H_{20}O$ $M^+$ $m/z$ 192.1513, found $M^+$ $m/z$ 192.1496.

**2,2,6,7-Tetramethylbicyclo[4.3.0]nona-4,7,9(1)-triene (1).** To a solution of **3** (1.0 g, 5.2 mmol) in pyridine (7 mL) was added dropwise phosphoryl chloride (0.53 mL, 5.3 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 45–50 °C for 30 min and then was poured into cold dilute HCl, and the organic substances were extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The residue was chromatographed on silica gel (hexane) to give 203 mg (22.4%) of **1** as a colorless oil. Analytical data (IR, $^1H$ NMR, MS, and GC retention time) were identical with those of a natural sample: HRMS calcd for $C_{13}H_{18}$ $M^+$ $m/z$ 174.1408, found $M^+$ $m/z$ 174.1429.

**8-Acetoxy-2,2,6,7-tetramethylbicyclo[4.3.0]nona-4,7,9(1)-triene (12).** A mixture of **2** and **10** (7.5 g, 39 mmol), isopropenyl acetate (25 g, 250 mmol), and $p$-toluenesulfonic acid (0.1 g) was refluxed for 6 h. The reaction mixture was directly distilled to give 8.5 g of a slight yellowish oil. This was chromatographed on silica gel (ether–hexane, 1:9) to give 7.5 g (82%) of **12** and 1.0 g of unreacted **2** and **10**, bp 121–122 °C/4 mmHg: IR (neat) 1760, 1659 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 1.24 (s, 6 H, $CH_3$), 1.26 (s, 3 H, $CH_3$), 1.71 (s, 3 H, $CH_3$), 2.16 (s, 3 H, $CH_3$), 1.80–2.40 (m, 2 H, $CH_2$), 5.32–5.80 (m, 2 H, CH=), 5.92 (s, 1 H, CH=); MS, $m/z$ (relative intensity) 232 ($M^+$, 16), 190 (89), 175 (100), 157 (17), 55 (16); HRMS calcd for $C_{15}H_{20}O_2$ $M^+$ $m/z$ 232.1462, found $M^+$ $m/z$ 232.1459.

**7α-((3-Chlorobenzoyl)oxy)-2,2,6β,7β-tetramethylbicyclo[4.3.0]nona-4,9(1)-dien-8-one (13).** To a solution of **12** (2.9 g, 12.5 mmol) in dichloromethane (30 mL) was added $m$-chloroperbenzoic acid (3.2 g of 70% assay, 13.0 mmol) in dichloromethane (60 mL) at −10 °C for 15 min. The mixture was stirred at 0 °C for 30 min and then was poured into a cold 5% aqueous NaOH, and the organic substances were extracted with dichloromethane. The organic layer was washed with a saturated sodium thiosulfate and brine and dried ($MgSO_4$). The residue was chromatographed on silica gel (ether–hexane, 15:85) to give 2.84 g (66%) of **13** as colorless crystals, mp 110.6–112.6 °C (from hexane): IR (KBr) 1734, 1715, 1603 $cm^{-1}$; $^1H$ NMR (360 MHz) $\delta$ 1.25 (s, 3 H, $CH_3$), 1.27 (s, 3 H, $CH_3$), 1.32 (s, 3 H, $CH_3$), 1.66 (s, 3 H, $CH_3$), 2.07 (dt, $J$ = 2.5 and 17 Hz, 1 H, $H_{ax}$–C(3)), 2.15 (ddd, $J$ = 1.2, 5, and 17 Hz, 1 H, $H_{eq}$–C(3)), 5.66 (d, $J$ = 10 Hz, 1 H, CH=), 5.76 (ddd, $J$ = 3, 5, and 10 Hz, 1 H, CH=), 5.86 (d, $J$ = 0.5 Hz, 1 H, CH=), 7.31 (t, $J$ = 8 Hz, 1 H, Ar H), 7.48 (ddd, $J$ = 1, 2.3, and 8 Hz, 1 H, Ar H), 7.77 (ddd, $J$ = 1, 2, and 8 Hz, 1 H, Ar H), 7.85 (t, $J$ = 2 Hz, 1 H, Ar H); MS, $m/z$ (relative intensity) 346 ($M^+$ + 2, 8), 344 ($M^+$, 22), 205 (47), 156 (46), 141 (58), 139 (100), 43 (71); HRMS calcd for $C_{20}H_{21}ClO_3$ $M^+$ $m/z$ 344.1178, found $M^+$ $m/z$ 344.1159.

**2,2,6β,7β-Tetramethylbicyclo[4.3.0]nona-4,9(1)-diene-7α,8α-diol (14).** To a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in ether (5 mL) was added dropwise a solution of **13** (350 mg, 1.0 mmol) in ether (5 mL) at 5–10 °C under argon atmosphere. The mixture was stirred at room temperature for 2 h. Excess hydride was decomposed by successive dropwise addition of water (0.1 mL), 15% NaOH (0.1 mL), and water (0.3 mL). The mixture was filtered off, and the filtrate was dried ($MgSO_4$) and condensed to give 305 mg of a colorless viscous oil, which was chromatographed on silica gel (ether–hexane, 1:4) to give 151 mg (73%) of **14** as colorless crystals, mp 61.7–62.8 °C (from hexane): IR (KBr) 3440, 3240, 1650 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 1.11 (s, 6 H, $CH_3$), 1.14 (s, 3 H, $CH_3$), 1.25 (s, 3 H, $CH_3$), 1.67 and 1.79 (two br s, 1 H, OH), 1.98 (m, 2 H, $CH_2$), 2.54 and 2.72 (two br s, 1 H, OH), 4.52 (dd, $J$ = 1.2 and 10 Hz, 1 H, CH) 5.20–6.00 (m, 3 H, CH=); MS, $m/z$ (relative intensity) 208 ($M^+$, 2), 175 (53), 135 (100), 119 (26), 43 (54); HRMS calcd for $C_{13}H_{20}O_2$ $M^+$ $m/z$ 208.1462, found $M^+$ $m/z$ 208.1409.

**7α,8α-*O*-Isopropylidene-2,2,6β,7β-tetramethylbicyclo[4.3.0]nona-4,9(1)-diene (15).** A mixture of **14** (61 mg, 0.3 mmol), $p$-toluenesulfonic acid (15 mg), anhydrous $MgSO_4$ (20 mg), and acetone (3 mL) was stirred at room temperature for 1 h. After the usual workup of the mixture, the residue was chromatographed on silica gel (ether–hexane, 1:9) to give 67 mg (92%) of **15** as a colorless oil: IR (neat) 1652, 1638 $cm^{-1}$; $^1H$ NMR (60 MHz) $\delta$ 1.09 (s, 3 H, $CH_3$), 1.16 (s, 6 H, $CH_3$), 1.26 (s, 3 H, $CH_3$), 1.36 (s, 3 H, $CH_3$), 1.40 (s, 3 H, $CH_3$), 1.96 (m, 2 H, $CH_2$), 4.88 (s, 1 H, CH), 5.29 (s, 1 H, CH=), 5.45–5.86 (m, 2 H, CH=); MS, $m/z$ (relative intensity) 233 ($M^+$ − 15, 6), 190 (60), 175 (100), 147 (36), 131 (33), 43 (47); HRMS calcd for $C_{13}H_{18}O$ $M^+$ − $C_3H_6O$ $m/z$ 190.1356, found $M^+$ − $C_3H_6O$ $m/z$ 190.1290.

**2,2,6β,7β-Tetramethylbicyclo[4.3.0]nona-4,9(1)-diene-7α,8β-diol (4).** In the same manner as described for the preparation of the alcohol **11**, **4** was obtained in 52% yield from **14** as

colorless crystals, mp 85.9–86.8 °C (from hexane). Analytical data (IR, $^1$H NMR, MS, and GC retention time) were identical with those of natural 4. HRMS calcd for $C_{13}H_{20}O_2$ $M^+$ $m/z$ 208.1462, found $M^+$ $m/z$ 208.1474.

**Dehydration of 3,4-Didehydro-β-ionol (5).** A mixture of 5 (300 mg, 1.56 mmol) and 5% aqueous citric acid (60 mL) was refluxed for 1 h. After the usual workup of the mixture, the residue was chromatographed on silica gel (hexane) to give 217 mg (80%) of 1 as a colorless oil.

**X-ray Structure Determination of 13.** Slow evaporation of a petroleum ether solution afforded colorless crystals suitable for single-crystal X-ray diffraction. A specimen, approximately 0.47 × 0.34 × 0.32 mm, was used. Preliminary photographic data indicated the triclinic space group $P1$ or $P\bar{1}$; a successful structure determination was accomplished in $P\bar{1}$. **Unit cell parameters:** $a$ = 11.112 (2) Å, $b$ = 11.355 (3) Å, $c$ = 7.982 (2) Å, $\alpha$ = 105.36 (2)°, $\beta$ = 89.78 (2)°, $\gamma$ = 113.28 (2)°, $V$ = 886.3 (3) Å$^3$, $Z$ = 2, $D_x$ = 1.2922 (4) g cm$^{-3}$.

Intensities for the independent reflections for $2\theta < 50°$ were measured with the $\omega$–$2\theta$ continuous scan mode at a $2\theta$ rate of 4° min$^{-1}$ by use of graphite-monochromated Mo $K_\alpha$ radiation ($\lambda$ = 0.71069 Å). The scan width in $2\theta$ was (2.0 + 0.68 tan $\theta$)° with background counts of 15-s duration on either side of the peak. The intensities were corrected for Lorentz and polarization factors but not for absorption. Altogether, 3128 reflections were measured, and, of these, 2524 reflections with $|F_o| > 3\sigma(F_o)$ were considered observed and used for the structure determination.

The structure was solved by direct methods using the program MULTAN 78[18] and refined by the block-diagonal least-squares method with anisotropic temperature factors for all the nonhydrogen atoms and with isotropic ones for the hydrogen atoms. The final residual index $R$ was 0.043 and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$ was 0.066. The weighting scheme used in the final least-squares cycle was $1/w = a + |F_o| + c|F_o|^2$, where $a = 2F_o$ (min) and $c = 2/F_o$ (max). The final difference Fourier map was featureless. Figure 1 was drawn with local version of the ORTEP-II program.[19]

**Acknowledgment.** We are indebted to Professors Sigeru Torii and Kenji Uneyama of Okayama University for measurement of 100-MHz $^1$H NMR spectra and for their generous advice. We also thank Hideo Naoki and Dr. Tsutomu Sakai, Suntory Institute for Bioorganic Research, for measurement of 360-MHz $^1$H NMR spectra and for their helpful discussions, and Mr. Azusa Yoshioka of our laboratory for obtaining HRMS spectra.

**Supplementary Material Available:** Tables of fractional coordinates, temperature factors, bond distances, and bond angles for keto ester 13 (5 pages). Ordering information is given on any current masthead page.

(18) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN 78, University of York, England and Louvain, Belgium, 1978.
(19) Johnson, C. K. ORTEP-II, Report ORNL 5138, Oak Ridge National Laboratory, TN, 1976.

# Two Total Syntheses of Showdomycin and Related Studies

Anthony G. M. Barrett* and Howard B. Broughton

*Department of Chemistry, Northwestern University, Evanston, Illinois 60201*

Steven V. Attwood and A. A. Leslie Gunatilaka

*Department of Chemistry, Imperial College, London SW7 2AY, England*

*Received September 9, 1985*

After a series of model reactions, D-ribose (2) was reacted with 3-(triphenylphosphoranylidene)-2,5-pyrrolidinedione (**8a**) in THF at reflux to produce 3(*E*)-(2(*S*),3(*S*),4(*R*),5-tetrahydroxy-1-pentylidene)-2,5-pyrrolidinedione (**35**) (75%). Subsequent cyclization of **35** using phenylselenenyl chloride followed by hydrogen peroxide gave showdomycin (**1**) (13%) and *epi*-showdomycin (**36**) (41%). Using a similar strategy 2,3-*O*-isopropylidene-D-ribose (**37b**) was reacted sequentially with 1-(triphenylmethyl)-3-(triphenylphosphoranylidene)-2,5-pyrrolidinedione (**8b**), phenylselenenyl chloride, hydrogen peroxide, and trifluoroacetic acid to give 1 (3% overall).

Showdomycin (1) was first isolated from *Streptomyces showdoensis* by Nishimura et al. of the Shionogi Research Laboratory.[1] This C-glycoside is noted both for its antibiotic activity, especially against *Streptococcus hemolyticus*, and for its inhibition of Ehrlich ascites tumors in mice.[2] Several successful multistage total syntheses of 1 have been reported by using either protected carbohydrates including ribose[3-6] or furan–dienophile cycloadducts[7] as starting materials. Without exception, in these syntheses, the maleimide ring of 1 was introduced indirectly either via carbacyclic or acyclic β-anomeric substituents on the ribose ring. In addition only one synthesis[3] prior to our preliminary publication[8] produced the C-9 skeleton of 1 directly in the first step. Herein we report experimental details for the total synthesis of 1 by a two-step protocol and by a four-step protocol. In addition, synthetic studies on conceptually similar but unsuccessful routes will be summarized.

In principle showdomycin (1) should be available in one step from the condensation reaction of D-ribose (2) with a maleimide anion equivalent (3) or from δ-D-ribonolactone (**4a**)[9] and a succinimide anion equivalent (5). In addition

(1) Nishimura, H.; Mayama, M.; Komatsu, Y.; Kato, H.; Shimaoka, N.; Tanaka, Y. *J. Antibiot., Ser. A* **1964**, *17*, 148. Darnall, K. R.; Townsend, L. B.; Robins R. K. *Proc. Nat. Acad. Sci. U.S.A.* **1967**, *57*, 548. Nakagawa, Y.; Kanō, H.; Tsukuda, Y.; Koyama, H. *Tetrahedron Lett.* **1967**, 4105.
(2) Matsuura, S.; Shiratori, O.; Katagiri, K. *J. Antibiot., Ser. A* **1964**, *17*, 234.
(3) Inoue, T.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1980**, 251.
(4) Kane, P. D.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 657. Kane, P. D.; Mann, J. *J. Chem. Soc., Chem. Commun.* **1983**, 224.
(5) Kalvoda, L.; Farkas, J.; Sorm, F. *Tetrahedron Lett.* **1970**, 2297. Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Shanks, C. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 225. Trummlitz, G.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1841. Kalvoda, L. *J. Carbohydr., Nucleosides, Nucleotides* **1976**, *3*, 47. Katagiri, N.; Haneda, T.; Takahashi, N. *Heterocycles* **1984**, *22*, 2195.
(6) For an excellent general C-nucleoside review, see: Buchanan, J. G. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 243.
(7) Ito, Y.; Arita, M.; Adachi, K.; Shibata, T.; Sawai, H.; Ohno, M. *Nucleic Acids Symp. Ser.* **1981**, *10*, 45. Just, G.; Liak, T. J.; Lim, M.-I.; Potvin, P.; Tsantrizos; Y. S. *Can. J. Chem.* **1980**, *58*, 2024. Sato, T.; Ito, R.; Hayakawa, Y.; Noyori, R. *Tetrahedron Lett.* **1978**, 1829. Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1981**, *103*, 3923. Noyori, R.; Sato, T.; Hayakawa, Y. *Ibid.* **1978**, *100*, 2561. Sato, T.; Hayakawa, Y.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2515. Ohno, M.; Ito, Y.; Arita, M.; Shibata, T.; Adachi, K.; Sawai, H. *Tetrahedron* **1984**, *40*, 145.
(8) Barrett, A. G. M.; Broughton, H. B. *J. Org. Chem.* **1984**, *49*, 3673.

0022-3263/86/1951-0495$01.50/0 