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Synthesis and Chemistry of Unusual Bicyclic Endoperoxides Containing the Pyridazine Ring

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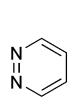
Inverse-Diels−Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with unsaturated bicyclic endoperoxides gave the bicyclic endoperoxides containing the pyridazine ring. The NEt_3 and CoTPP (TPP = tetraphenylporphyrin) catalyzed reaction of endoperoxide **8** resulted in the formation of hydroxy ketone **11** and *cis*-diol **9**. Cleavage of the peroxide linkage in **8** with thiourea provided *cis*-diol **9**. Oxidation of hydroxy ketone **11** and *cis*-diol **9** led to the phthalazine-5,8-dione **10**. Furthermore, the various transformations of the other endoperoxides **19**, **20**, **22**, **23**, and **30** resulted in the formation of pyridazine derivatives.

Introduction

The pyridazine (**1**) nucleus is of considerable interest because of its synthetic applications[1] and important pharmacological activities,[2] most of them related to the cardiovascular system.[2a,3] This six-membered heterocycle is also an integral part of many polynuclear heterocycles. Bicyclic endoperoxides, whose oxygen−oxygen (O−O) bond often plays a key role in the activity of a number of chemically and biologically relevant substances, are an important class of compounds.[4,5] For example, the prostaglandin endoperoxide (**2**) is a key intermediate in the biosynthesis of prostaglandins, prostacyclins, thromboxanes, and leukotrienes from fatty acids. Another example is the potent antimalarial 1,2,4-trioxane, artemisinin (**3**), and other related semisynthetic derivatives.[6]

In this paper, we report on the first synthesis of the phthalazine-type bicyclic endoperoxides containing both



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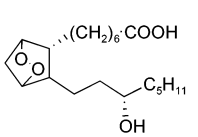

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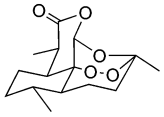

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pyridazine and peroxide units and their chemical transformations.[7] The methodology is based on the inverse-Diels−Alder reaction of tetrazine[8] with unsaturated bicyclic endoperoxides. With electron-withdrawing substituents (R = $COOCH_3$, CF_3, etc.), the reactivity of tetrazines is particularly high. Since some endoperoxides were not stable at the room temperature, the reactions were run at lower temperatures. To increase the reactivity of the tetrazine ring in the Diels−Alder reactions with inverse electron demand, we have used dimethyl 1,2,4,5-tetraazine-3,6-dicarboxylate as the diene component.

Results and Discussion

2,3-Dioxabicyclo[2.2.2]oct-5-ene[5] (**5**) reacted with tetrazine **4** in dry methylene chloride to give the isomeric adduct **7**, which is formed upon nitrogen extrusion from the initially formed tetracyclic adduct followed by a 1,3-hydrogen shift. Oxidation of the 1,4-dihydropyridazine mixture under the same reaction conditions with phenyliodosyl bis(trifluoroacetate) (PIFA)[9] produced the aromatized compound **8** in a 83% overall yield (Scheme 1).

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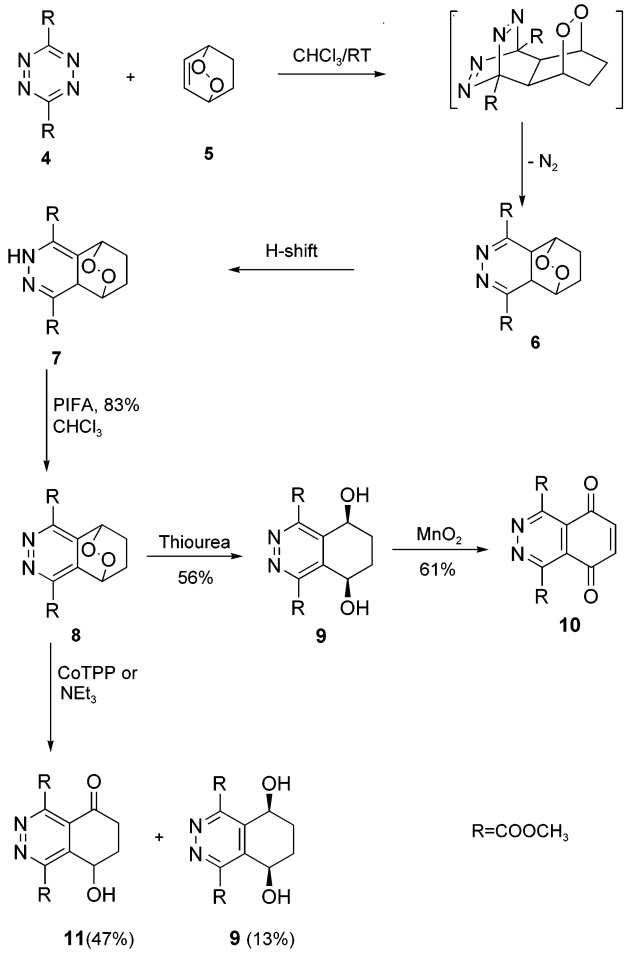
SCHEME 1



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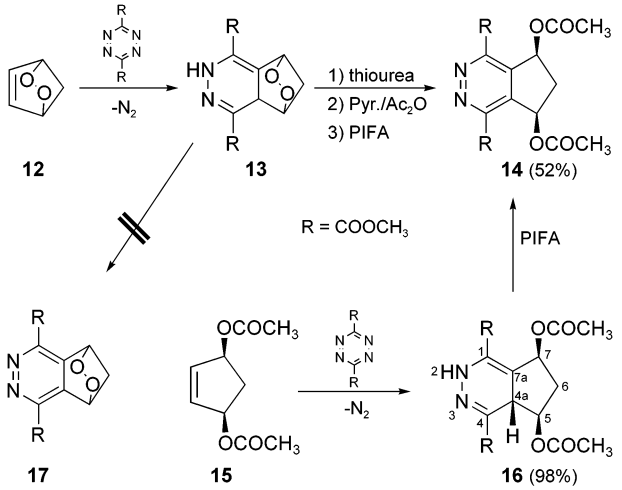

After successful isolation and characterization of the bicyclic endoperoxide **8**, we turned our attention to the chemistry of the peroxide functionality. We were interested in the synthesis of phthalazine derivatives,[10] especially phthalazinequinone **10**. The parent compound, phthalazine-5,8-quinone, was first synthesized by Parrick et al.[11] Some derivatives of this skeleton were used as medication for the treatment of inflammation, migraine, and shock.[12] Furthermore, other analogues have been shown to be effective in their DNA-degrading ability.[13]

The peroxide linkage is highly susceptible to reductive cleavage by a variety of reductants.[5] Selective reduction of the peroxide linkage in **8** was performed with thiourea under very mild conditions to produce the *cis*-diol **9** in 56% yield (Scheme 1). Since only the oxygen−oxygen bond breaks in this reaction, it preserves the configuration of alkoxy carbon atoms. Oxidation of diol **9** with active MnO_2 resulted in the formation of phthalazinequinone **10** in a yield of 61%.

The triethylamine-catalyzed reaction[5,14] of the endoperoxide **8** in $CHCl_3$ provided a mixture of the expected hyroxy ketone **11** and diol **9** in a 3:2 ratio (Scheme 1). The formation of the diol **9** can be rationalized by a mechanism in which the tertiary amine probably attacks the peroxide linkage directly and acts as a reducing reagent[14b,15] and reduces the peroxide linkage to diol **9**. Next, we treated endoperoxide **8** with cobalt(II) tetraphenylporphyrin (CoTPP)[16,17] and also obtained a mixture consisting of **9** and **11** in a 1:4 ratio.

In an analogous manner, we synthesized the endoperoxide **13** starting from the cyclopentadiene endoperoxide **12** (Scheme 2).[18] All efforts to obtain the corresponding pyridazine derivative **17** failed. However, the synthesis of **14**, a reduction product of **17**, was readily accomplished by two different approaches. Selective reduction of the peroxide linkage in **13** with thiourea followed by oxidation with PIFA and acetylation resulted in the formation of **14** (15% overall yield). In the second approach, we started from *cis*-1,3-diacetoxycyclopent-2-ene **15**,[18] which was synthesized from the reduction of cyclopentadiene endoperoxide with thiourea followed by acetylation. An addition of **15** to tetrazine **4** gave the 1,4-dihydropyridazine derivative **16** (Scheme 2).

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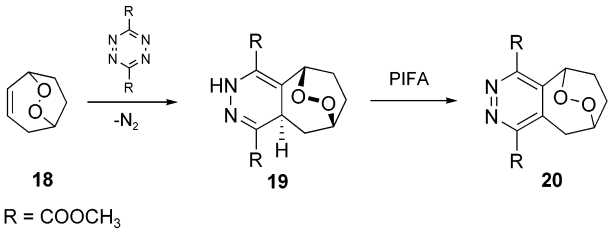
SCHEME 3



The assignment of the relative configuration of **16** was accomplished by ^{1}H- and ^{13}C NMR spectral data and NOE measurements. The stereochemistry of doubly allylic proton H_{4a} was confirmed by the observation of NOE effects. Irradiation at the resonance signal of the doubly allylic proton H_{4a} (at 3.60 ppm) caused a signal enhancement at the resonance signal of the adjacent proton H_5 at 5.54 ppm and the methylenic proton H_{6endo} at 1.91 ppm. However, there was no signal enhancement at the resonance signal of the proton H_7 indicating the cis orientation of the proton H_{4a} with respect to the acetyl groups. The oxidation of 1,4-dihydropyridazine derivative **16** supplied the compound **14** in 52% yield (Scheme 2).

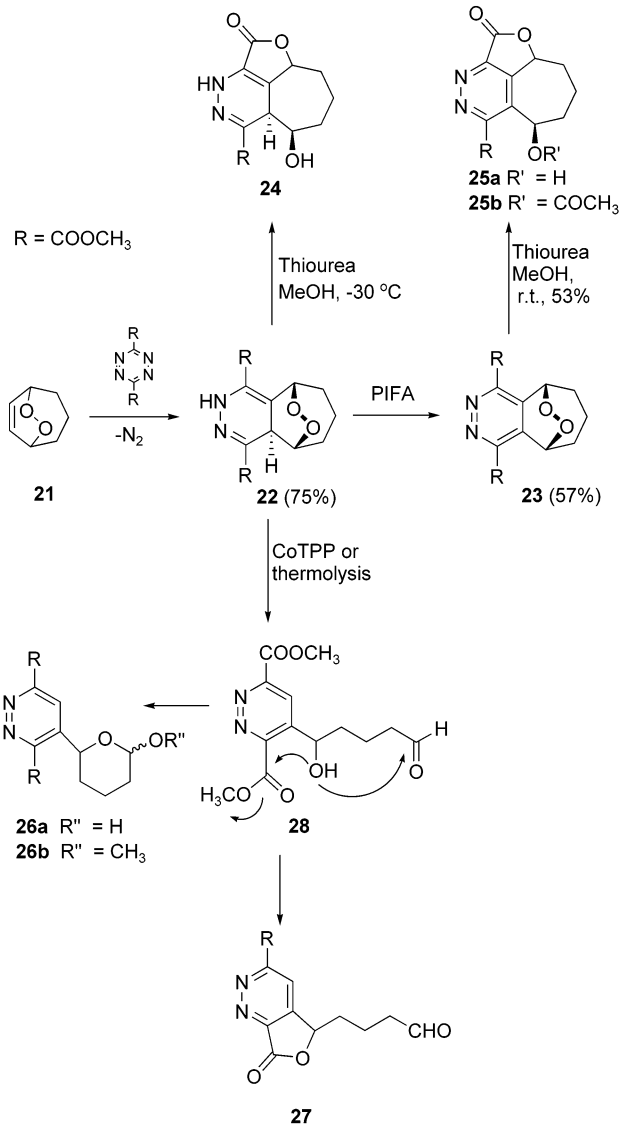
In a similar manner, the synthesis of **20** (Scheme 3) and **23** (Scheme 4) was achieved upon the addition of the endoperoxides **18** and **21**[19] to tetrazine **4** followed by PIFA oxidation. Although the stereochemistry of 1,4-dihydropyridazine endoperoxides **19** and **22** was not determined, we assume that tetrazine approaches the endocyclic double bond unit in **18** and **21** also from the *exo*-face, the sterically less crowded face of the molecule, to form the products **19** and **22**, respectively.

The reaction of **22** and **23** with thiourea furnished the cyclization products **24** and **25a**, respectively. One of the hydroxy groups of the diol formed upon the reduction of **22** (**23**) with thiourea attacks the neighboring ester group to form the lactone **24** (**25a**).

Treatment of **22** with CoTPP or thermolysis at 77 °C produced the isomeric pyranyl pyridazine derivative **26a** (in a ration of 1:1) as the major product besides the lactone **27** (Scheme 4). For the characterization of **26a**, the isomeric mixture was converted to the methoxyl derivative **26b**. The CoTPP-catalyzed reaction as well as the thermolysis of the bicyclic endoperoxides can lead to the formation of the products derived from an initial C−C cleavage.[16b,20] We assume that the primarily formed open-chain aldehyde **28** underwent intramolecular cyclization where the hydroxyl group attacks either ester carbonyl group or the aldehyde carbonyl group to produce the transesterification product **27** and the pyranyl derivative **26a**, respectively (Scheme 4).

As the last endoperoxide we studied the reaction of the cycloheptatriene endoperoxide **29**[19,21] with tetrazine **4.** The addition was accomplished by the treatment of

SCHEME 4



tetrazine with CHT-endoperoxide **29** in methylene chloride at room temperature for 1 day. Tetrazine **4** was only added to the double bond, which was incorporated into the six-membered ring and exclusively produced **30** (Scheme 5).

The *exo*-configuration of the proton H_7 was supported by a NOE experiment. The irradiation of the doubly allylic proton in the pyridazine ring at 3.50 ppm caused an enhancement of the bridgehead proton H_8 at 5.07 ppm and one of the methylene protons at 2.70 ppm. This finding indicated that the tetrazine approached the double bond in **29** from the *exo*-face of the molecule.

The base-catalyzed rearrangement of the endoperoxide **30** with NEt_3 produced a complex mixture that underwent polymerization or decomposition upon treatment with any column material. However, an isolable product **32** was obtained by the treatment of **30** with thiourea.

The CoTPP-catalyzed reaction of endoperoxide **30** or its thermolysis gave the isomeric pyranyl pyridazine derivative **33** (in a 3:7 ratio). The exact position of the double bond in **33** was determined by double resonance experiments. The position of the double bond provides

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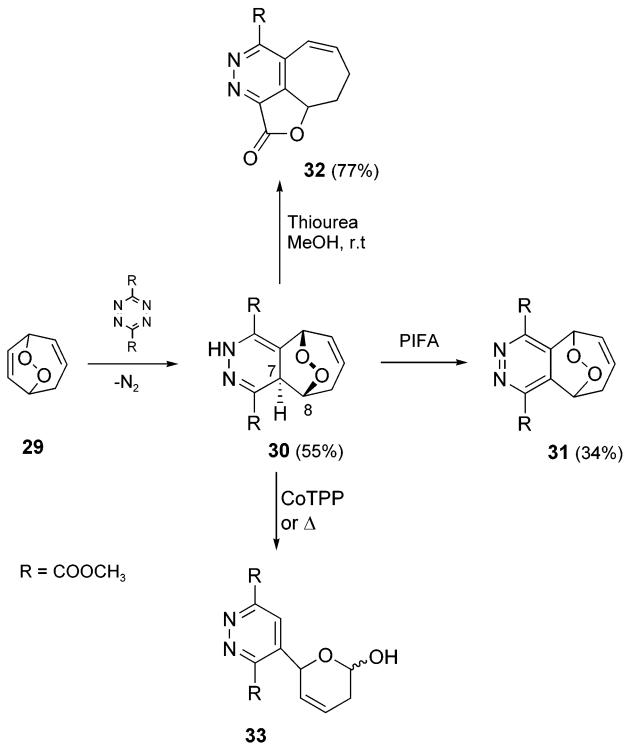
SCHEME 5



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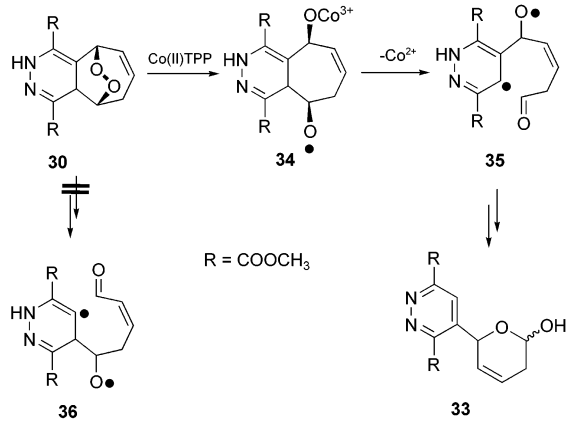

information about the cleavage mode of CoTPP catalyzed reaction or thermolysis. Presumably such reactions of the decomposition of endoperoxides, proceed via radical pathways. The formation of the isomeric **33** is reasonably understood in terms of the mechanism outlined in Scheme 6.

The radical, depicted as **34** resulting from the electron-transfer reaction between Co^{2+} species and endoperoxide, serves as a key intermediate. Cleavage of the C−C bond can form the allylic radical **35**. Subsequently, the proton abstraction and ring closure of an open-chain aldehyde ultimately delivers the isomeric pyranosyl derivative **33**. The other possible intermediate **36**, which is a vinyl radical, will not be as stable as the radical **35**.

In conclusion, we have described a simple method of access to bicyclic endoperoxides containing the pyridazine ring in which allow diverse transformations of the peroxide functional group. Transformations of these endoperoxides open a new way to heterocyclic compounds, such as the phthalazine and pyridazine derivatives.

Experimental Section

General Methods. Solvents were concentrated at reduced pressure. Melting points were determined on a capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 200 (50) MHz spectrometer and are reported in δ units with $SiMe_4$ as internal standard. Mass spectra (electron impact) were recorded at 70 eV on an MS spectrometer.

Dimethyl 9,10-Dioxa-4,5-diazatricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene-3,6-dicarboxylate (8). A solution of endoperoxide **5** (60 mg, 0.53 mmol), tetrazine **4** (150 mg, 0.75 mmol), and PIFA (270 mg, 0.63 mmol) in 15 mL of CH_2Cl_2 was stirred at room temperature for 4 days. The reaction mixture was diluted with water, and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL), washed with water, and dried over $CaCl_2$. After removal of the solvent, the residue was filtered on a short silica gel column (15 g) eluting with CCl_4/hexane (1:1), and 112 mg of iodobenzene was obtained as the first fraction. Further elution with ethyl acetate/hexane (1:4) furnished the product **8** (125 mg, 83%): pale yellow crystals from $CHCl_3$/ether; mp 133−134 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.15 (m, OCH, 2H), 4.11 (s, OCH_3, 6H), 2.67 (AA′ part of AA′XX′ methylene, 2H), 1.66 (XX′ part of AA′XX′ system, methylene, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.4 (CO) 146.7, 139.2, 69.7, 54.1, 21.0; IR (KBr, cm^{-1}) 3000, 2930, 2845, 1720, 1440, 1365, 1270, 1235, 1215, 1170, 1055, 925; Mass spectrum m/z (M^+) 280 (88), 264 (13), 249 (100), 233 (35), 222 (100), 190 (65), 175 (38), 163 (65). Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.33; H, 4.16; N, 9.89.

Thiourea Reduction of 8: Dimethyl 5*R*(*S*),8*S*(*R*)-5,8-Dihydroxy-5,6,7,8-tetrahydrophthalazine-1,4-dicarboxylate (9). To a stirred solution of **8** (200 mg, 0,72 mmol) in 10 mL of methanol was added a solution of thiourea (162 mg, 2.14 mmol) in methanol. After the addition was complete, stirring was continued for 2 h. The precipitated sulfur was filtrated and the solvent was evaporated. Crystallization of the residue (152 mg) from CH_2Cl_2/ether gave a dark brown powder (116 mg, 56%): mp 115−117 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.92 (m, OCH, 2H), 4.26 (m, OH, 2H), 3.99 (s, OCH_3, 6H), 2.15−1.85 (m, methylene, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.2, 155.3, 141.0, 65.4, 55.7, 28.4; IR (KBr, cm^{-1}) 3285, 3157, 2953, 2876, 2723, 1753, 1625, 1548, 1446, 1395, 1293, 1268, 1191, 1165, 1089, 1038, 961, 834. Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.25; H, 4.90; N, 9.83.

Oxidation of 9: Dimethyl 5,8-Dioxo-5,6,7,8-tetrahydrophthalazine-1,4-dicarboxylate (10). To a solution of diol **9** (or a mixture of **9** and **11**) (100 mg, 0.36 mmol) in 50 mL of CH_2Cl_2 was added 620 mg (7.14 mmol) of MnO_2. The reaction mixture was stirred at rt for 6 days. The solids were removed by filtration, and the solvent was evaporated. The crystallization of the residue from CH_2Cl_2/ether gave **10** as brown powder (60 mg, 61%): mp 163−166 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15 (s, =CH, 2H), 4.13 (s, OCH_3, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.7, 166.2, 153.3, 140.2, 124.6, 55.9; IR (KBr, cm^{-1}) 3068, 2960, 1753, 1702, 1607, 1445, 1391, 1375, 1291, 1260, 1221, 1183, 1106, 1067, 967, 859. Anal. Calcd for $C_{12}H_8N_2O_6$: C, 52.18; H, 2.92; N, 10.14. Found: C, 52.07; H, 2.85; N, 10.01.

CoTPP-Catalyzed Reaction of 9,10-Dioxa-4,5-diazatricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene-3,6-dicarboxylic Acid Dimethyl Ester (8). To a magnetically stirred solution of the endoperoxide **8** (250 mg, 0.89 mmol) in CH_2Cl_2 (50 mL) was added a catalytic amount of cobalt *meso*-tetraphenylporphyrin (CoTPP) at room temperature. The mixture was stirred for 3 days at rt and then evaporated. Chromatography of residue on silica gel (30 g) eluting with CH_2Cl_2/acetone (95:5) yielded the hydroxy ketone **11** as the first fraction.

Dimethyl 5-hydroxy-8-oxo-5,6,7,8-tetrahydrophthalazine-1,4-dicarboxylate (11): dark brown powder from CH_2Cl_2/ether (132 mg, 47%); mp 135−137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.17 (q, J = 7.7 Hz, H_5, 1H), 4.10 (s, OCH_3, 3H), 4.08 (br.s, OH, 1H), 4.04 (s, OCH_3, 3H), 3.25−3.07 (ddd, A part of AB system, J = 17.4 Hz, 12.6 Hz, 4.9 Hz, H_{7a}, 1H), 2.76−2.63 (dt, B part of AB system, J = 17.4, 4.2 Hz, H_{7b}, 1H), 2.56−2.24 (m, H_6, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.7, 167.6, 167.3, 154.8, 154.1, 143.6, 126.9, 63.6, 56.1, 55.5, 35.3, 30.5; IR (KBr, cm^{-1}) 3234, 2953, 2851, 2697, 1753, 1702, 1548, 1446, 1395, 1344, 1293, 1268, 1217, 1165, 1114, 1063, 961, 885. Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.25; H, 4.22; N, 10.15.

Continued elution with CH_2Cl_2/acetone (60:40) afforded the *cis*-diol **9** (36 mg, 13%).

NEt$_3$-Catalyzed Rearrangement of Dimethyl 9,10-Dioxa-4,5-diazatricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene-3,6-dicarboxylate (8). A solution of the endoperoxide **8** (100 mg, 0.36 mmol) in 20 mL of CH_2Cl_2 containing 3 drops of triethylamine was stirred at room temperature for 4 h. After removal of the solvent, the ^{1}H NMR of the residue showed the formation of a mixture of **9**/**11** (3:2) in quantitative yield. The mixture was separated as described above or used for the synthesis of **10** without further purification.

Synthesis of Dimethyl 5*R*(*S*),7*S*(*R*)-5,7-Bis(acetyloxy)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine-1,4-dicarboxylate (14). Method A. A solution of 1,4-diacetoxycyclopentene **15** (592 mg, 3.22 mmol) and tetrazine **4** (700 mg, 3.50 mmol) in 15 mL of CH_2Cl_2 was stirred at room temperature for 96 h. Filtration of the residue on a short Florisil column (8 g) eluting with ethyl acetate (100 mL) furnished **dimethyl 5,7-bis(acetyloxy)-4a,5,6,7-tetrahydro-2*H*-cyclopenta[*d*]pyridazine-1,4-dicarboxylate (16):** colorless crystals (1.11 g, 98%) from CH_2Cl_2/ether; mp 131−132 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.45 (bs, NH, 1H), 6.21 (bd, J = 5.8 Hz, H_7, 1H), 5.54 (ddd, J = 8.1, 5.0, 3.0 Hz, H_5, 1H), 3.85 (s, OCH_3, 3H), 3.81 (s, OCH_3, 3H), 3.60, (d, J = 5.0 Hz, H_{4a}, 1H), 2.33 (ddd, A part of AB system, J = 15.8, 8.1, 5.8 Hz, H_{6a}, 1H), 2.10 (s, CH_3, 3H), 2.06 (s, CH_3, 3H), 1.91 (bd, B part of AB system, J =15.8 Hz, H_{6b}, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 172.2, 171.9, 165.8, 162.7, 132.1, 126.6, 120.4, 77.8, 74.2, 55.0, 54.6, 43.6, 39.9, 23.1 (2 × CH_3); IR (KBr, cm^{-1}) 3340, 2995, 2940, 1720, 1590, 1430, 1240, 1125, 1110, 1030, 940, 815. Anal. Calcd for $C_{15}H_{18}N_2O_8$: C, 50.85; H, 5.12; N, 7.91. Found: C, 50.98; H, 5.22; N, 8.03.

A solution of **16** (520 mg, 1.47 mmol) and PIFA (900 mg, 2.1 mmol) in 25 mL of CH_2Cl_2 was stirred at room temperature for 3 h. The reaction mixture was diluted with water, and the aqueous solution was extracted with CH_2Cl_2 (75 mL), washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was filtered on a short Florisil column (10 g) eluting with CH_2Cl_2 (100 mL), and 320 mg of iodobenzene was obtained as the first fraction. Further elution with ethyl acetate (100 mL) furnished the product **14** (270 mg, 52%) as pale yellow crystals from CH_2Cl_2/ether: mp 170−171 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.60 (dd, J = 7.7, 2.8 Hz, H_5 and H_7, 2H), 4.05 (s, OCH_3, 6H), 3.06 (dt, A part of AB system, J = 15.7, 7.7 Hz, H_{6a}, 1H), 2.09 (dt, B part of AB system, J = 15.7 Hz, 2.8 Hz, H_{6b}, 1H), 2.06 (s, CH_3, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.3, 165.1, 152.6, 145.6, 77.8, 55.5, 41.3, 22.5; IR (KBr, cm^{-1}) 2995, 2940, 1720, 1425, 1365, 1250, 1200, 1050, 1030, 950, 810, 780; MS m/z (M$^+$) 352 (48) 321 (7), 279 (33), 250 (61), 237 (45), 220 (100), 207 (20), 192 (81). Anal. Calcd for $C_{15}H_{16}N_2O_8$: C, 51.14; H, 4.58; N, 7.95. Found: C, 51.00; H, 4.67; N, 8.09.

Method B. To a solution of cyclopentadiene (203 mg, 3.07 mmol) in 50 mL of CCl_4 was added 10 mg of TPP. The resulting mixture was irradiated with a projection lamp (150 W) while dry oxygen was being passed through the solution, and the mixture was stirred for 2.5 h at −20 °C. Later, to the stirred solution of cyclopentadiene endoperoxide **12** was added 507 mg (2.56 mmol) of tetrazine **4** at 10 °C. After complete addition (1−2 min), the mixture was stirred for 3.5 h at 10 °C. To the resulting mixture was added 310 mg (4.08 mmol) of thiourea in 40 mL of methanol and the mixture stirred for 3 h. After the precipitated sulfur was filtrated, the solvent was evaporated. The crude product (650 mg) was dissolved in 10 mL of pyridine, and Ac_2O (2 g, 0.02 mol) was added to the resulting mixture. The reaction mixture was stirred at rt for 16 h. The mixture was cooled to 0 °C, 100 mL of 1 N HCl solution was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were washed with $NaHCO_3$ solution (100 mL) and water (100 mL) and then dried ($MgSO_4$). After removal of the solvent, the crude product (354 mg) was oxidized with PIFA (600 mg, 1.39 mmol) in 30 mL of CH_2Cl_2 for 1 h. The reaction mixture was diluted with water, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL), washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was filtered on a short Florisil column (10 g) eluting with CH_2Cl_2 (50 mL) to give 270 mg of iodobenzene as the first fraction. Further elution with ethyl acetate (100 mL) furnished the product **14** (140 mg, 15%, overall yield).

Dimethyl 10,11-Dioxa-4,5-diazatricyclo[7.2.2.0^{2,7}]trideca-2,4,6-triene-3,6-dicarboxylate (20). A solution of endoperoxide **18** (250 mg, 1.98 mmol) and tetrazine **4** (471 mg, 2.38 mmol) in 15 mL of CH_2Cl_2 was stirred at room temperature for 45 h. After removal of the solvent, the residue was filtered on a short Florisil column (5 g) eluting with CH_2Cl_2 (150 mL) to furnish the crude product **19** (522 mg). The oxidation of the crude product (522 mg) to **23** was realized as described for the preparation of **8**: pale yellow crystals (216 mg, 37%) from $CHCl_3$/ether; mp 135−136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.79 (m, H_1, 1H), 4.84−4.77 (m, H_9, 1H), 4.06 (s, OCH_3, 3H), 4.05 (s, OCH_3, 3H), 3.60 (d, A part of AB-system, J =19.7 Hz, H_{8a}, 1H), 3.57 (dd, B part of AB-system, J = 19.7, 5.2 Hz, H_{8b}, 1H), 2.80−2.61 (m, CH_2, 1H), 2.40−2.21 (m, CH_2, 2H), 1.60−1.43 (m, CH_2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 166.7, 156.1, 151.9, 144.9, 141.0, 79.2, 76.7, 55.6, 55.4, 40.6, 25.3, 22.6; IR (KBr, cm^{-1}) 2940, 2890, 1730, 1440, 1240, 1215, 1150, 990, 950, 815, 765; MS m/z (M$^+$) 294 (35) 279 (18), 263 (69), 237 (88), 206 (100). Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.75; H, 4.57; N, 9.43.

Dimethyl 12,13-Dioxa-4,5-diazatricyclo[6.3.2.0^{2,7}]trideca-2,5-diene-3,6-dicarboxylate (22). A solution of the endoperoxide **21** (126 mg, 1 mmol) and tetrazine **4** (198 mg, 1 mmol) in 20 mL of CH_2Cl_2 was stirred at room temperature for 24 h. The residue was filtered on a short Florisil column (5 g). Elution with CCl_4 (40 mL) furnished the endoperoxide **22**: pale yellow colorless crystals from CCl_4 (222 mg, 75%); mp 131−133 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.73 (bs, NH, 1H), 5.73 (m, H_1, 1H), 5.68 (m, H_8, 1H), 3.80 (s, OCH_3, 3H), 3.76 (s, OCH_3, 3H), 2.67 (s, H_7, 1H), 2.18−1.17 (m, CH_2, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2, 162.7, 132.2, 129.8, 114.2, 77.7, 77.2, 54.8, 54.4, 37.0, 36.8, 34.8, 21.8; IR (KBr, cm^{-1}) 3285, 2973, 2953, 2927, 1753, 1702, 1625, 1472, 1446, 1370, 1293, 1268, 1242, 1191, 1140, 1114, 1089, 1063, 961, 808. Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.85; H, 5.57; N, 9.61.

Dimethyl 12,13-Dioxa-4,5-diazatricyclo[6.3.2.0^{2,7}]trideca-2,4,6-triene-3,6-dicarboxylate (23). The pyridazine derivative **22** (645 mg, 2.2 mmol) was oxidized with PIFA (1.2 g, 2.8 mmol) as described for the preparation of **8**. The residue was crystallized from CH_2Cl_2/ether to give pale yellow crystals (440 mg, 57%): mp 141−142 °C: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.05 (m, H_1 and H_8, 2H), 4.09 (s, OCH_3, 6H), 2.30 (m, CH_2, 4H), 1.75−1.16 (m, CH_2, 1H), 0.78−0.59 (m, CH_2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.4, 148.0, 137.0, 76.7, 54.1, 32.0, 19.1; IR (KBr, cm^{-1}) 3030, 2930, 2920, 2860, 1725, 1440, 1370, 1285, 1235, 1230, 1200, 1140, 1010, 780; MS m/z (M$^+$) 294 (8) 280 (4), 262 (100), 247 (23), 232 (52), 204 (35). Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.24; H, 4.91; N, 9.67.

Thiourea Reduction of 22: Methyl 5a*R*(*S*),6*R*(*S*),9a*S*-(*R*)-6-Hydroxy-2-oxo-2,3,5a,6,7,8,9,9a-octahydro-1-oxa-

3,4-diazabenzo[*cd*]azulene-5-carboxylate (24). A solution of **22** (210 mg, 0.7 mmol) and thiourea (320 mg, 4.2 mmol) in 10 mL of methanol was stirred at −30 °C. At the same temperature, stirring was continued for 4 days. The precipitated sulfur was filtrated, and the solvent was evaporated. The residue was crystallized from methanol to give **24** (51 mg, 27%) as yellow crystals: mp 149−151 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.21 (s, NH, 1H), 5.07 (bt, J = 5.5 Hz, H_{9a},1H), 4.17 (m, H_6, 1H), 3.94 (m, H_{5a}, 1H), 3.87 (s, OCH_3, 3H), 2.36 (m, OH, 1H), 2.35−1.24 (m, 6H), 2.10−1.89 (m, 3H), 1.61−1.51 (m, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 166.9, 166.6, 134.1, 131.5, 129.0, 82.9, 71.1, 53.5, 37.9 (2C), 33.5, 17.8; IR (KBr, cm^{-1}) 3565, 3514, 3361, 3285, 2953, 2876, 1778, 1753, 1727, 1702, 1625, 1600, 1472, 1446, 1395, 1370, 1293, 1268, 1217, 1140, 1114, 1063, 987.

Thiourea Reduction of 23: Methyl 6*R*(*S*),9a*S*(*R*)-6-Hydroxy-2-oxo-2,6,7,8,9,9a-hexahydro-1-oxa-3,4-diazabenzo[*cd*]azulene-5-carboxylate (25a). To a stirred solution of **23** (100 mg, 0,34 mmol) in 10 mL of CH_2Cl_2 was added a solution of thiourea (104 mg, 1.36 mmol) in 10 mL of methanol. After the addition was complete, stirring was continued for 4 days. The precipitated sulfur was filtrated, and the solvent was evaporated. The residue was crystallized from methanol to give **25a** as a yellow crystals (47 mg, 53%): mp 186−188 °C); ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.35 (d, J = 5.1 Hz, OH,-1H), 5.72 (dd, H_{9a}, J = 9.3 Hz, 5.1 Hz, 1H), 5.0 (m, H_6, 1H), 3.89 (s, OCH_3, 3H), 2.37−2.31 (m, 1H), 2.10−1.89 (m, 3H), 1.61−1.51 (m, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 168.5 (+), 167.4 (+), 154.3 (+), 149.3 (+), 146.9 (+), 140.9 (+), 82.2 (−), 71.1 (−), 54.5 (−), 38.5 (+), 31.8 (+), 23.7 (+); IR (KBr, cm^{-1}) 3463, 3412, 3029, 2953, 2876, 1804, 1753, 1625, 1574, 1446, 1395, 1344, 1293, 1242, 1191, 1140, 1114, 1089, 1063, 1012, 987, 936, 859.

6-Acetoxy-2-oxo-2,6,7,8,9,9a-hexahydro-1-oxa-3,4-diazabenzo[*cd*]azulene-5-carboxylic Acid Methyl Ester (25b). To a stirred solution of **25a** (90 mg, 0.34 mmol) in 1.5 g pyridine was added Ac_2O (300 mg, 2.94 mmol) at 0 °C. The reaction mixture was stirred at the room temperature for 18 h. The mixture was cooled to 0 °C, 40 mL of 2 N HCl solution was added, and the mixture was extracted with ethyl acetate (3 × 35 mL). The combined organic layers were washed with $NaHCO_3$ solution (2 × 50 mL) and water (100 mL) and then dried (Na_2SO_4). The residue was chromatographed on a short silica gel column (5 g). Elution with $CHCl_3$ gave **25b** as colorless crystals from CH_2Cl_2/ether (54 mg, 37%): mp 181−182 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.19 (dd, J = 10.1 Hz, 1.8 Hz, H_6, 1H), 5.55 (dd, J = 12.2 Hz, 4.5 Hz, H_{9a}, 1H), 4.06 (s, OCH_3, 3H), 2.70−2.60 (m, 1H), 2.16 (s, $OCCH_3$, 3H), 2.33−1.25 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 167.4, 166.4, 153.7, 149.8, 146.4, 136.3, 81.4, 72.7, 55.3, 34.9, 32.9, 23.8, 22.5; IR (KBr, cm^{-1}) 3004, 2978, 2953, 2902, 1829, 1778, 1600, 1446, 1395, 1319, 1242, 1140, 1063, 1038, 910, 808. Anal. Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.74; H, 471; N, 9.34.

Thermolysis Reaction of 22. A magnetically stirred solution of the endoperoxide **22** (300 mg, 1 mmol) in CCl_4 (40 mL) was refluxed for 10 h. While the lactone **27** was separated as a yellow viscose oil (41 mg, 14%), pyranyl pyridazine derivative *cis*/*trans*-**26a** remained in CCl_4 solution. The solvent was removed and the *cis*/*trans*-**26a** was obtained as the pale brown oil (230 mg, 77%). Thermolysis products (*cis*/*trans*-**26a** and **27**) were not stable toward column materials, and crystallization failed.

Dimethyl 4-(6-hydroxytetrahydropyran-2-yl)pyridazine-3,6-dicarboxylate (*cis*/*trans*-26a): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.30 (s, 1H), 5.40 (m, 2H), 4.99 (d, J = 10 Hz, 1H), 4.88 (d, J = 8.6 Hz, 1H), 4.02 (s, OCH_3, 3H), 4.01 (s, OCH_3, 3H), 3.99 (s, OCH_3, 3H), 3.98 (s, OCH_3, 3H), 2.09−1.19 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.7 (2C), 165.9, 165.7, 154.3, 154.1, 153.5, 152.7, 146.5, 145.8, 127.9 (2C), 98.8, 94.2, 74.5, 67.7, 55.3 (4C), 34.7, 33.9 (2C), 31.3, 24.4, 19.5.

Methyl 7-oxo-5-(4-oxobutyl)-5,7-dihydrofuro[3,4-*c*]-pyridazine-3-carboxylate (27): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.75 (bs, 1H), 8.43 (s, 1H), 5.70 (m, 1H), 4.09 (s, OCH_3, 3H), 2.60 (t, J = 6.5 Hz, 2H), 2.00−1.74 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.5, 166.4, 165.5, 153.9, 151.9, 148.2, 124.0, 81.0, 55.6, 44.7, 35.1, 19.5; IR (KBr, cm^{-1}) 3463, 3080, 2953, 2876, 2723, 2263, 1778, 1727, 1600, 1446, 1421, 1344, 1268, 1217, 1114, 1063, 987, 910. Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.34; H, 2.32; N, 10.45.

4-(6-Methoxytetrahydropyran-2-yl)pyridazine-3,6-dicarboxylic Acid Dimethyl Ester (*cis*/*trans*-26b). A solution of *cis*/*trans*-**26a** (1:1 ratio, 180 mg, 0.61 mmol) and *p*-toluensulfonic acid (20 mg, 0.066 mmol) in 20 mL of methanol was refluxed for 12 h. After evaporation of the solvent, 50 mL of CH_2Cl_2 was added to the residue. The formed organic layer was separated, washed with water (2 × 50 mL), and dried over anhydrous $CaCl_2$, and the solvent was evaporated. The residue was chromatographed on a short neutral Al_2O_3 column (15 g, activity 3). Elution with ether (100 mL) gave a mixture of *cis*/*trans*-**26b** as a brown oil (133 mg, 71%, 3:7 ratio): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.51 (s, 2H), 5.30 (dd, J = 11.2 Hz, 1.6 Hz, 1H), 5.07 (dd, J = 11.0 Hz, 1.7 Hz, 1H), 4.87 (m, 1H), 4.06 (s, OCH_3, 3H), 4.04 (s, OCH_3, 3H), 3.46 (s, OCH_3, 3H), 3.31 (s, OCH_3, 3H), 2.08−1.21 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.8, 166.6, 165.9, 165.8, 154.4, 153.0, 152.7, 146.3, 145.4, 127.8, 127.6, 105.6, 101.0, 74.4, 67.8, 58.1, 56.8, 55.2 (2), 55.1 (2C), 35.0, 34.1, 32.5, 31.2, 24.4, 20.2. Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.03; H, 5.75; N, 9.18.

CoTPP-Catalyzed Reaction of 22. The CoTPP-catalyzed reaction of **22** was performed as described for **8**. After 2 h, the products **26a** and **27** were formed in a ratio of 5:1 in quantitative yield.

Dimethyl 1*R*(*S*),7*S*(*R*),8*R*(*S*)-12,13-Dioxa-4,5-diazatricyclo[6.3.2.0^{2,7}]trideca-2,5,9-triene-3,6-dicarboxylate (30). A solution of endoperoxide **29** (176 mg, 1.98 mmol) and tetrazine **4** (283 mg, 1.43 mmol) in 15 mL of $CHCl_3$ was stirred at room temperature for 27 h. After removal of the solvent, the residue was chromatographed on a short neutral Al_2O_3 column (15 g, activity 3). Elution with $CHCl_3$ gave **30** as pale yellow crystals from CH_2Cl_2/ether (230 mg, 55%): mp 99−100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.39 (bs, NH, 1H), 6.25 (bd, J = 3.1 Hz, OCH, 1H), 6.10−6.02 (m, =CH, 1H), 5.88−5.79 (m, =CH, 1H), 5.07 (m, OCH, 1H), 3.90 (s, OCH_3, 3H), 3.85 (s, OCH_3, 3H), 3.50 (s, CH, 1H), 3.05 (bd, A part of AB system, J = 18.8 Hz, CH_2, 1H), 2.78 (dt, B part of AB system, J = 18.8, 5.3 Hz, CH_2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.6, 161.4, 138.9, 133.0, 128.1, 125.03, 115.0, 80.7, 73.4, 53.5, 53.0, 37.3, 34.7; IR (KBr, cm^{-1}) 3390, 3020, 2940, 2880, 2840, 1700, 1595, 1450, 1335, 1250, 1110, 900; MS m/z (M^+) 294 (28), 276 (30), 265 (81), 250 (100), 235 (94), 225 (47), 217 (49), 205 (49), 193 (56). Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.93; H, 4.66; N, 9.43.

Dimethyl 1*R*(*S*),8*S*(*R*)-12,13-Dioxa-4,5-diazatricyclo-[6.3.2.0^{2,7}]trideca-2,4,6,9-tetraene-3,6-dicarboxylate (31). The oxidation of **30** to **31** was carried out as described for **8** starting with 310 mg (1 mmol) of **30** and 500 mg (1.16 mmol) of PIFA. The residue (310 mg) was crystallized from CH_2Cl_2/ether to give pale yellow crystals (120 mg, 34%): mp 155−156 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.36−6.27 (m, 3H), 5.80 (dt, B part of AB-system, J = 10.2, 3.6 Hz, =CH, 1H), 4.10 (s, OCH_3, 6H), 3.30 (bd, A part of AB-system, J = 20.0 Hz, CH_2, 1H), 2.68 (bd, B part of AB-system, J = 20.0 Hz, CH_2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8 (2C), 150.0, 147.4, 141.7, 137.2, 134.3, 130.0, 76.6, 74.3, 55.7 (2C), 37.4; IR (KBr, cm^{-1}) 3035, 2925, 2900, 1765, 1440, 1415, 1362, 1320, 1310, 1270, 1230, 1164, 1100, 1025, 975, 945, 825. Anal. Calcd for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.45; H, 4.08; N, 9.68.

Thiourea Reduction of 30: Methyl 2-Oxo-2,8,9,9a-tetrahydro-1-oxa-3,4-diazabenzo[*cd*]azulene-5-carboxylate (32). To a stirred solution of **30** (100 mg, 0,34 mmol) in 10 mL of $CHCl_3$ was added a solution of thiourea (52 mg, 0.68

mmol) in 10 mL of methanol. After the addition was complete, stirring was continued for 18 h. The precipitated sulfur was filtrated, and the solvent was evaporated. The residue was chromatographed on a short silica gel column (5 g). Elution with $CHCl_3$ gave **32** as yellow crystals (65 mg, 77%) from CH_2Cl_2/ether: mp 136−137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (dt, A part of AB system, H_6, J = 12.3 Hz, 2.2 Hz, 1H), 6.58 (dt, B part of AB system, H_7, J = 12.3 Hz, 4.4 Hz, 1H), 5.50 (dd, J = 12.1 Hz, 2.9 Hz, H_{9a}, 1H), 4.06 (s, OCH_3, 3H), 2.91−2.70 (m, 3H), 2.01−1.83 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.3, 166.6, 151.9, 149.7, 147.8, 146.0, 131.2, 121.9, 80.4, 55.6, 30.6, 30.5; IR (KBr, cm^{-1}) 3285, 2953, 2927, 1804, 1753, 1727, 1625, 1600, 1497, 1446, 1395, 1344, 1293, 1263, 1217, 1140, 1114, 1012, 961, 936. Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.41; H, 4.00; N, 11.23.

CoTPP-Catalyzed Reaction 30: Dimethyl 4-(6-Hydroxy-5,6-dihydro-2*H*-pyran-2-yl)pyridazine-3,6-dicarboxylate (33). To a magnetically stirred solution of the endoperoxide **30** (100 mg, 0.34 mmol) in CH_2Cl_2 (20 mL) was added a catalytic amount 10 mg of CoTPP at room temperature. The mixture was stirred for 1 day at rt, and then the solvent was evaporated. Cleavage product *cis*/*trans*-**33** was formed quantitatively. The ^{1}H NMR analysis of the crude product showed the presence of a mixture of *cis*/*trans*-**33** in a ratio of 3:7. The crystallization of the residue from methanol gave *cis*/*trans*-**33** (55 mg, 55%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.37 (s, 1H), 5.92−5.71 (m, 6H), 5.46 (m, 1H), 5.28 (m, 1H), 4.07 (s, OCH_3, 3H), 4.06 (s, OCH_3, 3H), 4.05 (s, OCH_3, 3H), 4.03 (s, OCH_3, 3H), 3.98 (d, OH, 1H), 3.88 (m, OH, 1H), 2.59−2.14 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9 (2C), 160.0, 165.9, 154.5, 154.2, 154.1, 153.3, 144.9, 144.8, 128.8, 128.6, 128.2, 127.3 (2C), 125.8, 95.2, 92.5, 73.3, 67.7, 55.5 (4C, OCH_3), 33.7, 32.0.

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