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Diels–Alder reaction of maldoxin with an isopropenylallene

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Abstract

The Diels–Alder reaction of maldoxin with an isopropenylallene at 60–75 °C afforded an adduct closely related to chloropestolide A (24%) and a second adduct (0–11%) that underwent an ene reaction to generate the chloropupukeanolide D (11–22%) skeleton. The Diels–Alder reaction occurred with good selectivity (>5:1) from a single face of maldoxin under much milder conditions than previously reported for the analogous dimethoxycyclohexadienone. Furthermore, the ene reaction took place under mild conditions whereas the analogous Diels–Alder adduct from the dimethoxycyclohexadienone did not undergo an ene reaction.

Keywords

inverse electron demand Diels–Alder reaction; biomimetic synthesis; ene reaction; allene; 2,4-cyclohexadienone

1. Introduction

Liu, Che and co-workers recently reported the isolation of the cytotoxic natural products chloropestolide A (**3**),^{1b} chloropupukeanolide D (**5**),^{1c} chloropupukeananin (**7**),^{1a} chloropupukeanolide C (**8**),^{1c} and more highly oxygenated analogs^{1c,d} from the fermentation of the plant endophytic fungus *Pestalotiopsis fici* (see Scheme 1). These compounds were suggested to arise by an inverse electron demand Diels–Alder reaction between maldoxin (**1b**)² as the diene and isopropenylallene **2**, which was also isolated from *Pestalotiopsis fici*, as the dienophile.¹ Diels–Alder reaction from the ether face of maldoxin with the allene adding endo gives chloropestolide A (**3**). Diels–Alder reaction from the ether face with the allene adding exo affords **6**, which undergoes an intramolecular ene reaction to give chloropupukeanolide C (**8**). Diels–Alder reaction from the carboxylate face of maldoxin with the allene adding exo provides adduct **4**, which undergoes an intramolecular ene reaction to give chloropupukeanolide D (**5**), which rearranges to chloropupukeananin (**7**).

Fermentation on 1 Kg of rice gave 30 mg of chloropupukeananin (**7**) and 6 mg of chloropestolide A (**3**).^{1b} Fermentation on 3 Kg of rice afforded 15 mg of chloropupukeanolide D (**5**) and 3 mg of chloropupukeanolide C (**8**).^{1c} Although the Diels–

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Supplementary data

Discussion of the conformation of **5**, **8**, and **35b**, tables of NMR data, and copies of ¹H and ¹³C NMR spectral data. Supplementary data associated with this article can be found, in the online version, at ...

Alder reaction occurs on both the carboxylate face (**5** and **7**) and the ether face (**3** and **8**), the product ratios suggest that reaction from the carboxylate face is preferred by a factor of 5.

Suzuki and Kobayashi prepared dimethoxycyclohexadienone **9** as a model for maldoxin (**1b**) and investigated its Diels–Alder reactions with model isopropenylallene **10** (see Scheme 2).³ They found that reaction in toluene at reflux for 48 h afforded the desired Diels–Alder adducts **12** (10.5%) and **13** (3.5%) in modest yields accompanied by adduct **11** (11%) resulting from the addition of **9** as the dienophile to isopropenylallene **10** as the diene. They also found that carrying out the Diels–Alder reaction under high pressure (0.8 GPa) in CH₂Cl₂ for 24 h improved both the yield and the selectivity for the desired inverse electron demand Diels–Alder adducts **12** (43%) and **13** (27%) and gave slightly less (10%) of the undesired adduct **11**. An intramolecular ene reaction of **13** did not occur under either set of Diels–Alder conditions. Treatment of **13** with 80% aqueous TFA/CH₂Cl₂ effected the desired ene reaction, but was accompanied by hydrolysis of both the ketal and enol ether to give **14** in 88% yield (see Scheme 3). Three additional steps were needed to regenerate the enol ether to complete the synthesis of a chloropupukeananin model.

These experiments partially validate the biosynthetic hypothesis, but leave several questions unanswered because nature cannot achieve either the high pressures or temperatures used in the Diels–Alder reaction of **9** and **10**. The ene reactions of **4** and **6** to give **5** and **8**, respectively, appear to occur readily in nature since the initial Diels–Alder adducts **4** and **6** weren't isolated, whereas **13** only reacts further with strong acid. These differences suggest that there are important differences between the Diels–Alder reaction of **1b** and **2** and maldoxin model **9** and isopropenylallene model **10**. Furthermore, the questions of facial selectivity with maldoxin (**1b**) cannot be explored with the symmetrical dimethoxy ketal **9**. We therefore synthesized maldoxin (**1b**)⁴ to explore its Diels–Alder reaction with model isopropenylallene **10**.

The Diels–Alder reactions of unsymmetrically 6,6-di-substituted 2,4-cyclohexadienones have been extensively studied, but are not fully understood.^{5,6,7} For instance, 6-methyl-6-hydroxy-2,4-cyclohexadienone **16**, generated by oxidation of phenol **15**, spontaneously dimerizes to give Diels–Alder adduct **17** in 48% yield (see Scheme 4).^{6e} However, the acetate of **16** does not dimerize. Similarly, oxidation of phenol **18** with PhI(OAc)₂ in the presence of AcOH gives stable 6-acetoxy-6-methoxycyclohexadienone **19** in 95% yield, whereas oxidation of phenol **18** with PhI(O₂CCF₃)₂ in the presence of MeOH affords the unstable 6,6-dimethoxycyclohexadienone **20**, which dimerizes to give **21** (see Scheme 5).^{6b,e}

The stereospecific formation of **17** as a single diastereomer, even though **16** is racemic, has been explained by suggesting there is a strong preference for reaction from the face opposite the more electron donating methyl substituent at the 6 position for both the diene and dienophile. The acetate ester of **16** does not dimerize because the acetate group in the preferred orientation blocks the approach of the dienophile.^{6e} Presumably, the acetate is sufficiently electron withdrawing to electronically retard dimerization from the methyl face. The dimerization of **20** is analogous to that of **16** indicating that a methoxy group is still sufficiently electron donating to allow dimerization from the opposite face. Acetate **19** is stable because the acetate sterically blocks cycloaddition from the acetate face and is sufficiently electron withdrawing to retard dimerization from the methoxy face.

Quideau reported that anodic oxidation of **22** afforded dimethyl ketal **23**, which was hydrolyzed with aqueous acid to give cyclohexadienone 1,3-dioxolan-4-one **24**, which spontaneously dimerized to give a single dimer in 78–100% yield (see Scheme 6).^{6d,e} The stereochemistry of **25**, R = H and *n*-Pr, was established by crystal structure determination.

The compound lacking the geminal dimethyl groups of **23** could not be prepared by anodic oxidation so the effect of the geminal methyl groups on the Diels-Alder reaction stereochemistry could not be evaluated.^{6c,d} On the other hand, Deslongchamps reported that the stable cyclohexadienone 1,3-dioxolan-4-one **26** underwent Diels-Alder reactions with methyl vinyl ketone and ethyl vinyl ether with no facial selectivity affording 1:1 mixtures of **27** and **28** (see Scheme 7).⁷ Liao also reported that a cyclohexadienone 1,3-dioxolan-4-one lacking the cyclopentane ring of **26** affords mixtures of Diels-Alder adducts with a variety of dienophiles.^{5a}

2. Results and Discussion

Diels-Alder reactions of cyclohexadienone 1,3-dioxan-4-ones with the maldoxin skeleton have not been examined. We therefore initially explored the oxidative cyclization of readily available 2-(2-hydroxyphenyl)benzoic acid (**29**).⁸ Treatment of **29** with $\text{PhI}(\text{OAc})_2$ in $\text{CF}_3\text{CH}_2\text{OH}$ generated unstable maldoxin analogue **30**, which dimerized to give **31** in 60% yield (see Scheme 8). We were unable to trap **30** by carrying out the oxidative cyclization in the presence of excess 2,3-dimethyl-1,3-butadiene, methyl acrylate, or 2-methoxypropene, which indicates that **30** is very reactive as both a diene and a dienophile. The stability of **1b** and reactivity of **30** are consistent with the known stabilizing effect of substituents on the dienone ring.⁵⁻⁷ As in the dimerization of **16** and **24**, a single adduct **31** is formed from the dimerization of like enantiomers of racemic **30**. Although **31** is solid, we were unable to obtain single crystals suitable for X-ray structure determination. The stereochemistry of **31** was therefore tentatively assigned by analogy to **25** and the expectation that cycloaddition should occur from the face opposite the more electron donating ether oxygen.

The Diels-Alder reaction of maldoxin (**1b**)⁴ with isopropenylallene **10**³ occurred readily (see Scheme 9). Heating in 1:1 $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ for 18 h at 60 °C afforded a 1:1:2:1:1 mixture of recovered **1b**, **32b**, **33b**, **34b**, and **35b**, respectively. Heating for 24 h at 75 °C provided a 1:1:1 mixture of **32b**, **33b**, and **35b**, respectively. HPLC analysis showed minor components (<20% of the isolated products) that may be stereoisomers at the spiro center. The structure of **32b** in which maldoxin reacted as a dienophile was assigned by analogy to **11**. The 18 Hz geminal coupling constant for the allylic methylene group is characteristic of this ring system. The spectral data of Diels-Alder adduct **33b** with an endo allene correspond closely to those of both chloropestolide A (**3**) and **12**. The methylene protons absorb at δ 2.60 and 2.28 with a 13.6 Hz geminal coupling constant. The spectral data of Diels-Alder adduct **34b** with an exo allene correspond closely to those of **13**. The methylene protons absorb at δ 2.99 and 1.82 with a 13.6 Hz geminal coupling constant. The conversion of **34b** to ene adduct **35b** at 70 °C confirmed the exo allene stereochemistry. The spectral data of **35b** correspond closely to those of ene adducts chloropupukeanolides C (**8**) and D (**5**).

Dimethyl ketal **9** is much less reactive than maldoxin (**1b**) in the Diels-Alder reaction with **10** affording only 25% total yield of adducts after 48 h in toluene at reflux.³ Dimethyl ketal **9** also gives a greater percentage of the adduct in which isopropenylallene **10** is the diene, not dienophile, unless high pressure conditions are used. The facile reaction of **1b** with **10** at 60 °C is consistent with the Diels-Alder reaction of **1b** and **2** occurring under physiological conditions without enzymatic catalysis.

The absence of a chlorine has a marked effect on the Diels-Alder reactivity of dechloromaldoxin (**1a**).⁴ The Diels-Alder reaction of **1a** and **10** required much higher temperatures and longer times (90 °C, 4 d) and gave only the undesired adduct **32a** (23%) in which dechloromaldoxin reacted as the dienophile. As in **32b**, the 18 Hz geminal coupling constant for the allylic methylene group is characteristic of this ring system. The chlorine of

1b accelerates the Diels-Alder reaction to give **32b** only slightly, but greatly accelerates the desired inverse electron demand Diels-Alder reactions leading to **33b** and **34b**. An explanation of this phenomenon will require a full theoretical analysis of the molecular orbitals and transition state structures as reported by Dory and Deslongchamps for the reaction shown in Scheme 7.⁷

The stereochemistry at the spiro center is tentatively assigned as shown based on several considerations. In the major natural products, the Diels-Alder reaction occurred from the carboxylate face as proposed for **32–35**. Precedent also suggests that the dienophile should approach from the face opposite the more electron donating ether group.⁶ The proposed stereochemistry is consistent with that determined crystallographically for **25**.^{6d,e} Most of the differences between the ¹H NMR data of ene adducts **5**, **8**, and **35b** can be attributed to the presence of additional substituents on the cyclohexene rings of **5** and **8**. However, H₉ absorbs at δ 5.49 in **35b**, δ 5.51 in **5** and δ 5.76 in **8**. Since these protons are far removed from the cyclohexene substituents, the difference in chemical shifts are probably due to the proximity of H₉ to the phenyl ether oxygen in **35b** and **5** and carboxylate oxygen in **8**. The difference in the chemical shift of H₃₁ in **3** (δ 6.45) and **33b** (δ 6.31) is consistent with the assigned opposite stereochemistry at the spiro center. Finally, the crystal structure of dechloromaldoxin shown in Figure 1 indicates that the ether is pseudoaxial blocking that face and the carboxylate is pseudoequatorial allowing access to that face.^{4,9}

3. Conclusion

In conclusion, the Diels-Alder reaction of maldoxin (**1b**) with isopropenylallene **10** at 60 °C afforded adduct **33b** (24%) closely related to chloropestolide A and a second adduct **34b** (0-11%) that underwent an ene reaction to generate **35b** (11-22%) with the chloropupekeanolide D skeleton. The Diels-Alder reaction occurred with good selectivity (>5:1) from a single face of maldoxin under much milder conditions than previously reported for dimethoxycyclohexadienone **9**. Furthermore, adduct **34b** underwent an ene reaction under mild conditions whereas the analogous adduct **13** formed from **9** did not undergo an ene reaction. Finally, we found that the chlorine is essential because **1a** reacted only as a dienophile with **10** to give **32a** (23%) whereas **1b** reacted as a diene with **10** to give **33b–35b** (46%) in addition to **32b** (20%).

4. Experimental

4.1. General methods

Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase “concentrated” refers to removal of solvents by means of a rotary evaporator attached to a diaphragm pump (15-60 Torr) followed by removal of residual solvents at < 1 Torr with a vacuum pump. Flash chromatography was performed on silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F-254 pre-coated glass plates (0.25 mm). TLC Plates were analyzed by short wave UV illumination, or by dipping in vanillin stain (27 g of vanillin in 380 mL of EtOH, 50 mL of water and 20 mL of concentrated sulfuric acid) and heating on a hot plate. THF and ether were dried and purified by distillation from sodium/benzophenone. CH₂Cl₂, DIPEA, MeOH, and MeCN were distilled from CaH₂. ¹H and ¹³C NMR spectra were obtained on a 400 MHz spectrometer in CDCl₃ unless otherwise indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). For spectra obtained in CDCl₃, chemical shifts are referenced to the TMS peak at δ 0.00 in ¹H NMR and the residual solvent peak of CDCl₃ at δ 77.00 in ¹³C NMR. For spectra obtained in acetone-*d*₆, chemical shifts are referenced to the residual solvent peaks at δ 2.05 (¹H) and 29.92 (¹³C). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t

(triplet), q (quartet), p (pentet), m (multiplet) and br (broad). IR spectra were acquired on an FT-IR spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra were obtained using the following ionization techniques: chemical ionization (CI), electron impact (EI), electrospray ionization analyzed by quadrupole time of flight (QToF).

4.2. Diels-Alder dimer **31**

To a stirred solution of 2-(2-hydroxyphenoxy)-benzoic acid⁸ (**29**) (110 mg, 0.48 mmol) in $\text{CF}_3\text{CH}_2\text{OH}$ (10 mL) was added $\text{PhI}(\text{OAc})_2$ (186 mg, 0.58 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 1 h and diluted with CH_2Cl_2 (100 mL). The organic layer was washed with saturated NaHCO_3 solution (10 mL) and brine (10 mL), dried over MgSO_4 , and concentrated to yield 195.6 mg of crude **31**. Flash chromatography on MeOH-deactivated silica gel (3:1 to 2:1 hexanes/EtOAc) gave 65.8 mg (60%) of **31** containing less than 10% of a minor isomer as a white solid: mp (decomp); ^1H NMR 7.96 (dd, 1, $J = 7.3, 1.8$), 7.95 (dd, 1, $J = 7.3, 1.8$), 7.54 (ddd, 1, $J = 8.5, 7.3, 1.8$), 7.49 (ddd, 1, $J = 8.5, 7.3, 1.8$), 7.16 (br dd, 1, $J = 7.3, 7.3$), 7.13 (br dd, 1, $J = 7.3, 7.3$), 6.89 (br d, 1, $J = 8.5$), 6.86 (br d, 1, $J = 8.5$), 6.65 (dd, 1, $J = 10.4, 4.3$), 6.52 (dd, 1, $J = 8.6, 6.1$), 6.13 (dd, 1, $J = 8.6, 6.1$), 6.08 (dd, 1, $J = 10.4, 1.2$), 4.07 (br dd, 1, $J = 6.1, 1.8$), 3.92 (dd, 1, $J = 7.9, 1.8$), 3.72-2.67 (m, 1), 3.44 (dd, 1, $J = 6.1, 2$); ^{13}C NMR 197.4, 187.6, 159.7, 159.1, 155.4, 153.7, 146.9, 136.7, 136.3, 132.1, 129.7 (2 C), 128.5, 128.0, 123.8, 123.5, 116.4, 116.11, 114.5, 113.4, 99.9, 96.6, 50.9, 41.8, 41.1, 38.2; IR (neat) 2970, 1753, 1466, 1365, 1299, 1242, 1077; HRMS (Qtof) calcd for $\text{C}_{26}\text{H}_{17}\text{O}_8$ (MH^+) 457.0923, found 457.0924; HRMS (Qtof) calcd for $\text{C}_{26}\text{H}_{16}\text{O}_8\text{Na}$ (MNa^+) 479.0743, found 479.0745.

4.3. Diels-Alder adduct **32a** from dechloromaldoxin (**1a**)

Isopropenylallene **10** (5.1 mg, 0.034 mmol) was transferred to a resealable tube containing dechloromaldoxin (**1a**) (4.0 mg, 0.0116 mmol) in 0.6 mL of a 1:1 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ mixture. The tube was sealed and heated in a 90 °C oil bath for 4 days. The mixture was cooled and evaporated to give 11 mg of crude product. Preparative TLC (5:1 hexanes/EtOAc) gave undesired Diels-Alder adduct **32a** (1.3 mg, 23%) followed by recovered dechloromaldoxin (**1a**) (2.0 mg, 50%).

Data for **32a**: ^1H NMR 9.96 (br s, 1, OH), 6.43 (br s, 1), 6.33 (br s, 1), 6.28 (s, 1), 5.28 (s, 1), 4.92 (s, 1), 3.70 (s, 3), 3.68 (s, 3), 3.00 (d, 1, $J = 18$), 2.27 (s, 3), 2.42-2.28 (m, 4), 2.22 (d, 1, $J = 18$), 1.70-1.46 (m, 6), 1.77 (s, 3); ^{13}C NMR (partial, determined from HSQC and HMBC spectra, see Table S1) 185.7, 178.4, 168.9, 160.3, 153.5, 149.2, 141.3, 131.1, 120.9, 118.4, 112.1, 107.5, 102.3, 98.3, 97.0, 57.1, 54.6, 53.1, 39.5, 31.9, 30.4, 30.2, 28.4, 27.1, 26.5, 23.6, 22.5; IR (neat) 2924, 2851, 1711, 1640, 1585, 1460, 1355, 1201; HRMS (Qtof) calcd for $\text{C}_{28}\text{H}_{16}\text{O}_8$ (MH^+) 495.2019, found 495.2016; HRMS (Qtof) calcd for $\text{C}_{28}\text{H}_{30}\text{O}_8\text{Na}$ (MNa^+) 517.1838, found 517.1837.

4.4. Diels-Alder adducts **32b-35b** from maldoxin (**1b**)

Isopropenylallene **10** (2.8 mg, 0.019 mmol) was transferred to a resealable tube containing maldoxin (**1b**) (1.8 mg, 0.0047 mmol) in 1 mL of 1:1 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ mixture. The tube was sealed and heated in a 60 °C oil bath for 18 h. The mixture was cooled and evaporated to give 5 mg of crude product. ^1H NMR spectral analysis showed the presence of a 1:1:2:1:1 mixture of recovered **1b**, **32b**, **33b**, **34b**, and **35b**.

A similar reaction was carried out using isopropenylallene **10** (3.4 mg, 0.023 mmol) and maldoxin (**1b**) (2.3 mg, 0.0060 mmol) in a 75 °C oil bath for 1 day. ^1H NMR spectral analysis showed the presence of a 1:1:1 mixture of **32b**, **33b**, and **35b**.

The crude reaction mixtures were combined and purified by HPLC on XBridge™ Prep C18, 5 μ m OBD™, 19 $\times$ 250 mm; eluting with a gradient of 70:30:0.1 CH₃CN/H₂O/formic acid to 88:12:0.1 CH₃CN/H₂O/formic acid over 25 min (UV monitoring at 269 nm) to give 1.3 mg (22%) of **35b** (t_r = 9.1 min), 1.2 mg (20%) of **32b** (t_r = 16.1 min), 1.4 mg (24%) of **33b** (t_r = 18.7 min), and 0.4 mg (7%) of a 6:1:1 mixture of **34b** (t_r = 20.3 min), an uncharacterized Diels–Alder adduct (t_r = 19.5 min), and **35b**, respectively.

Data for **32b**: ¹H NMR 9.87 (br s, 1, OH), 6.45 (br s, 1), 6.33 (br s, 1), 6.31 (s, 1), 4.91 (s, 1), 4.12 (s, 3), 3.69 (s, 3), 3.03 (d, 1, J = 18), 2.27 (s, 3), 2.42–2.26 (m, 4), 2.16 (d, 1, J = 18), 1.70–1.45 (m, 6), 1.77 (s, 3); ¹³C NMR (partial, determined from HSQC and HMBC spectra, see Table S2) 173.4, 168.3, 160.6, 152.9, 149.6, 142.0, 131.1, 121.1, 118.3, 112.4, 108.4, 107.4, 98.0, 62.3, 53.9, 53.2, 40.8, 31.8, 30.4, 30.2, 28.2, 28.1, 26.7, 23.4, 22.5; IR (neat) 2925, 2850, 1741, 1642, 1569, 1449, 1366, 1203; HRMS (Qtof) calcd for C₂₈H₃₀ClO₈ (MH⁺) 529.1629, found 529.1632; HRMS (Qtof) calcd for C₂₈H₂₉ClO₈Na (MNa⁺) 551.1449, found 551.1453.

Data for **33b**: ¹H NMR 9.81 (br s, 1, OH), 6.46 (br s, 1), 6.22 (br s, 1), 5.51 (s, 1), 4.99 (s, 1), 3.76 (s, 3), 3.73 (s, 3), 2.60 (d, 1, J = 13.6), 2.28 (d, 1, J = 13.6), 2.27 (s, 3), 2.21–2.02 (m, 4), 1.70–1.41 (m, 6), 1.27 (s, 3); ¹H NMR (acetone-*d*₆) 6.53 (br s, 1), 6.31 (br s, 1), 5.65 (s, 1), 5.03 (s, 1), 3.77 (s, 3), 3.75 (s, 3), 2.53 (d, 1, J = 13.6), 2.40 (d, 1, J = 13.6), 2.31 (s, 3), 2.21–2.02 (m, 4), 1.70–1.41 (m, 6), 1.25 (s, 3); ¹³C NMR (partial, determined from HSQC and HMBC spectra, see Table S3) 198.7, 169.3, 160.7, 154.8, 150.7, 150.3, 112.0, 107.5, 107.2, 97.4, 96.3, 96.0, 94.6, 81.2, 56.6, 53.1, 51.0, 44.2, 39.3, 31.4, 30.4, 27.4, 26.7, 24.9, 24.4, 22.5; IR (neat) 2922, 2851, 1739, 1710, 1639, 1583, 1462, 1365, 1202; HRMS (Qtof) calcd for C₂₈H₃₀ClO₈ (MH⁺) 529.1629, found 529.1624; HRMS (Qtof) calcd for C₂₈H₂₉ClO₈Na (MNa⁺) 551.1449, found 551.1450.

Data for **34b**: ¹H NMR 9.83 (br s, 1, OH), 6.45 (br s, 1), 6.21 (br s, 1), 5.57 (s, 1), 5.03 (s, 1), 3.78 (s, 3), 3.74 (s, 3), 2.99 (d, 1, J = 13.6), 2.27 (s, 3), 2.30–2.08 (m, 4), 1.82 (d, 1, J = 13.6), 1.64–1.50 (m, 6), 1.16 (s, 3); IR (neat) 2920, 2850, 1708, 1642, 1584, 1461, 1203; HRMS (Qtof) calcd for C₂₈H₃₀ClO₈ (MH⁺) 529.1629, found 529.1631; HRMS (Qtof) calcd for C₂₈H₂₉ClO₈Na (MNa⁺) 551.1449, found 551.1450.

Partial data for the uncharacterized adduct were determined from the 6:1:1 mixture of **34b** (t_r = 20.3 min), the uncharacterized Diels–Alder adduct, and **35b**: ¹H NMR 9.79 (br s, 1, OH), 6.48 (br s, 1), 6.30 (br s, 1), 5.52 (s, 1), 4.96 (s, 1).

Data for **35b**: ¹H NMR 9.95 (br s, 1, OH), 6.39 (br s, 1), 6.32 (br s, 1), 6.13 (s, 1), 5.80 (s, 1), 5.48 (s, 1), 3.77 (s, 3), 3.72 (s, 3), 2.76 (br s, 1, OH), 2.67 (d, 1, J = 13.6), 2.29 (s, 3), 2.21–2.14 (m, 2), 2.00–1.92 (m, 2), 1.76–1.70 (m, 1), 1.64–1.58 (m, 1), 1.58–1.50 (m, 2), 1.46 (d, 1, J = 13.6), 1.16 (s, 3); ¹H NMR (acetone-*d*₆) 10.05 (br s, 1, OH), 6.38 (br s, 1), 6.38 (br s, 1), 6.21 (s, 1), 5.84 (s, 1), 5.49 (s, 1), 5.15 (br s, 1, OH), 3.69 (s, 3), 3.69 (s, 3), 2.56 (d, 1, J = 13.6), 2.27 (s, 3), 2.21–2.14 (m, 2), 2.00–1.92 (m, 2), 1.76–1.70 (m, 1), 1.64–1.58 (m, 1), 1.58–1.50 (m, 2), 1.46 (d, 1, J = 13.6), 1.13 (s, 3); ¹³C NMR (partial, determined from HSQC and HMBC spectra, see Table S4) 170.2, 160.5, 156.2, 152.4, 150.2, 142.6, 133.6, 131.2, 128.0, 110.6, 107.4, 106.4, 97.1, 95.6, 92.7, 90.1, 56.4, 55.2, 53.0, 46.1, 41.8, 26.1, 25.9, 22.7, 22.7, 22.5, 21.7; IR (neat) 2924, 2851, 1742, 1643, 1584, 1455, 1366, 1205; HRMS (Qtof) calcd for C₂₈H₃₀ClO₈ (MH⁺) 529.1629, found 529.1624; HRMS (Qtof) calcd for C₂₈H₂₉ClO₈Na (MNa⁺) 551.1449, found 551.1449.

The small amount of **35b** present in **34b** probably results from an ene reaction during solvent removal. The 6:1:1 mixture of **35b**, the uncharacterized adduct, and **34b** isomerized to a 5:1:2 mixture on storage in CDCl₃ for 1 month (at -20 °C, except when NMR data was being acquired). Heating the 1:2:1:1 mixture of **32b**, **33b**, **34b**, and **35b** obtained at 60 °C

(after removal of isopropenylallene **10**) for 18 h in a 70 °C oil bath gave a 1:2:0:2 mixture of **32b**, **33b**, **34b**, and **35b**. The Diels-Alder reaction with the isopropenylallene **10** as the diene that gives **32b** is slightly preferred at higher temperatures relative to those with the isopropenylallene as the dienophile that gives **33b** and **34b** because we obtained a 2:2:0:2, not 1:2:0:2 mixture, of **32b**, **33b**, **34b**, and **35b** when the reaction was started at 75 °C instead of starting at 60 °C and then increasing the temperature to 70 °C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

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9. NOEs were observed between the cyclohexene and aromatic ring protons of **8**, but not **5**.^{1c} We did not observe analogous NOEs in **35b**, but this is probably not useful for assigning the stereochemistry at the spiro center. The absence of cyclohexene substituents changes the conformation so that these NOEs should not be observed in either **35b** or the diastereomer at the spiro center. A full discussion is provided in the Supplementary data.

Scheme 1.

Isolation and biogenesis of chloropestolide A (**3**), chloropupukeanolides C (**8**) and D (**5**), and chloropupukeananin (**7**).

Scheme 2.
Diels-Alder reactions of **9** and **10**.

Scheme 3.
Acid catalyzed hydrolysis and ene reaction of **13**.

Scheme 4.
Facial selectivity in the dimerization of **16**.

Scheme 5.
Comparison of the reactivity of **19** and **20**.

Scheme 6.
Stereospecific dimerization of **24**.

Scheme 7.

Lack of facial selectivity in the inverse electron demand Diels-Alder reactions of **26**.

Scheme 8.
Generation and dimerization of benzo[1,3]dioxin-4-one **30**.

Scheme 9.
Diels–Alder reaction of maldoxin (**1b**) and **10**.

Figure 1.

X-Ray crystal structure of dechloromaldoxin (**1a**).⁴ The torsion angle between the cyclohexadienone oxygen and the ether oxygen is 81.3° whereas the torsion angle between the cyclohexadienone oxygen and the carboxylate oxygen is 42.0°.