mentary material. The crystal belonged to the monoclinic system and the data collected were consistent only with space group $P2_1/c$ (No. 14).[20] From a total of 2735 reflections collected in a complete quadrant of data, 1317 were accepted as statistically above background. In the data refinement, described in the supplementary material, 170 parameters were varied for the 1317 observations. The full-matrix least-squares refinement converged at $R = 0.097$ and $R_w = 0.091$. A perspective view of the oxime 7 is presented in Figure 3. Lists of the final atomic coordinates and the bond distances and angles are available in the supplementary material as Tables 5 and 6.

Supplementary Material Available: Descriptions of the determination of crystal structures for the syn-cis ketone **14**, the anti-cis ketoxime **18**, and the syn-cis ketoxime **7**, including tables of atomic coordinates, bond distances, and bond angles for each compound and Figures 9 and 10, perspective drawings of additional low-energy conformers calculated with the MM2 program for the diastereoisomeric olefins **20** and **21** (14 pages). Ordering information is given on any current masthead page.

Chemistry of 1,3,5-Tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene, a β-Tricarbonyl Trianion Equivalent

T. H. Chan* and D. Stössel

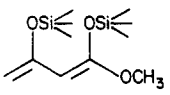
Department of Chemistry, McGill University, Montreal, P.Q., Canada H3A 2K6

Received September 23, 1985

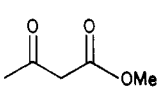
The title compound has been synthesized and its chemistry studied. Condensation with orthoesters, acid chlorides, or imidazolides gave aromatic compounds in a 5C + 1C condensation. A formal synthesis of lasiodiplodin has been completed.

It is well recognized that in nature condensation of poly-β-carbonyl compounds is a major pathway for the biogenesis of aromatic natural products.[1,2] Collie, as early as the 1890's, was the first to recognize the formation of benzenoid derivatives from polyketide acids.[3] Subsequently, numerous efforts to mimic this reaction in the laboratory have met with varying degrees of success.[1,2] The main difficulty has been to control the specificity of the direction of condensation.[2]

Recently the use of 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (**1**) as the dianion equivalent of methyl acetoacetate (**2**) has been introduced.[4] The use of **1** as



1



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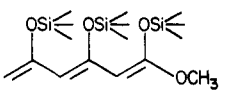

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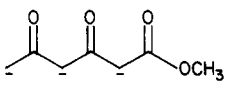

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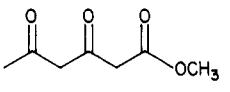
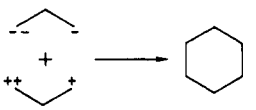


5

a dicarbonyl unit in forming benzenoid aromatic compounds has been quite successful. Specifically, a new cycloaromatization reaction was demonstrated on the basis of the reaction of **1** with various 1,3-dielectrophiles under Lewis acid catalyzed conditions.[5,6] Essentially, the reaction involves the union of two three-carbon units according to eq 1, and the regiochemistry is controlled by the different reactivities of the reaction sites.



(1)

We have demonstrated the utility of this approach by the synthesis of sclerin,[7] a plant growth promoter, and Δ^1-tetrahydrocannabinol,[8] the active component of marijuana.

In this paper, we report on the study of 1,3,5-tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene (**3**), the equivalent of the trianion **4** of the tricarbonyl compound methyl triacetate (**5**).

Results and Discussion

A. Preparation of 1,3,5-Tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene. The starting point was the synthesis of methyl triacetate (**5**) from dehydroacetic acid (**6**), which has been described in the literature.[9] Although **5** was reported to be indefinitely stable at room temperature, we have noted that crude **5** dimerizes after 2 to 3 months to give two aromatic compounds, **7** and **8**, in approximately a 1 to 1 ratio. These compounds may be separated easily by column chromatography.

The next step involved the conversion of **5** to the bis silyl enol ether **9** utilizing literature procedures with a slight variation.[6] The bis silyl enol ether **9** was then transformed into 1,3,5-tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene (**3**) through a minor modification of literature procedure.[6]

(1) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441.
(2) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
(3) Collie, J. N.; Myers, W. S. *J. Chem. Soc.* **1893**, *122*, 329.
(4) Chan, T. H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578. The correct stereochemistry of 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (**1**) is the one shown in this paper. The assignment was based on the NOE effect. See: Bell, S. H.; Cameron, D. W.; Feutrill, G. I.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **1985**, *26*, 6519.
(5) Chan, T. H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.
(6) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688.
(7) Chan, T. H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1981**, 20.
(8) Chan, T. H.; Chaly, T. *Tetrahedron Lett.* **1982**, *23*, 2935.
(9) Batelaan, J. G. *Synth. Commun.* **1976**, *6*(2), 81.

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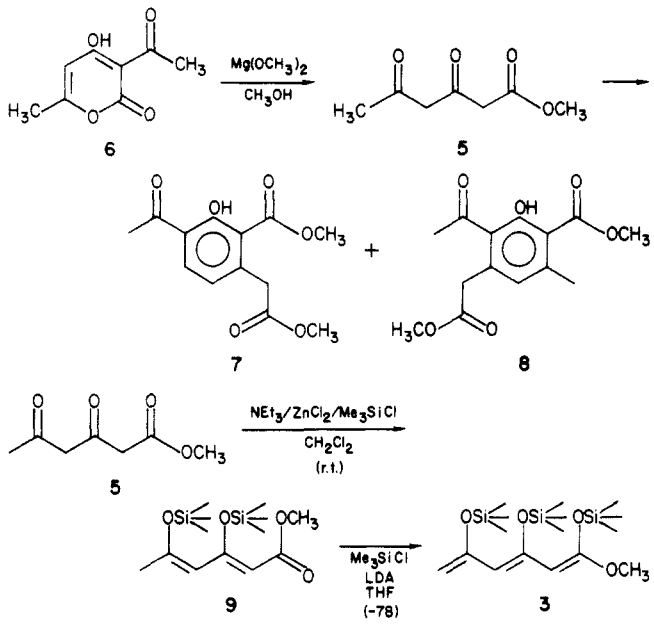
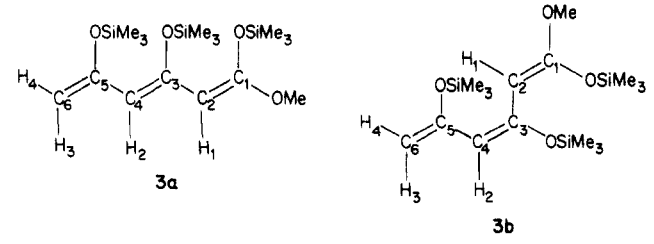
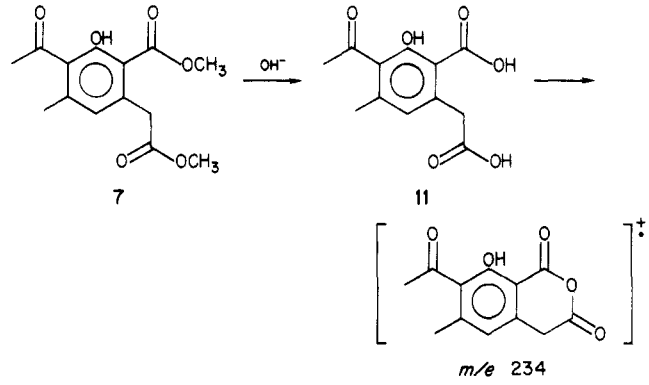


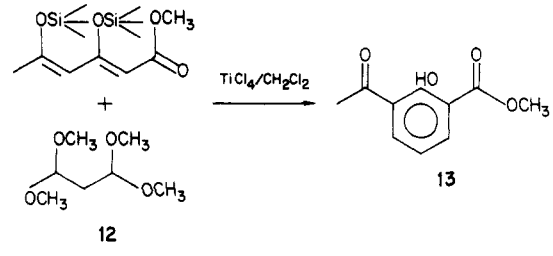
The silyl enol ethers **9** and **3** are sufficiently stable so that they may be kept in the refrigerator, the diene **9** for at least 3 months without appreciable decomposition, and the triene **3** for at least 1 month, if they are stored under nitrogen and precautions are taken to exclude moisture. In the case of **3** it is essential that moisture be excluded rigorously as it is hydrolized very readily. Both the proton and the silicon-29 NMR confirm that the diene **9** and the triene **3** are present as one major isomer. For the determination of the stereochemistry of **3** use was made of the NOE effect and of $^3J_{CH}$. Upon irradiation of the methoxy signal, a 20% enhancement was observed for the H_1 signal, thus establishing their relative cis position. The assignment of the signals in the ^{13}C NMR was done with the help of ^1H–^{13}C Heterocorrelation.[10a] For the configuration about C_3–C_4, $^3J(C_2$–$H_2)$ was measured as 2.9 ± 1.0 Hz for the major isomer, **3a**, with a cis relationship between C_2 and H_2, and as 7.4 ± 1.0 Hz for the minor isomer, **3b**, with a trans relationship between C_2 and H_2. The approximate ratio of **3a** to **3b** was 3 to 1. This assignment was based on previous findings[10b] where it was determined that in general $^3J_{CH}$(trans) > $^3J_{CH}$(cis), and that it was possible to assign the stereochemistry unambiguously if both isomers were available. In the case of diene **9** there was no significant NOE effect and only one isomer was available, so that the assignment of stereochemistry was not possible. The diene **9** is thermally stable so that it may be distilled. The triene **3** is used without any further purifications.



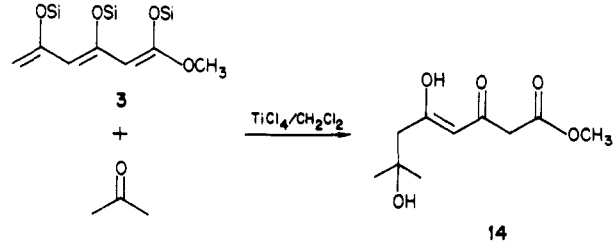
The bis silyl enol ether **9** did not react with acetone, benzaldehyde, or trimethyl orthoformate in the presence of titanium tetrachloride. However, in addition to the recovery of **5**, the diene **9** underwent dimerization under these Lewis acid conditions to give the same aromatic compounds **7** and **8** obtained from the dimerization of the triacetate ester **5** (not unexpectedly), also in a ratio close to 1 to 1. The dimerization reaction became the major pathway when the concentration of the diene in solution was high (close to 1 M); however, in more dilute solution (approximately 0.2 M), the dimers were not formed. The dimers **7** and **8** have different properties and different NMR spectra. To distinguish between the two, they were submitted to basic hydrolysis to give the corresponding dicarboxylic acids **10** and **11**. In the mass spectra, however, only **11** derived from **7** showed an intense peak at m/z 234 for the corresponding anhydride as it has both of the acid functions in ortho positions of each other.



On the other hand, diene **9** reacted with malonaldehyde bis(dimethyl acetal) (**12**) in the presence of $TiCl_4$ to give the aromatic compound **13** in 30% yield. This result suggests that either of the two enol silyl ether positions (C-2 and C-4) is capable of acting as a nucleophilic center.



B. Reactions of 3 with Carbon Electrophiles. Compound **3** proved to be more reactive than the diene **9** and several of its reactions were studied. The first was to learn if upon reaction with a simple electrophile such as acetone, one of the possible three nucleophilic sites (C-2, C-4, and C-6) would be more reactive. This was found to be the case and the alcohol **14** was obtained upon reaction in the presence of titanium tetrachloride.

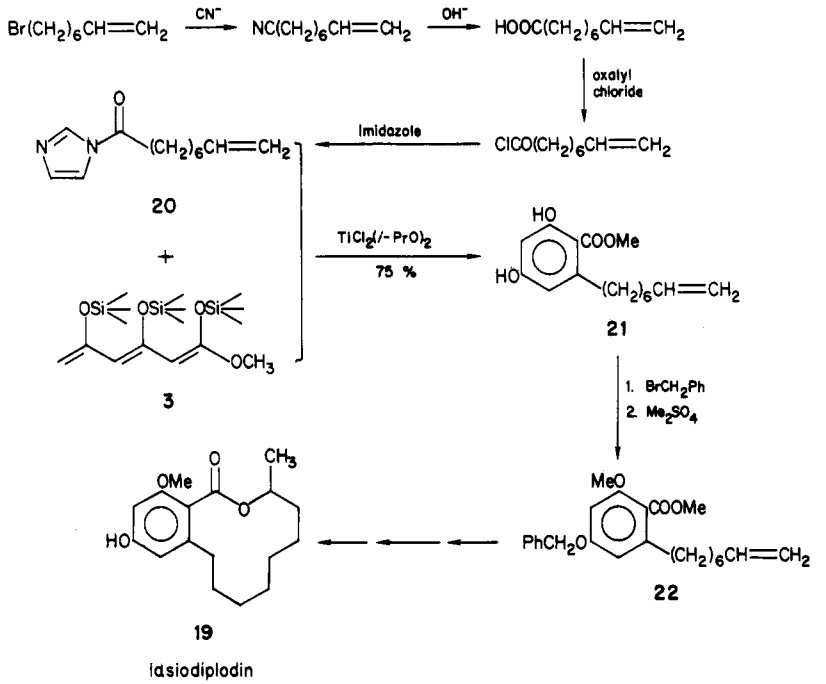


The triene **3** thus reacts with carbon electrophiles with ϵ-selectivity. The α- vs. γ-regioselectivity in the reaction of 1-siloxybutadiene with electrophiles has been a subject of considerable recent interest.[11] Whereas dienolates generally react with electrophiles at the α-position, 1-siloxydienes react selectively at the γ-position. While the two siloxy groups at C-3 and C-5 may have enhanced the

(10) (a) Maudsley, A. A.; Muller, L.; Ernst, R. R. *J. Magn. Reson.* **1977**, *28*, 463. Bodenhausen, G.; Freeman, R. *Ibid.* **1977**, *28*, 471. (b) Gregory, B.; Hinz, W.; Jones, R. A.; Arques, J. S. *J. Chem. Res., Synop.* **1984**, 311.

(11) Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*, 5252.

Scheme I. Formal Synthesis of Lasiodiplodin

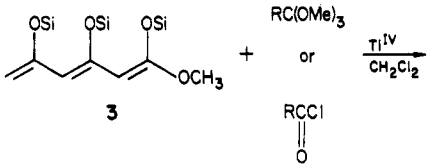


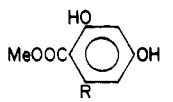
regioselection, one may postulate that 1-siloxytrienes should react preferentially at the ϵ-position.

The reactions of **3** with several monoelectrophiles were next examined. The first group of electrophiles studied was the orthoesters. Upon reaction with trimethyl orthoformate in the presence of $TiCl_4$, orsellinic acid methyl ester (**15a**) was obtained. This reaction may be envisaged as the formation of a six-membered ring through the condensation of a five-carbon nucleophilic unit and a one-carbon electrophilic unit, i.e., a 5C + 1C condensation.

The 5C + 1C condensation was also performed with trimethyl orthoacetate, orthobutyrate, and orthovalerate. In all cases, the corresponding products **15** were obtained in 40–50% yield after purification by column chromatography.

The next group of electrophiles examined was the acid chlorides. In this case a modification of the reaction conditions was necessary. Instead of using titanium tetrachloride alone as a catalyst, as no aromatic products were formed, a 1 to 1 molar ratio of titanium tetrachloride and titanium isopropoxide was used. Even so, the yields of products **15** after purification was around 25% except for dichloroacetyl chloride for which it was 40%. The acid chlorides may be considered as hard electrophiles and the possibility that they react through the oxygen of the trimethylsiloxy group instead of at carbon may explain the lower yields as compared to the condensation with the orthoesters.

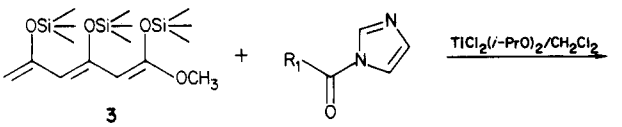




15a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = $CHCl_2$
e, R = *n*-Bu
f, R = $(CH_2)_5CH_3$
g, R = $(CH_2)_7CH_3$
h, R = *n*-Pr
i, R = $(CH_2)_4CH_3$

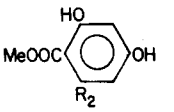
In order to improve the yield the imidazolides **16** were tried. These may be prepared very easily from acid chlorides and are often crystalline and easy to handle. Aliphatic imidazolides undergo the 5C + 1C condensation to give the expected aromatic products **15** in better than 50% yield after purification by column chromatography. The reaction conditions were similar to the ones for the acid chlorides.

The condensation between **3** and 1,1′-carbonyldiimidazole (**17**) gave the expected product, methyl 2,4,6-trihydroxybenzoate (**18**) in 47% yield.



16b, $R_1 = CH_3$
g, $R_1 = (CH_2)_7CH_3$
i, $R_1 = (CH_2)_4CH_3$

17, R_1 = 



15b, $R_2 = CH_3$
g, $R_2 = (CH_2)_7CH_3$
i, $R_2 = (CH_2)_4CH_3$

18, R_2 = OH

Other azolides were tried: propionyl 1,2,4-triazolide behaved in the same way as the imidazolides, giving similar yields (50%). However, the benzotriazolides and benzimidazolides were not as effective. The ester derived from propionic acid and *o*-nitrophenol (and also *p*-chlorophenol) did not give any of the expected product upon reaction with **3**.

It was found that increasing the amount of **3** so that 100% excess of it is used, the yield in its condensation with imidazolides can be increased to 75%.

C. A Formal Synthesis of Lasiodiplodin (19). The macrocyclic lactone lasiodiplodin (**19**) is a plant growth

inhibitor. It has been synthesized in several laboratories.[12,13] Of interest is the recent synthesis by Danishefsky et al.[13] in which the construction of the benzene moiety was achieved by the Diels–Alder reaction. In the percent case, the condensation of **3** with the imidazolide **20** gave the aromatic compound **21** in 75% yield. The formation of **21** may be considered as biomimetic in the sense that it is formed by a poly-β-carbonyl condensation reaction. The two hydroxy groups in **21** may be differentiated readily by benzylation followed by methylation to give **22**. Compound **22** has been previously converted to lasiodiplodin.[12,13]

Conclusion

It is clear from this study that the silyl enol ether approach to control poly-β-carbonyl condensations can be successfully applied to the synthesis of benzenoid natural products. We are currently exploring the possibility of using **3** for the synthesis of naphthalenoid natural products.

Experimental Section

All the chemicals used were reagent grade. Solvents were dried prior to use: methylene chloride was dried over phosphorus pentoxide, THF was dried over sodium metal/benzophenone, and hexanes were dried over sodium metal/benzophenone. Melting points were taken with a Gallenkamp apparatus and are uncorrected. Nuclear magnetic resonance spectra were taken with a Varian T-60 or XL-200 spectrometer using tetramethylsilane as internal standard. NMR spectra are reported in ppm with respect to Me_4Si and in parentheses the multiplicity and the number of hydrogens. ^{29}Si NMR were taken with the XL-200 using the decoupled Inept pulse sequence.[14] IR spectra were taken with a Perkin-Elmer Model 297 and reported in cm^{-1}. Mass spectra were taken at 60 eV with a Dupont 21-492B instrument and are reported as m/z (relative intensity in percent). All reactions were usually run in a nitrogen atmosphere and all equipment dried in an oven. Purifications involving column chromatography were performed with Merck silica gel 60 (230–400 mesh) using flash chromatography.[15] Microanalyses were performed by Guelph Chemical Laboratories Ltd.

Triacetic ester **5** was prepared according to literature procedure[9] and its identity confirmed by NMR, IR, and MS analysis.

Methyl 3,5-Bis(trimethylsiloxy)hexa-2,4-dienoate (9). Dry triethylamine (24 mL, 172 mmol) and dried zinc chloride were stirred at 0 °C in methylene chloride (30 mL). Triacetic ester **5** (6.0 mL, 40 mmol) and trimethylchlorosilane (26 mL, 204 mmol) were added in succession. The mixture was allowed to stir for 1 h at 0 °C and then overnight at room temperature. The solvent was distilled under reduced pressure, and the solid was extracted 5 times with freshly distilled hexanes and filtered. The combined extracts and filtrate were concentrated under reduced pressure and the resulting black oil was distilled under vacuum to give **9** in 80–85% yield (bp 110–120 °C at 0.5 mm): IR (neat) 2960, 1700, 1630, 1560, 1400, 1200, 850, 760; ^1H NMR (CCl_4) δ 0.1–0.3 (b, 18 H), 2.0 (s, 3 H), 3.6 (s, 3 H), 4.6 (s, 1 H), 6.6 (s, 1 H); ^{29}Si NMR ($CDCl_3$) δ 20.6, 18.8; ^{13}C NMR ($CDCl_3$) δ 21.5, 50.2, 96.1, 103.8, 160.8, 165.2, 167.5; MS, 302 (18, M^+), 287 (60), 271 (52), 157 (52), 73 (100); exact mass for $C_{13}H_{26}O_4Si_2$ calcd 302.137, found 302.134.

1,3,5-Tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene (3). In a 100-mL flask at 0 °C was placed a mixture of THF (20 mL), diisopropylamine (1.80 mL, 12 mmol), and *n*-butyllithium (5.2 mL of a 2.5 M solution in hexanes). The mixture was cooled to −78 °C and the bis silyl enol ether **9** added (3.0 mL, 10 mmol). The mixture was stirred for 5 min and excess trimethylchlorosilane added (8.0 mL). The reaction mixture was stirred for 15 min at −78 °C and then allowed to warm up to room temperature (10 min). The solvent and excess Me_3SiCl were evaporated off using a high vacuum pump. Freshly distilled hexane was added, and the mixture was filtered. The filtrate was concentrated in a high vacuum pump to give the title compound in 80–90% yield: IR (neat) 2960, 1650, 1300, 840; ^1H NMR (CCl_4) δ 0.2–0.6 (br, 27 H), 3.7 (s, 3 H), 4.1 (s, 1 H), 4.4 (d, J = 2 Hz, 1 H), 4.8 (s, 1 H), 5.4 (d, J = 2 Hz, 1 H); ^{29}Si NMR ($CDCl_3$) δ 22.4, 17.5, 15.7; ^{13}C NMR ($CDCl_3$) δ 54.4, 54.6, 76.3, 78.6, 92.6, 92.7, 106.0, 106.2, 148.3, 149.9, 153.7, 155.0, 157.8, 158.0; MS, 359 (11, $M^+ - CH_3$), 302 (39), 287 (78), 271 (46), 147 (50), 28 (100); exact mass for $C_{15}H_{31}O_4Si_3$ found 359.151, calcd 359.153.

Dimerization of Methyl 3,5-Bis(trimethylsiloxy)hexa-2,4-dienoate. In a 10-mL flask a mixture of methylene chloride (3 mL) and bis silyl enol ether (0.60 mL, 2 mmol) was added. The mixture was cooled to −78 °C and titanium tetrachloride (4 mmol, 0.44 mL) added. The mixture was stirred for 3 h at −78 °C and overnight at room temperature. To the reaction mixture was added aqueous sodium bicarbonate. The mixture was left stirring for several hours at the end of which it was extracted with ethyl ether. The ethereal solution was dried with anhydrous sodium sulfate and evaporated to dryness. The residue was separated on a column with 1/1 ethyl ether/petroleum ether to give the two dimers **7** and **8** each in 20% yield.

Methyl (4-acetyl-3-hydroxy-2-(methoxycarbonyl)-5-methyl)phenylacetate (7): mp 83–84.5 °C; IR (KBr) 900, 800, 1750, 1690; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 2.25 (s, 3 H), 3.40 (s, 5 H), 3.70 (s, 3 H), 6.05 (s, 1 H), 11.2 (s, 1 H); MS, 280 (68, M^+), 248 (60), 220 (88), 201 (100), 188 (69), 160 (62); exact mass for $C_{14}H_{16}O_6$ found 280.094, calcd 280.095. Anal. Found for $C_{14}H_{16}O_6$: C, 60.28; H, 6.09. Calcd C, 60.04; H, 5.76.

Methyl (2-acetyl-3-hydroxy-4-(methoxycarbonyl)-5-methyl)phenylacetate (8): mp: 81–82.5 °C; IR (KBr) 1740, 1680, 910, 800; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.40 (s, 3 H), 3.50 (s, 3 H), 3.60 (s, 2 H), 3.65 (s, 3 H), 6.10 (s, 1 H), 11.4 (s, 1 H); MS, 280 (M^+, 75), 248 (60), 220 (72), 201 (90), 188 (70), 160 (17); exact mass for $C_{14}H_{16}O_6$ found 280.099, calcd 280.095. Anal. Found for $C_{14}H_{16}O_6$: C, 59.89; H, 5.67. Calcd: C, 60.04; H, 5.76.

Hydrolysis of the Dimerization Products 7 and 8. The dimers **7** and **8** were each refluxed in 20% NaOH aqueous solution for an hour, and the mixtures were slowly neutralized dropwise with HCl to give the corresponding dicarboxylic acids **10** and **11**.

2-Acetyl-3-hydroxy-4-(hydroxycarbonyl)-5-methylphenylacetic acid (10) (derived from 8): mp 170–175 °C dec; IR (KBr) 3610, 3400, 1720, 1660, 1270, 1200, 840; ^1H NMR (acetone-d_6) δ 2.51 (s, 3 H), 2.61 (s, 3 H), 3.71 (s, 2 H), 6.79 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 24.0, 31.8, 38.7, 96.6, 107.7, 112.1, 126.6, 129.3, 139.7, 144.3, 162.0, 171.7, 174.2, 203.7; MS, 149 (28), 70 (43), 61 (30), 43 (100).

4-Acetyl-3-hydroxy-2-(hydroxycarbonyl)-5-methylphenylacetic acid (11) (derived from 7): mp 180–183 °C dec; IR (KBr) 1700, 1690, 1650, 1250, 1200; ^1H NMR (acetone-d_6) δ 2.23 (s, 3 H), 2.50 (s, 3 H), 4.00 (s, 2 H), 6.77 (s, 1 H); MS, 234 (41), 219 (52), 206 (68), 201 (100), 193 (39); exact mass for $C_{12}H_{10}O_5$ found 234.051, calcd 234.053.

Methyl 2-Hydroxy-3-acetylbenzoate (13). To a 25-mL flask equipped with magnetic stirrer under nitrogen was added a solution of metylene chloride (3 mL) and 1,1,3,3-tetramethoxypropane (0.15 mL, 1 mmol). The mixture was cooled to −78 °C and $TiCl_4$ was added (0.22 mL, 2 mmol). Then 1 mmol of silyl enol ether **9** was added (0.3 mL). The rection mixture was stirred for 3 h at −78 °C, quenched with sodium bicarbonate solution, and extracted with ether. The ether fraction was dried with anhydrous magnesium sulfate and concentrated to give **13** in 30% yield after purification by column chromatography using ethyl acetate/hexanes as eluent (2/8 v/v). The compound had mp 53.5–55 °C: IR (Nujol) 1680, 1260, 1145, 765, 715; ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 4.0 (s, 3 H), 6.9 (t, J = 8 Hz, 1 H), 8.0 (m, 2 H), 12.5 (s, 1 H); MS 194 (M^+, 43), 179 (43), 163 (38), 147 (100), 134 (33); exact mass for $C_{10}H_{10}O_4$ found 194.056, calcd 194.058.

Methyl 7-Hydroxy-7-methyl-3,5-dioxooctanoate (14). In a 25-mL flask under a nitrogen atmosphere, acetone (5 mmol, 0.40 mL) and methylene chloride (10 mL) were cooled to −78 °C, and titanium tetrachloride was added (5 mmol, 0.55 mL). Then tris silyl enol ether **3** was added (5 mmol, 2.0 mL), and the reaction

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mixture was stirred for 3 h at −78 °C and overnight at room temperature. The dark red solution was quenched with aqueous sodium bicarbonate and stirred for several hours. Then it was extracted 5 times with ether. The ether extracts were dried and filtered to give an oil which was purified by column chromatography using ethyl acetate/petroleum ether as eluents (4/6 v/v). After purification, methyl 7-hydroxy-7-methyl-3,5-dioxooctanoate was obtained in 15% yield: IR (neat) 1740, 1670, 1610; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 6 H), 2.5 (s, 2 H), 3.2 (s, 2 H), 3.8 (s, 3 H), 5.4 (s, 1 H); MS, 198 ($M^+ - H_2O$, 51), 183 (56), 143 (91), 101 (88); exact mass for $M^+ - 18$ ($C_{10}H_{14}O_4$) found 198.089, calcd 198.089.

General Procedure for the Condensation of 1,3,5-Tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene with Electrophiles. The electrophile (n mmol) and the tris silyl enol ether **3** (n mmol) were added to methylene chloride (20n mL) at −78 °C. Titanium tetrachloride was added to the mixture (for the orthoester group, 2n mmol in 4–5 mL of methylene chloride), or titanium tetrachloride and titanium tetraisopropoxide were mixed together in 4–5 mL of methylene chloride at 0 °C in a 2n to 2n mmolar ratio and added to the mixture (for the acid chlorides and the imidazolides). The reaction mixture was stirred for 2–3 h at −78 °C and overnight at room temperature. Then the reaction was carefully quenched with aqueous sodium bicarbonate and extracted 5 times with ether. The ether solution was dried, concentrated, and purified through column chromatography (eluents: 20/80 to 40/60 ethyl acetate/petroleum ether v/v) to give the product (in ca. 25% yield for the acid chlorides, ca. 40% yield for the orthoesters, and ca. 50% for the imidazolides).

2,4-Dihydroxybenzoic acid, methyl ester (15a, R = H) was obtained in 35% yield from the condensation of **3** with trimethyl orthoformate: mp 117–118 °C (lit.[16] mp 118–119 °C).

2,4-Dihydroxy-6-methylbenzoic acid, methyl ester (orsellinic acid methyl ester, 15b, R = CH_3) was obtained in 35% yield from the condensation of **3** with trimethyl orthoacetate or in 48% yield from the condensation of **3** with acetylimidazolide: mp 144–145 °C (lit.[17] mp 142 °C).

2,4-Dihydroxy-6-ethylbenzoic acid, methyl ester (15c, R = Et) was obtained in 20% yield from the condensation of **3** with propionyl chloride: mp 113–115 °C; IR (KBr) 3000, 2500, 1640, 1610, 1440, 1160, 850; ^{1}H NMR (acetone-d_6) δ 0.9 (t, J = 7 Hz, 3 H), 2.5 (q, J = 7 Hz, 2 H), 3.6 (s, 3 H), 6.0 (s, 2 H); MS, 196 (M^+, 40), 164 (100), 136 (54), 121 (37); exact mass for $C_{10}H_{12}O_4$ found 196.073, calcd 196.074. Anal. Found for $C_{10}H_{12}O_4$: C, 61.28; H, 6.17. Calcd: C, 61.26; H, 6.17.

2,4-Dihydroxy-6-(dichloromethyl)benzoic acid, methyl ester (15d, R = $CHCl_2$) was obtained in 35% yield from the condensation of **3** with dichloroacetylchloride: mp 120–122 °C; IR (KBr) 1650, 1620, 1590, 1330, 1260, 940; ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 6.4 (d, J = 3 Hz, 1 H), 7.0 (d, J = 3 Hz, 1 H), 7.7 (s, 1 H), 9.6 (s, 1 H), 11.2 (s, 1 H); MS, 250/252 (M^+, 18/32), 220 (36), 218 (61), 104 (26), 28 (100); exact mass for $C_9H_8O_4Cl_2$ found 249.980, calcd 249.980. Anal. Found for $C_9H_8O_4Cl_2$: C, 43.13; H, 3.48. Calcd: C, 43.24; H, 3.23.

2,4-Dihydroxy-6-n-butylbenzoic acid, methyl ester (15e, R = n-C_4H_9) was obtained in 22% yield from the condensation of **3** with pentanoyl chloride or in 38% yield from the orthoester: mp 90–92 °C; IR (KBr) 2960, 2940, 1650, 1620, 1580, 1320, 1260; ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 3 H), 1.2–1.6 (broad, 4 H), 2.8 (m, 2 H), 3.9 (s, 3 H), 6.2 (s, 2 H), 11.8 (s, 1 H); MS, 224 (M^+, 61), 192 (76), 182 (50), 163 (29), 150 (100); exact mass for $C_{12}H_{16}O_4$ found 224.105, calcd 224.105.

2,4-Dihydroxy-6-n-hexylbenzoic acid, methyl ester (15f, R = n-C_6H_{13}) was obtained in 20% yield from the condensation of **3** with heptanoyl chloride: IR (neat) 2960, 2940, 2880, 2860, 1740, 1650, 1110, 900; ^{1}H NMR ($CDCl_3$) δ 0.9 (s, 3 H), 1.0–1.6 (b, 8 H), 2.6–2.9 (m, 3 H), 3.9 (s, 3 H), 6.2 (s, 2 H), 11.4 (s, 1 H); MS, 252 (M^+, 27), 220 (44), 182 (55), 150 (44); exact mass for $C_{14}H_{20}O_4$ found 252.136, calcd 252.136.

2,4-Dihydroxy-6-n-octylbenzoic acid, methyl ester (15g, R = n-C_8H_{17}) was obtained in 22% yield from the condensation of **3** with nonanoyl chloride and in 49% yield from the imidazolide: IR (neat) 2960, 1940, 2880, 2860, 1650, 800; ^{1}H NMR ($CDCl_3$) δ 0.8–1.8 (m, 15 H), 2.7–3.1 (m, 2 H), 3.9 (s, 3 H), 6.2 (s, 3 H); MS, 280 (M^+, 3), 149 (18), 141 (36), 116 (62), 100 (45), 85 (51), 28 (100); exact mass for $C_{16}H_{24}O_4$ found 280.169, calcd 280.167.

2,4-Dihydroxy-6-n-propylbenzoic acid, methyl ester (15h, R = n-C_3H_9) was obtained in 23% yield from the condensation of **3** and butanoyl chloride and in 35% yield from the orthoester: mp 82–84 °C (lit.[19] mp 78 °C).

2,4-Dihydroxy-6-n-pentylbenzoic acid, methyl ester (15i, R = n-C_5H_{11}, methyl olivetolate) was obtained in 21% yield from the condensation of **3** and hexanoyl chloride and in 52% yield from the imidazolide: IR (neat) 2960, 2860, 1650, 790; ^{1}H NMR ($CDCl_3$) δ 0.9 (s, 3 H), 1.2–1.7 (b, 6 H), 2.8 (m, 2 H), 4.0 (s, 3 H), 6.2 (s, 2 H); MS, 238 (M^+, 47), 206 (47), 199 (29), 182 (54), 150 (49); exact mass for $C_{13}H_{18}O_4$ found 238.119, calcd 238.117.

Methyl 2,4,6-Trihydroxybenzoate (18). In a 25-mL flask, 2.25 mmol (0.365 g) of 1,1′-carbonyldiimidazole was added. Then 10 mL of methylene chloride was added and the solution was cooled to −78 °C. The tris silyl enol ether **3** was added (2.25 mmol, 0.9 mL). The mixture of catalysts was then added: titanium(IV) tetrachloride (4.5 mmol, 0.50 mL) and titanium(IV) tetraisopropoxide (4.5 mmol, 1.5 mL) (the catalysts were mixed at 0 °C in 5 mL of methylene chloride). The mixture was stirred at −78 °C for 5 h and overnight at room temperature. It was quenched with sodium bicarbonate solution and extracted with ether. The ether solution was dried and purified by column chromatography with 35:65 ethyl acetate/petroleum ether as solvent to give 47% isolated yield of methyl 2,4,6-trihydroxybenzoate: mp 176–177 °C (lit.[20] mp 174–176 °C).

Preparation of the Imidazolides. The imidazolides were prepared according to literature procedure:[18] the acid chloride and imidazole were mixed in a one to two molar ratio in THF and stirred for 15 h at room temperature. The resulting precipitate of imidazolinium chloride was discarded and the filtrate concentrated to give the product, which was often used crude. If desired, the imidazolide may be recrystallized from ethyl acetate/petroleum ether. The structures of all the imidazolides were checked by NMR.

Preparation of Other Azolides. 1,2,4-Propionyltriazole was prepared in a manner similar to the preparation of the imidazolides except that 1,2,4-triazole was used instead of imidazole. Propionylbenzimidazole and propionylbenzotriazole were prepared in a similar fashion. All the structures were checked by NMR.

Improved General Method for the 5C + 1C Condensation Involving 3 and the Imidazolides. The same order of addition as before was used but the proportion of the reagents was changed as follows: a ratio of 1:2:4:4 of imidazolide/silyl enol ether/titanium tetrachloride/titanium tetraisopropoxide was used (molar ratios). In this way, the yield of aromatic product can be increased to about 75%.

Preparation of 8-Nonenoylimidazole (20) from 8-Bromo-1-octene. This transformation was accomplished in four stages: (i) To a solution of sodium cyanide in water (4.5 g, 92 mmol in 20 mL) was added dropwise a solution of 8-bromo-1-octene in methanol using a dropping funnel (11.4 mL, 68 mmol in 110 mL). The mixture was refluxed for 46 h. The solvent was evaporated under reduced pressure and the residue extracted with ethyl acetate, dried, filtered, and concentrated to give the nitrile: IR (neat) 3080, 2950, 2930, 2240, 910; ^{1}H NMR ($CDCl_3$) δ 10.5 (b, 1 H), 5.5–6.2 (m, 1 H), 4.9–5.2 (m, 1 H), 4.8 (m, 1 H), 1.2–2.4 (b, 12 H).

(ii) To a solution of KOH (35 g in 105 mL of ethanol and 35 mL of water) was added the nitrile, and the mixture was heated to reflux for 4 days. The mixture was extracted with ether, dried, filtered, and concentrated to give 8-nonenoic acid in 50% yield starting from the bromide: IR (neat) 3080, 2950, 2930, 1700, 910; ^{1}H NMR ($CDCl_3$) δ 5.5–6.2 (m, 1 H), 4.9–5.2 (m, 1 H), 4.8 (m, 1 H), 1.2–2.4 (b, 12 H).

(iii) The 8-nonenoic acid was dissolved in 100 mL of dry benzene, and oxalyl chloride was added (35 mmol, 3.05 mL). The mixture was refluxed for 2 h and allowed to cool, and the solvent was removed on the rotavap to give 8-nonenoyl chloride (5.62 g,

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32.2 mmol, 94% from the acid): IR (neat) 3080, 2950, 2930, 1730, 910; ^{1}H NMR ($CDCl_3$) δ 5.4–6.1 (m, 1 H), 4.8–5.1 (m, 2 H), 4.7 (m, 1 H), 2.6–2.9 (t, J = 8 Hz, 2 H), 1.1–2.2 (b, 10 H).

(iv) To 8-nonenoyl chloride was added 100 mL of dry THF and 4.38 g (64.4 mmol) of imidazole. The mixture was stirred overnight at room temperature, filtered, concentrated, and recrystallized from hexanes–ethyl acetate to give 8-nonenoylimidazole (80% yield): mp 43–45 °C; IR (neat) 3080, 2950, 2930, 1680, 910; ^{1}H NMR ($CDCl_3$) δ 8.1 (s, 1 H), 7.4 (s, 1 H), 7.0 (s, 1 H), 5.7–5.9 (m, 1 H), 4.8–5.1 (m, 3 H), 2.6–2.8 (t, J = 7 Hz, 2 H), 1.9–2.1 (b, 2 H), 1.6–1.9 (b, 2 H), 1.2–1.5 (b, 8 H); MS, 206 (M^+, 3), 138 (23), 96 (48), 84 (25), 68 (100), 60 (30), 55 (70), 54 (21); exact mass for $C_{12}H_{18}N_2O$ found 206.143, calcd 206.142.

2,4-Dihydroxy-6-(7-octenyl)benzoic Acid, Methyl Ester (21). The title compound was obtained in 75% yield from the condensation of the tris silyl enol ether **3** and the imidazolide **20**. The product was purified with flash chromatography using 35:65 ether/petroleum ether as eluent: IR (neat) 2920, 2840, 1710, 1100; ^{1}H NMR ($CDCl_3$) δ 6.2 (b, 2 H), 5.2–6.0 (m, 1 H), 4.8 (b, 1 H), 5.2 (b, 1 H), 3.9 (s, 3 H), 2.6–3.0 (b, 2 H), 1.7–2.2 (b, 2 H), 1.1–1.7 (b, 8 H); MS, 278 (M^+, 21), 230 (24), 182 (58), 163 (37), 150 (37), 28 (100); exact mass for $C_{16}H_{22}O_4$ found 278.152, calcd 278.152.

Methyl 4-(Benzyloxy)-2-methoxy-6-(7-octenyl)benzoate (22). 2,4-Dihydroxy-6-(7-octenyl)benzoic acid, methyl ester (**21**) was subjected to benzylation to selectively give the 4-benzyl derivative: to a solution of 0.4 mmol of the 2,4-dihydroxy compound in acetone (2 mL) and anhydrous potassium carbonate (4 mmol, 0.6 g) was added 0.4 mmol of benzyl bromide in 1 mL acetone during 0.5 h. The reaction was left stirring overnight at room temperature and was purified by using column chromatography with 10:90 ether/petroleum ether to give 80 mg (60%) of the 4-benzyloxy derivative: ^{1}H NMR ($CDCl_3$) δ 11.7 (s, 1 H), 7.3 (m, 5 H), 6.4 (q, J = 2 Hz, 2 H), 5.9 (m, 2 H), 5.1 (s, 2 H), 5.0 (b, 2 H), 4.9 (b, 1 H), 3.9 (s, 3 H), 2.8 (t, J = 2 Hz, 2 H), 2.0 (m, 2 H), 1.4–1.7 (b, 8 H).

The 4-benzyloxy derivative was dissolved in acetone (20 mL), and dry potassium carbonate was added (6 mmol, 0.9 g), followed by excess dimethyl sulfate (1 mmol, 0.1 mL). The mixture was refluxed for 15 h. The mixture was cooled, filtered, and evaporated to give 70 mg (90%) of the 2-methoxy-4-benzyloxy derivative: IR (neat) 3065, 3030, 1725, 1603, 1456, 1324, 1264, 1234, 1193, 1040, 958, 942, 910, 831; ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 6.4 (s, 2 H), 5.5–6.2 (m, 1 H), 5.1 (s, 2 H), 5.0 (b, 2 H), 4.9 (b, 1 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 2.4–2.7 (b, 2 H), 1.0–2.2 (b, 10 H); MS, 382 (M^+, 16), 286 (12), 196 (11), 163 (17), 149 (28), 91 (100), 92 (27); exact mass for $C_{24}H_{30}O_4$ found 382.209, calcd 382.214.

Acknowledgment. We thank NSERC and FCAC for financial support of this work. D.S. thanks NSERC for the award of a scholarship.

Registry No. **3**, 102342-54-1; **5**, 29736-80-9; **7**, 102342-55-2; **8**, 102342-56-3; **9**, 102342-53-0; **10**, 102342-57-4; **11**, 102342-58-5; **12**, 102-52-3; **13**, 77527-00-5; **14**, 102342-59-6; **15a**, 2150-47-2; **15b**, 3187-58-4; **15c**, 102342-60-9; **15d**, 102342-61-0; **15e**, 102342-62-1; **15f**, 102342-63-2; **15g**, 102342-64-3; **15h**, 55382-52-0; **15i**, 58016-28-7; **16b**, 2466-76-4; **16g**, 102342-65-4; **16i**, 60988-34-3; **18**, 3147-39-5; **19**, 32885-81-7; **20**, 102342-67-6; **21**, 102342-68-7; **21** (4-benzyloxy deriv.), 102342-69-8; **22**, 71819-29-9; $HyC(OHe)_3$, 149-73-5; $CH_3C(OMe)_3$, 1445-45-0; C_2H_5COCl, 79-03-8; $Cl_2CHCOCE$, 79-36-7; *n*-BuCOCl, 638-29-9; *n*-$BuC(OMe)_3$, 13820-09-2; $CH_3(CH_2)_5COCl$, 2528-61-2; $CH_3(CH_2)_7COCl$, 764-85-2; *n*-PrCOCl, 141-75-3; *n*-$PrC(OMe)_3$, 43083-12-1; $CH_3(CH_2)_4COCl$, 142-61-0; $Br(CH_2)_6CH{=}CH_2$, 2695-48-9; $NC(CH_2)_6CH{=}CH_2$, 5048-34-0; $HOOC(CH_2)_6CH{=}CH_2$, 31642-67-8; $ClCO(CH_2)_6CH{=}CH_2$, 102342-66-5.

Synthesis of Oxygenated Metabolites of Indeno[1,2,3-*cd*]pyrene

Joseph E. Rice* and Edmond J. LaVoie

Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595

Dan J. McCaustland,† Daniel L. Fischer, and James C. Wiley, Jr.

Chemsyn Science Laboratories, Lenexa, Kansas 66215

Received December 20, 1985

The syntheses of *cis*- and *trans*-1,2-dihydro-1,2-dihydroxyindeno[1,2,3-*cd*]pyrene, 1,2-dihydroindeno[1,2,3-*cd*]pyrene 1,2-epoxide, and 1-, 2-, 6-, 7-, 8-, 9-, and 10-hydroxyindeno[1,2,3-*cd*]pyrene are described. UV and high-resolution NMR spectral data are reported for each compound synthesized.

Indeno[1,2,3-*cd*]pyrene (1) (Figure 1) has been detected throughout the environment in automobile and diesel engine exhaust, coal-derived liquids, river sediments, ground water, charcoal-broiled foods, and cigarette smoke condensate.[1-7] Indeno[1,2,3-*cd*]pyrene is listed as a priority pollutant by the Environmental Protection Agency and has been recommended for analysis by the World Health Organization's European Standards for Drinking Water.[8] This compound has been shown to be active as a carcinogen both on mouse skin and in rat lung.[9-12]

Recently we have undertaken a study on the metabolism and mechanism of activation of 1 to a carcinogen.[13-16] The availability of synthetic reference samples of indeno[1,2,3-*cd*]pyrene metabolites is essential to these studies. In this paper we describe the synthesis of the major metabolites of 1 as formed both in vitro in rat liver homogenate and in vivo in mouse skin.

† Formerly with Midwest Research Institute, Kansas City, MO.

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