three weeks at −20 °C. This procedure yielded a mixture of dark cubic crystals of **3**·2MeCN and a brick-red powder. The powder was partially removed by swirling the solution and decanting the fine powder suspension. This was repeated several times with fresh MeCN to give nearly pure **3**. The crystals were separated manually from the remainder of the powder to give analytically pure **3**·2MeCN. Yield: 0.53 g (63% based on Te). Compound **3** is insoluble in most common organic solvents but does give unstable solutions in DMSO. IR (DMSO): $\tilde{\nu}_{CO}$ = 2067 (vs), 2027 (s), 1981 (m, sh) cm^{-1}. Analysis calcd for **3**·2MeCN: 6.1 mmol CO per gram. Found: 6.2 mmol CO per gram.

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[5] Crystal structure data for **3**·2MeCN ($C_{14}H_6N_2O_9Br_4Fe_3Te_5$): M_r = 1471.40, orthorhombic, space group *Pcmn* (No. 62), $Z = 4$, a = 17.698(4) Å, b = 18.444(4) Å, c = 9.530(2) Å, V = 3110.8(12) Å^3, ρ_{calcd} = 3.142 gcm^{-3}, $Mo_{K\alpha}$-Strahlung, λ = 0.71069 Å, μ = 11.157 mm^{-1}. A total of 2127 independent reflections (of 3895 measured) were collected on a Rigaku AFC5S diffractometer at 223(2) K, 2θ-ω scans ($2.21 < \theta < 24.82°$), absorption correction by azimuthal (ψ) scans. The structure was solved by direct methods (Siemens SHELXTL-PC) and refined (SHELXL-93, G. M. Sheldrick) by full-matrix least-squares on F^2 to final residuals of R = 0.0268 (F) and wR = 0.0541 (F^2) for 1579 observed reflections ($I > 2\sigma(I)$, GOF = 1.026). Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein- Leopoldshafen (Germany), on quoting the depository number CSD-406 538.

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Synthesis of the Bicyclic Core of CP-225,917 and CP-263,114 by an Intramolecular Diels–Alder Reaction**

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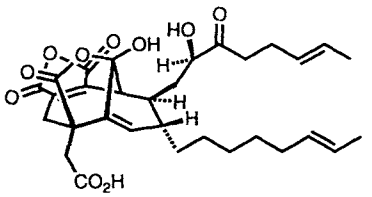
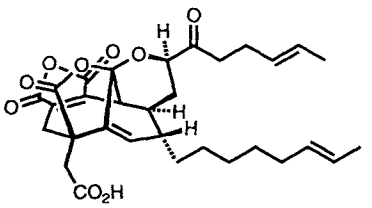
CP-225,917 (**1**) and CP-263,114 (**2**) are two structurally unusual natural products that were recently isolated from an unidentified fungus by a Pfizer research group.[1, 2] These molecules—which contain bicyclo[4.3.1]dec-1(9),4-dien-10-one, maleic anhydride, and γ-lactol ring systems—are both novel and challenging to synthetic chemists. Their biological activity includes inhibition of squalene synthase[1, 3] and Ras farnesyl transferase.[1, 4] Therefore, they constitute intriguing lead compounds for the development of useful agents for medical intervention, particularly for lowering cholesterol levels[5] and for cancer chemotherapy.[5, 6] Their presumed biosynthesis[1, 2] and mode of action add to their appeal as synthetic targets, since they provide additional opportunities for contributions to biology and medicine. Here we report an approach to the novel bicyclic core of these naturally occurring substances based on an intramolecular Diels–Alder reaction.[7]



1 CP-225,917



2 CP-263,114

Inspection of the structures of **1** and **2** reveals that the basic carbon skeleton can be reduced to model system **3** (Scheme 1), which contains the key and challenging bicyclic core as well as anchor groups for elaborating the remaining functionalities and side chains. Applying a retro Diels–Alder reaction to **3** leads to the open-chain triene **4** as a potential precursor (Scheme 1). Since the absolute stereochemistry of **1** and **2** is not yet known, this issue was put aside for now. The construction of **4** was guided by the strategic bond disconnections shown in Scheme 1 and involved a nucleophilic acylation reaction[8] and a directed aldol condensation.[9]

Scheme 2 summarizes the synthesis of **3a**, **b** from 1,4-butanediol (**5**). Monosilylation of **5** with NaH and *tert*-butyldimethysilyl chloride in THF proceeded in 90% yield to afford the corresponding hydroxysilyl ether **6**, which was smoothly oxidized to aldehyde **7** with SO_3·pyridine/DMSO/Et_3N. Alkylation of **7** via its *N*-cyclohexylimine derivative **8** with LDA and

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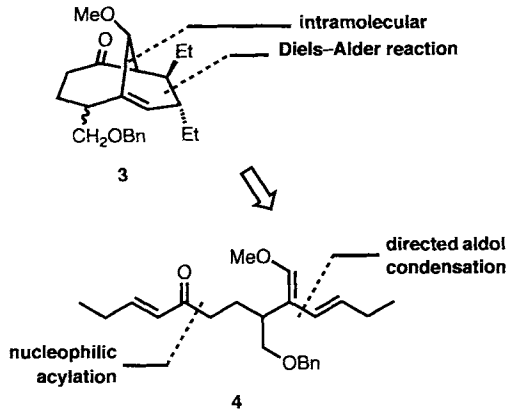


Scheme 1. Model compound **3** and the retrosynthetic analysis.

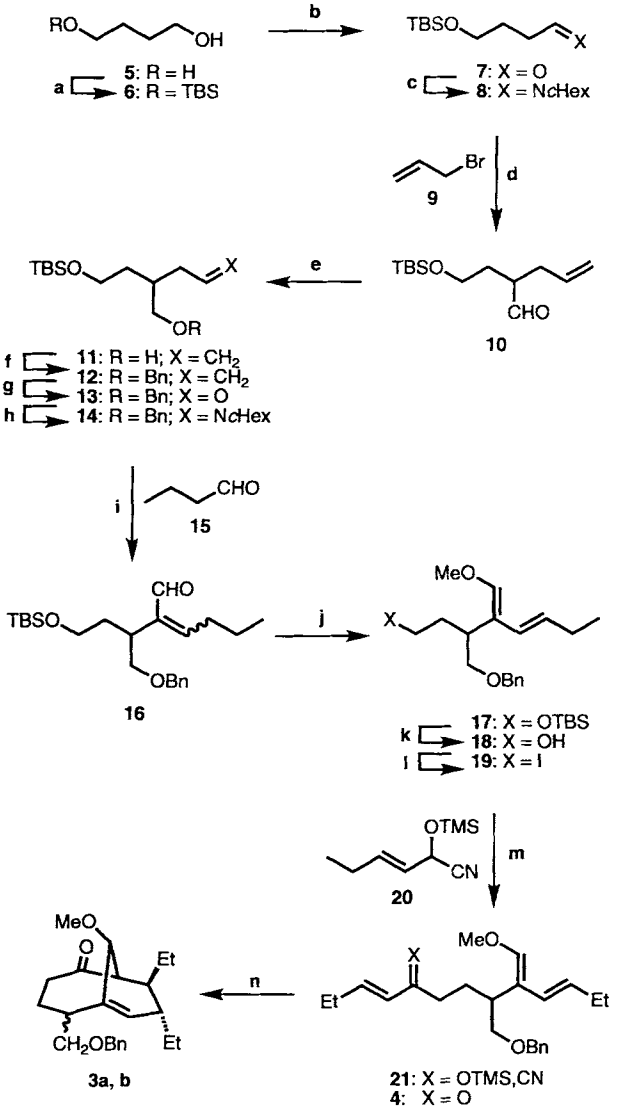
allyl bromide (**9**) furnished **10**, which was reduced with $NaBH_4$ in methanol to afford primary alcohol **11** (58% overall yield from **7**). After benzylation of **11**, the terminal olefin was cleaved with ozone/Ph_3P to give aldehyde **13** in 84% yield. Formation of the imine of **13** by reaction with cyclohexylamine in benzene under anhydrous conditions followed by anion generation, condensation with *n*-butanal (**15**), and acidic workup furnished aldehyde **16** in 74% overall yield as a mixture of isomers (*E*:*Z* ca. 1:1). Methylation of **16** with Me_2SO_4 in the presence of KH and HMPA proceeded smoothly to afford diene **17** in 96% yield as the single geometrical isomer. Desilylation of **17** with TBAF in aqueous THF led to alcohol **18**, which was converted to the corresponding iodide **19** with I_2/Ph_3P/imidazole in 78% yield. Finally, reaction of **19** with the lithio derivative of the TMS-protected cyanohydrine **20**,[4] followed by exposure to TBAF in aqueous THF led to triene **4** via **21** in 86% overall yield (see Table 1).

Table 1. Selected physical properties of **4** and **3a,b** [10].

4: R_f 0.18 (silica gel, hexane/ether 4/1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32-7.22$ (m, 5H, phenyl group), 6.81 (td, 1H, $J_1 = 9.50$, $J_2 = 15.84$ Hz, C*H*=CHCO), 6.08 (s, 1H, MeOC*H*=C), 6.03 (dd, 1H, $J_1 = 1.50$, $J_2 = 16.00$ Hz, CH=C*H*CO), 5.74 (d, 1H, $J = 15.59$ Hz, =C(C)C*H*=CH), 5.55 (td, 1H, $J_1 = 5.70$, $J_2 = 15.50$ Hz, =C(C)CH=C*H*CH$_2$), 4.48 and 4.49 (2s, 2H, OCH_2Ph), 3.57 (m, 2H, C(H)(C)CH_2OBn), 3.54 (s, 3H, OCH$_3$), 2.90 (m, 1H, =C(C)C(C)*H*CH$_2$OBn), 2.49 (m, 2H, C(O)CH_2CH$_2$), 2.19 (d of pseudo quint., 2H, $J_1 = 1.50$, $J_2 = 6.75$ Hz, H$_3$CCH_2CH=CHC(O)), 2.04 (pseudo quint., 2H, $J = 6.88$ Hz, =C(C)CH=CHCH_2CH$_3$), 1.93 and 1.83 (2m, 2H, C(O)CH$_2$CH_2CH(C)), 1.03 (t, 3H, $J = 7.42$ Hz, CH$_2$CH_3), 0.95 (t, 3H, $J = 7.44$ Hz, CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 201.1$, 148.1, 147.6, 138.8, 129.4, 128.1, 128.1, 128.0, 127.5, 127.2, 126.7, 126.7, 117.9, 72.7, 72.6, 59.8, 38.2, 36.8, 26.1, 25.4, 24.4, 14.0, 12.2; IR (Film): $\tilde{\nu}$ = 3027, 2962, 2872, 1669, 1630, 1455, 1364, 1230, 1114, 978, 740, 699 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{32}O_3Na$ [M+Na$^+$]: 379.2249, found: 379.2243.

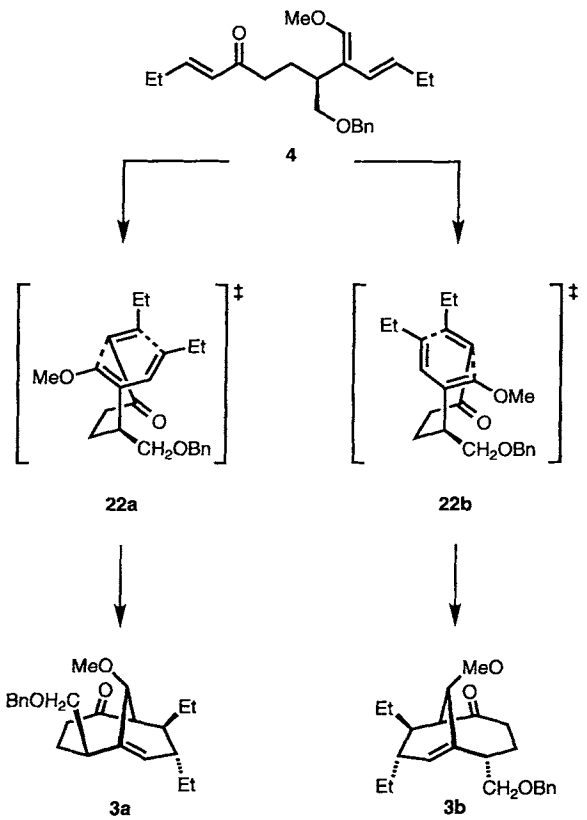
3a,b (major isomer): R_f 0.25 (silica gel, hexane/acetone 94/6); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.33-7.23$ (m, 5H, phenyl group), 5.59 (dd, 1H, $J_1 = 2.00$, $J_2 = 4.00$ Hz, C(C)=C*H*CH(C)), 4.54 (s, 2H, OCH_2Ph), 3.90 (dd, 1H, $J_1 = 2.00$, $J_2 = 4.00$ Hz, H$_3$COC*H*(C)), 3.82 (dd, 1H, $J_1 = 7.75$, $J_2 = 9.25$ Hz, CH(C)C*H*HOBn), 3.59 (dd, 1H, $J_1 = 6.75$, $J_2 = 9.25$ Hz, CH(C)CH*H*OBn), 3.25 (s, 3H, OCH$_3$), 2.85 (dd, 1H, $J_1 = 2.00$, $J_2 = 4.00$ Hz, bridgehead proton), 2.80 (pseudo quint., 1H, $J = 8.17$ Hz, CH$_2$C*H*(C)CH$_2$OBn), 2.34 (m, 2H, CH_2C(O)), 1.83 (m, 2H), 1.75–1.58 (m, 3H), 1.33–1.18 (m, 3H), 0.97 (t, 3H, $J = 7.25$ Hz, CH$_2$CH_3), 0.95 (t, 3H, $J = 7.50$ Hz, CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 214.2$, 141.3, 138.7, 132.4, 128.3, 127.6, 127.4, 80.3, 72.9, 72.6, 58.5, 57.0, 48.2, 46.2, 41.3, 40.1, 26.6, 26.1, 25.5, 12.1, 11.3; IR (film): $\tilde{\nu}$ = 2958, 2945, 2869, 1691, 1457, 1383, 1317, 1257, 1204, 1112, 739, 698 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{33}O_3$ [M+H$^+$]: 357.2429, found: 357.2423.

3a,b (minor isomer): R_f 0.28 (silica gel, hexane/acetone 94/6); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.33-7.24$ (m, 5H, phenyl group), 5.26 (pseudo t, 1H, $J = 2.24$ Hz, C(C)=C*H*CH(C)), 4.54 und 4.53 (2s, 2H, OCH_2Ph), 3.66 (pseudo t, 1H, $J = 2.25$ Hz, H$_3$COC*H*(C)), 3.59 (dd, 1H, $J_1 = 7.00$, $J_2 = 9.00$ Hz, CH(C)C*H*HOBn), 3.46 (dd, 1H, $J_1 = 6.25$, $J_2 = 9.25$ Hz, CH(C)CH*H*OBn), 3.43 (s, 3H, OCH$_3$), 3.12 (m, 2H), 2.48 (d, 1H, $J = 2.00$ Hz), 2.22 (m, 1H), 2.12 (m, 1H), 1.73 (m, 1H), 1.54 (m, 2H), 1.47 (m, 1H), 1.34–1.05 (m, 3H), 0.98 (t, 3H, $J = 7.50$ Hz, CH$_2$CH_3), 0.90 (t, 3H, $J = 7.50$ Hz, CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 215.0$, 146.8, 138.4, 128.4, 127.6, 125.3, 78.3, 73.2, 71.1, 57.5, 57.2, 44.4, 41.9, 41.7, 37.5, 36.3, 26.3, 25.7, 12.4; IR (film): $\tilde{\nu}$ = 3030, 2928, 2858, 1696, 1456, 1380, 1321, 1210, 1112, 1025, 914, 738, 698 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{32}O_3Na$ [M+Na$^+$]: 379.2237, found: 379.2237.



Scheme 2. Synthesis of the bicyclic core of CP-225,917 (**1**) and CP-263,114 (**2**). Reagents and reaction conditions: a) TBSCl (1.0 equiv), NaH (1.05 equiv, 60% dispersion in mineral oil, washed with hexane), THF, 0°C, 2h, 90%; b) SO_3·pyridine (3.0 equiv), DMSO (8.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0°C, 3h, 80%; c) cyclohexylamine (1.05 equiv), 4 Å molecular sieves, benzene, 22°C, 15h; d) LDA (1.0 equiv), THF, −5°C, 0.5h, then **9** (1.1 equiv) in THF, −78 → 22°C, 15h; e) $NaBH_4$ (2.0 equiv), MeOH, 22°C, 10 min, 58% over 3 steps; f) BnBr (1.1 equiv), NaH (1.1 equiv, 60% dispersion in mineral oil, washed with hexane), nBu_4NI (0.25 equiv), DMF, 0°C, 15h, 88%; g) O_3, CH_2Cl_2, −78°C, then excess Ph_3P, −78 → 22°C, 15h, 84%; h) cyclohexylamine (1.05 equiv), 4 Å molecular sieves, benzene, 22°C, 15h, 98%; i) LDA (1.05 equiv), THF, −5°C, 0.5h, then **15** (1.5 equiv) in THF, −78 → 22°C, 4h, then 6% oxalic acid in H_2O, 22°C, 0.5h, 74%; j) KH (2.0 equiv, 35% dispersion in mineral oil, washed with hexane), DME, 0°C, 0.5h, then Me_2SO_4 (2.0 equiv) in HMPA, 0°C, 0.5h, 96%; k) TBAF (1.5 equiv), THF/H_2O 95/5, 22°C, 3h, 96%; l) I_2 (1.2 equiv), Ph_3P (1.5 equiv), imidazole (2.0 equiv), CH_2Cl_2, 22°C, 5 min, 78%; m) **20** (2.0 equiv), LiHMDS (2.0 equiv), THF, −78°C, then immediately 0°C, 30 min, TBAF (2.0 equiv), THF/H_2O 95/5, 0°C, 5 min, 86%; n) Me_2AlCl (0.5 equiv), CH_2Cl_2, −10°C, 40 min, 86%, two isomers in a ratio of about 3:1. TBSCl = *tert*-Butyldimethylsilyl chloride, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, DMF = *N*,*N*-dimethylformamide, DME = 1,2-dimethoxyethane, HMPA = hexamethyl phosphoramide, TBAF = tetra-*n*-butylammonium fluoride, LiHMDS = lithium hexamethyldisilazide.

Although **4** was rather stable under thermal conditions (toluene, 110 °C, several hours), it smoothly underwent intramolecular Diels–Alder reaction in the presence of Me_2AlCl in CH_2Cl_2 at −10 °C. The resulting mixture of cycloadducts **3a, b** was chromatographically separated (silica gel, 6% acetone in hexane). The components **3a** and **3b** (R_f 0.25, 66% yield and R_f 0.28, 20% yield, stereochemistry unassigned) are presumably formed via the favored transition states **22a** and **22b**, respectively (Scheme 3). Variation of the substituents on the backbone of **4** and of the reaction conditions and catalyst is expected to improve the stereochemical outcome of the cycloaddition reaction, as desired for a total synthesis of the target molecules.



Scheme 3. Favored Diels–Alder transition states **22a** and **22b** leading to **3a** and **3b**, respectively (a racemic mixture was used; only one enantiomer is shown).

The chemistry described defines a possible strategy for the total synthesis of **1** and **2**, and opens the way for construction of simpler biological mimics of this class of compound for biological investigations.

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[10] All new compounds exhibited satisfactory spectral and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

Metal-Free Bacterial Haloperoxidases as Unusual Hydrolases: Activation of H_2O_2 by the Formation of Peracetic Acid**

Martin Picard, Jürgen Gross, Ellen Lübbert, Sabine Tölzer, Susanne Krauss, Karl-Heinz van Pée, and Albrecht Berkessel*

Dedicated to Professor Waldemar Adam on the occasion of his 60th birthday

Haloperoxidases catalyze the formation of hypohalites from hydrogen peroxide and chloride, bromide, or iodide [Eq. (1)].

$$H_2O_2 + Hal^- \xrightleftharpoons[\text{Hal: I, Br, Cl}]{\text{haloperoxidase}} OHal^- + H_2O \qquad (1)$$

The electrophiles thus formed are able to halogenate suitable organic substrates[1–3] and can thus play an important role in the biosynthesis of halogenated natural products. Haloperoxidases can also catalyze the transfer of oxygen from hydrogen peroxide to organic substrates such as olefins or thioethers.[4] Therefore, this class of enzymes has been intensively studied with respect to preparative transformations, for example, the asymmetric epoxidation of olefins and sulfoxidation of thioethers.[4] Furthermore, hydrogen peroxide is a readily available, mild, and environmentally friendly terminal oxidant.

Most haloperoxidases require a cofactor to catalyze the redox reaction shown in Equation 1. The type of cofactor is used to classify these enzymes into heme-containing, vanadium-containing, and metal-free haloperoxidases. So far only the heme-containing haloperoxidases have proven suitable for preparative applications, for example the chloroperoxidase from the fungus *Caldariomyces fumago*.[4] Although good yields and enantioselectivities could be achieved with some substrates, for a wider application the limited stability of this enzyme (temperature, cosolvents, pH, H_2O_2) is a serious drawback.

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