δ 1.46 (dd, 1 H, J = 1.5 Hz, 8.9 Hz), 1.62 (d, 1 H, J = 8.9 Hz), 2.69 (dd, 1 H, J = 1.3, 4.1 Hz), 3.13 (br s, 1 H), 3.27 (br s, 1 H), 3.38 (t, 1 H, J = 4.0 Hz), 3.65 (s, 3 H), 3.72 (s, 3 H), 6.07 (dd, 1 H, J = 2.7, 5.5 Hz), 6.29 (dd, 1 H, J = 3.2, 5.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.7, 173.5, 137.4, 135.0, 52.0, 51.7, 47.7, 47.7, 47.5, 47.5, 47.2, 47.0, 46.9, 45.5, 45.5. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.93; H, 6.75.

Methyl (4*R*)-1-methylcyclohexene-4-carboxylate: IR (neat) 1741 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.59–1.76 (m, 1 H), 1.65 (s, 3 H), 1.98–2.02 (m, 3 H), 2.21–2.23 (m, 2 H), 2.45–2.53 (m, 1 H), 3.68 (s, 3 H), 5.38 (br s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.5, 133.7, 119.2, 51.6, 39.1, 29.3, 27.7, 25.5, 23.5. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.00; H, 9.17.

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Registry No. 1, 137435-03-1; 2, 137492-77-4; (*R*,*R*)-hydrobenzoin, 52340-78-0; dimethyl fumarate, 624-49-7; methyl acrylate, 96-33-3; 2,3-dimethyl-1,3-butadiene, 513-81-5; 2-methyl-1,3-butadiene, 78-79-5; 1,3-butadiene, 106-99-0; cyclopentadiene, 542-92-7; dimethyl (4*S*,5*S*)-1,2-dimethylcyclohexene-4,5-dicarboxylate, 137492-78-5; dimethyl (4*S*,5*S*)-1-methylcyclohexene-4,5-dicarboxylate, 137492-79-6; dimethyl (4*S*,5*S*)-cyclohexene-4,5-dicarboxylate, 137492-80-9; dimethyl (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate, 135357-64-1; methyl (2*R*)-bicyclo[2.2.1]-hept-5-ene-2-carboxylate, 72203-34-0; (+)-α-terpineol, 7785-53-7.

An Improved Procedure of the Pechmann Condensation in the Synthesis of 8-Ethyltrimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]-pyran-6-ones Structurally Related to the Aglycon of Gilvocarcins

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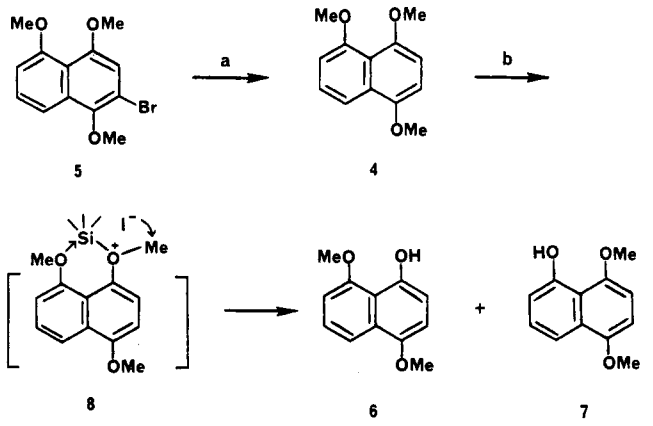
The antitumor and antibiotic activities of gilvocarcins,[2] chrysomycin,[3] and ravidomycins[4] have prompted several syntheses of defucogilvocarcins[5] and the related *C*-glycosides.[6] We have recently described the synthesis of the 12-demethoxydefucogilvocarcin ring system[7] via the Pechmann condensation[8] and subsequent regioselective oxidation with selenium dioxide. The use of the Pechmann condensation in the preparation of benzo[*d*]naphtho[1,2-*b*]pyran-6-ones from dihydroxynaphthalenes and 2-carbethoxycyclohexanones was first reported by Chebaane[8a] and subsequently by Daves[6b] and McGee.[5f] We now report a concise synthesis, utilizing an improved Pechmann condensation procedure, of trimethoxy-8-ethyl-6*H*-benzo-[*d*]naphtho[1,2-*b*]pyran-6-ones such as **1** and **2**, structurally related to the aglycon of gilvocarcins, and describe the related unexpected products formed in the condensation reaction.

Initially, we attempted to prepare the required 4,5-dimethoxy-1-naphthol (**3**) from the monodemethylation of 1,4,5-trimethoxynaphthalene (**4**),[9] obtained from the debromination of 2-bromo-1,4,5-trimethoxynaphthalene (**5**)[5a] with 10% Pd/C in formic acid and DMF (86% yield) (Scheme I). However, monodemethylation of **4** with trimethylsilyl iodide[10] gave only the undesired isomers **6** and **7** (94% yield) in a ratio of 3:1. Spectral data and melting points of **6**[11] and **7**[12a] are identical with those reported. Presumably, the C-4 and C-5 oxygens chelated via a trimethylsilyl group as depicted in structure **8** led to

Scheme I[a]



[a] (a) 10% Pd/C, HCO_2H, DMF, 150 °C; (b) Me_3SiI, $CHCl_3$, 25 °C, 48 h.

Scheme II

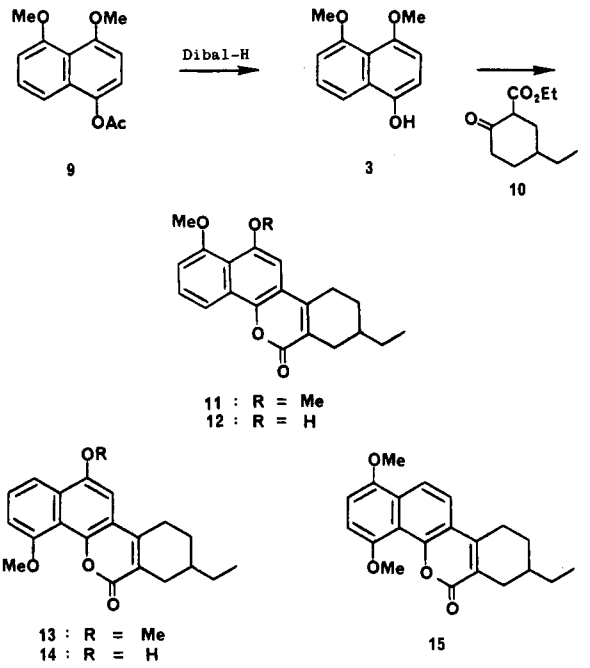


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Table I. Pechmann Condensation of Naphthols (3, 6, and 7) and β-Keto Ester 10

entry	naphthol	reaction conditions	products, % yield 11	12	13	14	15
1	3	H_2SO_4, 0 → 25 °C, 4 h		8	20	40	
2	3	*p*-TsOH, 120 °C, 12 h		30		20	
3	3	5 equiv of $CH_3CO_2NH_4$, 185 °C, 2 h		25		18	
4	3	2 equiv of CF_3CO_2H, 2 equiv of H_2SO_4, 0 → 22 °C, 5 h	81			10	
5	6	H_2SO_4, 0 → 25 °C, 4 h		5	40	17	
6	6	2 equiv of CF_3CO_2H, 2 equiv of H_2SO_4, 0 → 22 °C, 5 h			93		
7	7	2 equiv of CF_3CO_2H, 2 equiv of H_2SO_4, 0 → 22 °C, 5 h					86

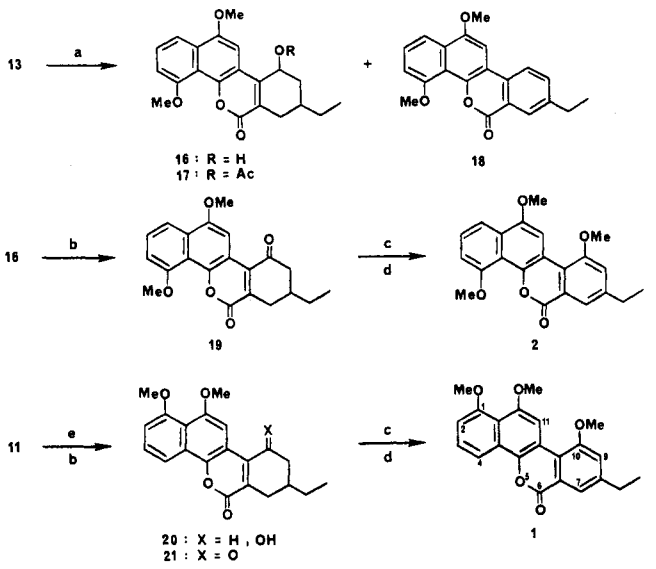
attack of iodide on the *O*-methyl of either C-4 or C-5. Other hydrolytic agents, such as 48% HBr in refluxing acetic acid, gave mixtures of the corresponding dihydroxy- and trihydroxynaphthalenes. We then prepared naphthol **3**[13] by the deacetylation of 1-acetoxy-4,5-dimethoxynaphthalene (**9**)[11] with Dibal-H in THF (95% yield) (Scheme II).

We have first tempted to prepare tetracyclic lactone **11** under usual Pechmann conditions. Surprisingly, when naphthol **3** and ethyl 5-ethyl-2-oxocyclohexanecarboxylate (**10**)[14] were treated with concentrated H_2SO_4 at 0 °C and then at 25 °C,[7] the C-4-OH condensation products, **13** and **14**, were formed as the major products while C-12-*O*-demethyl lactone **12** was obtained in only 8% yield (Table I, entry 1). Possibly, in the presence of H_2SO_4, **3** underwent rapid demethylation of the C-4 methoxy group followed by electrophilic aromatic addition at C-3 (predominantly) with keto ester **10**. Results similar to those provided by **3** were obtained when the isomeric naphthol, 1,5-dimethoxy-4-naphthol (**6**), was treated with **10** in concentrated H_2SO_4 (entry 5). Milder acidic media were investigated. Treatment of a mixture of **3** and **10** with 5 equiv of *p*-toluenesulfonic acid at 120 °C (entry 2) or 5 equiv of ammonium acetate[8f] at 185 °C (entry 3) similarly led to hydroxy compounds **12** (25–30% yields) and **14** (18–20% yields). Other systems for the condensation of **3** with **10**, such as *p*-toluenesulfonic acid in refluxing toluene, P_2O_5, and $POCl_3$ in refluxing toluene, produced **11** in only 5–10% yields. An 81% yield of **11**, the expected product, was eventually obtained from a mixture of **3** and **10** treated with 2 equiv of CF_3CO_2H and 2 equiv of H_2SO_4 at 0 °C and then at 22 °C (entry 4). A small amount of **14** (10%) was also formed. On the other hand, while isomeric naphthols **6** and **7**, when treated with **10** in CF_3CO_2H–H_2SO_4 also gave the expected coupling products **13** and **15** in 93% and 86% yields, respectively, no demethylation products were obtained (entries 6 and 7).

The regiochemistry of **13** was determined by converting it into benzonaphthopyrone **2** (vide infra), which was analyzed by X-ray diffraction.[15] Alcohols **12** and **14**, respectively, were methylated with sodium hydride and methyl iodide in DMF to provide **11** (95% yield) and **13** (92% yield).

Various methods have been investigated for C-10 hydroxylation of **11** and **13**. Regioselective oxidation of **13** with selenium dioxide[16] in refluxing acetic acid[7] provided a 31% yield of alcohol **16**, 9% yield of acetate **17**, and 6%

Scheme III[a]



[a] (a) SeO_2, AcOH, 120 °C; (b) PCC, CH_2Cl_2; (c) $(MeO)_3CH$, MeOH, *p*-TsOH; (d) DDQ; (e) SeO_2, diglyme, 185 °C, 30 min.

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(9) 1,4,5-Trimethoxynaphthalene (**4**) has also been synthesized by anodic oxidation of 1,5-dimethoxynaphthalene: Jackson, D. K.; Swenton, J. S. *Synth. Commun.* **1977**, *7*, 333.

(10) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

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(12) (a) Laatsch, H. *Liebigs Ann. Chem.* **1985**, 1847. A recent synthesis of **7**: (b) Sibi, M. P.; Dankwardt, J. W.; Snieckus, V. *J. Org. Chem.* **1986**, *51*, 273. Spectral data were not fully reported, however.

(13) An alternative preparation of naphthol **3** has been reported recently from 5-hydroxynaphthalene-1,4-dione in 13% yield: Malesani, G.; Ferlin, M. G. *J. Heterocycl. Chem.* **1987**, *24*, 513. However, spectral data of **3** and **4** were not fully reported. Since the reported[13] melting point for naphthol **3** is significantly lower than that of our material, full characterization of **3** is described here.

(14) Ester **10** was prepared from ethoxycarbonylation of 4-ethylcyclohexanone with LDA in THF at −78 °C followed by ethyl cyanoformate (64% yield). For the preparation of β-keto esters (from ketones, diethyl carbonate, and sodium hydride) and use of ethyl cyanoformate, see: (a) Rhoads, S. J.; Gilbert, J. C.; Decora, A. W.; Garland, T. R.; Spangler, R. J.; Urbigkit, M. J. *Tetrahedron* **1963**, *19*, 1625. (b) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, 5425. Ester **10** has been prepared by Daves[6b] utilizing the method reported by Rhoads.[14a]

(15) Robinson, P. D.; Hua, D. H.; Roche, D.; Saha, S. *Acta Crystallogr., Sect. C.* In press.

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yield of pyrone **18**, with 30% of **13** being recovered (Scheme III). Oxidation of **11**, however, afforded only a 7% yield of desired alcohol **20** and 4% yield of the corresponding C-10,11-diol; 51% of starting material **11** was recovered. Acetate **17** was converted into **16** by treatment with K_2CO_3 in MeOH (92% yield). Pyrone **18** was formed from the dehydration of **16** or elimination of acetic acid from **17** followed by aromatization through elimination of H_2. These pathways were supported by treating **16** or **17** with selenium dioxide in refluxing acetic acid; **18** was formed slowly. Allylic deprotonation of **13** with 2 equiv of LDA·HMPA complex[17] in THF followed by 4.6 equiv of oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH)[18] provided a 30% yield of alcohol **16** and 70% recovery of **13**. However, when **11** was treated under the same conditions, only 5% of desired alcohol **20** along with 88% of starting **2** were obtained. Finally, oxidation of **11** under McGee and Confalone's conditions[5f] with 3 equiv of selenium dioxide in diglyme at 200 °C for 30 min generated a 60% yield of alcohol **20**, and 25% of **11** was recovered. Compounds **16**, **17**, and **20** are mixtures of cis and trans isomers. The regiochemistry is evidence from the X-ray analysis of **2**,[15] and the ^1H NMR spectra of **1** and **2** in which C-7 and C-9 hydrogens appear as doublets with $J_{7,9}$ = 1 Hz (1,3-coupling). Oxidation of alcohol **16** with pyridinium chlorochromate (PCC) in methylene chloride[19] gave ketone **19**. The aromatization of **19** was performed by the method of McGee.[5f] Ketalization of ketone **19** with methyl orthoformate and then aromatization with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded a 56% overall yield of **2** (Scheme III). Similar treatment of **20** furnished dibenzo[*b*,*d*]pyran **1** in 51% overall yield (from **20**).

A convenient regioselective construction of 8-ethyltrimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-ones is now provided by an improved Pechmann condensation of naphthols with ethyl 5-ethyl-2-oxocyclohexanecarboxylate carried out under mild conditions followed by oxidation of the resulting 6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans with selenium dioxide. Compounds **1**, **2**, and **11–21** have not previously been reported.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were obtained in deuteriochloroform on a Bruker WM-400 (400 MHz in ^1H and 100 MHz in ^{13}C) spectrometer and are reported in ppm (δ units) downfield of internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer and are reported in wavenumbers (cm^{-1} units). Mass spectra were determined on a Finnigan 4000 automated gas chromatograph/EI-CI mass spectrometer and a JEOL JMS-DX303HF mass spectrometer. EI MS were taken under the conditions of 75 eV, 300 μA, and 3 kV, and FAB MS were taken in Xe gas, 2 kV, using glycerol and *m*-nitrobenzyl alcohol as matrixes. Davisil silica gel, grade 643 (200–425 mesh), was used for the flash chromatographic separation.

1,4,5-Trimethoxynaphthalene (4). A mixture of 2.0 g (6.73 mmol) of 3-bromo-1,4,8-trimethoxynaphthalene (**5**)[5a] and 0.35 g (0.33 mmol) of 10% Pd/C in 3.5 mL of 85% HCO_2H and 17.5 mL of DMF was stirred at 150 °C for 5 h, cooled to 25 °C, diluted with 150 mL of ether, and filtered through Celite. The filtrate was washed with H_2O (30 mL), saturated aqueous $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated to give 1.26 g (86% yield) of **4**, mp 116–117 °C (lit.[13] mp 119 °C).

1,5-Dimethoxy-4-naphthol (6) and 1,4-Dimethoxy-5-naphthol (7). To a solution of 0.7 g (3.2 mmol) of 1,4,5-trimethoxynaphthalene (**4**) in 20 mL of $CHCl_3$ under argon was added 0.7 g (3.52 mmol) of Me_3SiI. The solution was stirred at 25 °C for 48 h, diluted with 5 mL of H_2O and 10 mL of saturated aqueous NH_4Cl solution, and extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and CH_2Cl_2 as eluant to give 0.458 g (70.5% yield) of **6** (more polar) and 0.153 g (23.5% yield) of **7** (less polar). **6**: mp 150–151 °C (lit.[11] mp 155.5–156.5 °C). **7**: mp 102–103 °C (lit.[12] mp 105 °C).

8-Ethyl-12-hydroxy-1-methoxy-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (12), 4,12-Dimethoxy-8-ethyl-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]-pyran-6-one (13), and 8-Ethyl-12-hydroxy-4-methoxy-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (14) (entry 5 of Table I). A mixture of 1.86 g (9.12 mmol) of 1,5-dimethoxy-4-naphthol (**6**) and 2.71 g (13.69 mmol) of ethyl 5-ethyl-2-oxocyclohexanecarboxylate (**10**) was stirred vigorously at 25 °C for 15 min and then cooled to 0 °C. To it was added slowly 4.65 mL of concentrated H_2SO_4, and the mixture was stirred vigorously for 3 h at 0 °C. The mixture was diluted with 30 mL of ice–H_2O and 50 mL of CH_2Cl_2, neutralized with saturated aqueous $NaHCO_3$ to pH 7, and extracted five times with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using mixtures of hexane, CH_2Cl_2, and ethyl acetate as eluant to give 1.233 g (40% yield) of **13**, 0.502 g (17% yield) of **14**, and 0.148 g (5% yield) of **12**.

13: mp 199–200 °C; ^1H NMR ($CDCl_3$) δ 7.87 (d, J = 8 Hz, 1 H, C1-H), 7.51 (t, J = 8 Hz, 1 H, C2-H), 7.04 (d, J = 8 Hz, 1 H, C3-H), 6.83 (s, 1 H, C11-H), 4.08 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 2.98–2.7 (m, 2 H, C7-Hs), 2.1–2.04 (m, 2 H, C10-Hs), 1.6–1.4 (m, 5 H), 1.02 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 161.82 (s, CO), 157.8 (s), 151.8 (s), 147.15 (s), 144.2 (s, C=), 129.1 (s), 127.85 (d), 122.41 (s), 118 (s, C=), 115.5 (s), 114.15 (d), 108.39 (d), 97.42 (d), 56.43 (q, OMe), 55.79 (q, OMe), 34.53 (d), 30.23 (t), 28.72 (t), 27.51 (t), 26.24 (t), 11.42 (q); CI MS m/e 339 (M + 1, 80); EI MS m/e 339 (M + 1), 338 (M^+, 100), 323, 306, 279, 254, 218, 167, 149. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.47; H, 6.78.

14: mp 188–189 °C; ^1H NMR (DMSO-d_6) δ 10.23 (s, 1 H, OH), 7.77 (d, J = 8 Hz, 1 H, C1-H), 7.51 (t, J = 8 Hz, 1 H, C2-H), 7.13 (d, J = 8 Hz, 1 H, C3-H), 7.0 (s, 1 H, C11-H), 3.95 (s, 3 H, C12-OMe), 2.9–2.6 (m, 3 H), 1.93 (m, 2 H), 1.6–1.3 (m, 4 H), 0.95 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 160.69 (s, CO), 156.70 (s), 148.96 (s), 147.14 (s), 142.23 (s, C=), 127.86 (s), 127.5 (d), 121.33 (s), 115.39 (s), 114.84 (s, C=), 114.29 (d), 108.34 (d), 101.15 (d), 56.14 (q, OMe), 33.72 (d), 29.84 (t), 28.19 (t), 26.89 (t), 25.43 (t), 11.21 (q); FAB MS m/e 325 (M + 1), 277, 185, 137, 93, 75. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22. Found: C, 73.89; H, 6.47.

12: mp 244–245 °C; ^1H NMR ($CDCl_3$) δ 9.18 (s, 1 H, OH), 8.14 (d, J = 8 Hz, 1 H, C4-H), 7.47 (t, J = 8 Hz, 1 H, C3-H), 6.94 (d, J = 8 Hz, C2-H), 6.89 (s, 1 H, C11-H), 4.1 (s, 3 H, OMe), 2.9 (m, 2 H), 2.7 (m, 1 H), 2.1 (m, 2 H), 1.45 (m, 4 H), 1.02 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 159 (s, CO), 155.79 (s), 150.47 (s), 147.41 (s), 141.5 (s, C=), 129 (s), 126.98 (d), 123.83 (s), 117 (s), 116.1 (d), 110 (s), 106.5 (d), 102.34 (d); FAB MS m/e 325 (M + 1), 277, 246, 229, 212, 185 (100), 154, 137, 93, 75. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22. Found: C, 73.97; H, 6.31.

4,12-Dimethoxy-8-ethyl-10-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (16), 10-Acetoxy-4,12-dimethoxy-8-ethyl-7,8,9,10-tetrahydro-6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one (17), and 4,12-Dimethoxy-8-ethyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (18). A solution of 1.0 g (2.96 mmol) of **13** and 1.313 g (11.8 mmol) of selenium dioxide in 100 mL of acetic acid was stirred under reflux for 12 h under argon. The solution was then cooled to 25 °C, diluted with 100 mL of CH_2Cl_2, neutralized with 70 g (1.748 mol) of NaOH in 320 mL of H_2O, and extracted with CH_2Cl_2 three times. The combined extracts were washed with H_2O and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using mixtures of hexane, CH_2Cl_2, and ethyl acetate as eluant

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to give 59 mg (6% yield) of **18**, 0.105 g (9% yield) of acetate **17**, 0.30 g (30% recovery) of **13**, and 0.325 g (31% yield) of alcohol **16**.

16 [a mixture of cis and trans isomers (1:2.5)]: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8 Hz, 1 H, C1-H, trans), 7.54 (d, J = 8 Hz, 1 H, C1-H, cis), 7.45 (t, J = 8 Hz, 1 H, C2-H, trans), 7.42 (t, J = 8 Hz, 1 H, C2-H, cis), 7.41 (s, 1 H, C11-H, cis), 7.11 (s, 1 H, C11-H, trans), 6.96 (d, J = 8 Hz, 1 H, C3-H, trans), 6.92 (d, J = 8 Hz, 1 H, C3-H, cis), 5.06 (br s, 1 H, CHO, cis and trans), 4.03 (s, 3 H, OMe, trans), 4.01 (s, 3 H, OMe, trans), 4.0 (s, 3 H, OMe, cis), 3.98 (s, 3 H, OMe, cis), 2.94 (dd, J = 18, 4 Hz, 1 H, C7-H, trans), 2.73 (dd, J = 17, 4 Hz, 1 H, C7-H, cis), 2.5 (m, 1 H, cis), 2.44 (d, J = 10 Hz, 1 H, cis), 2.39 (d, J = 7 Hz, 1 H, trans), 2.20 (d, J = 14 Hz, 1 H, trans), 2.1–1.85 (m, 2 H), 1.5 (m, 3 H), 1.06 (t, J = 7 Hz, 3 H, Me, trans), 1.0 (t, J = 7 Hz, 3 H, Me, cis); ^{13}C NMR ($CDCl_3$) δ 162.02 (s, CO), 157.22 (s, trans), 157.14 (s, cis), 151.53 (s, trans), 150.78 (s, cis), 148.01 (s, cis), 145.87 (s, trans), 145.02 (s, =C), 128.92 (s, trans), 128.74 (s, cis), 128.02 (d, trans), 127.9 (d, cis), 123.7 (s, trans), 123.64 (s, cis), 115.6 (s, trans), 115.5 (s, cis), 114.56 (s, cis), 114.4 (s, trans), 114.14 (d, trans), 114.04 (d, cis), 108.26 (d, trans), 108.0 (d, cis), 100.56 (d, cis), 98.2 (d, trans), 67.54 (d, CHO, cis), 64.16 (d, CHO, trans), 56.29 (q, OMe, trans), 56.21 (q, OMe, cis), 55.84 (q, OMe, trans), 55.74 (q, OMe, cis), 39.49 (d, CH, cis), 37.13 (d, trans), 33.73 (t, cis), 30.53 (t, trans), 29.69 (t, trans), 29.07 (t, cis), 28.94 (t, trans), 28.64 (t, cis), 15.25 (q, cis), 11.22 (q, trans); FAB MS m/e 355 (M + 1, 20), 354 (M^+), 277, 246, 229, 212, 185 (100), 167, 154, 137. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.23; H, 6.05.

17 [a mixture of cis and trans isomers (1:4)]: mp 199–200 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8 Hz, 1 H, C1-H), 7.53 (t, J = 8 Hz, 1 H, C2-H), 7.05 (d, J = 8 Hz, 1 H, C3-H), 6.77 (s, 1 H, C11-H, trans), 6.52 (s, 1 H, C11-H, cis), 6.32 (br s, 1 H, CHO, trans), 6.30 (br s, 1 H, CHO, cis), 4.06 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 2.98 (dd, J = 13, 3 Hz, 1 H, trans), 2.8 (dd, J = 13, 3 Hz, 1 H, cis), 2.4 (m, 1 H, cis), 2.07 (s, 3 H, CH_3CO), 2.0–1.4 (m, 6 H), 1.01 (t, J = 7 Hz, 3 H, Me, trans), 0.97 (t, J = 7 Hz, 3 H, Me, cis); ^{13}C NMR ($CDCl_3$) δ 170.37 (s, CO of OAc), 161.56 (s, CO), 157.35 (s), 151.5 (s, cis), 151.22 (s, trans), 144.83 (s, =C), 143.47 (s, cis), 142.52 (s, trans), 128.83 (s), 128.11 (d), 127.99 (s), 125.76 (s), 115.6 (s), 114.09 (d), 108.38 (d), 97.8 (d, cis), 97.05 (d, trans), 67.44 (d, CHO, cis), 65.23 (d, CHO, trans), 56.35 (q, OMe), 55.65 (q, OMe, trans), 55.56 (q, OMe, cis), 34.42 (d, trans), 34.03 (d, cis), 32.8 (t, cis), 30.2 (t, trans), 29.96 (t, cis), 29.56 (t, trans), 28.81 (t, trans), 27.93 (t, cis), 21.15 (q, OAc), 11.48 (q, cis), 11.13 (q, trans); CI MS m/e 397 (M + 1), 353, 339 (100), 147, 129; EI 396 (M^+), 352 (M – Ac), 338, 269, 129 (100), 112. Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.41; H, 6.35.

18: ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1 H, C7-H), 8.0 (d, J = 8 Hz, 1 H, C1-H), 7.86 (dd, J = 8, 1 Hz, C9-H), 7.64 (dd, J = 8, 2 Hz, 1 H, C10-H), 7.47 (t, J = 8 Hz, C2-H), 7.27 (s, 1 H, C11-H), 7.03 (d, J = 8 Hz, 1 H, C3-H), 4.1 (s, 3 H, OMe), 4.09 (s, 3 H, OMe), 2.8 (q, J = 7 Hz, 2 H, CH_2), 1.33 (t, J = 7 Hz, 3 H, Me); EI MS m/e 335, 334 (M^+, 10), 319 (M – Me), 275 (100), 185. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.37; H, 5.28.

4,12-Dimethoxy-8-ethyl-10-oxo-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (19). To a mixture of 90 mg (0.254 mmol) of alcohol **16** and 0.4 g of 3-Å molecular sieves in 20 mL of CH_2Cl_2 under argon was added 0.110 g (0.508 mmol) of pyridinium chlorochromate. The mixture was stirred at 25 °C for 4 h and filtered through a Florisil column using a 1:1 mixture of ethyl acetate and ether as eluant, and the filtrate was concentrated to give 95 mg of the crude product. Column chromatographic purification of this crude material on silica gel using 3% ethyl acetate in CH_2Cl_2 as eluant gave 72 mg (80% yield) of ketone **19** as orange solids: mp 154–155 °C; IR (CH_2Cl_2) ν 3080, 2920, 2850, 1690 (strong, C=O), 1600, 1370, 1070 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1 H, C11-H), 7.77 (d, J = 8 Hz, 1 H, C1-H), 7.45 (t, J = 8 Hz, 1 H, C2-H), 6.95 (d, J = 8 Hz, 1 H, C3-H), 4.0 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 3.10 (dd, J = 20 Hz, 5 Hz, 1 H, CH_2CO), 2.74 (dd, J = 20 Hz, 3 Hz, 1 H, CH_2CO), 2.42 (d, J = 11 Hz, 1 H, CH_2C=), 2.37 (dd, J = 11, 3 Hz, 1 H, CH_2C=), 2.08 (m, 1 H, CH), 1.5 (m, 2 H, CH_2CH_3), 0.96 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 201 (s, CO), 161.9 (s, CO), 158 (s), 152 (s), 145.8 (s), 137.6 (s), 134 (s), 129.3 (s), 128.76 (d), 115.8 (s), 114.31 (d), 112 (s), 108.53 (d), 100.34 (d), 56.62 (q, OMe), 56.02 (q, OMe), 46.58 (t, CH_2CO), 35.91 (d, CH), 31.06 (t), 28.83 (t), 11.21 (q, Me); CI MS m/e 353 (M + 1, 90), 325, 135 (100), 119, 107; EI MS m/e 353, 352 (M^+, 100), 337, 324, 309, 225, 197, 179, 149, 133, 105. Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.29; H, 5.81.

8-Ethyl-4,10,12-trimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (2). The procedure described by McGee and Confalone was followed;[5f] a 56% yield of **2** (red crystals) was obtained from ketone **19**: mp 159–160 °C; IR (CH_2Cl_2) ν 3060, 2930, 2840, 1700 (strong, C=O), 1598, 1450, 1360, 1160, 1130, 1080, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1 H, C11-H), 7.92 (d, J = 1 Hz, 1 H, C7-H), 7.83 (dd, J = 8, 1 Hz, 1 H, C1-H), 7.45 (t, J = 8 Hz, 1 H, C2-H), 7.08 (d, J = 1 Hz, 1 H, C9-H), 7.0 (dd, J = 8, 1 Hz, 1 H, C3-H), 4.09 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 4.0 (s, 3 H, OMe), 2.75 (q, J = 7 Hz, 2 H, CH_2), 1.32 (t, J = 7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 161.8 (s, CO), 157.29 (s), 157.05 (s), 150.7 (s), 150 (s), 145.53 (s), 128.08 (s), 127.21 (d), 122.79 (s), 121.23 (d), 116.93 (d), 116.03 (s), 115 (s), 114.01 (d), 113.4 (s), 108.29 (d), 102.86 (d), 56.6 (q, OMe), 56.2 (q, OMe), 55.53 (q, OMe), 28.87 (t), 15.09 (q); FAB MS m/e 365 (M + 1), 364, 338, 277 (100), 246, 212, 196, 185, 154, 137, 93. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.27; H, 5.67.

4,5-Dimethoxy-1-naphthol (3). To a cold (–78 °C) solution of 1.67 g (6.8 mmol) of **9**[11] in 60 mL of THF under argon was added 20.3 mL (20.3 mmol) of diisobutylaluminum hydride in THF (1.0 M). The solution was stirred at –78 °C for 40 min, 0 °C for 2 h, and then 25 °C for 10 h, diluted with 200 mL of CH_2Cl_2 and 1.84 g of acetic acid in 200 mL of H_2O, and stirred well. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give 1.311 g (95% yield) of white solids: mp 163–165 °C (recrystallized from ethyl acetate) (lit.[13] mp 109 °C); ^{1}H NMR 7.76 (d, J = 8 Hz, 1 H, C-8 H), 7.40 (t, J = 8 Hz, 1 H, C-7 H), 6.9 (d, J = 8 Hz, 1 H, C-6 H), 6.75 (d, J = 8 Hz, 1 H, C-3 H), 6.71 (d, J = 8 Hz, 1 H, C-2 H), 3.98 (s, 3 H, OMe), 3.91 (s, 3 H, OMe); ^{13}C NMR 156.87 (s), 151.2 (s), 145.36 (s), 127.7 (s), 125.97 (d), 118.56 (s), 114.37 (d), 108.94 (d), 107.26 (d), 107.0 (d), 57.53 (q), 56.44 (q); EI MS m/e 205 (M + 1), 204 (M^+, 100), 189. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.30; H, 6.23.

*The following experiment serves as the general procedure for the reaction of naphthols **3**, **6**, and **7** with β-keto ester **10** under CF_3CO_2H–H_2SO_4 conditions (entries 4, 6, and 7 of Table I).*

1,12-Dimethoxy-8-ethyl-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (11). To a well-stirred mixture of 0.5248 g (2.57 mmol) of naphthol **3** and 1.018 g (5.14 mmol) of ester **10** at 0 °C was added a solution of 0.59 g (5.14 mmol) of CF_3CO_2H and 0.50 g (5.14 mmol) of H_2SO_4. The solution was gradually warmed to 22 °C over 30 min, stirred at 22 °C for 4.5 h, diluted with CH_2Cl_2, and neutralized with $NaHCO_3$. The methylene chloride layer was separated, washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using mixtures of hexane, CH_2Cl_2, and ethyl acetate as eluant to give 0.704 g (81% yield) of **11** and 83 mg (10% yield) of **14**.

11: orange solid, mp 172–174 °C; IR (CH_2Cl_2) 2910, 1690 (s, C=O), 1590, 1570, 1390, 1370, 1125, 1075; ^{1}H NMR 8.17 (dd, J = 8, 1 Hz, 1 H, C-4 H), 7.52 (t, J = 8 Hz, 1 H, C-3 H), 7.01 (dd, J = 8, 1 Hz, 1 H, C-2 H), 6.82 (s, 1 H, C-11 H), 4.0 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 2.99 (br d, J = 18 Hz, 1 H), 2.89 (dd, J = 18, 4 Hz, 1 H), 2.77 (m, 1 H), 2.16 (m, 1 H), 2.1 (m, 1 H), 1.6 (m, 1 H), 1.49 (m, 3 H), 1.03 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR 161.96 (s, CO), 156.94 (s), 153.63 (s), 147.29 (s), 142.97 (s), 132.5 (s), 127.72 (d), 126.63 (s), 123.57 (s, C=), 118.15 (s, C=), 114.83 (d), 108.68 (d), 98.94 (d), 57.01 (q, OMe), 56.5 (q, OMe), 34.56 (t), 30.28 (d), 28.73 (t), 27.31 (t), 25.84 (t), 11.39 (q); MS EI m/e 338 (M^+, 100), 306, 279. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.32; H, 6.87.

1,4-Dimethoxy-8-ethyl-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (15): mp 162–164 °C; ^{1}H NMR 8.09 (d, J = 9 Hz, 1 H, C-12 H), 7.58 (d, J = 9 Hz, 1 H, C-11 H), 6.91 (d, AB, J = 8 Hz, 1 H, C-2 H), 6.86 (d, AB, J = 8 Hz, 1 H, C-3 H), 4.03 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 3.01 (br d, J = 19 Hz, 1 H), 2.88 (dd, J = 19, 5 Hz, 1 H), 2.8 (m, 1 H), 2.15 (m, 1 H), 2.1 (m, 1 H), 1.62 (m, 1 H), 1.48 (m, 3 H), 1.02 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR 161.69 (s, CO), 151.28 (s), 149.02 (s), 147.3 (s), 127.72 (s), 125.84 (s), 122.6 (s), 121.48 (s), 119.8 (d), 117.97 (d), 116.8 (s), 108.09 (d), 106.27 (d), 57.18 (q, OMe), 55.92 (q, OMe), 34.52 (t), 30.17 (d), 28.74 (t), 20.45 (t), 26.05 (t), 11.39 (q, Me); EI MS m/e 338 (M^+). Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.79; H, 6.23.

1,12-Dimethoxy-8-ethyl-10-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (20). A procedure similar to those described by McGee and Confalone[5f] starting from 11 and using SeO_2 in diglyme at 200 °C for 30 min was followed. However, a 60% yield of alcohol **20** (and 25% recovery of **11**) was obtained instead of the corresponding selenic ester.[5f] Mp and ^1H and ^{13}C NMR spectra of alcohol **20** are identical with those of that derived from SeO_2–AcOH oxidation or LDA·HMPA–MoOPH hydroxylation: mp 212–214 °C; IR (CH_2Cl_2) 3400, 1710; ^1H NMR 8.03 (dd, J = 8, 1 Hz, 1 H, C-4 H), 7.48 (t, J = 8 Hz, 1 H, C-3 H), 7.1 (s, 1 H, C-11 H), 6.98 (dd, J = 8, 1 Hz, 1 H, C-2 H), 5.09 (br s, 1 H, CHO), 3.99 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 2.96 (dd, J = 18, 3 Hz, 1 H), 2.2 (br d, J = 13 Hz, 1 H), 2.06 (m, 1 H), 1.9 (m, 1 H), 1.2 (m, 3 H), 1.06 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR 162 (s, CO), 156.78 (s), 153.7 (s), 145.76 (s), 139.8 (s), 137.7 (s), 127.67 (d), 125.1 (s), 121.9 (s), 118.14 (s), 114.67 (d), 109.01 (d), 99.49 (d), 63.84 (d, CO), 56.96 (q, OMe), 56.58 (q, OMe), 36.99 (t), 30.62 (d), 29.17 (t), 28.91 (t), 11.23 (q); FAB MS m/e 355, 354 (M^+), 353, 246, 185, 154, 137, 93. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.37; H, 6.01.

1,12-Dimethoxy-8-ethyl-10-oxo-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (21). A procedure similar to those described for the oxidation of alcohol **16** with PCC was followed. Starting from 0.235 g (0.66 mmol) of alcohol **16**, 0.187 g (80% yield) of **21** was isolated as red orange solids: mp 161–163 °C; IR (CH_2Cl_2) 2950, 2920, 2850, 1698 (s, CO), 1680, 1585, 1555, 1383, 1080; ^1H NMR 8.19 (s, 1 H, C-11 H), 8.12 (d, J = 8 Hz, 1 H, C-4 H), 7.52 (t, J = 8 Hz, 1 H, C-3 H), 7.03 (d, J = 8 Hz, 1 H, C-2 H), 4.02 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 3.2 (dd, J = 19, 4 Hz, 1 H), 2.84 (dd, J = 16, 4 Hz, 1 H), 2.47 (m, 2 H), 2.19 (m, 1 H, C-8 H), 1.58 (quintet, J = 7 Hz, 2 H, CH_2), 1.03 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR 200.29 (s, C-10), 161.82 (s, C-6), 156.57 (s), 153.88 (s), 144.01 (s), 136.79 (s), 135.27 (s), 127.69 (d), 126.06 (s), 118.25 (s), 114.63 (d), 112.0 (s), 109.26 (d), 100.98 (d), 56.54 (q, OMe), 46.09 (q, OMe), 35.57 (2 C, t, C-7, 9), 30.86 (d), 28.48 (t), 10.9 (q); FAB MS m/e 353, 352 (M^+), 338, 246, 185, 154, 137, 93. Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.61; H, 6.03.

8-Ethyl-1,10,12-trimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]-pyran-6-one (1). A procedure similar to that described by McGee and Confalone[5f] using trimethyl orthoformate–*p*-TsOH and then DDQ was followed; an 89% yield of **1** (yellow crystals) was obtained from ketone **21**: mp 241–243 °C; IR (CH_2Cl_2) 3040, 2960, 2950, 2840, 1706 (s, CO), 1605, 1580, 1380, 1125, 1120; ^1H NMR 8.42 (s, 1 H, C-11 H), 8.22 (d, J = 8 Hz, 1 H, C-4 H), 7.98 (d, J = 1 Hz, C-7 H), 7.51 (t, J = 8 Hz, 1 H, C-3 H), 7.18 (d, J = 1 Hz, 1 H, C-9 H), 6.99 (d, J = 8 Hz, 1 H, C-2 H), 4.09 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 2.79 (q, J = 7 Hz, 2 H, CH_2), 1.34 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR 161.55 (s, CO), 157.31 (s), 156.66 (s), 152.81 (s), 146.02 (s), 140.55 (s), 127.15 (d), 126.5 (s), 123.3 (s), 122.21 (s), 121.56 (d), 117.52 (s), 117.08 (d), 114.86 (d), 113.73 (s), 107.98 (d), 104.43 (d), 56.75 (q, OMe), 56.52 (q, OMe), 56.23 (q, OMe), 28.93 (t), 15.1 (q, Me); EI MS m/e 364 (M^+), 277, 197, 196. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.39; H, 5.87.

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Supplementary Material Available: Spectral data for compounds **4**, **6**, and **7** (1 page). Ordering information is given on any current masthead page.

Synthesis of Annulated Furanoses by Free-Radical Cyclization of Haloalkenes Derived from Diacetone Glucose

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In the last years the synthesis of carbocycles from carbohydrates has attracted considerable interest.[1] The free-radical route is an extremely efficient strategy for the cyclization of carbohydrate derivatives.[2] Some authors have recently advanced and demonstrated the merits of performing the free-radical cyclization without disturbing the anomeric center.[3] Following this idea, Fraser-Reid and co-workers have developed the concept and synthetic applications of annulated furanoses.[4] The publication of two recent reports[5,6] on the synthesis of new annulated furanoses prompts us to disclose our recent results on this subject.[7]

We describe here the synthesis and free radical cyclization of the chiral radical precursors **2–7** (Scheme I). These compounds can be obtained from readily available diacetone glucose **1**. They are conveniently functionalized to yield, after 6-exo[8] free-radical cyclization,[9] annulated furanoses. In these compounds, the carbocycle is trans fused at carbons C3 and C4 of the sugar moiety and the substitution in the ring can be modified by changing the type of acceptor in the intramolecular free-radical cyclization. In this process a new stereocenter can be formed and the sugar provides an ideal chiral template for achieving a good diastereoselection.[10] In addition, annulated furanoses are useful chiral polyfunctional building blocks for further development.[11]

With this scenario in mind we have synthesized and cyclized the radical precursors **2–7** (Scheme I).

The aldehyde **2** has been designed in view of the ability of aldehydes to function as acceptors.[12] We have synthesized it from 3-*C*-(carbomethoxymethyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose[13] by first bromination and then reduction (DIBAH, toluene, −78 °C) of the resulting compound. The cyclization of compound **2** under typical conditions (see Experimental Section) did not yield the expected products; we obtained in turn the uncyclized compounds **8** and **9** (Scheme II). Compound **8** showed in the ^1H NMR spectrum signals at δ 1.21 (d, J = 6.7 Hz) and 1.14 (d, J = 6.7 Hz) for the methyls attached to C3/C5; H5 appears at δ 4.01 (dq, $J_{5,4}$ = 3.1 Hz, $J_{5,6}$ = 6.7 Hz). Compound **9** showed in the ^1H NMR spectrum signals at δ 9.79 (*H*COR) and 5.40 (OC*H*(OH)R), 1.29 (d, J = 6.2 Hz) and 1.23 (d, J = 6.5 Hz) corresponding to the methyl (C6), in the open or hemiacetalic form. Product **8** probably arises by intramolecular 1,7-hydrogen transfer,[14] decarbonylation, and hydrogen trapping. The absence of cyclized products in this case is surprising in view of some recent results.[15] This also proves that the success of the aldehyde as acceptor in free-radical cyclizations is very dependent on the structure.

Oxime ethers are known as more reliable acceptors.[16] So, the radical precursor **3** has been obtained from compound **2** (Scheme I) by the routine method (*O*-benzylhydroxylamine hydrochloride, pyridine, methylene chlo-

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