under nitrogen for 15 h. The solvent was evaporated, and the product mixture was chromatographed on silica gel with 5% ether–hexane as an intial eluent. The first fraction afforded a mixture of **13** and **14** that was separated on GC. The first product was **13** (0.41 g, 21%): IR (film) 2940 (C–H), 1670, 810 cm^{-1} (C=CH); ^1H NMR δ 5.31 (t, 1, 2 H), 2.6–1.4 (m, 6, 3 H, 4 H, and 5 H), 1.3, 1.25, 1.00, 0.95, 0.90 (s, 3 each, five methyls); mass spectrum, *m/e* (rel intensity) 178 (M^+, 28) 163 (M – CH_3, 7), 135 (100), 121 (7), 119 (7), 107 (35), 96 (35), 93 (38), 91 (15), 81 (34), 79 (22); high-resolution mass spectrum calculated for $C_{13}H_{22}$ 178.1724, found 178.1735. The second product was 1-isopropenyl-6-isopropyl-6-methylcyclohexene (**14**) (0.17 g, 9%): ^1H NMR δ 5.57 (t, 1, 2 H), 4.73 (m, 2, isopropenyl olefinic protons), 1.88 (s, 3, isopropenyl methyl), 1.2 (s, 3, 6-methyl), 0.85, 0.78 (d, 3 each, isopropyl methyls); UV (MeOH) λ_{max} 228 nm (ϵ 8080); mass spectrum, *m/e* (relative intensity), 178 (M^+, 15), 165 (7), 135 (100), 119 (28), 107 (47), 105 (11), 93 (49), 91 (31); high-resolution mass spectrum calculated for $C_{13}H_{22}$ 178.1724, found 178.1725.

Further elution afforded starting material **11** (1 g, 50%) and finally **12** (0.12 g, 6%): ^1H NMR δ 3:1 (t, 1, 5 H), 1.81, 1.64 (s, 3 each, olefinic methyls), 1.2 (s, 3, methyl on C-1), 0.98, 0.89 (s, 3 each, methyls on C-7); mass spectrum, *m/e* (relative intensity) 206 (M^+, 92), 191 (M– CH_3, 100), 178 (M – CO, 26), 163 (M– CH_3, CO, 62), 150 (31), 121 (77), 107 (72), 93 (88), 91 (98); high-resolution mass spectrum calculated for $C_{14}H_{22}O$ 206.1671, found 206.1694.

Irradiation of **12** for about 5 h and analysis of the product mixture by GC showed the formation of **11** together with other photolysis products.

4,4,15,15,17,17-Hexamethylandrost-8(14)-en-16-one (15). To a suspension of potassium hydride (26% in oil, ~0.3 g) in dimethoxyethane (25 mL) was added **3** (200 mg) and the mixture was refluxed under nitrogen for 3 h. The mixture was cooled to room temperature and then methyl iodide (4 mL) was added and the mixture was stirred at room temperature under nitrogen overnight. The excess potassium hydride was destroyed by slow addition of water and the product was extracted with ether. The ether dried ($MgSO_4$) and was evaporated to leave an oil which was flash chromatographed over silica, using hexane and then 10% ether–hexane, to afford **15**. Recrystallization from ether–methanol gave the pure material (165 mg, 70%): mp 147–149 °C; IR (KBr) 1740 cm^{-1} (C=O); UV (MeOH) λ_{max} 300 (ϵ 40); ^1H NMR (recorded on a Bruker WH-360/180 NMR spectrometer) δ 1.35 (s, 3), 1.25 (s, 3), 0.93 (s, 6), 0.91 (s, 3), 0.89 (s, 3), 0.86 (s, 3), 0.83 (s, 3); mass spectrum, *m/e* (rel intensity) 356 (M^+, 50), 341 (M – CH_3, 28), 232 (20), 217 (14), 216 (13), 204 (10), 202 (11), 191 (18), 137 (100), metastable peak at 326.6 (356 → 341).

Anal. Calcd for $C_{25}H_{40}O$: C, 84.27; H, 11.23. Found: C, 84.09; H, 10.97.

Photolysis of 4,4,15,15,17,17-Hexamethylandrost-8(14)-en-16-one (15). Photolysis of **15** in pentane, methanol, and acetone for 40 h proceeded with the slow disappearance of starting material but no new products could be identified.

Photolysis of 4,4-Dimethylandrost-8(14)-en-17-one (16b). A solution of **16b**[2] (100 mg) [λ_{max} 292 (ϵ 55) (MeOH)] in anhydrous benzene (100 mL) was stirred with a stream of nitrogen and was irradiated with a 450-W Hanovia lamp through a Pyrex filter. The course of the reaction was followed by removing small aliquots at various intervals and examining them by GC. After 15 min, a photostationary state consisting of approximately 14% of **17**, 6% of **16a** and 78% of **16b** was attained. A total of 500 mg of this mixture from combined runs was chromatographed on preparative scale thin-layer silica plates. Elution with 10% ether–hexane afforded 60 mg of pure **17** (14%), which was recrystallized from ether–methanol; mp 150–151 °C; IR (KBr) 1740 (C=O), 1665 cm^{-1} (C=C); UV (MeOH) λ_{max} 297.5 (ϵ 31); ^1H NMR δ 2.56 (m, 4, 15 H and 16 H), 1.68 (br s, 3, 18 H), 0.93 (s, 3, 21 H), 0.88 (s, 3, 20 H), 0.80 (s, 3, 19 H); mass spectrum, *m/e* (rel intensity) 300 (M^+, 53), 285 (M – CH_3, 9), 272 (M – CO, 12), 257 (11), 243 (12), 187 (11), 176 (20), 150 (37), 137 (100).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.74. Found: C, 84.3; H, 10.69.

The second product was extracted with ethyl acetate and yielded 18 mg of **16a** (6%); mp 120–121 °C; IR (KBr) 1745 cm^{-1}; ^1H NMR δ 1.23 (s, 3, 18 H), 0.88 (s, 6, 20 H and 21 H), 0.81 (s, 3, 19 H); mass spectrum, *m/e* (rel intensity) 300 (M^+, 91), 285 (34), 272 (8), 257 (8), 243 (5), 190 (16), 176 (47), 150 (45), 137 (100); high-resolution mass spectrum calculated for $C_{21}H_{32}O$ 300.2453, found 300.2442; $[\alpha]_D$ –108.6° ($CHCl_3$); CD ($CHCl_3$) $[\theta]_{306}$ –3806 deg cm^2 $dmol^{-1}$; $\Delta\epsilon$ –1.15.

The third material isolated ws unreacted **16b** (390 mg, 78%).

Irradiation of **17** foı 15 min also gave a mixture of **16b**, **17**, and **16a**, in which **16b** was the major product.

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Registry No. **3**, 81535-11-7; **5a**, 6560-99-2; **5b**, 81535-12-8; **5c**, 81535-13-9; **5d**, 81535-14-0; **5e**, 81535-15-1; **5f**, 81535-16-2; **5g**, 81535-17-3; **6**, 81535-18-4; **7a**, 81535-19-5; **7b**, 81535-20-8; **8a**, 81535-21-9; **8b**, 81600-19-3; **9**, 81535-22-0; **10**, 81535-23-1; **11**, 81535-24-2; **12**, 81535-25-3; **13**, 81535-26-4; **14**, 81535-27-5; **15**, 81553-84-6; **16a**, 81600-20-6; **16b**, 66500-27-4; **17**, 81535-28-6; 17β-hydroxy-4,4-dimethylandrost-5-ene, 6560-97-0; 4,4-dimethylandrost-7-en-16β-yl benzoate, 81535-29-7; 4,4-dimethylandrost-7-en-16-ol, 81535-30-0; 1,3a-dimethyl-4,5,6,7-tetrahydroindan-2-one, 60415-97-6.

Total Synthesis of Frustulosin and Aurocitrin

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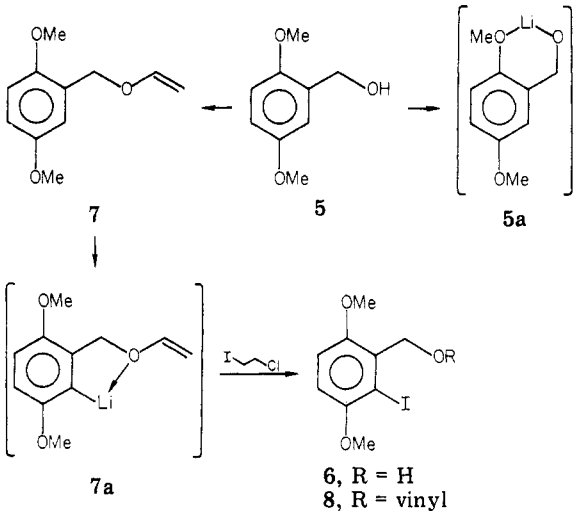
The regioselective total syntheses of the novel fungal antibiotics frustulosin (**1**) and aurocitrin (**2**) were accomplished from 3,6-dihydroxy-2-iodobenzaldehyde (**10**) which was prepared by a regiodirected metalation of 2,5-dimethylbenzyl vinyl ether to establish the 1,2,3,4-tetrasubstitution pattern of these compounds. The unsaturated side chains of these hydroquinone antibiotics were attached by using the iodo aldehyde functionalities. The structures of these antibiotics are confirmed by synthesis.

Frustulosin (**1**)[1,2] and aurocitrin (**2**)[3] are two hydroquinone antibiotics recently isolated by Nair and coworkers from fungal sources. Frustulosin and related compounds were obtained from *Stereum frustulosum*; aurocitrin was obtained from *Hypocrea citrina*. These

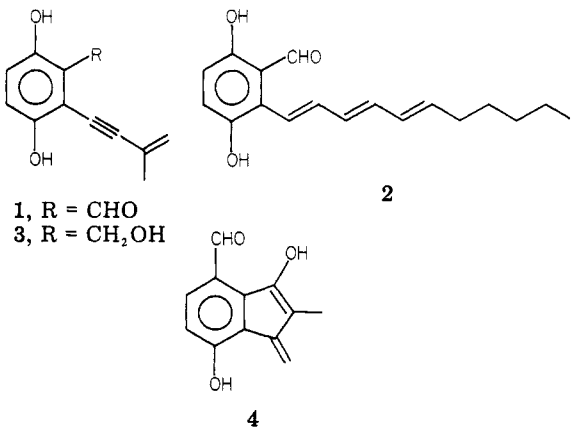
(1) Nair, M. S.; Anchel, M. *Tetrahedron Lett.* **1975**, 2641–2642.
(2) Nair, M. S.; Nachel, M. *Phytochemistry* **1977**, 16, 390–392.
(3) Nair, M. S.; Carey, S T. *Tetrahedron Lett.* **1979**, 3233–3236.

0022-3263/82/1947-2541$01.25/0

Scheme I



antibiotics have a relatively broad spectrum of antimicrobial activities, inhibiting *Staphylococcus aureus*, several *Bacilli*, and *Vibrio cholera* in the microgram per milliliter concentration range. The structures of these compounds were determined by a combination of spectral and chemical investigations. Originally, frustulosin was formulated as the unusual benzofulvene 4[1], but subsequent work re-



sulted in revision to the acetylenic structure 1. This was confirmed independently by two groups.[4,5] We describe herein regioselective total syntheses of frustulosin (1)[4] and aurocitrin (2) from a common intermediate readily obtained by a regiodirected metalation. This work also confirms the structure proposed by Nair and Carey[3] for aurocitrin.

Our initial synthetic strategy was prompted by two series of reports: the first described the regiodirected lithiation of 3-methoxybenzyl alcohols to afford the more sterically hindered phthalides on carbonation;[6] the second was catalytic substitution of aryl iodides with terminal acetylenes to afford arylacetylenes in high yield.[7] Our intention was to use the regiodirected metalation of an appropriately substituted benzyl alcohol to introduce regioselectively an iodo substituent between the hydroxymethyl and methoxyl substituent and then to use the iodo group as the point of attachment for the side chains.

While preliminary studies with 3-methoxybenzyl alcohol showed that metalation employing Uemura's conditions (*n*-BuLi–TMEDA) followed by quenching with iodine afforded 2-iodo-3-methoxybenzyl alcohol, albiet in only modest yields, application of this method to 2,5-dimethoxybenzyl alcohol (**5**) failed to produce any of the desired iodo derivative **6** (Scheme I). Upon closer examination it became apparent that the *o*-methoxy group was coordinating the lithium benzyl alkoxide **5a** and preventing the desired ring metalation from occurring. When tetrahydrofuran was used as a solvent instead of hexane, the ring metalation occurred rapidly with concomitant formation of a deep red color; however, the metalation was not regioselective, and 35:27 mixture of 2- and 4-iodo derivatives was obtained. Incidently, the formation of the deep red color upon ring metalation makes 2,5-dimethoxybenzyl alcohol a highly useful self-indicating primary standard for the determination of organolithium reagents.[8]

To avoid the problems associated with alkoxide formation, we protected the hydroxyl as the vinyl ether **7** by transvinylation with a tenfold excess of ethyl vinyl ether in the presence of a catalytic amount of mercuric acetate. Although under these conditions only a 60–70% conversion could be achieved, the vinyl ether **7** was easily separated from unreacted alcohol by filtration through silica gel with dichloromethane as an eluant. Of the various common hydroxyl protecting groups, only the vinyl ether proved to be stable to the subsequent metalation conditions: silyl ethers and methoxymethyl ethers were cleaved readily to the alkoxides during attempted metalation.

With protection of the hydroxyl group the benzylic protons became more susceptible to attack by the metalating reagent (*n*-BuLi–TMEDA), resulting in poor yields of ring-metalated product. After several trials it was found that *n*-butyllithium in pentane at 0 °C resulted in the slow formation of a yellow-brown granular precipitate that was principally the desired metalated species **7a**. An excess of *n*-butyllithium and at least 6 h were required for maximal conversion to the anion **7a**. More powerful metalating species such as *tert*-butyllithium, higher temperatures, or ethereal solvents (ether, THF) resulted in very poor conversions. After metalation in pentane was complete, the precipitate was allowed to settle, and then the supernatant was drawn off, leaving a yellow-brown residue. This material was readily soluble in ether or tetrahydrofuran, and solutions appeared to be quite stable. Unreacted **7** could be recovered from the supernatant.

Reaction of **7a** with iodine[9] (I_2) resulted in a mixture of the iodovinyl ether **8** contaminated with significant amounts of **6** in which the vinyl ether had been cleaved. Furthermore, the yields were unacceptably low (10–15%), and large amounts of **5** and **7** were recovered. Since care was taken to ensure that acidic conditions were avoided in the workup, it was clear that cleavage of the vinyl ether was occurring by attack of the iodine on the highly reactive vinyl ether. When a less electrophilic halogen–metal exchange reagent was employed such as *tert*-butyl iodoacetate, the yield of **8** rose to 20–30%; although lithium–hydrogen exchange seriously competed with iodination, large amounts of **7** were obtained. Significantly, the cleavage of the vinyl ether was eliminated. The lithium–hydrogen exchange reaction was finally suppressed by iodination with ethylene iodochloride.[10]

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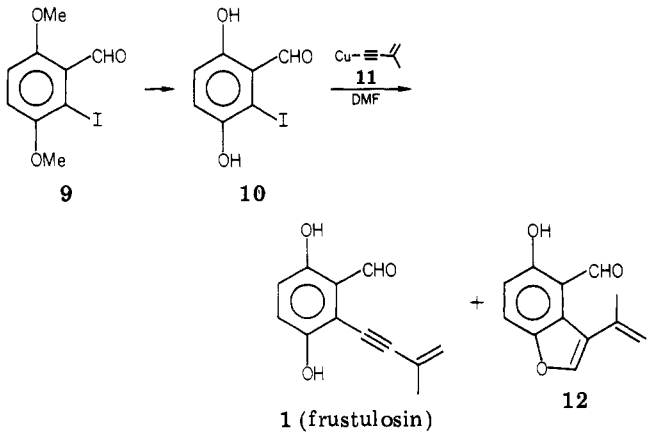
Scheme II



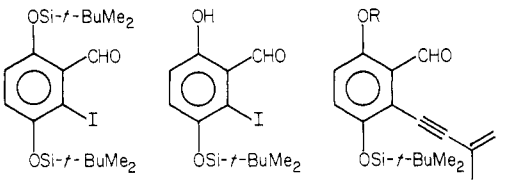
This reagent was conveniently prepared by bubbling ethylene into a dichloromethane solution of freshly distilled iodine monochloride. When an ethereal solution of anion **7a** was treated with 1.1 equiv of ethylene iodochloride at room temperature, there was a rapid evolution of a gas (ethylene) and formation of a white precipitate (LiCl). Column chromatography of the product on silica gel afforded a 54% yield of crystalline **8** (mp 68–72 °C). The vinyl protecting group was then removed by treatment with dilute aqueous HCl in aqueous tetrahydrofuran to afford the iodo alcohol **6** as slightly tan prisms from CH_2Cl_2–hexane (mp 108.5–110 °C). A somewhat higher yield procedure involves cleavage of the vinyl group in methanol by using $Hg(OAc)_2$ (reverse transvinylation); however, care must be taken to remove acid impurities or a mixed methyl acetal results.

Oxidation of the iodobenzyl alcohol **6** to the aldehyde **9** was readily accomplished with pyridinium chlorochromate in 1:1 dichloromethane–acetone at room temperature. Acetone was used as a cosolvent for the benzyl alcohol; however, dichloromethane was required to achieve oxidation. The oxidation required 2 equiv of reagent and 24 h for completion (83% yield). If 5 equiv of oxidant was employed, the reaction required about 50 min, and a 73% yield of **9** was obtained. There was no evidence of any overoxidation.

Removal of the methoxy groups afforded the key dihydroxyiodobenzaldehyde **10** (Scheme II), the central intermediate for the synthesis of frustulosin (**1**) and aurocitrin (**2**). In model studies with 2-iodo-3-methoxybenzaldehyde, demethylation with boron tribromide resulted in the formation of benzal bromides.[11] These studies led us to investigate boron triiodide for the demethylation of methoxy aldehydes under mild conditions.[11] Treatment of **9** with a 1 M solution of BI_3 in dichloromethane at room temperature for 105 s resulted in complete removal of the methyl groups. Chromatography of the crude product oil afforded the yellow crystalline aldehyde **10** in 46% yield. In our studies on the synthesis of benzal bromides with BBr_3 we had observed that the presence of an *o*-methoxy substituent made these compounds relatively unstable with respect to hydrolysis to the aldehydes. Thus, we investigated the reaction of **10** with BBr_3 and found that at 0 °C mainly the methoxyl ortho to the carboxaldehyde was removed after 50 min with less than 2 equiv of reagent. This selectivity was similar to that observed with BCl_3.[12] With an excess of reagent at room temperature both methyl ethers were cleaved within 4 h.

The dihydroxy aldehyde **10** proved to be extremely labile in base which, unfortunately, precluded the use of the excellent catalytic methods for side-chain introduction by using low-valent palladium complexes.[7] Even in diethylamine the iodo aldehyde was instantly and irreversibly degraded to a reddish brown polymeric material. Substitution of the iodine was accomplished by using Castro's method.[13] Treatment of **10** with copper(I) isopropenylacetylide (**11**) in DMF resulted in the slow formation of two less polar products (Scheme II). After 2 h at 70–90 °C the more polar product, which corresponded to frustulosin[14] by thin-layer chromatography, reached a maximum concentration. The reaction temperature was critical; below 70 °C the substitution did not occur, and above 90 °C there was exclusive formation of a less polar product which was shown to be the benzofuran **12**. By this method about 35% yield of frustulosin was obtained after chromatography and recrystallization.

To minimize formation of the benzofuran **12** during the coupling step, we masked the phenolic hydroxyls with the *tert*-butyldimethylsilyl group. Treatment of the iodo aldehyde **10** with *tert*-butyldimethylsilyl chloride in DMF with imidazole as the catalyst afforded the disilyl derivative **13** in 74% yield after recrystallization. The hydroxyl group



ortho to the aldehyde carbonyl was the most difficult to derivatize, presumably due to hydrogen bonding, and required a 45–55 °C reaction temperature with excess reagent for completion. Although the monosilyl aldehyde **14** would probably have served for the synthesis or frustulosin, we also intended to use **13** as an intermediate for the synthesis of aurocitrin. Aldehydes **13** and **14** were indistinguishable by TLC, but **14** showed a distinct singlet for the hydrogen bonded phenol at δ 12.0 in the NMR spectrum. Aldehyde **14** exhibited a strong carbonyl band at 1640 cm^{-1} in the infrared; however, the hydroxyl band was so broadened as to be unobservable.

When the disilyl iodide **13** was treated with cuprous isopropenylacetylide in DMF at 90–110 °C for 2 h, it was converted to a yellow oily material, **15**, with identical TLC mobility as the starting material. Infrared analysis of this oil showed the presence of two carbonyl bands at 1685 and 1645 cm^{-1}, and the NMR spectrum showed a diminished signal for the silyl resonances, although the isopropenyl resonances relative to the aromatic protons appeared to be in the correct ratio. This strongly suggested that the silyl group ortho to the aldehyde carbonyl had been partially cleaved to form **15a**. As will be seen in the subsequent work with aurocitrin, the lability of the ortho siloxy group proved to be a serious difficulty. Attempts to minimize the silyl cleavage during the acetylide coupling met with little success. Lower reaction temperatures or shorter reaction time gave increased amounts of unreacted starting material. The coupling, however, appeared to

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(11) Lansinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341–349.
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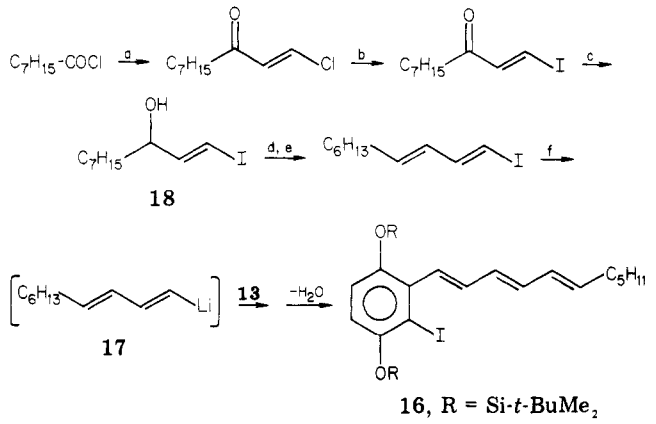
(14) WE thank Dr. Nair of the New York Botanical Garden, Bronx, NY for generous samples of both frustulosin and aurocitrin.

Scheme III[a]



[a] (a) C_2H_2, $AlCl_3$; (b) NaI, Me_2CO, H^+; (c) LAH, Et_2O; (d) HBr(aq); (e) DBU, CH_2Cl_2; (f) *t*-BuLi, −120 °C.

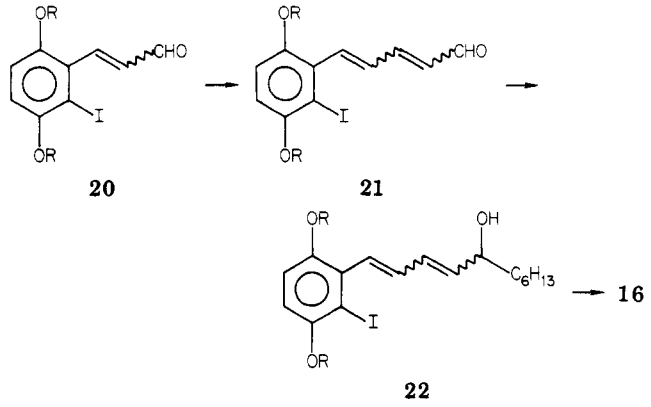
occur in about 90% yield as judged by the amount of frustulosin obtained after removal of the silyl groups from the crude reaction product.

Initially, treatment of the coupled product **15–15a** with tetra-*n*-butylammonium fluoride in tetrahydrofuran afforded only a small amount of frustulosin, even though the starting material had all reacted. Since frustulosin appears to be quite labile in basic solution, the increasing alkalinity of the reaction mixture due to the fluoride cleavage was suspected as the cause of the poor conversion. Indeed, when a small amount of acetic acid was added, a marked improvement in the amount of frustulosin produced was observed. With 2 equiv of fluoride in tetrahydrofuran–acetic acid (50:1) silyl removal was complete within 0.5 h, and a 92% yield of frustulosin[14] was obtained after preparative thin-layer chromatography.

Conversion of frustulosin to the related metabolite frustulosinol was accomplished by borohydride reduction. Although this reduction has been previously reported,[2,5] no experimental details have been published. When frustulosin was treated with borohydride in methanol at room temperature, only a trace of the desired alcohol was obtained. Reduced temperatures were shown to be beneficial, and we were able to develop a reproducible procedure for this reduction. Treatment of **1** with 1.0 equiv of $NaBH_4$ in methanol for 6 min at −78 °C resulted in a nearly complete reaction with only a trace of starting material remaining. Excess borohydride and/or longer reaction times resulted in reduced yields of **3**. Even so, **3** required extensive chromatography to yield a completely colorless crystalline product. Recrystallization from CH_2Cl_2–hexane afforded frustulosinol **3**: mp 88–89.5 °C;[2,14] 68% yield.

With successful synthesis of frustulosin (**1**) and frustulosinol (**3**), attention was turned to the conversion of the iodo aldehyde **13** to aurocitrin (**2**). The strategy for aurocitrin was to use the aldehyde carbonyl as the point of attachment of the side chain and then by a metalation procedure to use the iodine of the resulting undecatrienyl iodide **16** to afford the aldehyde carbonyl of aurocitrin (Scheme III). Initially, the decadienyllithium reagent **17** was selected since addition to the carbonyl would produce a readily dehydratable dienyl benzyl alcohol. The reagent was readily prepared by chlorovinylation of octanoyl chloride,[15] halogen exchange to the iodovinyl ketone (NaI/acetone, TsOH),[16] and reduction to the iodo alcohol

Scheme IV[a]



[a] R = Si-*t*-BuMe$_2$.

18 ($LiAlH_4/Et_2O$). Conversion of **18** to the extremely sensitive iodo diene was accomplished by bromination with saturated aqueous HBr at 0 °C, followed by dehydrohalogenation with DBU (2 equiv in CH_2Cl_2) and rapid filtration through silica gel with pentane as an eluant. The iododiene was extremely sensitive to heat and light, decomposing with liberation of iodine. It was converted to the dienyllithium reagent **17** by treatment with 2 equiv of *tert*-butyllithium at −120 °C.[17] When this reagent was allowed to react with the iodo aldehyde **13**, the principal products were those of halogen–metal exchange rather than carbonyl addition. Furthermore, the small amounts of carbonyl adducts that were obtained appeared to be phenolic, where the *tert*-butyldimethylsilyl group had migrated to the more basic benzyl alkoxide.[18]

To avoid the halogen–metal exchange reaction, we needed a more stabilized anion. The enolate of α-(trimethylsilyl)-*tert*-butylaldimine[19] added to the carbonyl of **13** at −78 °C to afford a complex mixture of products from which a 3:2 mixture of *trans*- and *cis*-cinnamaldehydes **20** was obtained in about 54% yield. As in the case with dienyllithium reagent, phenolic products were obtained, presumably arising from silyl migration from the phenolic oxygen. That silyl migration was a consequence of forming an alkoxide anion in the benzylic position, rather than due to hydrolytic cleavage of the silyl protecting group, was shown when the cinnamaldehydes **20** were subjected to the homologation procedure. Even though the product was a complex mixture of stereoisomers, the dienyl aldehyde structure **21** (Scheme IV) was produced in 89% yield, indicating that loss of the phenolic protecting group was due to silyl migration. Reaction of the dienylaldehyde with hexylmagnesium bromide resulted in the diethyl alcohol **22** which was dehydrated with concomitant isomerization by using a trace of iodine in refluxing benzene[20] to form the *trans*-trienyl iodide **16**. Dehydration of **22** with $POCl_3$/pyridine or $SOCl_2$/pyridine afforded mixtures of trienyl iodides which could be isomerized to a single isomer (by TLC) with iodine.

The synthesis of the trienyl iodide by this route was somewhat cumbersome and suffered from the loss of the

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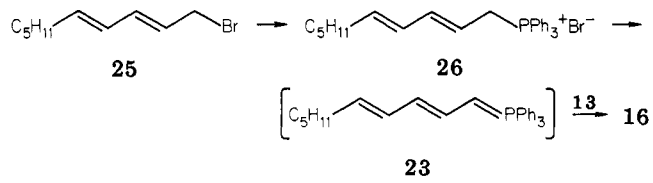
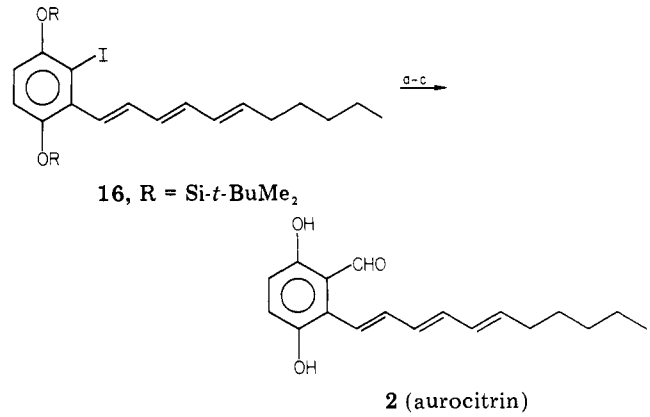
(20) Isler, O. U. S. Patent 2 451 739.

Scheme V



Scheme VI



silyl group in the first condensation step, which seriously affected the yield of the overall process. Furthermore, it was not a convergent approach to **16**. Since a stabilized anion was required to avoid halogen–metal exchange and intermediates in which the carbonyl adduct would collapse rapidly to avoid silyl migration were needed, we decided to investigate the Wittig reaction. The *all-trans*-decadienylphosphorane **23** does not seem to have been reported. The isomeric *trans,cis*-decadienylphosphorane had been prepared by a laborious route, but was reported to be inefficient in producing trienes by carbonyl addition.[21] The all-trans isomer was prepared from commercially available *trans,trans*-2,4-decadienal. Reduction with diisobutylaluminum hydride in ether afforded the *all-trans*-dienyl alcohol[22] **24** in 88% with apparently no over reduction to the saturated alcohols.

The alcohol was brominated with triphenylphosphine dibromide in CH_3CN at room temperature to yield the dienyl bromide **25** contaminated with a small amount of triene. When PBr_3 in lutidine was used, the triene was the major product. The dienyl bromide was readily separated from the triene by distillation at 50–55 °C (0.020 mm, Kugelrohr). This bromide does not appear to have been previously reported.

The dienyl bromide reacted readily with triphenylphosphine in tetrahydrofuran to form the phosphonium salt **26** (Scheme V) which crystallized when the solution was cooled to −78 °C. When the chilled solution was filtered and dried in vacuo for an extended period, white crystalline material (mp 55–59 °C) could be obtained in an 88% yield. Unless the phosphonium salt was protected from light and moisture it decomposed to a dark tarry mass.

Treatment of a slurry of the phosphonium salt in tetrahydrofuran at −78 °C with *n*-butyllithium resulted in the formation of the dark red-brown ylide **23**. At this temperature the phosphonium salt was slow to dissolve, and several hours were required for formation of the ylide. Addition of the iodo aldehyde **13** to the solution of the phosphorane **23** caused the ylide color to slowly fade, and from this reaction mixture could be obtained the iodo triene **16** after chromatography in 58% yield. This material appeared to be the all-trans isomer since treatment with I_2 in refluxing benzene produced no chromatographic or spectroscopic changes.

Aurocitrin (**2**) was obtained from iodo triene **16** (Scheme VI) by halogen–metal exchange with *n*-butyllithium in ether at −78 °C, followed by quenching of the intermediate aryllithium reagent with excess DMF. Thin-layer chromatography indicated that a complex mixture was obtained. Presumably this mixture was produced by the aforementioned silyl migrations, since the mixture was considerably simplified by treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran containing a trace of acetic acid. From this reaction mixture aurocitrin was obtained after chromatography on silica gel and recrystallization from hexane. The synthetic material was identical in all respects with an authentic sample of the natural antibiotic.[14]

16, R = Si-*t*-BuMe$_2$

2 (aurocitrin)

[a] (a) *n*-BuLi, Et_2O, −78 °C; (b) DMF; (c) *n*-$Bu_4N^+F^-$, AcOH, THF.

Experimental Section

General Methods. Melting point determinations were made in sealed evacuated capillaries by using a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on Beckman Model IR 18 or on Acculab 1 spectrophotometers. Spectra of liquid samples were obtained as films and of solid samples as KBr mulls unless otherwise noted. Nuclear magnetic resonance spectra were obtained in CCl_4 or $CDCl_3$ solution containing tetramethylsilane as an internal standard on either a Varian Associates Model EM-360 spectrophotometer or a Bruker WH 90 spectrophotometer. Gas chromatograms were obtained on a Packard-Becker Model 417 gas chromatograph using a 3 mm × 2.6 m glass column packed with 3% OV-17 on 80/100 Chromosorb W HP. Analytical thin-layer chromatograms were run on Merck precoated silica plates with 250-μm layers. Preparative thin-layer chromatograms were run on 20 × 20 cm plates coated with a 1.6-mm layer of Merck silica gel PF 254. Column chromatography was performed in a pumped system by using Merck 0.040–0.063-nm (230–400 mesh) silica gel 60 which was slurry packed into commercial glass columns. Combustion analyses were performed by Galbraith Laboratories.

2,5-Dimethoxybenzyl Vinyl Ether (7). A solution of 28.2 g (0.168 mol) of crude 2,5-dimethoxybenzyl alcohol (**5**) and mercury acetate (1.5 g, 4.8 mmol) in ethyl vinyl ether (Aldrich; 200 mL, 2.1 mol) was refluxed for 2 days. Unreacted ethyl vinyl ether was removed by distillation, and the residue was diluted with ether and washed with aqueous K_2CO_3. The ether solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to afford 31.5 g of a mixture of **5** and **7**. The mixture was chromatographed on 175 g of 60–200-mesh silica gel. The vinyl ether **7** eluted in the first 1.5 L of CH_2Cl_2 followed by the alcohol **5** in 1 L of 35% ether–65% dichloromethane. The vinyl ether fraction was concentrated and distilled at 90–99 °C (0.3 mm) to afford 19.2 g (60%) of clear colorless **7**. Concentration of the alcohol fractions afforded recovery of 9.87 g of **5**. Vinyl ether **7** had the following: NMR (CCl_4) δ 7.0 (s, 1 H), 6.85 (d, 2 H), 6.8–6.4 (q, 1 H), 4.85 (s, 1 H), 4.55–3.95 (m, 2 H), 3.88 (s, 3 H), 3.84 (s, 3 H); IR (neat) 3005, 2905, 2920, 2850, 1660, 1640, 1635, 1620, 1610, 1500, 1470, 1460, 1455, 1435, 1380, 1370, 1320, 1280, 1220, 1050, 1030, 810, 715 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.04; H, 7.22.

2-Iodo-3,6-dimethoxybenzyl Vinyl Ether (8). 2,5-Dimethoxybenzyl vinyl ether (**5**; 9.63 g, 49.6 mmol) was metalated at 0 °C with *n*-butyllithium (50 mL, 1.85 M, 92.5 mmol) in 300 mL of pentane in a 500-mL three-necked indented flask. After the mixture was stirred for 6 h, the flask was put in the refrigerator overnight to allow the anion to settle. The pentane was drawn off and the tan residue washed with a 20-mL portion of pentane. The residue was dissolved in anhydrous ether (150 mL) and the

(21) Bergelson, L. D.; Solodovnik, V. D.; Shemyalkin, M. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 843–850.
(22) Vig, B.; Mahajan, A. C.; Ram, B.; Kad, G. *Indian J. Chem.* **1973**, *11*, 207–208.

red-brown solution cooled to 0 °C. Ethylene iodochloride (10.0 g, 52.6 mmol) was added at a rate to keep the temperature of the solution below 15 °C. After 2 h the mixture was poured into water and extracted with three portions of ether. The combined extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated to afford a yellow orange oil.

The crude material was chromatographed on a 2.5 × 28 cm column containing 100 g of Merck silica gel (40–60-μm particle size). The column was eluted with a mixture of 10% ether in petroleum ether at a flow rate of 27 mL/min. Fractions containing the iodide were combined and concentrated to afford 6.69 g (51%) of crystalline iodide **8**: mp 72.5–74.5 °C; NMR (CCl_4) δ 7.1 (s, 2 H), 7.0–6.6 (q, 1 H), 5.15 (s, 2 H), 4.7–4.1 (m, 2 H), 4.0 (d, 6 H); IR (KBr) 2950, 2830, 1650, 1600, 1570, 1540, 1520, 1470, 1450, 1430, 1420, 1370, 1315, 1300, 1250, 1230, 1190, 1080, 1030, 990, 960, 940, 815, 790 cm^{-1}. Anal. Calcd for $C_{11}H_{13}IO_3$: C, 41.27; H, 4.09; I, 39.64. Found: C, 40.47; H, 3.98; I, 39.88.

4-Iodo-3,6-dimethoxybenzyl Alcohol from 2,5-Dimethoxybenzyl Alcohol. A solution of 2,5-dimethoxybenzyl alcohol (**5**; 168 mg, 1 mmol) in THF (5 mL) was metalated with 1.8 M *n*-butyllithium (1.6 mL, 2.8 mmol) at ambient temperature under a N_2 atmosphere for 35 min. The cloudy, light brown solution was transferred using a cannula into a chilled (0 °C) solution of ethylene iodochloride (780 mg, 4 mmol) in THF (2 mL). After the resultant clear yellow solution had been stirred for 0.5 h, the reaction was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated to afford 270 mg of yellow oily solids. This material was chromatographed on a silica gel preparative plate developed with 5% ether in CH_2Cl_2 to afford 103 mg (35%) of 2-iodo-3,6-dimethoxybenzyl alcohol **6** and 81 mg (27%) of 4-iodo-3,6-dimethoxybenzyl alcohol which was recrystallized from CH_2Cl_2/hexane: mp 99.0–100 °C; NMR ($CDCl_3$) δ 7.45 (s, 1 H), 4.8 (s, 2 H), 4.03–4.06 (d, 6 H), 2.4 (s, 1 H); IR (KBr) 3500–3100, 3000, 2960, 2940, 2880, 2840, 1600, 1485, 1460, 1430, 1380, 1355, 1280, 1200, 1170, 1060, 1050, 1020, 850, 825, 790, 700 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15. Found: C, 36.92; H, 3.88; I, 42.92.

2-Iodo-3,6-dimethoxybenzyl Alcohol (6). Method A. The chromatographed vinyl ether **8** (6.56 g, 20.5 mmol) was hydrolyzed in THF (35 mL) containing 10 mL of 5% v/v aqueous H_2SO_4. After 4 h the mixture was diluted with water and extracted with two portions of CH_2Cl_2. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated to a brownish solid. The crude product was chromatographed on a 2.5 × 28 cm column containing 100 g of Merck silica gel (40–60-μm particle size) and eluted at 37 mL/min with an ether–dichloromethane gradient starting with 2% ether and increasing in this component at the rate of 1% per void volume. Fractions containing the alcohol were combined to afford, after one recrystallization from dichloromethane and hexane, 3.83 g (64%) of alcohol **6**: mp 108.5–110 °C; NMR (CCl_4) δ 6.68 (s, 2 H), 5.03 (s, 2 H), 3.93 (s, 6 H), 2.52 (s, 1 H, exchangeable with D_2O); IR (KBr) 3450, 3350–3300, 2960–2940, 2840, 1590, 1570, 1470, 1430, 1310, 1300, 1250, 1220, 1195, 1170, 1140, 1080, 1030, 1010, 920, 805, 715 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_3$: C, 36.76, H, 3.77; I, 43.15. Found: C, 37.03; H, 3.82; I, 42.97.

Method B. The chromatographed vinyl ether **8** (1.39 g, 4.34 mmol) was dissolved in 20 mL of methanol containing $Hg(OAc)_2$ (50 mg). After 0.5 h the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated to a yellow solid. This was recrystallized once from ethyl acetate and once from CH_3CN to afford **6**: 1.09 g (85%); mp 108–110 °C.

2-Iodo-3,6-dimethoxybenzaldehyde (9). A solution of 2-iodo-3,6-dimethoxybenzyl alcohol (**6**; 1.17 g, 4.00 mmol) in acetone (6 mL) and CH_2Cl_2 (10 mL) was added to pyridinium chlorochromate (2.0 g) in acetone (5 mL). The mixture was allowed to stir overnight, diluted with aqueous NaOH, and extracted with two portions of ether. The combined extracts were washed with 5% aqueous H_2SO_4 and brine, dried with anhydrous $MgSO_4$, and concentrated. The crude product was dissolved in CH_2Cl_2, filtered through a short column of silica gel, and recrystallized from CH_2Cl_2–hexane to afford yellow rosettes: 958 mg (83%); mp 114–115 °C; NMR ($CDCl_3$) δ 10.4 (s, 1 H), 7.1 (s, 2 H), 3.95 (s, 6 H); IR (KBr) 3070, 2940, 2840, 1690, 1540, 1470, 1430, 1265, 1200, 1065, 1020, 910, 815 cm^{-1}. Anal. Calcd for $C_9H_9IO_3$: C, 37.01; H, 3.11; I, 43.45. Found: C, 36.88; H, 3.07; I, 43.47.

2-Iodo-3,6-dihydrobenzaldehyde (10). 2-Iodo-3,6-dimethoxybenzaldehyde (**9**) (0.436 g, 1.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with a 1.2 M solution of BBr_3 in CH_2Cl_2 (4.5 ml, 3.8 mmol) at ambient temperature under a N_2 atmosphere. The orange solution was allowed to stir for 4 h, quenched with H_2O, and extracted several times with CH_2Cl_2. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated to a yellow-gold solid. This was sublimed at 100–160 °C (0.10 mm) to afford 340 mg (86%) of bright yellow crystals: mp 150.0–151.0 °C; NMR (acetone-d_6) δ 12.95 (s, 1 H), 10.4 (s, 1 H), 9.2 (s, 1 H), 7.5–6.9 (m, 2 H); IR (KBr) 3260–3220, 1630, 1610, 1560, 1450, 1345, 1285, 1240, 1200, 1175, 1135, 975, 845, 785, 700 cm^{-1}. Anal. Calcd for $C_7H_5IO_3$: C, 31.84; H, 1.90; I, 48.07. Found: C, 31.99; H, 1.92; I, 48.30.

Copper(I) Isopropenylacetylide (11). The method of Castro was employed.[13] Hydrated $CuSO_4$ (12.5 g, 0.05 mol) in concentrated NH_4OH (50 mL) in a 1-L Erlenmeyer flask was added under N_2 to a solution of hydroxylamine hydrochloride (7 g, 0.1 mol) in water (200 mL). After 10 min the dark blue solution had been almost clear with only faint gray-blue color. Isopropenyl acetylene (3.3 g, 0.05 mol) was added, and a bright yellow precipitate formed immediately. The mixture was filtered, and the filter cake washed with water, ethanol, and ether and dried in vacuo to yield 3.62 g (56%) of a canary yellow powder.

Frustulosin (1). A mixture of 2-iodo-3,6-dihydroxybenzaldehyde (**10**; 26.4 mg, 0.1 mmol) and copper(I) isopropenylacetylide (25 mg, 0.19 mmol) in DMF was heated 3 h at 70–90 °C. The mixture was poured into water and extracted with ether three times. The combined extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated to a yellow-orange oil. The crude product was chromatographed on a silica gel preparative plate developed with 2% ether in CH_2Cl_2 to afford 7 mg of starting material **10**, 5 mg of frustulosin (**1**), and 4 mg of 2-isopropenyl-4-formyl-5-hydroxybenzofuran (**12**). The frustulosin was recrystallized from CH_2Cl_2–hexane to afford fine yellow needles: mp 136–138 °C; NMR ($CDCl_3$) δ 11.6–11.4 (d, 1 H), 10.7–10.5 (d, 1 H), 7.5–6.95 (m, 2 H), 5.8–5.4 (m, 2 H), 2.25–2.05 (m, 3 H); IR (KBr) 3300, 1640, 1600, 1585, 1465, 1440, 1410, 1380, 1330, 1305, 1280, 1200, 1150, 1060, 1020, 970, 910, 820, 710 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.06; H, 5.10. This material was identical in all respects with an authentic sample of frustulosin[14] and gave an undepressed mixture melting point. The benzofuran **12** sublimed at 85–90 °C (0.65 mm) to afford pale yellow crystals: mp 106.5–108 °C; NMR ($CDCl_3$) δ 11.6 (s, 1 H), 7.8–6.85 (m, 3 H), 5.95 (s, 1 H), 2.15 (s, 3 H); IR (KBr) 3600–3340, 3130, 3090, 2960, 2930, 2860, 1650, 1065, 970, 960, 905, 820, 750, 720, 680 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.06; H, 5.15.

3-Isopropenyl-4-formyl-5-hydroxybenzofuran (12). A mixture of 2-iodo-3,6-dihydroxybenzaldehyde (**10**: 44 mg, 0.16 mmol), copper(I) isopropenylacetylide (42 mg, 0.33 mmol), and 2 mL of DMF was heated to 90–105 °C under N_2 for 3 h. The cloudy, brown-gold mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to afford 16 mg of a golden solid. This material was sublimed at 85–95 °C (0.65 mm) to give 11 mg (33%) of a pale yellow crystalline solid, mp 106.5–108.0 °C.

2-Iodo-3,6-bis[(*tert*-butyldimethylsilyl)oxy]benzaldehyde (13). A solution of 2-iodo-3,6-dihydroxybenzaldehyde (**10**: mp 145.0–148.0 °C; 500 mg, 1.9 mmol), *tert*-butyldimethylsilyl chloride (723 mg, 4.8 mmol), and imidazole (517 mg, 7.6 mmol) in DMF (13 mL) was heated at 50 °C nitrogen for 10.5 h. The reaction mixture was poured into water and extracted with petroleum ether. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, and concentrated to afford 834 mg of a lemon-yellow crystalline solid which was chromatographed on an 8 × 15 cm column of 60–200-mesh silica gel eluted with 10% diethyl ether in petroleum ether. This removed minor polar compounds. The pale yellow product (mp 60.0–64.0 °C) was obtained from the first 100 mL of eluant. An analytical sample was obtained by sublimation at 130–135 °C (1.8 mm): mp 62.0–64.0 °C; NMR ($CDCl_3$) δ 10.35 (s, 1 H), 7.0–6.9 (d, 2 H),

1.15–1.10 (d, 18 H), 0.3–0.2 (d, 12 H); IR ($CHCl_3$) 2960, 2930, 2890, 2860, 1680, 1540, 1435, 1390, 1380, 1240, 910, 825 cm^{-1}. Anal. Calcd for $C_{19}H_{33}IO_3$: C, 46.33; H, 6.75; I, 25.77. Found: C, 46.55; H, 6.86; I, 25.80.

2-Iodo-3-[(*tert*-butyldimethylsilyl)oxy]-6-hydroxybenzaldehyde (14). A DMF solution (10 mL) of 2-iodo-3,6-dihydroxybenzaldehyde (**10**: mp 145.0–148.0 °C; (264 mg, 1 mmol), imidazole (216 mg, 3.2 mmol), and *tert*-butyldimethylsilyl chloride (181 mg, 1.2 mmol) was stirred for 12 h at room temperature under N_2. The yellow-orange solution was poured into water, and the crude product was extracted with petroleum ether. The combined petroleum ether extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, and concentrated to give 238 mg of a viscous yellow oil. This was chromatographed on a silica gel preparative plate developed with 15% ether in petroleum ether. The major band afforded 188 mg (47%) of **14** as a pale yellow oil which crystallized: mp 38.5–41.0 °C; NMR ($CDCl_3$) δ 12.0 (s, 1 H), 10.4 (s, 1 H), 7.2–6.9 (m, 2 H), 1.05 (s, 9 H), 0.25 (s, 6 H); IR ($CHCl_3$) 2950, 2930, 2890, 2860, 1640, 1570, 1450, 1280, 1250, 1165, 995, 875, 840, 820 cm^{-1}.

Bis(*tert*-butyldimethylsilyl)frustulosin 15. A mixture of 2-iodo-3,6-bis[(*tert*-butyldimethylsilyl)oxy]benzaldehyde (**13**: mp 60.0–64.0 °C; 90 mg, 0.18 mmol) and copper(I) isopropenylacetylide (46 mg, 0.36 mmol) in DMF (15 mL) under N_2 was placed in a 90 °C oil bath. Over a period of 2 h, the temperature was slowly increased to 107 °C. The mixture was poured into water and extracted with ether. The combined ethereal extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, and concentrated to afford a gold-brown oil (56 mg, 73%), which after bulb-to-bulb distillation [165–185 °C (0.6 mm)] gave 53 mg of a mixture of 3-*O*-(*tert*-butyldimethylsilyl)frustulosin **15a** and bis(*tert*-butyldimethylsilyl)frustulosin **15**: NMR ($CDCl_3$) δ 10.6 (s, 1 H), 7.2–6.8 (m, 2 H), 5.6–5.3 (m, 2 H), 2.1–2.0 (s, 3 H), 1.0 (s, 15 H); IR ($CHCl_3$) 2950, 2920, 2880, 2850, 1685, 1645, 1605, 1575, 1560, 1450, 1395, 1385, 1360, 1280, 1260, 1160, 1000, 980, 940, 930, 895, 830 cm^{-1}. The mixture (**15**, **15a**) was determined to be of adequate purity for further synthetic use.

Frustulosin (1). Method B. A solution of a mixture of **15** and **15a** [bp 165–185 °C (0.6 mm); 200 mg, 0.47 mmol] in 6 mL of THF was treated with 0.4 mL of glacial acetic acid and tetra-*n*-butylammonium fluoride (0.9 mL, 1 M in THF) at 0 °C for 0.5 h under nitrogen. The yellow mixture was poured into water and extracted with ether. The combined ethereal extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, and concentrated to give 97 mg of a yellow-gold solid. Chromatography on a silica gel preparative plate developed with 5% ether in CH_2Cl_2 afforded 5 mg of a less polar impurity and 87 mg (92%) of frustulosin (**1**): mp 136.5–138.5 °C (lit.[1] mp 139.0–140.0 °C).

Frustulosinol (3). Sodium borohydride (1.4 mg, 0.037 mmol) was added in one portion to a cold (−78 °C) solution of frustulosin (**1**: mp 136.5–138.5 °C; 30 mg, 0.15 mmol) in methanol (8 mL). The mixture was stirred for 6 min at −78 °C, quenched with a water–10% aqueous hydrochloric acid mixture (5:1), and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, and concentrated to give 36 mg of a tan-gold oil. Chromatography on a silica gel preparative plate developed with 15% ether in CH_2Cl_2 afforded 4 mg of frustulosin (**1**) and 21 mg of frustulosinol (**3**), which was obtained as gold film. The frustulosinol was recrystallized twice from CH_2Cl_2–hexane to give 15 mg (68%) of white crystalline solid: mp 88.0–89.5 °C (lit.[2] mp 87.0–89.0 °C); NMR ($CDCl_3$) δ 6.85 (s, 2 H), 5.55–5.35 (m, 3 H, 1 exchangeable H), 5.15 (s, 2 H), 2.15–1.95 (m, 3 H); IR ($CHCl_3$) 3590, 3520, 3470–3110, 3100, 3000, 2980, 2960, 2920, 2890, 1610, 1605, 1460, 1370, 1330, 1280, 1240, 1170, 1150, 1045, 960, 955, 900, 820 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.43; H, 5.83.

1-Chloro-1-decen-3-one. Anhydrous $AlCl_3$ (26 g, 0.2 mol) was suspended in CCl_4 (70 mL) in a 250-mL three-necked flask fitted with a fritted glass gas-inlet tube connected to an acetylene source, a $CaCl_2$ outlet tube, and an addition funnel containing octanoyl chloride (20 g, 0.12 mol) dissolved in CCl_4 (20 mL). The flask was cooled in an ice bath while the acid chloride solution was added to the acetylene-saturated $AlCl_3$ suspension. The acetylene stream was continued for 3 h while the mixture was allowed to warm to ambient temperature.

The black reaction mixture was poured into an ice–salt mixture and extracted with ether. The dark ether extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated to a brown oil. The oil was clarified by passing it through a column of silica gel (200 g) eluted with 5% ethyl ether in petroleum. Distillation afforded 18 g (79%) of a pale tan oil: bp 57–59 °C (0.3 mm); NMR ($CDCl_3$) δ 7.4 (d, 1 H, J = 14 Hz), 6.6 (d, 1 H, J = Hz), 2.55 (t, 2 H, J = 7 Hz), 1.8–1.0 (br m, 8 H), 0.9 (t, 3 H, J = 5 Hz); IR 3080, 2960, 2935, 2860, 1695 (C=O), 1680 (C=O), 1586 (C=C), 1470, 1145, 942 cm^{-1}.

1-Iodo-1-decen-3-one. 1-Chloro-1-decen-3-one (6.0 g, 32 mmol) was dissolved in acetone (30 mL) containing dry NaI (10 g). No precipitation of NaCl occurred until 10 mg of $AlCl_3$ was added. After the mixture was allowed stand overnight, the supernatant was decanted, diluted with water and the iodo ketone extracted with ether. The combined extracts were washed with water, brine, dried with anhydrous $MgSO_4$ and concentrated to afford a yellow green oil. Crystallization from pentane afforded 5.6 g (63%) of unstable, light sensitive pale, yellow-green leaflets: mp 46–47 °C; NMR (CCl_4) δ 7.95 (d, 1 H, 14 Hz), 7.25 (d, 1 H, 14 Hz), 2.55 (t, 2 H, J = 7 Hz), 1.8–1.1 (br m, H), 0.9 (t, 3 H, J = 6 Hz).

1-Iodo-1-decen-3-ol (18). To a solution of $LiAlH_4$ (0.5 g) in ether (100 mL) was added 1-iodo-1-decen-3-one (3.00 g, 10.7 mmol) at 0 °C. As soon as the addition was complete, the solution was allowed to warm to ambient temperature and then quenched with water. Anhydrous $MgSO_4$ was added to form a granular precipitate. The mixture was filtered and the filtrate concentrated to afford **18** (2.76 g, 91%) as a yellow oil: NMR (CCl_4) δ 6.9–6.2 (m, 2 H), 4.15 (m, 2 H), 2.2–1.1 (br m, 12 H) 0.9 (t, 3 H, J = 5 Hz); IR 3320 (OH), 2920, 2910, 2840, 1595 (w), 1450 cm^{-1}.

1-Iodo-1,3-decadiene. A solution of iodo alcohol **18** (270 mg, 0.96 mmol) in pentane (7 mL) was treated with saturated aqueous HBr at room temperature under N_2. After 10 min TLC on silica gel showed the reaction to be complete. The mixture was diluted with water and extracted into petroleum ether. The extracts were washed with water, dried with anhydrous magnesium sulfate, and concentrated to afford 433 mg of crude iodo bromide: NMR (CCl_4) δ 7.1–5.8 (br m, 2 H), 4.4 (br q, 1 H), 2–1.1 (br m, 12 H), 0.9 (br t, 3 H). The iodobromide was very unstable and was treated immediately with diazabicycloundecene (DBU; 0.30 mL, 2 equiv) in CH_2Cl_2 (0.5 mL). After 1.5 h the mixture was poured into water and quickly extracted with petroleum ether. The combined extracts were washed in succession with water, 10% HCl(aq), 10% NaOH(aq), water, and brine, dried with anhydrous $MgSO_4$, and concentrated. The resulting light- and heat-sensitive crude product was rapidly chromatographed on a short column of silica gel eluted with pentane to afford the diene 186 mg (74%) as an oil which immediately began to loose iodine upon exposure to air. NMR of the diene (CCl_4): δ 7.2–5.3 (br m, 4 H), 2.4–1.8 (br m, 2 H), 1.7–1.1 (m, 8 H), 0.9 (br t, 3 H). The iodo diene was immediately used in the following experiment.

Reaction of the Lithium Reagent 17 with the (Siloxy)iodo Aldehyde 13. The crude iodo diene (186 mg, 0.7 mmol) was dissolved in a mixture of THF (1.6 mL), ether (0.4 mL), and pentane (0.4 mL). The mixture was cooled under N_2 to −120 to −110 °C (liquid N_2, petroleum ether, 2-propanol, acetone slush), and a solution of *tert*-butyllithium (0.7 mL of 2 M solution, 1.4 mmol) was added. After 50 min the cooling bath was exchanged for a dry ice–acetone bath, and a solution of the bis(siloxy)iodo aldehyde **13** (300 mg, 0.61 mmol) in THF (2 mL) was added. The mixture was allowed to warm to −60 °C over a 5-min period and then quenched with H_2O. The reaction mixture was diluted with H_2O and extracted with ether. The combined ether extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated to a yellow gum. Analysis of this material by thin-layer chromatography showed it to be an extremely complex mixture of products.

2-Iodo-3,6-bis[(*tert*-butyldimethylsilyl)oxy]cinnamaldehyde (20). To a solution of LDA (3.35 mmol) in THF (10 mL) at 0 °C was added to a solution of α-(trimethylsilyl)-*tert*-butylaldimine[19] (523 mg, 3.05 mmol) in THF (4 mL). After 1 h the solution was cooled to −78 °C and the bis(silyloxy)iodo aldehyde **13** (1.003 g, 2.04 mmol) in THF (5 mL) was added dropwise. The mixture was maintained at −78 °C for 1 h and then allowed to warm to ambient temperature overnight. A solution of aqueous oxalic acid (20 mL, 1 M) was added, and after 1 h the

mixture was poured into water and extracted with ether. Then combined extracts were washed with water, saturated aqueous $NaHCO_3$, and brine, dried with anhydrous $MgSO_4$, and concentrated. Column chromatography of the crude material on silica gel eluted with 2.5% ether in petroleum ether afforded 570 mg (54%) of **20** as an oil: NMR ($CDCl_3$; trans isomer) δ 10.05 (d, 1 H, J = 9 Hz, CHO), 7.55 (d, 1 H, J = 11 Hz), 7.10 (s, 2 H, aryl), 6.45 (dd, 1 H, J_A = 9 Hz, J_B = 11 Hz), 1.20 (s, 9 H), 0.53 (s, 6 H), 0.35 (s, 6 H); IR 2950, 2930, 2890, 2860, 1680, 1450, 1250, 925 cm^{-1}. Anal. Calcd for $C_{21}H_{35}IO_3Si_2$: C, 48.64; H, 6.80. Found: C, 48.59; H, 6.92.

5-[2-Iodo-3,6-bis(*tert*-butyldimethylsiloxy)phenyl]-2,4-pentadienal (21). To a solution of LDA (1.35 mmol) in THF (10 mL) at 0 °C was added a solution of α-(trimethylsilyl)-*tert*-butylaldimine[19] (221 mg, 1.29 mmol) in THF (4 mL). After 1 h the mixture was cooled to −78 °C, and the cinnamaldehyde **20** (536 mg, 1.03 mmol) was added in THF (1 mL). After 1 h at −78 °C, the mixture was allowed to warm to ambient temperature overnight. A solution of aqueous oxalic acid (25 mL, 1 M) was added, and after 2 h the mixture was diluted with water and extracted with ether. The ether extract was washed with water, aqueous $NaHCO_3$, and brine, dried with anhydrous $MgSO_4$, and concentrated. Column chromatography of the crude material on silica gel eluted with 7.5% ether in petroleum ether afforded 505 mg (90%) of dienal **21** as a mixture of isomers: NMR ($CDCl_3$) δ 10.0 (d, 1 H, J = 10 Hz, CHO), 7.75–6.35 (m, 6 H, aryl and dienyl protons), 1.45 (s, 9 H), 1.23 (s, 9 H), 0.61 (s, 6 H), 0.47 (s, 6 H); IR 2950 (s), 2930, 2890, 2860, 1680 (s), 1550 (m), 1450 (s), 1250, 925 cm^{-1}. Anal. Calcd for $C_{23}H_{37}IO_3Si_2$: C, 50.72; H, 6.85. Found: C, 50.81; H, 6.95.

1-[2-Iodo-3,6-bis(*tert*-butyldimethylsiloxy)phenyl]-1,3-undecadien-5-ol (22). A solution of hexylmagnesium bromide was generated in ether (10 mL) from magnesium turnings (486 mg, 20 mmol) and hexyl bromide (1.65 g, 10 mmol). After the Grignard formation was complete, a 2.5-mL aliquot of the Grignard solution was transferred to a 25-mL round-bottomed flask. A solution of the dienal **21** (350 mg, 0.64 mmol) in 5 mL of ether was slowly added at room temperature. After 1 h the reaction was quenched with 1 N aqueous H_2SO_4 and extracted with ether. The ether extracts were washed with aqueous $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$, and concentrated to afford a heavy yellow oil. Filtration through a short column of silica gel gave **22** (353 mg, 88%) as a nearly colorless oil: NMR ($CDCl_3$) δ 7.5–5.7 (complex m, 6 H, aryl and vinyl), 4.42 (m, 1 H), 2.3–1.0 (overlapping signals with singlets at 1.27 and 1.37 and a broad aliphatic envelope at 1.55, 31 H), 0.55 (s, 6 H), 0.40 (s, 6 H); IR 3400 (s, OH), 2960 (s) 2940 (s) 2875 (s), 1450, 1250, 930, 845, 730 (w) cm^{-1}. Anal. Calcd for $C_{29}H_{51}IO_3Si_2$: C, 55.22; H, 8.15. Found: C, 55.12; H, 8.28.

***trans,trans*-2,4-Decadien-1-ol (24).** Technical *trans,trans*-2,4-decadienal (1.00 g, 6.58 mmol) was reduced in ether (20 mL) at 0 °C with a solution of DIBAL (1 M in hexane, 7 mL, 7 mmol). After 10 min the reaction was quenched with about 1 mL of water and stirred until the mixture set up as a gel. Anhydrous $MgSO_4$ was added to form a granular precipitate. The mixture was filtered and concentrated to afford 897 mg (88.5%) of dienol **24**,[22] which was used in the subsequent bromination without further purification.

***trans,trans*-1-Bromo-2,4-decadiene (25).** Bromine was added dropwise to be a solution of triphenylphosphine (900 mg, 3.43 mmol) in CH_3CN (15 mL) until a faint color just remained. A very small amount of triphenylphosphine was then added to remove the bromine color. The solution was cooled to ambient temperature, and a solution of the dienol **24** (500 mg, 3.25 mmol) in CH_3CN (5 mL) was added. After 5 min the mixture was poured into petroleum ether, and the CH_3CN layer was repeatedly extracted with petroleum ether. Concentration of the petroleum ether extracts afforded 670 mL of crude material (95%). Evaporative distillation (bulb to bulb) 50–55 °C (0.02 mm) yielded 617 mg (87.5%) of colorless dienyl bromide **25**: NMR (CCl_4) δ 6.5–4.9 (complex m, 4 H), 3.9 (d, 2 H, J = 8 Hz), 2.35–1.6 (m, 2 H), 1.6–1.1 (m, 6 H), 0.85 (br 3 H); IR 3000, 2930, 2910, 1640, 1450, 1190, 974. Anal. Calcd for $C_{10}H_{17}Br$: C, 55.30; H, 7.83. Found: C, 55.44; H, 7.84.

Triphenyl(*trans,trans*-2,4-decadienyl)phosphonium Bromide (26). Triphenylphosphine (700 mg, 2.67 mmol) was added to a solution of freshly distilled dietnyl bromide **25** (575 mg, 2.65 mmol) in THF (10 mL) in flask covered with foil to exclude light and maintained under a N_2 atmosphere. After being allowed to stand overnight, the solution was cooled to −78 °C for 1.5 h to crystallize the phosphonium salt. The mother liquor was then removed with a canula by N_2 pressure. Residual solvent was removed by a vacuum pump while the −78 °C bath was maintained until the crystals were dry. The phosphonium salt **26** was obtained as a white crystalline solid: 1.13 g (88%); mp 55–59 °C; NMR ($CDCl_3$) δ 8.5–7.2 (m, 17 H), 6.0–4.8 (complex m, 4 H), 2.2–1.8 (m, 2 H), 1.8–1.1 (br m, 6 H), 0.9 (br t, 3 H). The salt is very hydroscopic, rapidly becomes discolored, and forms a dark tarry mass on exposure to light and moisture. Anal. Calcd for $C_{28}H_{32}BrP \cdot H_2O$: C, 67.60; H, 6.84. Found: C, 67.35; H, 6.61.

1-[2-Iodo-3,6-bis(*tert*-butyldimethylsiloxy)phenyl]-1,3,5-undecatriene (16). A slurry of the phosphonium salt **26** (280 mg, 0.434 mmol) in THF (2 mL) at −78 °C under N_2 was treated with *n*-butyllithium (0.26 mL, 1.8 M solution, 0.47 mmol). The salt was slow to dissolve, but ylide formation was complete after 4 h, affording a dark brown-red ylide solution. The iodo aldehyde **13** (205 mg, 0.417 mmol) was added in THF (1.5 mL). This caused the ylide color to fade but not to disappear entirely.

After being stirred overnight, the reaction mixture was poured into water overlaid with petroleum ether and extracted with petroleum ether. The combined extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated to a yellow oil. This was chromatographed on a silica preparative plate developed twice with 3% ether in petroluem ether to afford **16** (149 mg, 58.4%) as a pale yellow oil: NMR ($CDCl_3$) δ 7.0–5.6 (br m, 8 H), 2.2 (br q, 2 H, J = 8 Hz), 1.6–1.0 (br m, 6 H), 1.29 and 1.32 (s, 18 H), 0.9 (br t, 3 H), 0.54 and 0.45 (s, 12 H); IR 3015, 2960, 2930, 2860, 1565, 1540 1440, 1290, 1238, 980, 910, 905, 820, 790, 762 cm^{-1}. Anal. Calcd for $C_{29}H_{49}IO_2Si_2$: C, 56.87; H, 8.00. Found: C, 56.90; H, 8.25.

1-[2-Iodo-3,6-bis(*tert*-butyldimethylsiloxy)phenyl]-1,3,5-undecatriene (16) from the Undecadienol 22. To a solution of 1-[2-iodo-3,6-bis(*tert*-butyldimethylsiloxy)phenyl]-1,3-undecadien-5-ol (**22**; 349 mg, 0.55 mmol) in dry benzene (10 mL) was added I_2 (100 mg). The solution was heated to reflux for 1 h, cooled, diluted with ether (50 mL), washed with dilute aqueous $Na_2S_2O_3$, 10% aqueous $NaHCO_3$, brine, dried with anhydrous $MgSO_4$, and concentrated to afford the triene **16** (298 mg, 88%) after filtration through a short column of silica gel eluted with 5% ether in petroleum ether.

Aurocitrin (2). The trienyl iodide **16** (70 mg, 0.114 mmol) was dissolved in ether (1 mL), and the solution was cooled to −78 °C under N_2. A solution of *n*-butyllithium was added (0.2 mL, 1.5 M, 0.3 mmol). After 2 min the reaction was quenched by the addition of DMF (210 μL in three equal portions), the cooling bath was removed, and 10% aqueous HCl was added (1 mL). When the reaction mixture had warmed to ambient temperature it was poured into water and extracted with ether. The ether extracts were washed with brine, dried with anhydrous magnesium sulfate, and concentrated to produce a yellow oil (65 mg). The crude product, a complex mixture by TLC, was immediately hydrolyzed to aurocitrin without further purification.

The crude product was dissolved in THF (1 mL); the solution began to darken within a few minutes. To this solution was added acetic acid (20 μL) followed by a solution of *n*-Bu_4NF (160 mL, 1 M in THF). Addition of the fluoride produced an immediate orange color. After 1 h the reaction mixture was poured into water overlaid with ether and extracted with ether. The ether extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated to afford 48 mg of a brownish orange oil. This was chromatographed on a silica gel preparative plate developed with 1% CH_3OH–30% ether in petroleum ether to afford 26 mg (79%) of crystalline aurocitrin. Recrystallization from hexane afforded 19 mg of orange plates, mp 104–106.5 °C. This material was identical in all respectes with an authentic sample[14] and gave an undepressed mixture melting point. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.52; H, 7.69. Found: C, 75.28; H, 7.73.

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Palladium-Catalyzed Reactions of Acyl Chlorides with (1-Alkynyl)tributylstannanes. A Convenient Synthesis for 1-Alkynyl Ketones

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Acyl chlorides couple with (1-alkynyl)tributylstannanes in the presence of catalytic amounts of palladium(II) or palladium(0) complexes to produce 1-alkynyl ketones in respectable yields. The couplings of isobutyryl, acetyl, benzoyl, and *p*-nitrobenzoyl chlorides with phenylethynyl-, (trimethylsilyl)ethynyl-, (carbomethoxy)ethynyl-, [3-[(*tert*-butyldimethylsilyl)oxy]-1-propynyl]-, and (3,3-diethoxy-1-propynyl)tributylstannanes were investigated in the presence of tetrakis(triphenylphosphine)palladium(0), benzylchlorobis(triphenylphosphine)palladium(II), dichlorobis(triphenylphosphine)palladium(II), or phenyliodobis(triphenylphosphine)palladium(II). The reactions are highly selective in that only the alkynyl groups are transferred from the stannane.

As a class, α,β-acetylenic carbonyl compounds are extremely versatile substrates for further synthetic elaboration. Numerous syntheses involving α,β-acetylenic carbonyl compounds have been reported,[2] and a significant number of them involve the synthesis of heterocyclic compounds. The facility with which α,β-acetylenic carbonyl compounds undergo nucleophilic additions and cyclizations[2c,d,3-6] makes them very desirable intermediates for elaboration to heterocyclic systems. Our interest in this class of compounds derives from their use as intermediates for *C*-nucleoside synthesis.[3-5] More specifically, we are interested in developing convenient, high-yield routes for converting carboxylic acids into 1-alkynyl ketones, which could serve as precursors to *C*-nucleosides.

A survey of the literature revealed the existence of several methods for carrying out such transformations; however, there are limitations with each of them. (1) The silver or copper(I) acetylide–acyl chloride routes[7-9] are quite variable in yield, and acetal or ester functions in the acetylide are often cleaved by the acyl chloride.[10] (2) The $AlCl_3$-catalyzed reaction of acyl chlorides with silylated alkynes[11] uses strongly acidic conditions. (3) The use of alkynylcadmium–acyl chloride[12] and of alkynyllithium–mixed anhydride[13] procedures gives low to moderate yields of 1-alkynyl ketones, and they place limitations on the functionalities allowed in the acetylene. (4) The copper(I) iodide–dichlorobis(triphenylphosphine)palladium(II)-catalyzed reaction of acyl chlorides with 1-alkynes[14] cannot be used with acyl chlorides that readily react with tertiary amines, which are necessary components of the reaction. (5) Thermal reactions between acyl chlorides and stannylated alkynes[15] give only moderate yields of 1-alkynyl ketones.

Since the above syntheses either give low yields of 1-alkynyl ketones or are of limited scope, we looked for a route to 1-alkynyl ketones that would be clean, produce high yields, and tolerate a wide variety of functional groups on both reactants. Most recently, the conversion of acyl chlorides into ketones by a palladium-catalyzed reaction with tetraorganotin reagents (eq 1) was reported.[16] The

$$R'_4Sn + RC(O)Cl \xrightarrow{\text{Pd catal}} RC(O)R' + R_3'SnCl \quad (1)$$

reaction is mild, tolerates a variety of functional groups, and produces ketones in high (usually >90%) yield. Furthermore, when vinyl- or aryltrialkylstannanes were used, only the vinyl or aryl group was transferred to form the corresponding ketones. We reasoned that an alkynyl

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