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Synthesis of a precursor to quassimarin

Abstract

An intermediate containing the ACE ring system of quassimarin was prepared. The isopropylidene malonate **8** reacted with diene **2** to afford two Diels-Alder adducts. The major adduct was converted into lactone **11** by a sequence involving epoxidation followed by acid-mediated epoxide opening and lactonization.

Disciplines

Chemistry | Environmental Chemistry | Inorganic Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments

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of toluene was heated at 100 °C in an NMR tube. The progress of the reaction was followed by ^{31}P NMR. After 30 h, all **6** had disappeared, and the only phosphorus species gave complex signals in the pyrophosphate region (δ -10 and -21). The dihydrophthalimide derivative **15**⁴ was identified in the solution by ^1H and ^{13}C NMR spectroscopy.

Reaction of 5,6-Oxaphosphabicyclo[2.2.2]octene Derivative **6 with Benzylamine.** A solution of 0.10 g (0.29 mmol) of benzylamine in 0.75 mL of toluene was heated at 100 °C for 75 min, by which time all **6** had disappeared (^{31}P NMR analysis) and only one phosphorus product (δ about +11) was present. On cooling, a crystalline product precipitated; it was collected by filtration and recrystallized from ethanol-ether to yield 0.075 g of **17** (66%); mp 128-130 °C dec; $\delta_{31\text{P}}$ (CDCl_3) +11.6. Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_2\text{P} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 64.28; H, 6.88; P, 7.90. Found: C, 64.18; H, 6.78; P, 7.71.

The reaction was also conducted at room temperature; after 14 days, all **6** had disappeared, and the only phosphorus product was **17**, isolated in 69% yield.

X-ray Crystal Structure Analyses of $3\mathbf{a} \cdot \text{H}_2\text{O}$ and **6.** Crystal data: $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_2\text{P}_2 \cdot \text{H}_2\text{O}$ ($3\mathbf{a} \cdot \text{H}_2\text{O}$), M_r 332.32, monoclinic, $a = 6.333$ (1) Å, $b = 17.220$ (3) Å, $c = 9.585$ (1) Å, $\beta = 125.19$ (1)°, $V = 854.3$ Å³, $Z = 2$, $D_{\text{calcd}} = 1.292$ g cm⁻³, μ (Cu K α radiation, $\lambda = 1.5418$ Å) = 24.3 cm⁻¹. Space group $Pc(C_2^2)$ or $P2_1/c(C_2^2)$ from the systematic absences $h0l$ when $l \neq 2n$, with $Z = 2$, an ordered structure demands the former as **3a** lacks either a center or twofold axis of symmetry. Sample dimensions: 0.07 × 0.12 × 0.70 mm (sealed inside a thin-walled glass capillary to prevent loss of water of crystallization).

$\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_4\text{P}$ (**6**), M_r 346.33, triclinic, $a = 8.013$ (1) Å, $b = 15.480$ (1) Å, $c = 7.084$ (1) Å, $\alpha = 91.26$ (1)°, $\beta = 108.30$ (1)°, $\gamma = 100.05$ (1)°, $V = 818.7$ Å³, $Z = 2$, $D_{\text{calcd}} = 1.405$ g cm⁻³, μ (Cu K α radiation) = 16.9 cm⁻¹. Space group $P1(C_1)$ or $P\bar{1}(C_1)$ from Laue symmetry; shown to be the latter by structure solution. Sample dimensions: 0.08 × 0.30 × 0.60 mm (mounted on the end of a thin glass fiber).

Oscillation, Weissenberg, and precession photographs yielded preliminary unit-cell parameters and space group information. Intensity data hkl for $3\mathbf{a} \cdot \text{H}_2\text{O}$; $\pm h \pm kl$ for **6** were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu K α radiation, incident-beam graphite monochromator; ω - 2θ scans, $\theta_{\text{max}} = 67^\circ$). From totals of 1554 and 2941 unique forms for $3\mathbf{a} \cdot \text{H}_2\text{O}$ and **6**, respectively, those 1076 and 2609 with $I > 3.0\sigma(I)$ were retained for the structure analyses. In addition to the usual Lorentz and polarization corrections, empirical absorption corrections, based on the ϕ dependence of the intensities of several reflections with χ ca. 90°, were also applied to the data. Refined unit-cell pa-

rameters were derived by least-squares treatment of the diffractometer setting angles for 25 reflections ($39^\circ < \theta < 65^\circ$ for $3\mathbf{a} \cdot \text{H}_2\text{O}$; $60^\circ < \theta < 67^\circ$ for **6**) widely separated in reciprocal space.

The crystal structure of $3\mathbf{a} \cdot \text{H}_2\text{O}$ was solved by the heavy-atom approach. Initial coordinates for the phosphorus atoms were derived from the three-dimensional Patterson map, and remaining non-hydrogen atom positions were obtained from a weighted F_o Fourier synthesis phased by the phosphorus atoms. Full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic thermal parameters, with hydrogen atoms included at their calculated positions in the later iterations, converged to $R = 0.045$ ($R_w = 0.059$).¹³ For **6**, the crystal structure was solved by use of direct methods.¹⁶ Approximate positions for all non-hydrogen atoms were obtained from an E -map. Hydrogen atoms were located in a difference Fourier synthesis evaluated at a late stage in the analysis. Full-matrix least-squares adjustment of atomic positional and thermal (anisotropic C, N, O, P; isotropic H) parameters converged to $R = 0.045$ ($R_w = 0.073$).¹³

Neutral atom scattering factors used in the structure-factor calculations were taken from ref 18. In the least-squares iterations, $\sum \omega \Delta^2 [w = 1/\sigma^2(|F_o|), \Delta = |F_o| - |F_c|]$ was minimized. All calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius SDP suite of programs.

Registry No. $3\mathbf{a} \cdot \text{H}_2\text{O}$, 103003-07-2; **3b**, 96548-52-6; **3c**, 103003-08-3; **4**, 103003-10-7; **5**, 103003-11-8; **6**, 103003-12-9; **7**, 103003-13-0; **11**, 92063-25-7; **12**, 103003-14-1; **13**, 103003-15-2; **14**, 103003-16-3; **15**, 75581-74-7; **17**, 103003-17-4; 1-(*N,N*-diethylamino)-3-methyl-3-phospholene 1-oxide, 3105-70-2; 1-piperidyl-3-methyl-3-phospholene 1-oxide, 7563-20-4; 3,4-dibromo-1-(*N,N*-dimethylamino)-3-methylphospholane 1-oxide, 103003-04-9; 3,4-dibromo-1-(*N,N*-diethylamino)-3-methylphospholane 1-oxide, 103003-05-0; 3,4-dibromo-1-piperidinyl-3-methylphospholane 1-oxide, 103003-06-1; 1-(*N,N*-dimethylamino)-3,4-dimethylphospholane 1-oxide, 103003-09-4; *N*-phenylmaleimide, 941-69-5; benzylamine, 100-46-9.

Supplementary Material Available: Tables of non-hydrogen atom positional and anisotropic thermal parameters, hydrogen atom parameters, interatomic distances and angles, torsion angles, and displacements of atoms from least-squares planes for $3\mathbf{a} \cdot \text{H}_2\text{O}$ and **6** (16 pages). Ordering information is given on any current masthead page.

(18) *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.

Synthesis of a Precursor to Quassamarin

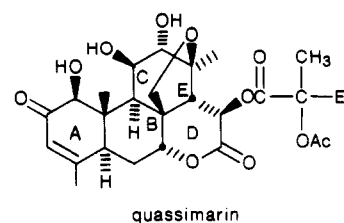
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Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received February 19, 1986

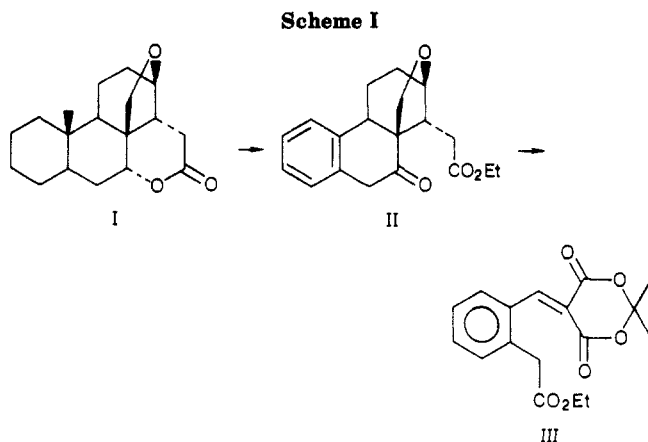
An intermediate containing the ACE ring system of quassamarin was prepared. The isopropylidene malonate **8** reacted with diene **2** to afford two Diels-Alder adducts. The major adduct was converted into lactone **11** by a sequence involving epoxidation followed by acid-mediated epoxide opening and lactonization.

The quassinoids are a diverse class of diterpenes that exhibit useful biological activity.¹ This fact, combined with their challenging structure, has made them frequent synthetic objectives. This is evidenced by the significant number of recent approaches. Grieco's elegant studies on quassinoid synthesis have led to total syntheses of quassin and castelanolide and the synthesis of an isomer of the pentacyclic quassinoid quassamarin.² Ganem has reported



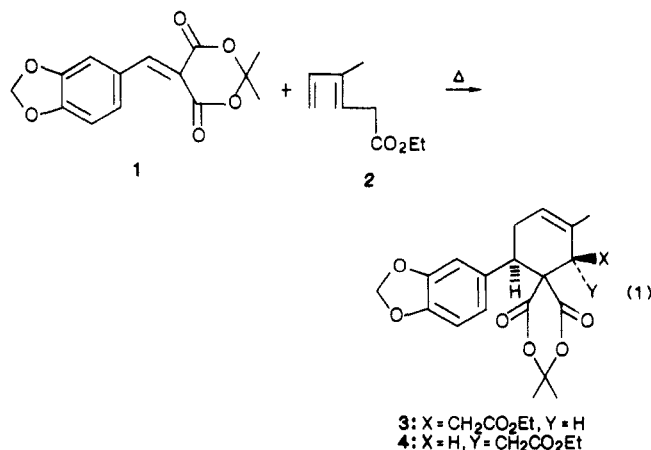
a clever approach to the pentacyclic member.³ Fuchs,⁴ Weller,⁵ Watt,⁶ and Heathcock⁷ have also reported very

(1) Polonsky, J. *Fortschr. Chem. Org. Naturst.* 1973, 30, 102.

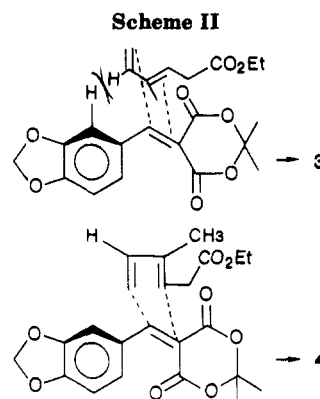


promising routes. We initially planned a Diels–Alder–based strategy in which the B ring stereochemistry was introduced by the cycloaddition of 2-carbomethoxybenzoquinone with a substituted diene.⁸ A more direct approach which would also address problems associated with the appendage of the A ring is outlined in Scheme I. The key step involves the cycloaddition of a sterically hindered isopropylidene malonate with a substituted diene.

Isopropylidene alkylidenemalonates have been employed as both dienes and dienophiles in the Diels–Alder reaction. Tietze has demonstrated that electron-rich alkenes undergo both intermolecular and intramolecular cycloadditions with isopropylidene alkylidenemalonates.⁹ Dauben has developed an efficient synthesis of δ -damascone using the adduct of an isopropylidene malonate and piperylene.¹⁰ In order to test the feasibility of our plan, the reaction between 1 and diene 2 was studied (eq 1).



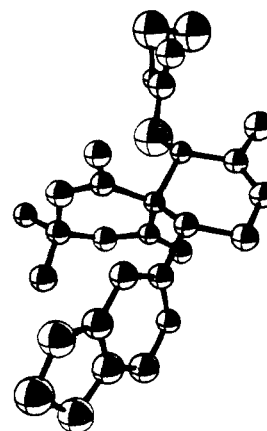
Compound 1 was prepared from isopropylidene malonate and piperonal by the method of Brown.¹¹ The Diels–Alder



reaction afforded products 3 and 4 in a 2:3 ratio in 60% yield. The two products were crystalline and readily separable. They were clearly stereoisomers as evidence by NMR and mass spectroscopy. Unambiguous assignment of the structure by NMR was complicated in that the two stereogenic centers were isolated from each other. However, a single-crystal X-ray determination¹² showed a cis relationship between the aryl group and the acetic acid ester portion in adduct 3. Adduct 4, therefore, has the desired trans relationship. In principle, a 1:1 ratio of adducts could have resulted, since both carbonyl groups activate equally. However, we anticipated that in the preferred conformation the aryl ring would be out of the plane of the alkylidenemalonate group and would interfere with the approach of the diene. This is shown in Scheme II. This disparity should increase as the number and size of the ortho substituents increases.

With adduct 4 readily available, the diacid became the next goal. Molecular models indicated that the isopropylidene malonate was fairly hindered, being flanked by both the aryl group and the acetic acid ester group. Indeed, upon treatment with excess methanolic potassium hydroxide the isopropylidene malonate moiety was not cleaved. Starting material was recovered when 4 was treated with aqueous HCl in THF. The reaction of 4 with *p*-toluenesulfonic acid in boiling benzene produced several products. Since the diacid was to be converted into an axial lactone, we set out to cleave the isopropylidene malonate intramolecularly and produce the lactone directly. This approach was successful, as depicted in eq 2. Ex-oxidation of the olefin with *m*-chloroperbenzoic acid followed by opening of the epoxide with perchloric acid produced lactone 5 in 98% yield. The absence of the

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(12)



(2) Quassin: Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* 1980, 102, 7586. Grieco, P. A.; Vidari, G.; Ferrino, S. *J. Am. Chem. Soc.* 1984, 106, 3539. Castelanolide: Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* 1984, 49, 2342.

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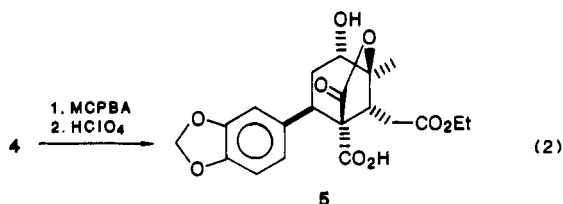
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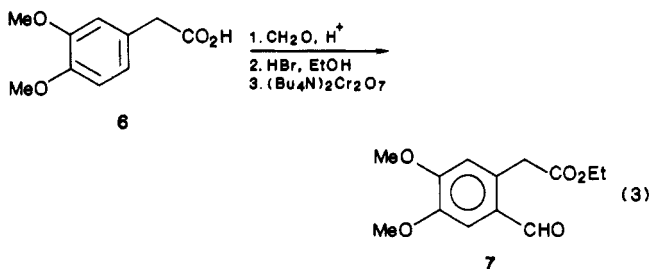
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(10) Dauben, W. G.; Kozikowski, A. P.; Zimmerman, W. T. *Tetrahedron Lett.* 1975, 515.

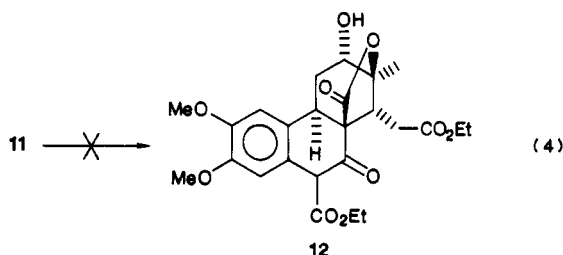


olefinic resonance in the NMR and the appearance of an IR absorption at 1775 cm^{-1} supported the structure.

With the formation of lactone acid **5**, the preliminary study was complete. The preparation of **II** now became the next objective. The synthesis of dienophile **8** required the preparation of aldehyde **7**. The most direct route to **7** is shown in eq 3. The commercially available acid **6** was



converted to the lactone using formaldehyde and acid. This lactone was cleaved to a bromo ester with HBr in ethanol.¹³ The benzylic bromide was then oxidized to aldehyde **7** with bis(tetrabutylammonium) dichromate.¹⁴ This aldehyde was easily transformed into **8**. The Diels-Alder reaction of **8** with diene **2** afforded the two adducts **9** and **10** in a 2:5 ratio in 84% yield (Scheme III). The increased stereoselectivity presumably reflects the presence of the acetic acid ester unit in the ortho position. The chemical shifts and multiplicities were essentially identical with those in the model system compounds **3** and **4**. Therefore, the structures assigned to **9** and **10** are well supported. Adduct **10** was treated with *m*-chloroperbenzoic acid followed by perchloric acid to generate the lactone acid which was esterified with diazomethane to produce triester **11** in 76% yield. Triester **11** was then subjected to several Dieckmann condensation conditions.¹⁵ Since the arylacetic ester moiety should be the most acidic group in **11**, the formation of a single β -keto ester was expected. Surprisingly, only starting material was recovered when triester **11** was treated with sodium hydride in THF or with potassium hydride in THF. The reaction with sodium methoxide yielded only transesterification products. The rationale for the failure of **11** to cyclize to **12** is not clear. Perhaps nonbonded interactions between the lactone carbonyl and the hydrogen on the carbanion carbon are responsible (eq 4).

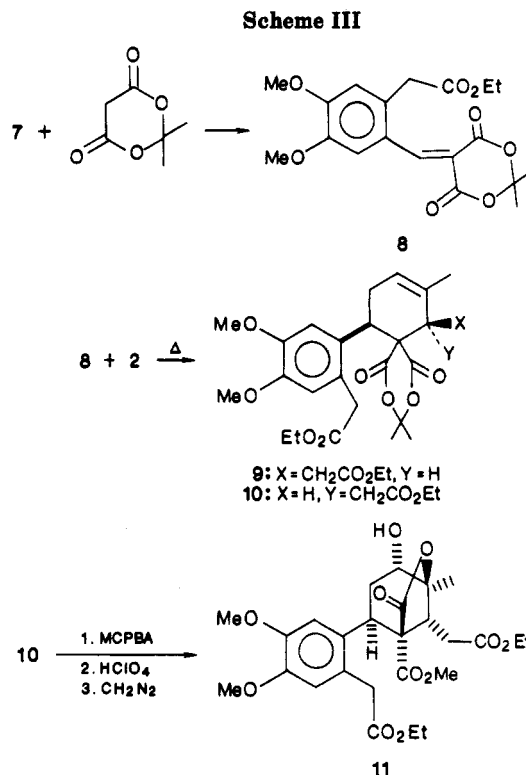


The synthesis of **5** and **11** in 35% and 26% yield, respectively, represents a direct entry to the ACE ring system

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of quassamarin. While a suitable reaction to append the B ring has yet to be found, the overall approach is a convergent one and alternative dienophiles can be readily generated. Compound **5** may be useful for the generation of secoquassinoids, compounds that could provide valuable insight into the structural requirements for biological activity.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from phosphorus pentoxide. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 60-MHz instrument and on a Nicolet 300-MHz instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform instrument. High resolution mass spectra were determined on a Kratos mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. Melting points were determined on a Fischer-Johns apparatus and are uncorrected.

General Procedure for the Formation of Alkylidene-malonates. The aldehyde (1.5 equiv) and 2,2-dimethyl-1,3-dioxane-4,6-dione (1.0 equiv) were dissolved in benzene (0.25 M with respect to the dioxanedione) at room temperature. Piperidine (0.19 equiv) and glacial acetic acid (1.1 equiv) were added and the solution was heated at reflux, using a Dean-Stark trap to remove water. After 3 h, the Dean-Stark trap was replaced with a distillation head and the reaction was concentrated to one-third of the original volume. After the concentrate had cooled, the product crystallized as bright yellow needles. The yield of **1** was 93%. The yield of **8** was 92%.

1: mp $178.5\text{--}179.5\text{ }^\circ\text{C}$; NMR (CDCl_3) 1.79 (s, 6 H), 6.08 (s, 2 H), 6.85 (d, $J = 8\text{ Hz}$, 1 H), 7.53 (dd, $J = 2\text{ and } 8\text{ Hz}$, 1 H), 8.04 (d, $J = 2\text{ Hz}$, 1 H), 8.30 (s, 1 H); ^{13}C NMR (CDCl_3) 27.57, 102.29, 104.11, 108.47, 111.98, 112.63, 126.68, 133.70, 148.40, 153.08, 157.50, 160.10; IR (CH_2Cl_2) 3050, 1720, 1570, 1560, 1450, 1240, 1080, 935 cm^{-1} .

8: 300-MHz NMR (CDCl_3) 1.23 (t, $J = 7\text{ Hz}$, 3 H), 1.80 (s, 6 H), 3.78 (s, 2 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 4.13 (q, $J = 7\text{ Hz}$, 2 H), 6.83 (s, 1 H), 8.03 (s, 1 H), 8.65 (s, 1 H); IR (CDCl_3) 3060, 1740, 1720, 1570, 1555, 1485, 1450, 1390, 1240, 1080, 995, 930 cm^{-1} .

General Procedure for the Diels-Alder Reactions. Equimolar amounts of the alkylidene-malonate and diene **2** were

dissolved in toluene (0.3 M with respect to 2) and heated for 72 h at reflux. The solution was then cooled and concentrated. The crude product was then separated by flash chromatography using 6:1 hexanes/ethyl acetate.

3: mp 149–151 °C; 300-MHz NMR (CDCl₃) 0.72 (s, 3 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.59 (s, 3 H), 1.71 (br s, 3 H), 2.06 (m, 2 H), 2.56 (dd, *J* = 4 and 9 Hz, 1 H), 2.82 (br t, *J* = 11 Hz, 1 H), 3.61 (dd, *J* = 3 and 7 Hz, 1 H), 3.78 (br s, 1 H), 4.14 (m, 2 H), 5.70 (br s, 1 H), 5.90 (s, 2 H), 6.71 (s, 3 H); ¹³C NMR (CDCl₃) 14.09, 21.35, 28.69, 29.36, 29.80, 35.20, 44.50, 46.85, 59.43, 61.17, 101.16, 106.21, 108.66, 109.83, 122.74, 123.39, 131.09, 133.03, 147.43, 148.04, 169.53, 171.50; IR (CDCl₃) 2990, 1770, 1740 sh, 1730, 1620, 1580, 1450, 1380, 1325, 1250, 1045 cm⁻¹. Anal. Calcd for C₂₃H₂₆O₈: C, 64.18; H, 6.09. Found: C, 64.20; H, 6.05.

4: mp 146.5–148 °C; 300-MHz NMR (CDCl₃) 1.27 (s, 3 H), 1.27 (t, *J* = 7 Hz, 3 H), 1.79 (br s, 3 H), 1.83 (br s, 3 H), 2.36 (d of m, *J* = 16 Hz, 1 H), 2.56 (d, *J* = 16 Hz, 1 H), 2.61 (m, 1 H), 3.07 (m, 2 H), 3.45 (dd, *J* = 4 and 6 Hz, 1 H), 4.14 (m, 2 H), 5.72 (br s, 1 H), 5.89 (d, *J* = 2 Hz, 2 H), 6.69 (s, 1 H), 6.72 (s, 1 H); ¹³C NMR (CDCl₃) 14.18, 22.50, 28.88, 29.11, 31.04, 35.23, 42.29, 42.54, 55.24, 60.85, 100.98, 105.17, 108.15, 109.83, 122.71, 123.62, 130.26, 133.04, 146.91, 147.53, 166.39, 167.65, 172.44; IR (film) 3005, 2995, 1770, 1730, 1620, 1505, 1445, 1380, 1260, 1230, 1180, 930 cm⁻¹. Anal. Calcd for C₂₃H₂₆O₈: C, 64.18; H, 6.09. Found: C, 64.19; H, 6.45.

9: 300-MHz NMR (CDCl₃) 0.86 (s, 3 H), 1.24 (t, *J* = 7 Hz, 3 H), 1.28 (t, *J* = 7 Hz, 3 H), 1.62 (s, 3 H), 1.71 (br s, 3 H), 2.18 (dd, *J* = 4 and 14 Hz, 1 H), 2.37 (br d, *J* = 14 Hz, 1 H), 2.59 (dd, *J* = 7 and 12 Hz, 1 H), 2.74 (br t, *J* = 12 Hz, 1 H), 3.42 (d, *J* = 15 Hz, 1 H), 3.85 (br s, 6 H), 3.94 (m, 2 H), 4.08–4.23 (m, 5 H), 5.62 (br s, 1 H), 6.67 (s, 1 H), 6.77 (s, 1 H); ¹³C NMR (CDCl₃) 14.04, 14.17, 21.22, 28.91, 29.97, 31.02, 35.13, 38.26, 42.30, 44.97, 55.78, 55.87, 56.09, 58.41, 60.85, 61.14, 106.21, 111.24, 114.13, 123.84, 126.16, 130.66, 130.83, 148.13, 165.08, 169.75, 171.40, 171.69; IR (CDCl₃) 3020, 1770, 1735, 1695, 1610, 1450, 1370, 1200, 1025, 910 cm⁻¹; HRMS for C₂₃H₃₆O₁₀ requires 532.23086, measured 532.23245.

10: 300-MHz NMR (CDCl₃) 1.22 (t, *J* = 7 Hz, 3 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.35 (s, 3 H), 1.77 (s, 3 H), 1.83 (s, 3 H), 2.39 (br d, *J* = 8 Hz, 1 H), 2.62 (m, 2 H), 3.03 (m, 2 H), 3.35 (br d, *J* = 6 Hz, 1 H), 3.68–3.87 (m, 2 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.11 (m, 4 H), 5.71 (br s, 1 H), 6.64 (s, 1 H), 6.74 (s, 1 H); ¹³C NMR (CDCl₃) 14.08, 14.12, 22.42, 28.83, 29.12, 31.70, 35.06, 38.13, 38.78, 42.99, 53.37, 54.32, 55.59, 55.64, 60.69, 60.78, 105.05, 110.24, 114.09, 124.21, 126.39, 130.02, 130.89, 147.62, 167.00, 167.94, 171.86, 172.31; IR (CDCl₃) 3030, 1770, 1740, 1730, 1615, 1445, 1380, 1260, 1030 cm⁻¹.

General Preparation of the Lactones. The Diels–Alder adduct (1.0 equiv) was dissolved in methylene chloride (0.13 M). After the solution was cooled to 0 °C, MCPBA (1.05 equiv) was

added as a solid in one portion. The reaction mixture was slowly allowed to warm to room temperature over 2 h. The mixture was diluted with ether (twice the original volume) and washed with saturated sodium bicarbonate solution and then with brine. The organic layer was concentrated, dissolved in THF to make a 0.13 M solution, and treated with 3 N perchloric acid (4 mL/mmol of epoxide). After the solution had stirred for 12 h at room temperature, it was diluted with an equal volume of water and extracted twice with ether. The combined extracts were washed with brine, dried, and concentrated. In the case of the lactone derived from 10, it was dissolved in methylene chloride and treated with diazomethane in ether until gas evolution ceased. Lactone 5 was produced in 98% yield. Lactone 11 was produced in 76% yield.

5: 300-MHz NMR (CDCl₃) 1.28 (t, *J* = 7 Hz, 3 H), 1.57 (s, 3 H), 1.98–2.15 (m, 2 H), 2.36 (d, *J* = 3 Hz, 1 H), 3.04 (d, *J* = 4 Hz, 2 H), 3.22 (t, *J* = 4 Hz, 1 H), 3.99 (br s, 1 H), 4.14 (q, *J* = 7 Hz, 2 H), 5.90 (s, 2 H), 6.68 (d, *J* = 6 Hz, 1 H), 6.83 (d, *J* = 6 Hz, 1 H), 6.89 (s, 1 H); IR (CDCl₃) 3650–2400, 1775, 1740 sh, 1725, 1620, 1440, 1380, 1250, 905 cm⁻¹. Anal. Calcd for C₂₀H₂₂O₉: C, 59.11; H, 5.46. Found: C, 58.88; H, 5.43.

11: 300-MHz NMR (CDCl₃) 1.28 (t, *J* = 7 Hz, 6 H), 1.58 (s, 3 H), 2.10 (m, 2 H), 2.79 (br s, 1 H), 3.08 (m, 1 H), 3.24 (br t, *J* = 8 Hz, 1 H), 3.52 (s, 3 H), 3.70 (m, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.82–4.08 (m, 4 H), 4.14 (m, 4 H), 6.67 (s, 1 H), 7.13 (s, 1 H); ¹³C NMR (CDCl₃) 14.13, 20.65, 29.31, 31.02, 37.72, 39.33, 50.76, 52.38, 55.71, 55.84, 59.62, 60.91, 61.02, 67.90, 71.13, 84.12, 110.22, 113.88, 125.11, 128.15, 128.95, 132.12, 147.17, 168.49, 172.31, 172.63; IR (CDCl₃) 3030, 1780, 1740 sh, 1730, 1615, 1450, 1385, 1280, 1120, 1010 cm⁻¹; HRMS for C₂₆H₃₄O₁₁ requires 522.21012, measured 522.21083.

Synthesis of Aldehyde 7. The bromo ester (1.67 g, 5.30 mmol) was dissolved in 15 mL of chloroform at room temperature. Tetrabutylammonium dichromate (7.58 g, 10.60 mmol) was added and the mixture was heated at reflux for 2 h. The cooled mixture was filtered through 30 g of silica gel using 400 mL of ether to afford 1.24 g (93% yield) of pure 7: NMR (CDCl₃) 1.21 (t, *J* = 7 Hz, 3 H), 3.93 (s, 6 H), 3.96 (s, 2 H), 4.14 (q, *J* = 7 Hz, 2 H), 6.75 (s, 1 H), 7.35 (s, 1 H), 10.08 (s, 1 H); IR (CCl₄) 3030, 1740, 1730, 1695, 1680, 1470, 1280, 1170, 1115, 1030 cm⁻¹.

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BOP-Cl Mediated Synthesis of the Cyclosporine A 8–11 Tetrapeptide Fragment

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With the bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) coupling reagent, synthesis of the cyclosporine A 8–11 tetrapeptide has been carried out utilizing both Fmoc- and Cbz-N-protection of the intermediates. The former protecting group allows a very time efficient sequence where isolation of the free imino fragment is obviated and demonstrates the potential for applications to solid phase. Cbz protection is more economical for larger scale synthesis, however, and provides more stable intermediates. In both cases remarkable chemical efficiency was achieved, the fully protected tetrapeptide being obtained in 66% and 73% yields, respectively, from the constituent protected amino acids. By means of the Fmoc procedure, diastereomers at each stage of coupling have been separately prepared. HPLC analysis, using these compounds as internal standards, has shown that racemization in all cases was less than 1%.

The cyclosporines are a family of extensively N-methylated cyclic undecapeptides, first isolated as fungal

metabolites, a number of which possess strong, orally active immunosuppressive properties.¹ Due to the recent FDA