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MICHAEL-ADDITION REACTIONS OF LEVOGLUCOSENONE

FRED SHAFIZADEH, DAVID D. WARD, AND DAVID PANG
Wood Chemistry Laboratory, Department of Chemistry, University of Montana, Missoula, Montana 59812 (U.S.A.)

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ABSTRACT

The Michael-addition reactions of levoglucosenone with diethyl malonate, ethyl cyanoacetate, 2-nitropropane, and 2-methylcyclohexanone have been examined, using a variety of catalysts. This reaction may be conveniently used to prepare, in reasonable yields, 4-substituted levoglucosenone derivatives having the D-*erythro* configuration. Better yields of the diethyl malonate adduct were obtained on using bis(2,4-pentanedionate)-Ni(II) as the catalyst.

INTRODUCTION

Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose, **1**) may be used for a variety of reactions involving extension of the carbon skeleton in sugar molecules. In recent publications, we have examined the "4 + 2" cycloaddition[1] and oligomerization[2a] of this compound. In attempting to perform the former reaction with furan, we obtained a β-addition compound, rather than the expected product of cycloaddition; this led us to examine the Michael-addition reactions of **1**, using a variety of enolate anions that provide a convenient method for extending the carbon chain and functionality of **1** at C-4.

RESULTS AND DISCUSSION

Heating **1** in aqueous triethylamine has been shown to provide an 82% conversion of **1** into three self-condensation products, a dimer and two trimers, that were the subject of two previous publications[2a,b]. Such self-condensations are commonly observed in Michael reactions[3]. It has recently been shown that an aqueous solution of **1** in the presence of triethylamine will readily form the β-hydroxy derivative. Similarly, the β-methoxy compound is formed from a methanolic solution, and the corresponding phenylthio derivative may be obtained from a chloroform solution containing benzenethiol in the presence of triethylamine[4].

In this study, diethyl malonate (DEM) was chosen as the initial nucleophile. Compound **1** was dissolved in ethanol containing DEM, and piperidine was used as the catalyst. After heating for 3 h at 50°, no further change was detectable by t.l.c.,

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TABLE I

^{1}H-N.M.R.-SPECTRAL PARAMETERS[a] FOR LEVOGLUCOSENONE (1) AND SOME C-4 SUBSTITUTED DERIVATIVES

Substituent at C-4	*H-1*	*H-3a*	*H-3e*	*H-4*	*H-5*	*H-6exo*	*H-6endo*	*H-7*	*Other*
OH[b]	5.15(s)	2.93(dd)	2.43(dm)	4.20(m)	4.72(m)	← 4.0(m) →		—	4.20(b); OH
OMe[b]	5.18(s)	2.86(dd)	2.53(dm)	3.80(m)	4.87(m)	← 4.0(m) →		—	3.48(s), OMe
S-Ph[b]	5.17(s)	3.03(dd)	2.48(dm)	3.73(m)	4.68(m)	← 4.0(m) →		—	7.30–7.70(m), phenyl
Levoglucosenone[c] (10)	5.11(s)	3.97(q)	2.23(d)	3.43(d)	4.54(d)	4.03(q)	4.16(d)	—	5.40(s), H-1′; 7.08(d), H-4′; 5.06(t), H-5′; 3.71(d), H-6′endo; 3.88(q), H-6′exo
Furan[d]	5.10(s)	3.02(dd)	2.60(d)	3.53(dd)	4.80(m)	4.14(dd)	4.17(dd)	—	6.18(dd); 6.22(dd); 7.34(m) furan ring
CH(CO$_2$Et)$_2$[e] (3)	5.11(s)	2.85(dd)	2.31(bd)	2.92(dd)	4.74(bd)	4.04(dd)	4.10(dd)	3.68(d)	4.28–4.61, CH$_2$; 1.28(t), CH$_3$
				2.99–2.90	4.40			4.16	4.28 1.29
CHCNCO$_2$Et[d] (4)	5.05(bs)	2.59–2.23		———	——	← 4.21(m) →		——	—— CH$_2$ ester; ——(t), CH$_3$ ester
				3.18	4.35			3.93	4.24 1.27
CMe$_2$NO$_2$[e] (5)	5.11(s)	2.77(dd)	2.23(d)	2.94(ddd)	4.65(m)	← 4.02 →		—	1.71(s) CH$_3$; 1.63(s) CH$_3$

[a]All values in p.p.m. from Me$_4$Si. [b]60 MHz. [c]270 MHz. [d]90 MHz. [e]360 MHz. Key: dm, distorted multiplet.

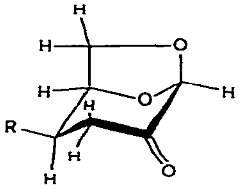
at which point the reaction was quenched. Purification by chromatography yielded the reaction product (**3**) as a yellow oil. Infrared analysis of this oil showed a shift of the carbonyl absorption of **1** to higher frequency (*i.e.*, from 1700, 1725 cm^{-1} for **1** to 1745 cm^{-1} for **3**); this is consistent with loss of conjugation present in the α,β-unsaturated system of **1**. Mass-spectral analysis showed no parent ion at the expected 286 m.u., nor was there a peak at 256 m.u., frequently observed[1,2,4] on loss of C=O in adducts of **1**. The results of microanalysis were, however, correct for the desired $C_{13}H_{18}O_7$. P.m.r.-spectral study of this material indicated that only one isomer had been formed. Loss of the vinylic resonances observed[5] for **1**, and the appearance of a methylene group (readily observable by chemical shift[1,4] and geminal coupling) adjacent to the C=O functionality indicated that β-addition had occurred. The p.m.r. spectrum of this material was consistent with those of similar types of compounds (see Tables I and II), previously described[2,4]. Two isomers (**2** and **3**) are possible with this compound, as depicted.

TABLE II

SELECTED, ^{1}H-N.M.R. COUPLING-CONSTANTS FOR COMPOUNDS LISTED IN TABLE I

Substituent at C-4	$J_{3a,3e}$	$J_{4,3a}$	$J_{4,3e}$	$J_{4,5}$	$J_{4,7}$
OH	17.0	5.0	small	^{a}	—
OMe	17.5	5.0	2	^{a}	—
S-Ph	17.0	7.0	small	^{a}	—
$CH(CO_2Et)_2$	16.6	8.3	v. small	^{a}	8.7
Levoglucosenone	16.0	9.0	v. small	^{a}	—
Furan	16.6	7.8	<1	0.5	—
CMe_2CN	16.5	8.8	3.0	^{a}	—

^{a}Not observed.



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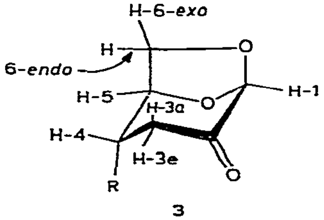

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R = $-CH(CO_2Et)_2$

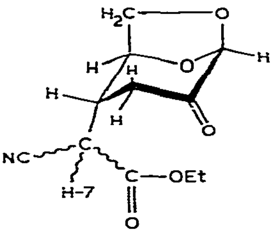
From the coupling constants observed for H-3, 4, and 5, it appeared that isomer **3** had been formed. A Dreiding model of **3** showed the dihedral angle between H-4 and H-5 to be ~70°, and this is consistent with the lack of observable coupling between these two protons. Decoupling experiments showed that coupling exists between H-4 and H-3*a* (J 8.25 Hz) and between H-4 and H-3*e* (J ~0.5 Hz), and this is consistent with models of **3**, as the dihedral angle between H-4 and H-3*a* appears to be ~10°, whereas that of H-4, H-3*e* is ~115°. Had structure **2** been obtained, couplings of the order $J_{4,5}$ ~2, $J_{4,3a}$ ~9, and $J_{4,3e}$ ~6 Hz might have been expected, but these were not observed. A doublet integrating to one proton at δ 3.68, and coupled by 8.74 Hz to H-4, indicated that reaction had occurred, as expected at the methylene protons of diethyl malonate. A doublet at δ 53.66 in the ^{13}C, off-resonance spectrum confirmed this.

Geminal coupling observed between H-3*a*, H-3*e* is large (negative), relative to that for most carbohydrates[6] (see Table II). Similar coupling has been observed for analogous compounds, and may possibly be explained by the adjacent, electron system of the carbonyl functionality, which has been shown to decrease *J geminal* (*i.e.*, become more negative, or increase its absolute value)[7,8]. Vicinal coupling between H-4, H-3*a* (equatorial, axial) is also large (8.25 Hz), relative to the generally accepted observation that, for hexopyranoses, $J_{a,e}$ is usually[9,10] 2–6 Hz.

It is worthy of note that most Michael reactions are conducted in an alcoholic solvent[11]. Because of the alcoholysis reactions previously observed with methanol[4], the reaction between **1** and DEM was initially studied by using *N*,*N*-dimethylformamide (DMF) as the solvent; however, no reaction could be induced at room, or elevated, temperature. It was further observed that, whereas methanol in the presence of triethylamine reacts with **1**, during 24 h at 50°, ethanol does not. Therefore, ethanol was chosen as the solvent in the preparation of **3**. Although triethylamine is a catalyst, use of piperidine was found to improve the yields.

Suitable reaction-conditions having been established, ethyl cyanoacetate was next examined as the nucleophile. After heating for 24 h at 86° in either ethanol or DMF, there was obtained, on purification, a yellow oil (**4**) the microanalysis of which gave values that agreed with those calculated for $C_{11}H_{15}NO_5$. The mass spectrum of this material displayed no parent ion, but other peaks, at 213 and 211 m.u., consistent with the loss of CN and CO, were observed. The infrared spectrum of **4** was similar to that of **3**, with the exception that the C=O absorbances were not quite so intense, and the expected C≡N stretch appeared at 2250 cm^{-1}.

P.m.r. analysis of this oil suggested that an isomeric mixture was present. Two closely spaced (2.0 Hz) triplets due to the CH_3, and two quartets, resulting from the



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ester (CH_2), were observable, suggesting an isomeric mixture. G.l.c. analysis in a fused silica–OV-17 capillary column (50 m) showed two peaks in the ratio of almost 1 : 1, with retention times of 13.5 and 14.8 min. Extensive, preparative chromatography failed to separate these isomers. As discussed for **3**, two geometric isomers are possible. The similarities of the p.m.r. spectra of **3** and **4** suggested the stereochemistry depicted for **4**.

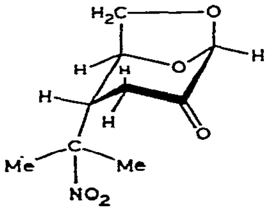
The isomeric nature of **4** seems best explained by the presence of a chiral center at C-7, making H-7, -CH_2-, and -CH_3 of the (*R*) isomer magnetically different from those of the (*S*) isomer.

As an example of a nitro-activated methylene compound, 2-nitropropane was examined. A number of examples of Michael additions using these types of nitro compound have been described[12–14], many producing nitro ketones[15], although some of the compounds are cyclized to nitrocyclohexanones[13].

In this instance, **1** was added to a solution of 2-nitropropane in dry 1,4-dioxane containing benzyltrimethylammonium hydroxide as the catalyst[13,14] (triethylamine may also be used)[16]. This mixture was heated for 48 h, and the reaction was monitored by t.l.c. On purification, a yellow oil was obtained which crystallized as a white solid (**5**) of sharp melting-point (87–88°), in 15% yield. Elimination of the solvent, and use of an excess of 2-nitropropane, increased the yield of **5** to 67%.

Good microanalytical results were obtained for a crystalline sample of **5**, although the mass-spectral analysis showed no parent ion, the first peak being observed at 187 m.u. ($M^{+\cdot} - CO$).

P.m.r.- and ^{13}C-n.m.r.-spectral analysis (see Tables I and II, and the Experimental section) indicated that only one of the two isomers possible was present, and that the expected γ-nitro ketone had indeed been formed. Very small coupling ($\leqslant 0.5$ Hz) between H-4 and H-5 was observable, and the values $J_{3a,4}$ 8.75 and $J_{3e,4}$ 3.0 Hz suggested that the stereochemistry of **5** is as depicted.



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The infrared spectrum exhibited the expected loss of the -C=C- stretch observed for **1**, and absorbances at 1535 and 1400 cm^{-1} indicated the presence of an NO_2 group.

In a recent publication on Michael additions[17], transition-metal complexes were used instead of the more strongly basic catalysts, with increased yields and a diminution in unwanted side-products. Bis(2,4-pentanedionate)-Ni(II) has been found to be a catalyst with β-diketones, β-keto esters, β-keto amides, and β-diesters[17], and therefore this catalyst was examined with the nucleophiles already mentioned. On heating **1** in an excess of DEM for 18 h at 180°, under reflux, with this catalyst, a 70% yield of **3** was obtained (after purification), and this was a substantial increase over the 54% yield obtained with piperidine. Chloroform and 1,4-dioxane were examined as solvents, but their reflux temperatures (62 and 82°, respectively) were not high enough to initiate the reaction.

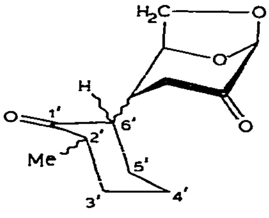
Bis(2,4-pentanedionate)-Ni(II) was examined as a potential catalyst for the reaction of **1** with ethyl cyanoacetate. On refluxing **1** with an equimolar amount of ethyl cyanoacetate in the presence of the Ni complex in chloroform, at ~63°, there was no reaction after 72 h. The use of an excess of ethyl cyanoacetate (instead of chloroform) raised the reflux temperature to 188°, and after 1 h, no further change was observable by t.l.c., but, on purification, only a 16% yield of **4** was obtained. Again, as observed before, an almost 1:1 mixture of two isomers had formed. The g.l.c., mass-, infrared-, and p.m.r.-spectral analyses compared well with those obtained previously. Obviously, this nickel complex is not the catalyst of choice here, as the yields of **4** were poor compared to those obtained by using piperidine. It was thought that the nickel complex was, perhaps, not acting as a catalyst at all; however, on heating **1** with an excess of ethyl cyanoacetate at 188° for similar periods of time, in the absence of the Ni(II) complex, no reaction was observed.

Finally, bis(2,4-pentanedionate)-Ni(II) was examined as a catalyst for the reaction of **1** with 2-nitropropane. Despite a variety of conditions examined, no reaction could be induced.

The Michael reaction between **1** and 2-methylcyclohexanone was, perhaps the most interesting. In a study of carbanions, House *et al.*[18,19] had reported the successful addition of 2-methylcyclohexanone to a variety of alkenes under strongly basic conditions. Their results indicated that the preponderant, monoalkylated product formed was the 2,2-disubstituted derivative of 2-methylcyclohexanone. This interested us, because of the reported success in acid-catalyzed ring closures used to form tetrahydroindanones[19], indicating that it might be possible to fuse 2-methylcyclohexanone to **1** *via* a five-membered, heterocyclic ring, at C-3 and C-4 in **1**.

With this in mind, **1** was added to a cooled solution of 2-methylcyclohexanone in *tert*-butanol containing an equimolar quantity of potassium *tert*-butoxide. Stirring for 45 min at room temperature produced a dark-brown solution containing a quantity of suspended material. T.l.c. indicated the presence of at least 15 compounds of which only 10 could be isolated after considerable chromatography. Shortening of the reaction time to less than 5 min, without cooling, appreciably diminished the number of compounds formed. From the organic extractable residue, four major fractions were obtained by p.l.c. on silica plates eluted with 1:3 1,4-dioxane–hexane; these displayed R_F values of 0.00–0.19, 0.24, 0.30, and 0.35.

The fraction having R_F 0.00–0.19 appeared to be a mixture of dimers and trimers, based on chromatographic studies with authentic samples reported previously[2]. The fraction having R_F 0.35 was a yellow oil that did not crystallize; the



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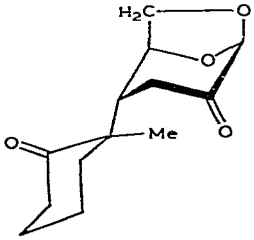
results of microanalysis were consistent with structure **6**, but the p.m.r. and ^{13}C-n.m.r. data indicated a mixture of isomers. In the ^{13}C-n.m.r. spectrum, 17 resonances were observed, instead of the expected 13. No carbonyl carbon atoms were observable, because of long relaxation-times. Based on the p.m.r. spectrum, and on comparison thereof with those of **3**, **4**, and **5**, we tentatively suggest structure **6** for it. Because of the chirality present at C-2′ and C-6′, four diastereoisomers are possible, and an indication of the presence of such isomers was seen on g.l.c. analysis in a fused silica–OV-17, capillary column (50 m); a retention time of 13.6 min was observed, with the resulting peak having a distinct shoulder on its trailing edge.

The material having an R_F value of 0.30 (present in the greatest quantity) also appeared to be isomeric. After chromatographic separation, a white, waxy solid was obtained. Fractional recrystallization of this material gave one of the two possible diastereoisomers, **7** or **8**, as a crystalline material of sharp melting point (129–130°). The results of microanalysis of both the white, waxy solid and the crystalline material were consistent with the formulas depicted. G.l.c. (in a capillary column) of the crystalline material produced a single peak having a retention time of 21.2 min. A similar analysis of the white, waxy solid afforded a similar peak, with the same retention time, but having the slightest hint of a shoulder on its leading edge.



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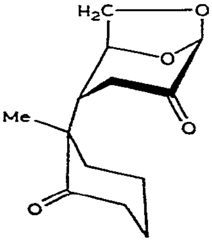

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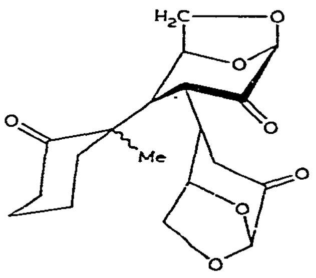
Finally, based on its p.m.r. and ^{13}C-n.m.r. spectra, the fraction having R_F 0.238 appeared to be a single compound having structure **9**. The production of this material was not surprising, as the dimer (**10**) had already been reported[2] to be formed under strongly basic conditions. Having isolated **9**, attempts were made to synthesize it from **10**. However, **10** was found to be insoluble in *tert*-butanol, the solvent originally used for this reaction. Reactions using oxolane (THF) and *tert*-



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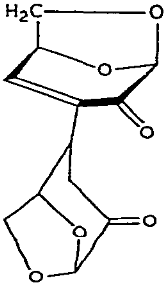

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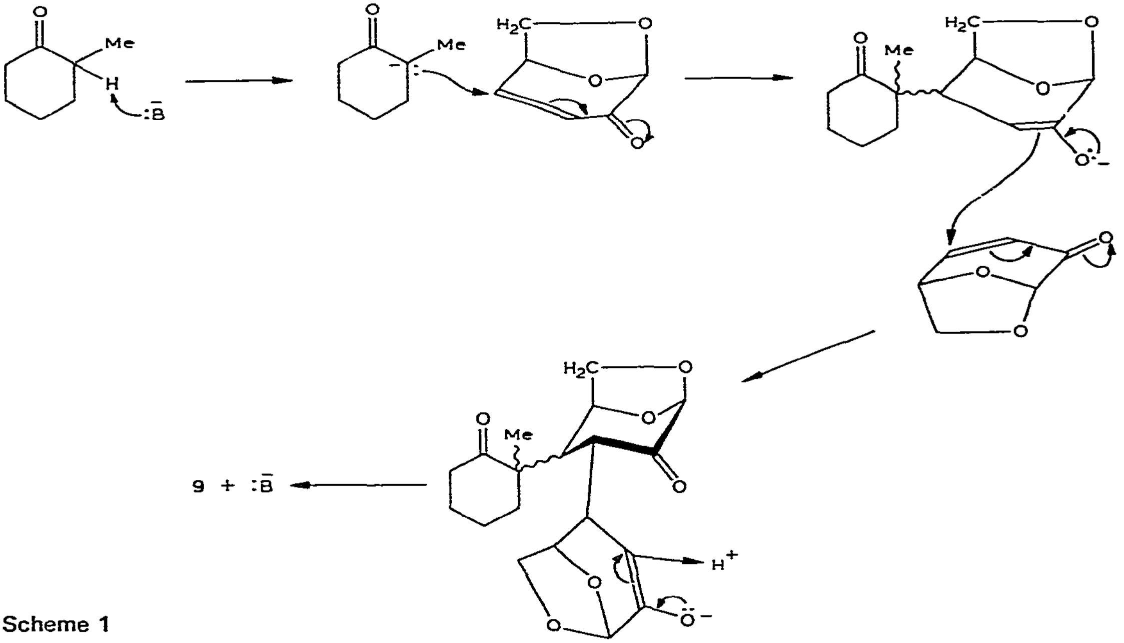
butanol, or THF alone, as the solvent were also unsuccessful. Thus, the mechanism shown in Scheme 1 for the formation of **9** is proposed.



Scheme 1

The foregoing study shows that the Michael additions of levoglucosenone follow a general pattern with respect to **1**. This type of reaction could be used to provide a variety of synthetically useful, organic molecules.

EXPERIMENTAL

General. — P.m.r. (90 MHz) and ^{13}C-n.m.r. (22.5 MHz) spectra were recorded with a JEOL FX-90Q instrument, except for those at 100, 25.0, and 360 MHz, which were recorded at the Colorado State University. Infrared spectra were recorded with a Nicolet MX-1 instrument, and mass spectra with a Varian M.A.T. III spectrometer. All t.l.c. assays were conducted on Baker-flex silica gel, IB2-F (J. T. Baker Chemical

Co.). In all instances, t.l.c. detection was achieved either by u.v. absorbance, or by spraying with 1:2:37 anisaldehyde–sulfuric acid–ethanol. Silica used for separations in chromatographic columns was supplied by E. Merck (Silica gel 60, 70–230 mesh).

Reaction of levoglucosenone with diethyl malonate. — A mixture of levoglucosenone (**1**; 7.9 mmol) with diethyl malonate (1.27 g), ethanol (15 mL), and piperidine (20 drops) was heated under reflux for 7.5 h at 110°; t.l.c. with 1:1 ethyl acetate–petroleum ether then showed the absence of **1**, and a spot at R_F 0.67. Purification was effected in a column (2 × 50 cm) of silica, eluted with 1:2 ethyl acetate–petroleum ether with 1.2% of MeCN added; this yielded 1.22 g (54%, based on initial **1**) of a straw-colored oil (**3**), which failed to crystallize; ν_{max}^{NaCl} 2990, 2945, 2915 (CH), 1745 (vs, C=O), and 1320–1120 cm^{-1} (s, C-O-C and C-O-CO-stretching); ^{1}H-n.m.r. (360 MHz, $CDCl_3$–Me_4Si): δ 5.11 (s, 1 H, H-1), 4.74 (bd, 1 H, H-5, $J_{5,6exo}$ 5.34, $J_{5,6endo}$ 0.92 Hz), 4.28–4.16 (m, 4 H, -CH_2-), 4.10 (dd, 1 H, H-6*endo*, $J_{6exo,endo}$ 7.85, $J_{5,6endo}$ 0.92 Hz), 4.04 (dd, 1 H, H-6*exo*, *J* as before), 3.68 (d, 1 H, H-7, $J_{4,7}$ 8.74 Hz), 2.92 (dd, 1 H, H-4, $J_{4,7}$ 8.74, $J_{4,3a}$ 8.25 Hz), 2.85 (dd, 1 H, H-3*a*, $J_{4,3a}$ 8.25, $J_{3a,3e}$ 16.6 Hz), 2.31 (bd, 1 H, H-3*e*, $J_{3a,3e}$ 16.6 Hz, no distinct coupling observed between H-3*e* and H-4), and 1.28 (t, 6 H, -CH_3); ^{13}C-n.m.r. (25.0 MHz, $CDCl_3$–Me_4Si): 197.93 (C-2), 167.57 (-CO-O), 101.18 (C-1), 74.50 (C-5), 67.84 (C-6), 61.89 (-CH_2-O), 53.66 (C-7), 40.17 (C-4), and 34.68 (C-3); *m/z*: no parent-ion was observed (286 m.u.), 260 (20%), 242 (14%), 214 (43%), 195 (20%), 186 (100%), 179 (40%), 153 (73%), and 152 (88%).

Anal. Calc. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.29. Found: C, 54.44; H, 6.36.

Reaction of levoglucosenone with ethyl cyanoacetate. — Compound **1** (1.0 g, 7.9 mmol) and ethyl cyanoacetate (1.0 g, 8.8 mmol) were dissolved in *N,N*-dimethylformamide or ethanol (10 mL), piperidine (20 drops) was added, and the mixture was heated under reflux for 24 h at 86°. Processing as just outlined, and chromatographic purification, provided a viscous yellow oil (**4**), R_F 0.56 on silica plates developed with 1:1 hexane–ethyl acetate; 49% yield (based on the initial quantity of **1**). N.m.r. analysis of this oil showed the probable presence of two isomers, but attempted separation by p.l.c. and g.l.c. in conventionally packed columns failed. G.l.c. analysis in an OV-17–fused silica capillary column (50 m) showed two distinct peaks, with retention times of 13.5 and 14.8 min, respectively, but preparative separation proved impossible. ^{1}H-N.m.r. analysis was difficult (because of the isomeric nature of this mixture), and thus, the assignments, where indicated, are tentative. Many of the assignments were made by comparing this spectrum with those of compounds **3** and **5**; ^{1}H-n.m.r. (90 MHz, $CDCl_3$–Me_4Si): δ 5.05 (s, H-1), 4.38 (m, H-5, w/2 5 Hz), 4.28 (q, -CH_2- ester, *J* 7.08 Hz), 4.21 (m, H-6*exo*,*endo* and, probably, H-7), 3.23–2.81 (m, H-4,3*a*), 2.59–2.23 (m, H-3*e*), and 1.29 (t, -CH_3, *J* 7.08 Hz; *m/z*: no parent-ion was observed at the expected 239 m.u.; 213 ($M^{+\cdot}$ — $CN^{\cdot}$, 5%), 211 ($M^{+\cdot}$ — CO or C_2H_4, 2%), 185 (213^{+} — C_2H_6, or $211^{+\cdot}$ — CO, 18%), 178 (23%), 152 (58%), and 151 (58%).

Anal. Calc. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.85. Found: C, 55.31; H, 5.67; N, 5.85.

Reaction of levoglucosenone with 2-nitropropane. — To a solution of freshly distilled 2-nitropropane (0.476 g, 5.35 mmol) in dry 1,4-dioxane (2 mL) was added benzyltrimethylammonium hydroxide (Triton B; 0.0179 g) as the catalyst (2%, relative to levoglucosenone). This mixture was heated to 60°, a solution of **1** (0.674 g, 5.35 mmol) in 1,4-dioxane was added dropwise, and the reaction was monitored by t.l.c. for the next 48 h. After 1 h, a spot appeared at R_F 0.51 (**1** has R_F 0.43) in 1:1 ethyl acetate–hexane. After 2 h, the temperature was raised to 75°, resulting in a slight increase in the intensity of the spot at R_F 0.51. After 5 h, the temperature was again raised, to 85°, with little obvious effect; it was then raised to 93°, and kept there for 18 h, at which time a threefold excess of 2-nitropropane was added. Little, if any, increase in the intensity of the spot at R_F 0.51 was observed, and, after a total of 48 h, the reaction was quenched. On cooling, the residue was washed with 1% aq. HCl, and extracted with diethyl ether (4 × 20 mL), and the extracts were combined, successively washed with saturated $NaHCO_3$ and distilled water, dried (sodium sulfate), and evaporated, to give a yellow oil. Purification was achieved in a silica column (1 × 100 cm) eluted with ethyl acetate–hexane, to give a yellow oil (**5**), which solidified on standing; yield 0.131 g, 6.09 mmol (15% based on the starting quantity of **1**), m.p. 87–88°; ν_{max}^{KBr} 2990, 2940, 2910, 2865 (CH), 1740, 1763 (C=O), 1535 (NO_2 asymmetric), 1400 (NO_2 symmetric), 1108, and 1133 cm^{-1} (COC); ^{1}H-n.m.r. (360 MHz, $CDCl_3$–Me_4Si): δ 5.11 (s, 1 H, H-1), 4.65 (m, 1 H, H-5, w/2 8 Hz), 4.02 (m, 2 H, 6*exo,endo*, w/2 5 Hz), 1.71 (s, 3 H, -CH_3), 1.63 (s, 3 H, -CH_3), 2.94 (ddd, 1 H, H-4, $J_{3a,4}$ 8.78, $J_{3e,4}$ 3.0, $J_{4,5}$ <0.5 Hz), 2.77 (dd, 1 H, H-3*a*, $J_{3a,4}$ 8.78, $J_{3a,3e}$ 16.5 Hz), and 2.23 (d, 1 H, H-3*e*, *J* 16.5 Hz); ^{13}C-n.m.r. (22.5 MHz, $CDCl_3$-Me_4Si): 198.41 (C-2), 100.93 (C-1), 91.30 (C-7), 73.09 (C-5), 69.13 (C-6), 47.60 (C-4), 32.78 (C-3), and 23.87 (2 -CH_3); *m/z* no parent peak observed at 215 m.u., 187 ($M^{+\cdot}$ — CO, 4%), 178 (10%), 152 (94%), 151 (100%), 123 (28%), and 109 (18%).

Anal. Calc. for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; O, 37.17. Found: C, 50.38; H. 6.04; O, 36.93.

Reaction of levoglucosenone with diethyl malonate using bis(2,4-pentanedionate)-Ni(II) as the catalyst. — To a solution of **1** (0.662 g, 5.2 mmol) and an equimolar amount (0.841 g) of diethyl malonate in chloroform was added bis(2,4-pentanedionate)-Ni(II) catalyst (1 mol%, based on starting **1**), which turned the solution yellow-green. After stirring for 4.5 h at room temperature, no reaction had occurred; the mixture was then refluxed for 23.5 h at 62°, but still no reaction had occurred. The solvent was then changed to 1,4-dioxane, increasing the reflux temperature to 82°, but with no effect. After 72 h with no appreciable reaction, the solvent was evaporated, and an excess of diethyl malonate was added and used as the solvent. Refluxing occurred at 180°, and after 18 h, no starting material was observed in t.l.c., whereupon, heating was discontinued. T.l.c. analysis showed four spots, at R_F 0.11, 0.22, 0.28, and 0.64 with 2:1 hexane–ethyl acetate on silica plates. The catalyst was removed by passing the mixture through a column of silica (5 × 5 cm) eluted with chloroform, and the eluate was separated on a column (5 × 30 cm) of silica. Four products were isolated; that having R_F 0.28 was the desired adduct (70% yield, based on the initial quantity of **1**). The infrared, ^{1}H-n.m.r., and mass spectra showed to be identical to **3**, already described. The ^{1}H-n.m.r. spectra of the remaining three fractions showed them to be hydrocarbons; they were not investigated further.

Reaction of levoglucosenone with ethyl cyanoacetate using bis(2,4-pentanedionate)-Ni(II) catalyst. — A solution of **1** (0.4870 g, 3.86 mmol), ethyl cyanoacetate (0.4372 g, 3.86 mmol), and bis(2,4-pentanedionate)-Ni(II) (0.0106 g, 386 μmol) in chloroform (5 mL) was boiled under reflux for 92 h, after which time, no observable reaction had occurred. The chloroform was evaporated, and an excess of ethyl cyanoacetate (5 mL) was added, refluxing now occurring at 188°. After 1 h, the color had turned from a pale yellow to orange-brown. On cooling, the mixture was passed through a column (5 × 5 cm) of silica and eluted with chloroform. Concentration of the eluate, and extensive chromatography in a column (1 × 55 cm) of silica eluted with hexane–ethyl acetate in various ratios resulted in the isolation of four compounds having the following R_F values: 0.71 (0.238 g), 0.66 (0.071 g), 0.56 (0.153 g), and 0.36 (0.019 g). The ^{1}H-n.m.r. spectra of these fractions showed that the material having R_F 0.56 was the desired Michaels adduct, consisting of an almost equimolar mixture of two isomers, as observed on preparation of **4** using piperidine. The material having R_F 0.77 was ethyl cyanoacetate, and that having R_F 0.66 appeared to be a condensation product of ethyl cyanoacetate, and to contain no **1**. The fraction having R_F 0.36, found during chromatography, was not observed in the t.l.c. of the initial, reaction product, and was not further investigated.

The desired Michaels adduct was obtained in 16% yield (based on **1**) and had R_F value, i.r. and n.m.r. spectra, and elemental analysis identical to those of **4** obtained previously.

Reaction of levoglucosenone with 2-methylcyclohexanone. — To a solution of potassium *tert*-butoxide (0.52 g, 4.66 mmol) in *tert*-butanol (5 mL) was added 2-methylcyclohexanone (0.52 g, 4.66 mmol). After cooling to room temperature, **1** (0.59 g) was added dropwise, with stirring. The color turned from a pale yellow to dark brown, and, after 45 min, no levoglucosenone was detectable by t.l.c. The mixture was then washed with 1% HCl (50 mL), and extracted with three 50-mL portions of diethyl ether. The extracts were combined, washed with water, dried (sodium sulfate), and evaporated, yielding a dark-brown residue. Crude separation was achieved by chromatography on a column (1 × 50 cm) of silica, eluted with 1:1 hexane–ethyl acetate; this yielded 0.162 g of organic material. On exhaustive elution of the column with methanol, 0.588 g of residue was obtained that was soluble only in methanol. Considerable experimentation indicated that 1:3 1,4-dioxane–hexane was the solvent system best suited to the separation of the material initially eluted. Extensive chromatography (both on a column and on p.l.c. plates) resulted in the isolation of ten fractions: R_F 0.622–0.88; 5 compounds, spots at 0.81, 0.75, 0.70, 0.65, and 0.62; none of these seemed to be u.v. active at either 254 or 366 nm. Poor resolution was obtained on various columns, although isolation of two compounds, R_F 0.70 and 0.62, was achieved.

The following were the characteristics of these components: R_F 0.70, non-u.v.-active, the anisaldehyde spray produced a turquoise-blue spot, yield 64 mg; R_F 0.62, non-u.v.-active, yield 1.01 mg; R_F 0.35, non-u.v.-active, an oil that turned light purple with the anisaldehyde spray, yield 3.67 mg; R_F 0.32, u.v.-active, a pale straw-colored spot with the anisaldehyde spray, yield 95 mg; R_F 0.29, non-u.v.-active, crystalline material appearing as a pink spot on spraying with anisaldehyde, yield 8.29 mg; R_F 0.30 u.v.-active, crystalline material, a deep straw-colored spot on spraying with anisaldehyde, and only sparingly soluble in $CDCl_3$, yield 29.52 mg; R_F 0.24, u.v.-active crystalline solid, a blue-black spot on spraying with anisaldehyde, yield 27.66 mg; R_F 0.19, a yellow oil, u.v.-active on t.l.c. plates, a black spot on spraying with anisaldehyde, yield 26.88 mg; and R_F 0.00–0.19, a u.v.-active streak containing at least five compounds; by using ethyl acetate–hexane, the R_F may be extended to ~0.50 (but isolation of pure material was not achieved), a yellow, sticky syrup, yield 45.89 mg; two components compare well, chromatographically, with authentic samples of the previously prepared, dimer and trimer[2] condensation-adducts of **1**.

In view of the small quantities involved, and the difficulties in purification, only the compounds having R_F 0.30, 0.24, and 0.19 were examined. After some experimentation, the reaction was repeated with double the quantities of starting materials: the reaction time was 5 min, and no cooling was employed. On processing, 1.66 g of organic-extractable material was obtained; this was placed on a column (2 × 50 cm) of silica, and eluted with hexane (20 mL), 6:1 hexane–1,4-dioxane (70 mL), 5:1 hexane–1,4-dioxane (60 mL), 7:1 hexane–1,4-dioxane (50 mL), and 3:1 hexane–1,4-dioxane. Elution was discontinued after ~300 mL of eluate had been collected, at which point no organic material was detectable therein. On evaporation, 0.37 g of organic material was obtained, which was shown by t.l.c. to contain four components, R_F 0.0–0.19, 0.24, 0.30, and 0.35. Further chromatography on silica plates resulted in separation of them; their characteristics were as follows.

(1) The material having R_F 0.0–0.19 (wt. 0.19 g) gave a black, streaked spot on spraying with the anisaldehyde reagent. It did not appear to contain any of the desired products (p.m.r. spectrum), and was not examined further.

(2) The material having R_F 0.24 (wt. 0.006 g) gave a blue-black spot on spraying with the anisaldehyde reagent. It was isolated as white crystals of **9**; recrystallized from chloroform, m.p. 233–234°, ν_{max}^{KBr} 3360, 3330, 3300, 2870 (CH stretch), 1740, 1710 (C=O), 1445, 1415, 1385, 1265, and 1115 cm^{-1} (COC); ^1H-n.m.r. (90 MHz, $CDCl_3$–Me_4Si): δ 5.21 (s, 1 H, H-1 of one anhydro ring), 5.15 (s, 1 H, H-1 of the second anhydro ring), 4.84 (m, 1 H, H-5 of one anhydro ring), 4.71 (m, 1 H, H-5 of the second anhydro ring), 3.86 (m, 4 H, H-6*exo,endo* of both anhydro rings, w/2 6 Hz), 3.59 (d, 1 H, *J* 6.83 Hz), 3.13 (ddd, 1 H, *J* 11.47, 4.0, 4.0 Hz), 2.86 (d, 1 H, *J* 11.47 Hz), 2.41 (dd, 1 H, *J* 10.99, 2.0 Hz), 2.13 (ddd, 1 H, *J* ~14.0, 4.0, 4.0 Hz), 1.83 (m, 6 H, w/2 22 Hz), 1.46 (dd, 2 H, *J* 11.72, 1.46 Hz), and 1.23 (s, 3 H, CH_3); ^{13}C-n.m.r.* (62.5 MHz; $CDCl_3$–Me_4Si): δ 207.8, 205.3, 198.5 (C=O), 100.3,

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*C-1, C-5, and C-6 refer to both pyranose rings, because they were not distinguished from each other.

99.1 (C-1), 76.7, 75.6 (C-5), 71.7, 71.4 (C-6), 49.5, 41.9, 40.8, 40.6, 33.6, 29.7, 27.6, 24.2, 23.2, and 21.6.

Anal. Calc. for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 63.79; H, 6.59.

(3) The material having R_F 0.30 (wt. 0.150 g) gave a a straw-yellow spot when sprayed with the anisaldehyde reagent. It was an isomeric mixture, **7** or **8**; however, some of one of the isomers crystallized, to provide a white solid, and this was recrystallized from MeOH–H_2O.

(*a*) Crystalline material (**7** or **8**), m.p. 129–130°; $\nu_{\max}^{\mathrm{KBr}}$ 3060, 3010, 2880 (CH), 1730, 1695 (C=O), 1130, and 1115 cm^{-1} (COC); ^{1}H-n.m.r. (90 MHz, $CDCl_3$–Me_4Si): δ 5.06 (s, 1 H, H-1), 4.70 (m, 1 H, H-5, w/2 8 Hz), 3.96 (m, 2 H, H-6*exo,endo*; a distorted doublet), 2.74 (d, 1 H, H-4, $J_{3a,4}$ 8.3 Hz), 2.46 (dd, 1 H, H-3*a*, $J_{3a,4}$ 8.3, $J_{3a,3e}$ 11.95 Hz). The remaining protons lay in a broad multiplet from δ 2.97–1.58, and were indiscernible in the 90-MHz spectrum, except those of the methyl group at δ 1.31 (s, 3 H, CH_3); ^{13}C-n.m.r. (62.5 MHz, $CDCl_3$–Me_4Si), chemical shift (appearance in off-resonance spectrum): 214.7 (s, C-2′), 202.0 (s, C-2), 100.9 (d, C-1), 74.2 (d, C-5), 70.3 (t, C-6), 52.5 (s, C-6′), 44.0 (d, C-4), 35.9 (t, C-3), 20.5 (q, CH_3), 38.8, 37.8, 27.0, and 20.9 (t, C-9,10,11,12).

Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.29; H, 7.50.

(*b*) The initial material obtained, R_F 0.30, appeared to be an isomeric mixture of **7** and **8**. A pure sample of both **7** and **8** could not be isolated; however, some information regarding their spectroscopic properties was obtainable by difference. The i.r. data were as just given; p.m.r. (90 MHz, $CDCl_3$–Me_4Si): δ 5.06 (s, H-1), 4.69 (m, H-5, w/2 16 Hz), 4.64, 3.96 (m, H-6*endo,exo*; little change in peak shape or position was observable here between this spectrum and that of (*a*), and 1.18 (s, 3 H, CH_3 of isomer *a*); the signals of the remaining protons lay in a complex multiplet in the region δ 2.97–1.58.

Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.66. Found: C, 65.32; H, 7.55.

(*4*) The material having R_F 0.35 (wt. 0.37 g) gave a purple spot with the anisaldehyde spray; it was compound **6**, a yellow oil that failed to crystallize; $\nu_{\max}^{\mathrm{NaCl}}$ 2986, 2932, 2857 (CH), 1732, 1705 (C=O), 1124, and 1108 cm^{-1} (COC); from the ^{1}H-n.m.r. spectrum (90 MHz, $CDCl_3$–Me_4Si) it was evident that two isomers were present: δ 5.05 (s, H-1; despite the apparent presence of two isomers, this resonance appeared as a sharp singlet), 4.68 (m, H-5, w/2 10 Hz; this was somewhat broader than expected for a single compound), 4.02 (d, H-6*endo*). From decoupling H-5, it appears that H-6*endo* for both isomers occurs at this point, whereas H-6*exo* (dd) falls in the region δ 4.05–3.89. All remaining protons, except those of CH_3 appeared in a complex multiplet from δ 2.97–1.13. The protons of CH_3 appeared as a doublet centered at δ 1.01, J 8.54 Hz. Decoupling at this point, in an attempt to locate the position of the adjacent proton, proved ineffective. ^{13}C-n.m.r. (22.5 MHz, $CDCl_3$–Me_4Si; chemical shift; appearance in off-resonance spectrum): 101.25 (s), 76.41 (d), 73.88 (d), 68.48 (t), 68.15 (t), 53.07, 51.83 (d), 46.17 (d), 38.73, 37.41, 37.46, 36.94, 33.23, 32.32, 31.98, 25.30 (t), and 14.31 (d). The carbonyl carbon atoms were not observed, due to long relaxation times. The mass spectrum further indicated the presence of two isomers; *m/z*: 238 (parent ion), 210 ($\mathrm{M}^{+\cdot}$ − CO, 34%), 165 ($210^{+\cdot}$ − $C_2H_5O^{\cdot}$, 35%), 149 (165^{+} − $O^{\cdot}$, 17%), 136 (165^{+} − $CHO^{\cdot}$, 10%), 112 (53%), and 99 (100%).

Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.48; H, 7.66.

Attempts at separation by g.l.c. failed; in a column (1.83 m) of 3% of SE-30, with temperature programmed from 75° at 8°.min^{-1}, retention time 13.1 min; in a capillary column (50 m) of OV-17 on fused silica under isothermal conditions at 220°, broad peak with slight shoulder on leading edge, retention time 21.24 min.

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