

INTRAMOLECULAR DIELS–ALDER CYCLOADDITIONS OF *cis*-CYCLOHEXADIENEDIOLS DERIVED ENZYMATICALLY FROM (2-AZIDOETHYL)BENZENE. CONSTRUCTION OF HIGHLY FUNCTIONALIZED BRIDGED ISOQUINOLINE SYNTHONSJosef ZEZULA¹, Tomáš HUDLICKÝ^{2,*} and Ion GHIVIRIGA^{3,+}*Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, U.S.A.; e-mail: ¹ jzezula@chem.ufl.edu, ² hudlicky@chem.ufl.edu, ³ ion@chem.ufl.edu*

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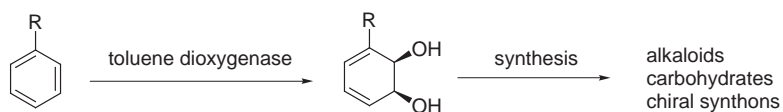
(3*aR*,7*aS*)-4-(2-Azidoethyl)-2,2-dimethyl-3*a*,7*a*-dihydrobenzo[1,3]dioxole (**22**) was converted in two steps to trienes **23** and **24**, which upon heating underwent intramolecular Diels–Alder reactions to give mixtures of isomeric 11,11-dimethyl-5-oxo-10,12-dioxo-4-azatetracyclo[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylates **25**, **26** and **27**, **28**, respectively. These products were separated and identified. For comparison, intermolecular Diels–Alder cycloaddition of diene **22** with maleic anhydride was carried out. Products of this reaction, 1-(2-azidoethyl)-4,4-dimethyl-3,5,10-trioxatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-ene-9,11-diones (**29** and **30**) were converted to methyl ester analogues of **31** and **32** in a two-step sequence. The stereochemical outcome of these cycloadditions is discussed as well as their possible utilization in organic synthesis, especially in total synthesis of some alkaloids.

Keywords: Biotransformations; Diels–Alder reactions; Bridged octahydroisoquinolones; Morphine; Asymmetric synthesis; Isoquinoline alkaloids; Total syntheses; Chemoenzymatic synthesis.

A recent review summarizes research in the area of chemoenzymatic synthesis originating in *cis*-cyclohexadienediols¹. Gibson's discovery of the remarkable enzymatic dearomatization² portrayed in Scheme 1 has led to the development of many applications of diol metabolites in asymmetric synthesis³. General methods of synthesis for inositols and their derivatives⁴, monosaccharides and their aza and pseudo analogs⁵, and oxygenated *Amaryllidaceae* alkaloids⁶ have been developed in response to the availability of the optically pure diols⁷ **1**. Through continuing efforts of Gibson and Boyd, as well as through those of our own group, new metabolites have

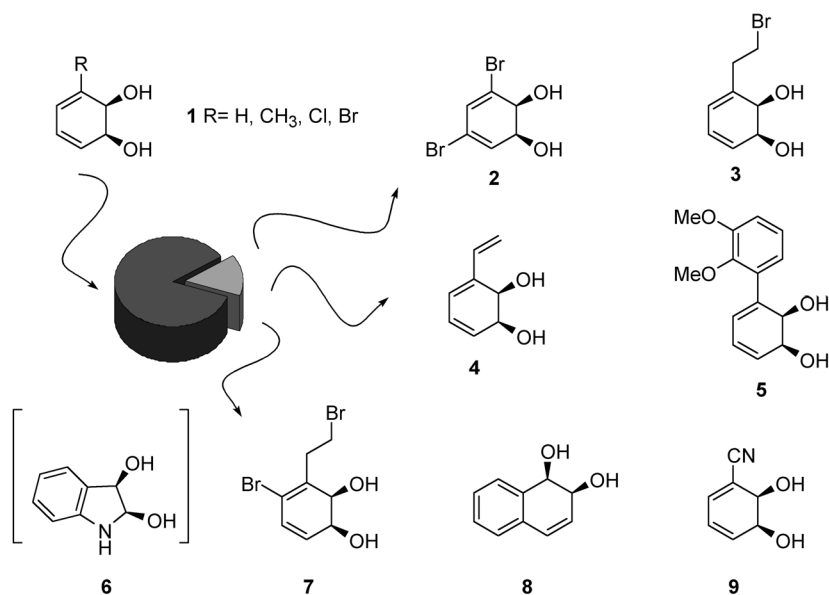
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been added to the growing portfolio of these synthons, now containing over 300 compounds⁸, only a few of which have been used in synthetic ventures.



SCHEME 1
Chemoenzymatic synthesis of natural products

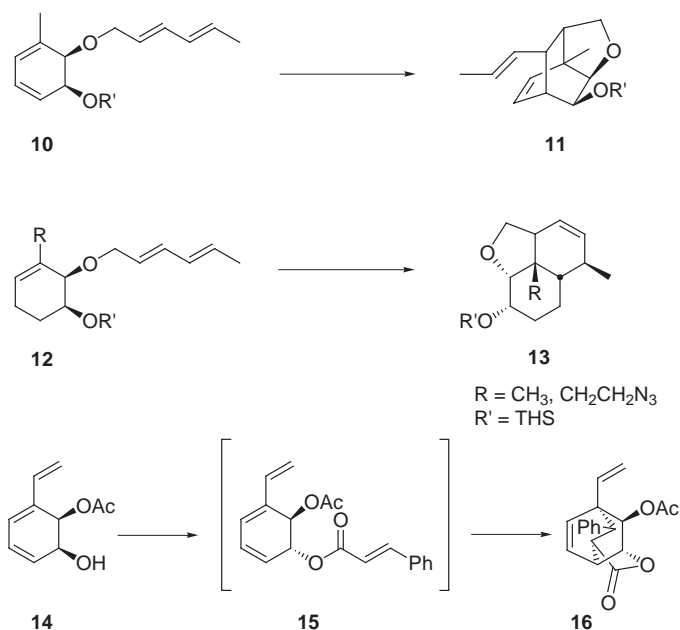
Over 85% of all synthetic activity in this area has stemmed from the diols derived from benzene, toluene and chloro- or bromobenzene (Scheme 2). The rest have capitalized on conversions of recently isolated diols with more elaborate functionality.



SCHEME 2
cis-Dienediol metabolites used in total synthesis

That the more complex diols were not readily available to the synthetic community until a just few years ago may explain the relative under-utilization of these powerful synthons. In the area of cycloadditions, many

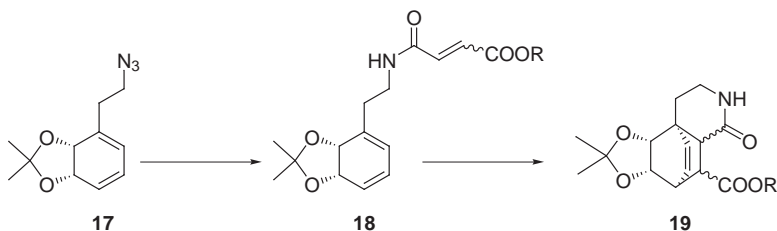
examples have been reported for intermolecular Diels–Alder cycloadditions of benzynes⁹, quinines¹⁰, acrylates¹¹, olefins, acetylenes¹¹, and other dienophiles¹², but only with those dienediols derived from toluene and halobenzenes. Creative use of Diels–Alder chemistry has been reported by Banwell, who applied it to the synthesis of steroids¹³ and to an approach to Taxol® (ref.¹⁴). Only three examples of intramolecular cycloadditions have been reported, all from our research group. We have employed dienophiles or dienes tethered through one of the hydroxy groups of a diol, as shown in Scheme 3.



SCHEME 3
Examples of intramolecular Diels–Alder cycloadditions

The first two examples, leading to the bridged system **11** and the tricyclic ether **13**, were aimed at the synthesis of morphinans¹⁵. The third example, employing the diol derived from styrene, is from our synthesis of zelylena¹⁶. In this manuscript we report the Diels–Alder cycloadditions of dienes **17** and **18**, each obtained by toluene dioxygenase-mediated oxidation of (2-azidoethyl)benzene¹⁷, followed by protection (for **17**) and conversion of the azide to the amide used as a tether for the dienophile (for **18**), Scheme 4.

Intra- and intermolecular cycloadditions with maleates, fumarates, and maleic anhydride are compared. Further synthetic applications are suggested for adducts **19**.



SCHEME 4

Diels-Alder cycloadditions of substrates tethered *via* side-chain substituents

EXPERIMENTAL

All non-hydrolytic reactions were carried out under an argon atmosphere, with standard techniques to exclude moisture. Analytical and preparative TLC was performed on Silicyle silica gel 60A plates. Flash chromatography was performed on chromatographic silica gel, 230–400 mesh (Lagand Chemicals). Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR instrument. Wavenumbers are given in cm^{-1} . ^1H and ^{13}C NMR spectra were obtained on a Varian 300 MHz or on a Varian Inova 500 MHz spectrometer with CDCl_3 -TMS as a solvent. ^1H chemical shifts are reported in ppm (δ -scale) relative to TMS (0.0 ppm). ^{13}C chemical shifts are reported in ppm (δ -scale) relative to the central line of the CDCl_3 triplet (77.23 ppm). Coupling constants (J) are reported in Hz. Optical rotations were recorded on a Perkin–Elmer 241 digital polarimeter (10^{-1} deg cm^2 g^{-1}). Melting points were obtained on a Thomas–Hoover capillary melting point apparatus and are uncorrected. High-resolution mass spectra and elemental analyses were performed at the University of Florida and Atlantic Microlab, Inc., respectively.

(3*aR*,7*aS*)-4-(2-Azidoethyl)-2,2-dimethyl-3*a*,7*a*-dihydrobenzo[1,3]dioxole (**22**)

To a solution of the crude diene diol derived from (2-azidoethyl)benzene¹⁷ (0.88 g, 4.9 mmol) (containing small amount of the corresponding phenol) in methylene chloride (6 ml) and 2,2-dimethoxypropane (6 ml, 49 mmol, 10 equiv.) was added catalytic amount of 4-methylbenzene-1-sulfonic acid. The reaction mixture was stirred at room temperature for 45 min, with monitoring by TLC. Upon completion, the reaction mixture was treated with 5 wt.% solution of sodium hydroxide (10 ml), followed by extraction with methylene chloride (4×20 ml). The combined organic layers were washed with brine (10 ml) and dried over anhydrous sodium sulfate. After filtration and removal of solvent, the oily residue was purified by column chromatography (hexane–EtOAc, 95 : 5). Compound **22** was obtained as yellow oil in 46% yield (0.50 g). ^1H NMR and IR data were in agreement with previously published data for this compound¹⁷.

General Procedure for the Staudinger Reduction¹⁸ Followed by DCC Coupling

To a solution of the diene **22** (0.204 g, 0.92 mmol) in tetrahydrofuran (3 ml) were added triphenylphosphine (0.254 g, 0.97 mmol, 1.05 equiv.) and water (26 μ l, 1.5 mmol, 1.5 equiv.), and the resulting mixture was stirred at room temperature. After 22 h tetrahydrofurane (5 ml) was added, and solution was dried over anhydrous magnesium sulfate. Following filtration and removal of solvent, the crude residue was used for the next step.

To a solution of monoethyl fumarate (0.147 g, 0.97 mmol, 1.05 equiv.) in methylene chloride (3 ml) were added dicyclohexylcarbodiimide (DCC) (0.220 g, 1.07 mmol, 1.1 equiv.) (a white precipitate forms) and catalytic amount of a DMAP. The reaction mixture was stirred at 0 °C for 5 min, then a solution of the crude amine (ca 0.2 g, 0.92 mmol) in the methylene chloride (3 ml) was added. After stirring at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 18 h. The white precipitate was filtered off and the solvent evaporated. The remaining dark brown oil was triturated with ether (15 ml), and the resulting solid was separated by filtration.

Ethyl (*E*)-(3a*R*,7a*S*)-3-{*N*-[2-(2,2-Dimethyl-3a,7a-dihydrobenzo[1,3]dioxol-4-yl)-ethyl]carbamoyl} Acrylate (**23**)

Diene **22** (0.204 g, 0.92 mmol) was reduced using the Staudinger protocol¹⁸ to the corresponding amine, which was immediately subjected to DCC coupling as described above. Silica was added to the filtrate, and solvent was removed under reduced pressure. The crude product thus adsorbed on silica was then purified by column chromatography (hexanes–EtOAc, 60 : 40, 50 : 50, 40 : 60). Product **23** was obtain as semicrystalline oil (0.174 g, 59%) and was stored under argon in the freezer. (It easily undergoes Diels–Alder reaction at room temperature.) R_F (hexanes–EtOAc, 1 : 1) 0.41; $[\alpha]_D^{29}$ -14.6 (c 0.0308 g ml⁻¹, CHCl₃). ¹H NMR: 6.84 and 6.77 (d, 2 H, $J = 15.6$); 6.44 (bs, 1 H); 5.95 (m, 1 H); 5.82 (m, 2 H); 4.76 (d, 1 H, $J = 8.4$); 4.49 (d, 1 H, $J = 8.4$); 4.24 (q, 2 H, $J = 6.9$); 3.57 (m, 2 H); 2.59 (m, 1 H); 2.38 (m, 1 H); 1.43 (s, 6 H); 1.31 (t, 3 H, $J = 7.2$). ¹³C NMR: 165.7, 163.7, 136.7, 134.2, 130.1, 124.4, 123.7, 121.9, 105.27, 71.3, 71.9, 61.3, 38.5, 34.3, 27.0, 25.0, 14.3. IR (neat): 3 287.2, 3 074.9, 3 049.4, 2 985.1, 2 934.1, 1 724.8, 1 667.5, 1 651.8, 1 298.9, 1 031.2. HRMS: calculated for C₁₇H₂₄NO₅ ([M + H]⁺): 322.1654, found: 322.1652.

Ethyl (*Z*)-(3a*R*,7a*S*)-3-{*N*-[2-(2,2-Dimethyl-3a,7a-dihydrobenzo[1,3]dioxol-4-yl)-ethyl]carbamoyl} Acrylate (**24**)

Diene **22** (0.270 g, 1.22 mmol) was reduced to the corresponding amine using the Staudinger protocol¹⁸ and immediately used for DCC coupling using the general procedure. Solvent was removed under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 70 : 30). Pure **24** was obtained as oil (0.101 g, 26%) and was stored under argon in the freezer. R_F (EtOAc) 0.74; $[\alpha]_D^{29}$ $+71.6$; (c 0.0145 g ml⁻¹, CHCl₃). ¹H NMR: 8.19 (bs, 1 H); 6.30 and 6.10 (2d, 2 H, $J = 12.9$); 5.96 (m, 1 H); 5.81 (m, 2 H); 4.71 (dd, 1 H, $J = 3.0, 8.6$); 4.56 (d, 1 H, $J = 8.4$); 4.23 (q, 2 H, $J = 7.2$); 3.56 (q, 2 H, $J = 6.3$); 2.51 (m, 2 H); 1.40 and 1.39 (2s, 6 H); 1.31 (t, 3 H, $J = 7.2$). ¹³C NMR: 166.2, 164.2, 138.3, 134.9, 125.5, 124.3, 123.8, 121.0, 105.3, 73.1, 71.6, 61.7, 38.0, 33.8, 27.0, 25.2, 14.2. IR (neat): 3 300.3, 3 047.5, 2 985.2, 2 935.1, 1 729.4, 1 661.7, 1 629.6, 1 211.4, 1 027.4. HRMS: calculated for C₁₇H₂₄NO₅ ([M + H]⁺): 322.1654, found: 322.1689.

Ethyl (1*R*,6*R*,7*S*,8*S*,9*R*,13*S*)-11,11-Dimethyl-5-oxo-10,12-dioxa-4-azatetracyclo-[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylate (**25**)

and Ethyl (1*R*,6*S*,7*R*,8*S*,9*R*,13*S*)-11,11-Dimethyl-5-oxo-10,12-dioxa-4-azatetracyclo-[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylate (**26**)

A solution of triene **23** (0.13 g, 0.4 mmol) in benzene (10 ml) was heated to reflux for 21 h, then the solvent was evaporated. Column chromatography (hexanes-EtOAc, 20 : 80) yielded pure **25** (0.030 g, 23%), pure isomer **26** (0.020 g, 15%), and a mixture of both isomers (0.048 g, 37%). The overall yield of reaction was 75%.

25: R_F (EtOAc) 0.46; $[\alpha]_D^{29} +10.7$ (c 0.0138 g ml⁻¹, CHCl₃). ¹H NMR (500 MHz): 6.30 (ddt, 1 H, $J = 8.3, 6.6, 0.9$); 6.03 (bs, 1 H); 5.95 (dt, 1 H, $J = 8.2, 1.3$); 4.24 (ddd, 1 H, $J = 7.1, 3.2, 1.0$); 4.22 (dq, 1 H, $J = 15.8, 7.2$); 4.20 (dq, 1 H, $J = 15.6, 7.2$); 4.03 (dd, 1 H, $J = 7.1, 2$); 3.50 (td, 1 H, $J = 12.3, 4.9$); 3.43 (ddt, 1 H, $J = 12.5, 6.4, 2.5$); 3.26 (dtd, 1 H, $J = 6.5, 3.3, 1.1$); 2.97 (dd, 1 H, $J = 5.9, 3.0$); 2.73 (d, 1 H, $J = 6.0$); 2.29 (ddd, 1 H, $J = 13.6, 4.6, 1.7$); 1.91 (ddd, 1 H, $J = 13.3, 12.2, 6.9$); 1.31 (s, 3 H); 1.30 (t, 3 H, $J = 7.3$); 1.26 (s, 3 H). ¹³C NMR (126 MHz, CDCl₃): 173.5, 172.8, 133.4, 130.7, 109.6, 82.0, 76.2, 61.5, 44.3, 43.0, 41.4, 39.3, 38.0, 27.7, 25.4, 25.1, 14.3. IR (neat): 3 311.84, 3 213.3, 3 056.6, 2 983.5, 2 937.2, 1 728.1, 1 668.2, 1 194.7. HRMS: calculated for C₁₇H₂₄NO₅ ([M + H]⁺): 322.1654, found: 322.1653. For C₁₇H₂₃NO₅ (321.4) calculated: 63.54% C, 7.21% H; found: 63.59% C, 7.30% H.

26: R_F (EtOAc) 0.40; $[\alpha]_D^{27} +17.2$ (c 0.0181 g ml⁻¹, CHCl₃). ¹H NMR: 5.99 (m, 2 H); 5.73 (bs, 1 H); 4.35 (dd, 1 H, $J = 3.2, 7.0$); 4.18 (m, 3 H); 3.56 (m, 1 H); 3.47 (m, 1 H); 3.32 (m, 1 H); 3.04 (dd, 1 H, $J = 1.7, 6.3$); 2.79 (d, 1 H, $J = 5.9$); 2.39 (m, 1 H); 2.14 (m, 1 H); 1.32(s, 3 H); 1.26 (s, 3 H); 1.26 (t, 3 H, $J = 7.1$). ¹³C NMR: 173.5, 172.8, 136.4, 129.2, 109.6, 78.5, 76.2, 61.5, 45.4, 41.3, 41.2, 39.0, 38.9, 27.3, 25.6, 25.3, 14.4. IR (neat): 3 307.9, 3 052.7, 2 981.6, 2 933.9, 1 731.8, 1 667.1, 1 058.7. HRMS: calculated for C₁₇H₂₄NO₅ ([M + H]⁺): 322.1654, found: 322.1653. For C₁₇H₂₃NO₅ (321.4) calculated: 63.54% C, 7.21% H; found: 63.84% C, 7.41% H.

Ethyl (1*R*,6*S*,7*S*,8*S*,9*R*,13*S*)-11,11-Dimethyl-5-oxo-10,12-dioxa-4-azatetracyclo-[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylate (**27**)

and Ethyl (1*R*,6*R*,7*R*,8*S*,9*R*,13*S*)-11,11-Dimethyl-5-oxo-10,12-dioxa-4-azatetracyclo-[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylate (**28**)

A solution of triene **24** (0.087 g, 0.27 mmol) in benzene (13 ml) was heated at reflux for 5 days. The solvent was evaporated, and the residue purified by column chromatography (EtOAc) to provide pure **28** (0.017 g, 20%), pure **27** (0.022 g, 25%) and a mixture of both isomers (0.035 g, 40%, **28** is prevailing component). The overall yield of the reaction was 85%. The ratio of cycloadducts (by integration of the ¹H NMR spectrum of the crude mixture) was 2 : 1 (**28** : **27**).

27: R_F (CHCl₃-MeOH, 9 : 1) 0.56; $[\alpha]_D^{30} +38.6$ (c 0.0092 g ml⁻¹, CHCl₃). ¹H NMR: 6.32 (t, 1 H, $J = 7.5$); 6.10 (d, 1 H, $J = 8.4$); 5.83 (bs, 1 H); 4.16 (dd, 1 H, $J = 8.1, 4.2$); 4.09 (q, 2 H, $J = 7.0$); 3.82 (d, 1 H, $J = 8.1$); 3.62 (dd, 1 H, $J = 10.2, 2.7$); 3.54 (dd, 1 H, $J = 12.3, 4.2$); 3.36 (m, 1 H); 3.24 (d, 1 H, $J = 10.2$); 3.11 (m, 1 H); 2.02 (dt, 1 H, $J = 13.3, 6.1$); 1.84 (dd, 1 H, $J = 13.1, 3.6$); 1.53 (s, 3 H); 1.35 (s, 3 H); 1.25 (t, 3 H, $J = 7.1$). ¹³C NMR: 174.0, 173.0, 133.9, 132.5, 113.1, 78.9, 74.9, 60.6, 41.3, 41.2, 41.1, 38.7, 38.6, 26.9, 26.5, 24.6, 14.3. IR (neat): 3 306.3, 3 046.5, 2 928.2, 2 856.1, 1 731.9, 1 666.5, 1 175.7. HRMS: calculated for C₁₇H₂₄NO₅ ([M + H]⁺): 322.1654, found: 322.1637.

28: R_F (CHCl₃–MeOH, 9 : 1) 0.51; $[\alpha]_D^{25}$ –29.6 (c 0.0100 g ml⁻¹, CHCl₃). ¹H NMR: 6.23 (t, 1 H, $J = 7.3$); 6.01 (d, 1 H, $J = 8.4$); 5.80 (bs, 1 H); 4.31 (dd, 1 H, $J = 2.8, 7.1$); 4.22 (dd, 1 H, $J = 3.8, 6.3$); 4.10 (q, 2 H, $J = 7.1$); 3.93 (d, 1 H, $J = 7.2$); 3.61 (dt, 1 H, $J = 12.6, 3.8$); 3.39 (m, 1 H); 3.10 (m, 2 H); 2.32 (m, 2 H); 1.33 (s, 3 H); 1.28 (s, 3 H); 1.25 (t, 3 H, $J = 7.1$). ¹³C NMR: 172.7, 171.0, 131.9, 129.7, 110.1, 83.0, 78.6, 60.9, 45.1, 43.5, 41.2, 39.4, 39.1, 28.4, 25.6, 25.4, 14.3. IR (neat): 3 310.5, 2 927.5, 2 855.7, 1 731.9, 1 666.9. HRMS: calculated for C₁₇H₂₄NO₅ ($[M + H]^+$): 322.1654, found: 322.1628. For C₁₇H₂₃NO₅ (321.4) calculated: 63.54% C, 7.21% H; found: 63.18% C, 7.13% H.

(1*R*,2*R*,6*S*,7*S*,8*R*,12*R*)-1-(2-Azidoethyl)-4,4-dimethyl-3,5,10-trioxatetracyclo-
[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-ene-9,11-dione (**29**)

and (1*R*,2*R*,6*S*,7*S*,8*S*,12*S*)-1-(2-Azidoethyl)-4,4-dimethyl-3,5,10-trioxatetracyclo-
[5.5.2.0^{2,6}.0^{8,12}]tetradec-13-ene-9,11-dione (**30**)

To a solution of diene **22** (0.212 g, 0.96 mmol) in benzene (7 ml), maleic anhydride (0.099 g, 1.0 mmol, 1.05 equiv.) was added. The reaction mixture was stirred under argon atmosphere at room temperature for 68 h, and the reaction progress was monitored by TLC. The benzene was evaporated under reduced pressure, and the resulting oil was purified by column chromatography (hexanes–EtOAc, 80 : 20) to yield the expected cycloadducts: **29** as a white solid (0.051 g, 17%) and **30** as a yellow oil (0.121 g, 39%). The ratio of cycloadducts (by integration of the ¹H NMR spectrum of the crude mixture) was 1.6 : 1 (**30** : **29**). The reaction was also carried out at reflux temperature with similar results.

29: R_F (hexanes–EtOAc, 70 : 30) 0.33; m.p. 116–117 °C; $[\alpha]_D^{29}$ +2.3 (c 0.0104 g ml⁻¹, CHCl₃). ¹H NMR: 6.18 (dd, 1 H, $J = 8.3, 6.2$); 5.91 (d, 1 H, $J = 8.4$); 4.33 (dd, 1 H, $J = 7.2, 3.3$); 4.20 (d, 1 H, $J = 7.1$); 3.67 (m, 2 H); 3.48 (m, 1 H); 3.10 (m, 2 H); 2.39 (m, 2 H); 1.31 and 1.29 (s, 6 H). ¹³C NMR: 171.0, 169.9, 134.5, 129.8, 110.4, 78.24, 77.2, 47.3, 43.1, 42.2, 36.2, 30.0, 25.3, 25.0. IR (KBr): 2979.0, 2 105.0, 1 846.9, 1 776.1. HRMS: calculated for C₁₅H₁₈N₃O₅ ($[M + H]^+$): 320.1246, found: 320.1244.

30: R_F (hexanes–EtOAc, 70 : 30) 0.55; $[\alpha]_D^{31}$ + 44.5 (c 0.0121 g ml⁻¹, CHCl₃). ¹H NMR: 6.26 (dd, 1 H, $J = 8.3, 6.5$); 6.04 (d, 1 H, $J = 8.3$); 4.19 (dd, 1 H, $J = 8.2, 3.9$); 4.01 (d, 1 H, $J = 8.3$); 3.6 (m, 3 H); 3.42 (m, 2 H); 2.32 (m, 2 H); 1.48 (s, 3 H); 1.35 (s, 3 H). ¹³C NMR: 173.2, 172.1, 136.2, 131.7, 113.1, 76.6, 74.4, 47.5, 43.6, 41.9, 39.9, 37.0, 32.0, 26.5, 24.4. IR (KBr): 2 986.0, 2 095.8, 1 841.6, 1 770.4. HRMS: calculated for C₁₅H₁₈N₃O₅ ($[M + H]^+$): 320.1246, found: 320.1235.

General Procedure for the Staudinger Reduction¹⁸ Followed by Esterification

To a solution of compound **29** (0.083 g, 0.26 mmol) in tetrahydrofuran (3 ml) were added triphenylphosphine (0.072 g, 0.27 mmol, 1.05 equiv.) and water (5 μl, 0.52 mmol, 2 equiv.). The reaction mixture was heated to approximately 60 °C for 54 h (monitored by TLC) (a white precipitate forms during the reaction). The solvent was evaporated under reduced pressure, and the residue treated with a cold solution of diazomethane in ether (3 ml). (During the reaction the initially insoluble residue dissolves.) After stirring at room temperature for 30 min, more diazomethane solution (3 ml) was added, and stirring was continued for 17 h. Methanol (1 ml) was added and solvents were removed under reduced pressure.

Methyl (1*R*,6*R*,7*R*,8*S*,9*R*,13*S*)-11,11-Dimethyl-5-oxo-10,12-dioxa-4-azatetracyclo-[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylate (**31**)

Compound **29** (0.083 g, 0.26 mmol) was reduced and converted to the corresponding ester according to the general procedure described above. The residue was purified by column chromatography (EtOAc–hexanes, 3 : 1, with 0.5% Et₃N). Product **31** was obtained as a white crystalline material (0.050 g, 63%); m.p. 172–173 °C; *R_F* (EtOAc) 0.39; [α]_D²⁷ +19.9 (c 0.0122 g ml⁻¹, CHCl₃). ¹H NMR: 6.16 (bs, 1 H); 5.99 (m, 2 H); 4.34 (dd, 1 H, *J* = 7.2, 3.3); 4.18 (d, 1 H, *J* = 7.2); 3.71 (s, 3 H); 3.56 (m, 1 H); 3.47 (m, 1 H); 3.30 (m, 1 H); 3.04 (dd, 1 H, *J* = 6.2, 1.5); 2.77 (d, 1 H, *J* = 6.0); 2.37 (m, 1 H); 2.14 (m, 1 H); 1.32 and 1.26 (s, 6 H). ¹³C NMR: 174.0, 172.8, 136.4, 129.2, 109.5, 78.4, 76.1, 52.7, 45.5, 41.1, 38.9, 38.7, 27.2, 25.6, 25.3. IR (KBr): 3 416.7, 3 224.8, 1 744.6, 1 648.2, 1 195.2. HRMS: calculated for C₁₆H₂₂NO₅ ([M + H]⁺): 308.1498, found: 308.1496. For C₁₆H₂₁NO₅ (307.3) calculated: 62.53% C, 6.89% H; found: 62.84% C, 6.80% H.

Methyl (1*R*,6*S*,7*S*,8*S*,9*R*,13*S*)-11,11-Dimethyl-5-oxo-10,12-dioxa-4-azatetracyclo-[6.5.2.0^{1,6}.0^{9,13}]pentadec-14-ene-7-carboxylate (**32**)

Compound **30** (0.48 g, 1.5 mmol) was reduced and converted to the corresponding ester as described above. The residue was purified by column chromatography (5% Et₃N in EtOAc). Product **32** was obtained as a white crystalline material (0.31 g, 70%); m.p. 173–174 °C; *R_F* (EtOAc) 0.18; [α]_D²⁸ +48.6 (c 0.0107 g ml⁻¹, CHCl₃). ¹H NMR: 6.34 (t, 1 H, *J* = 7.2); 6.11 (d, 1 H, *J* = 8.4); 6.01 (bs, 1 H); 4.15 (dd, 1 H, *J* = 8.0, 4.3); 3.82 (d, 1 H, *J* = 8.1); 3.64 (s, 3 H); 3.56 (m, 1 H); 3.36 (m, 1 H); 3.24 (d, 1 H, *J* = 10.2); 3.09 (m, 2 H); 2.03 (m, 2 H); 1.85 (m, 1 H); 1.52 and 1.34 (s, 6 H). ¹³C NMR: 174.6, 172.8, 134.0, 132.4, 113.0, 78.8, 75.0, 51.9, 41.4, 41.1, 41.0, 38.6, 29.9, 26.9, 26.5, 24.6. IR (KBr): 3 354.1, 3 060.3, 2 931.0, 1 736.9, 1 660.5, 1 208.0. HRMS: calculated for C₁₆H₂₂NO₅ ([M + H]⁺): 308.1498, found: 308.1497. For C₁₆H₂₁NO₅ (307.3) calculated: 62.53% C, 6.89% H; found: 62.65% C, 6.88% H.

(1*R*,8*S*,9*R*,13*S*)-1-(2-Azidoethyl)-11,11-dimethyl-10,12-dioxatetracyclo-[6.5.2.0^{2,7}.0^{9,13}]pentadeca-2,4,6,14-tetraene-3,6-diol (**33**)

and (1*R*,2*S*,7*S*,8*S*,9*R*,13*S*)-1-(2-Azidoethyl)-11,11-dimethyl-10,12-dioxotetracyclo-[6.5.2.0^{2,7}.0^{9,13}]pentadeca-4,14-diene-3,6-dione (**34**)

To a solution of diene **22** (0.12 g, 0.53 mmol) in benzene (3 ml) was added freshly sublimed 1,4-benzoquinone (0.058 g, 0.47 mmol, 1.1 equiv.) and the reaction mixture was stirred at room temperature for 3 days. A black precipitate formed during reaction. The reaction mixture was evaporated, and the residue was purified by preparative TLC (hexanes–EtOAc, 9 : 1; 3 elutions). The aromatized product **33** was isolated (0.013 g, 7.6%) along with the expected cycloadduct **34** (0.015 g, 8.6%).

33: *R_F* (hexanes–EtOAc, 60 : 40) 0.27. ¹H NMR: 6.50 (d, 1 H, *J* = 8.7); 6.48 (t, 1 H, *J* = 7.5); 6.39 (d, 1 H, *J* = 8.7); 6.21 (dd, 1 H, *J* = 7.8, 1.2); 4.48 (m, 1 H); 4.28 (dd, 1 H, *J* = 7.2, 3.3); 4.08 (d, 1 H, *J* = 6.9); 3.81 (m, 1 H); 3.61 (m, 1 H); 2.71 (m, 2 H); 1.38 (s, 3 H); 1.26 (s, 3 H). ¹³C NMR: 146.2, 145.1, 135.7, 132.6, 129.6, 127.9, 115.9, 114.8, 112.4, 82.0, 79.3, 50.0, 49.7, 38.3, 31.2, 29.1, 25.7. IR (neat): 3 426.3, 2 977.8, 2 930.1, 2 094.5, 1 642.0. HRMS: calculated for C₁₇H₂₀N₃O₄ ([M + H]⁺): 330.1454, found: 330.1476.

34: *R_F* (hexanes–EtOAc, 70 : 30) 0.35. ¹H NMR: 6.69 (d, 1 H, *J* = 10.5); 6.65 (d, 1 H, *J* = 10.5); 6.19 (t, 1 H, *J* = 8.1); 6.20 (dd, 1 H, *J* = 8.3, 8.1); 5.91 (d, 1 H, *J* = 7.8); 4.15 (dd, 1 H, *J* =

8.1, 3.9); 3.90 (d, 1 H, $J = 8.7$); 3.68 (m, 1 H); 4.50 (m, 2 H); 3.42 (d, 1 H, $J = 8.7$); 2.16 (m, 1 H); 1.86 (m, 1 H); 1.35 (s, 3 H); 1.25 (s, 3 H). ^{13}C NMR: 143.2, 141.9, 136.2, 132.1, 112.5, 78.0, 74.5, 47.7, 44.9, 43.5, 40.8, 33.7, 29.7, 26.4, 24.4. IR (neat): 2 982.9, 2 928.3, 2 097.0, 1 688.3, 1 682.8, 1 606.9.

(1*R*,2*R*,7*S*,8*S*,9*R*,13*S*)-1-(2-Azidoethyl)-11,11-dimethyl-10,12-dioxatetracyclo-
[6.5.2.2.0^{2,7}.0^{9,13}]pentadeca-4,14-diene-3,6-diol (**35**)

To a solution of diene **22** (0.076 g, 0.34 mmol) in benzene (5 ml) was added freshly sublimed 1,4-benzoquinone (0.038 g, 0.34 mmol, 1.1 equiv.), and the reaction mixture was heated to reflux for 18 h under argon atmosphere. The resulting dark brown mixture containing a black precipitate was concentrated, and the residue was dissolved in 5 ml of a 1 : 1 mixture of methylene chloride and methanol. Ceric(III) chloride heptahydrate (0.129 g, 1 equiv.) was added and, after 5 min at ambient temperature, sodium borohydride (0.013 g, 1 equiv.) was added in one portion. After stirring for an additional 30 min at ambient temperature, pH was adjusted to neutral with dilute hydrochloric acid. Water (10 ml) was added, and the mixture was extracted with ether (4 × 15 ml). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 1 : 1). Product **35** was obtained as an oil (0.028 g, 25%, containing a trace of aromatized product). R_F (hexanes–EtOAc, 1 : 1) 0.3. ^1H NMR: 6.47 (m, 2 H); 6.12 (t, 1 H, $J = 7.5$); 5.87 (d, 1 H, $J = 7.8$); 4.26 (m, 2 H); 4.03 (d, 1 H, $J = 7.2$); 3.57 (m, 2 H); 2.87 (m, 1 H); 2.59 (d, 1 H, $J = 8.7$); 2.25 (m, 1 H); 2.05 (m, 1 H); 1.91 (dd, 1 H, $J = 11.1$, 3.9); 1.68 (dd, 1 H, $J = 10.8$, 4.2); 1.33 (s, 3 H); 1.27 (s, 3 H). ^{13}C NMR: 136.6, 136.3, 132.2, 128.2, 109.0, 81.3, 79.7, 65.2, 61.9, 48.0, 46.0, 43.0, 41.1, 31.4, 30.9, 29.7, 29.6. IR (neat): 3 358.8, 3 052.97, 2 978.7, 2 924.1, 2 855.0, 2 096.7, 1 661, 1 208.3, 1 066.3. HRMS: calculated for $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_4$ ($[\text{M} + \text{H}]^+$): 334.1767, found: 334.1742.

N-[2-(2,2-Dimethyl-(3*aR*,7*aS*)-dihydrobenzo[1,3]dioxol-4-yl)ethyl]acetamide (**36**)

Compound **22** (0.25 g, 1.1 mmol) in thioacetic acid (0.4 ml, 4.4 mmol, 4 equiv.) was stirred at 0 °C for 1 h, and then allowed to warm to room temperature. Stirring was continued for 17 h, then the mixture was concentrated and the residue purified by column chromatography (EtOAc). Product **36** was obtained as yellow oil (0.12 g, 46%). R_F (EtOAc) 0.33. ^1H NMR: 6.21(bs, 1 H); 5.96 (m, 1 H); 5.80 (m, 2 H); 4.72 (dd, 1 H, $J = 8.7$, 3.3); 4.52 (d, 1 H, $J = 8.7$); 3.45 (m, 2 H); 2.48 (m, 1 H); 2.36 (m, 1 H); 1.96 (s, 3 H); 1.41 (s, 6 H). ^{13}C NMR: 170.0, 134.5, 123.8, 123.7, 121.0, 104.9, 72.9, 71.5, 37.7, 37.1, 26.7, 24.7, 23.1. IR (neat): 3 298.4, 3 087.9, 2 985.7, 2 935.0, 1 651.5, 1 557, 1 434.3.

(1*R*,2*R*,7*R*,8*S*,9*R*,13*S*)-*N*-[2-(11,11-Dimethyl-3,6-dioxo-10,12-dioxatetracyclo-
[6.5.2.0^{2,7}.0^{8,9}]pentadeca-4,14-diene-1-yl)ethyl]acetamide (**37**)

and (1*R*,2*S*,7*S*,8*S*,9*R*,13*S*)-*N*-[2-(11,11-Dimethyl-3,6-dioxo-10,12-dioxatetracyclo-
[6.5.2.0^{2,7}.0^{8,9}]pentadeca-4,14-diene-1-yl)ethyl]acetamide (**38**)

To a stirred solution of **36** (0.048 g, 0.2 mmol) in benzene (7 ml) was added 1,4-benzoquinone (0.033 g, 0.3 mmol, 1.5 equiv.). The reaction mixture was stirred at ambient temperature for 4 days (with monitoring by TLC). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (EtOAc). The isolated compound (0.047 g) was shown by ^1H NMR to be a mixture of the two isomers **37** and **38** (ca

2 : 1). Further attempt to separate the isomers by column chromatography (hexanes–acetone, 2 : 1) was unsuccessful. Partial ^1H NMR of the mixture (signals belonging to the exo adduct **38** are in italics): 6.60 (s, 2 H); 6.65 (s, 2 H); 6.28 (bs, 1 H); 6.19 (dd, 1 H, $J = 6.3, 8.1$); 6.09 (t, 1 H, $J = 8.1$); 5.99 (bs, 1 H); 5.91 (d, 1 H, $J = 8.1$); 5.73 (d, 1 H, $J = 8.4$); 1.98 (s, 3 H); 1.97 (s, 3 H); 1.51 and 1.35 (s, 6 H); 1.30 and 1.28 (s, 6 H). HRMS: calculated for $\text{C}_{19}\text{H}_{24}\text{NO}_5$ ($[\text{M} + \text{H}]^+$): 346.1654, found: 346.1618.

RESULTS AND DISCUSSION

β -Functionalized ethylbenzenes have been shown to be good substrates for toluene dioxygenase overexpressed in the recombinant organism *E. coli* JM109 (pDTG601), developed by Gibson¹⁹. The absolute stereochemistry of the diols derived from (2-bromoethyl)benzene²⁰, 1-bromo-2-(2-bromoethyl)benzene²¹, and (2-azidoethyl)benzene¹⁷, isolated in yields of 0.1–0.5 g l⁻¹ from the whole-cell fermentations, has been established. These compounds have been used previously in our approaches to morphine²² through radical, cationic, and Heck-type cyclizations²³, as well as the aforementioned Diels–Alder cycloadditions tethered through one of the hydroxy groups.

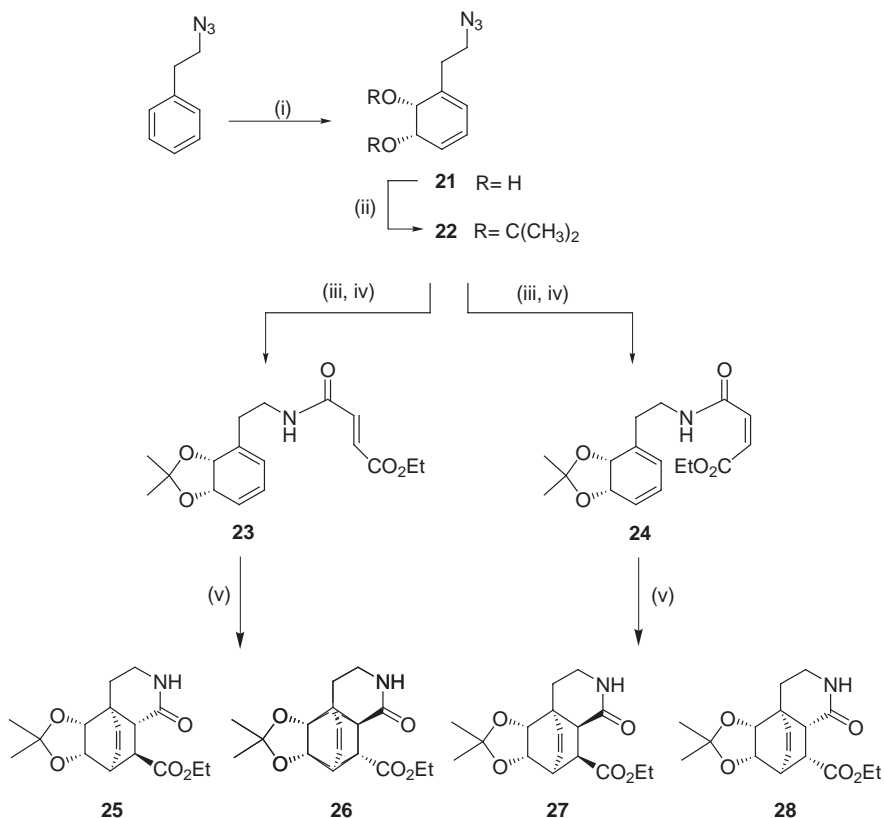
We chose to study cycloadditions where a nitrogen-linked tether would deliver the dienophile and to compare the stereoselectivity of the intramolecular process with an analogous intermolecular cycloaddition. To this end, (2-azidoethyl)benzene was converted to the *cis* diol with *E. coli* JM109 (pDTG601) in 10-l fermentor (3 g l⁻¹) and immediately protected as an acetonide, as shown in Scheme 5. Aware of the propensity of diene diols acetonides to dimerize *via* Diels–Alder cycloadditions²⁴, we quickly subjected the azide to the Staudinger protocol and converted the resulting amine to either fumaroyl or maleoyl amide in 59% and 26% yield, respectively. Heating **23** or **24** in benzene at reflux for 1 or 5 days led to a mixture of cycloadducts **25** and **26** in 75%, and **27** and **28** in 85% total yield.

Separation of isomers was difficult because of the small R_F difference (*e.g.*, 0.06 for **25** and **26**); nevertheless, analytical samples of pure isomers were obtained along with mixtures of both isomers with various ratios. The ratios of **25** to **26** and **27** to **28** in crude mixtures were determined from ^1H NMR spectra to be approximately 1.3 : 1 and 1 : 2, respectively. The trienes were stored at low temperature to avoid cycloadditions. Even so, after 30 days at –30 °C and under Ar atmosphere, triene **23** showed noticeable contamination by cycloaddition products in the NMR spectrum. Triene **23** (in CDCl_3) readily underwent cycloaddition at room temperature within a few days.

The relative stereochemistry of adducts **25** and **26** were determined by means of 2D-NMR techniques. For example, the assignment of the ^1H NMR spectrum of **25** was straightforward from the DQCOSEY experiment (Fig. 1).

NOEs to the protons at 4.03 and 4.24 ppm identified the acetonide methyl *cis* to them as 1.26. It is the other methyl at 1.30 which displays NOEs with the protons in the olefinic bridge, thus establishing that the acetonide ring is *exo*.

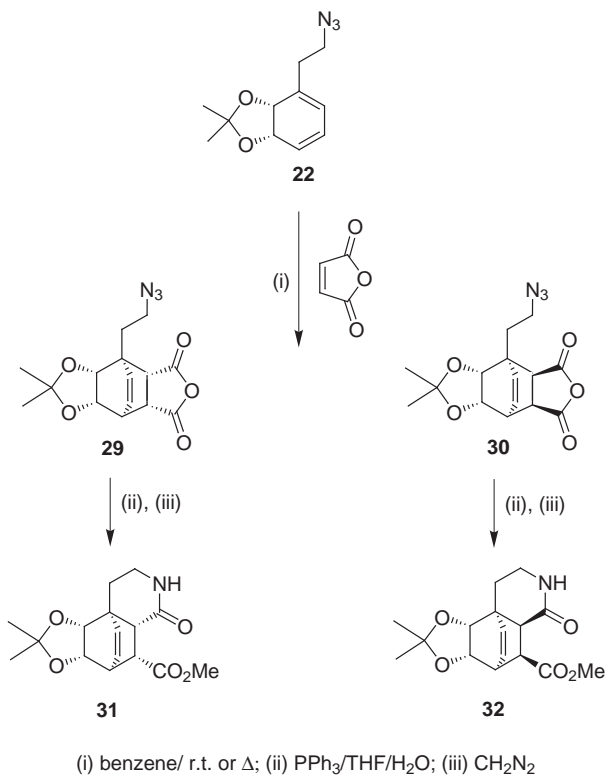
A large coupling constant (12.3) between the signals 3.43 and 1.91 indicates that the piperidone ring has a chair conformation and that these protons are axial. The protons at 1.91, 4.03 and 2.73 display large NOEs, comparable in intensity with the one between 4.03 and 4.24, indicating



(i) *E. coli* JM109 (pDTG601); (ii) DMP/TsOH; (iii) $\text{Ph}_3\text{P/THF/H}_2\text{O}$; (iv) DCC/ ethyl fumaric or ethyl maleic acid; (v) benzene/ Δ

SCHEME 5
Synthesis of trienes **23** and **24** and their cycloadditions

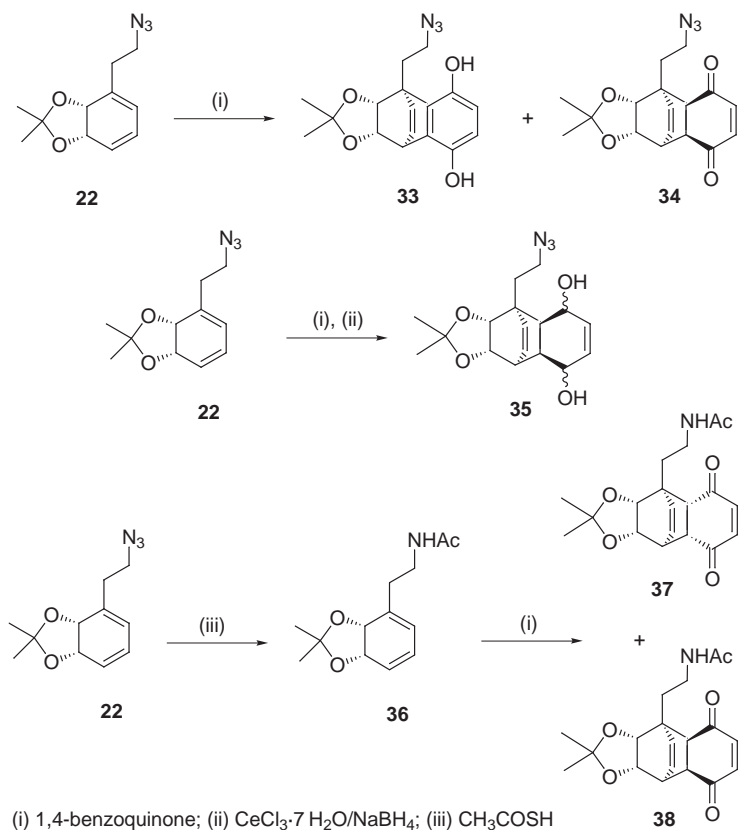
Banwell has carried out cycloadditions on similar diene systems (*e.g.*, the dienediol derived from toluene), with 1,4-benzoquinone¹³ (refluxing benzene) or with maleic anhydride⁹ (in methylene chloride at 0–18 °C) as dienophiles. He observed a different outcome from ours; in both cases he reported a single isomer resulting from the endo process (55 and 68% yields, respectively). We have attempted the reaction of diene **22** with 1,4-benzoquinone using Banwell's conditions, but the reactions produced complex mixtures; however, we isolated in low yields aromatized hydroquinone product **33** along with expected cycloadduct **34**. To prevent aromatization, we attempted to reduce the crude reaction mixture following cycloaddition under Luche conditions. The reduction product **35** was isolated in low yield.



SCHEME 6
Intermolecular cycloaddition of diene **22**

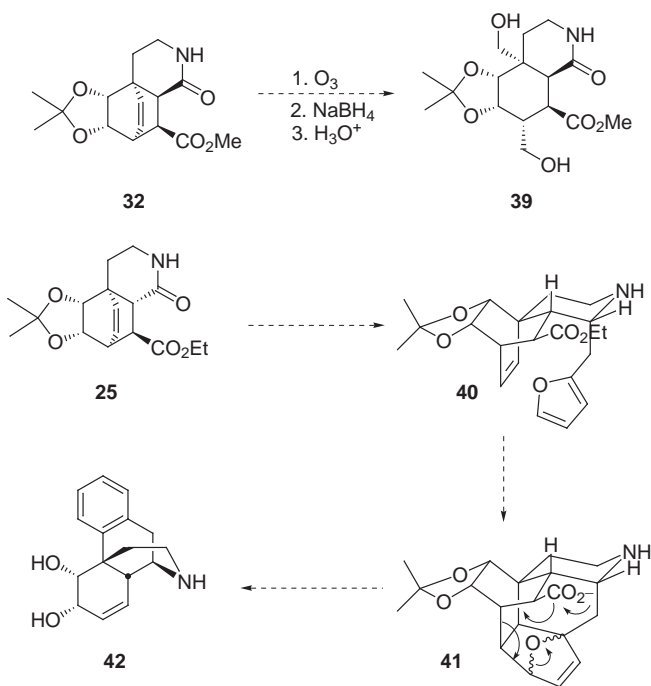
Because we suspected side reactions such as 1,3-dipolar cycloaddition of the azide moiety, we reduced the azide **22** to acetamide **36**, which was then used for cycloaddition with 1,4-benzoquinone, (Scheme 7). The isolated product appeared as a single spot on TLC; however, the ^1H NMR spectrum showed that it is actually a mixture of both isomers **37** and **38** with a ratio of *ca* 2 : 1. In this case, the endo cycloadduct **37** predominated, in contrast to our observations of the cycloaddition with maleic anhydride. Further attempts to separate these compounds were not successful.

Compounds **25–28**, and **31** and **32** are unique in two regards. First, the isoquinoline skeleton is functionalized at all but one carbon atom, and it is easy to envision, for example, an oxidative cleavage of the bridge in **32** to



SCHEME 7
Cycloadditions of diene **22** with 1,4-benzoquinone

provide an interesting scaffold (*i.e.* **39**) for parallel synthesis as shown in Scheme 8. Second, adduct **25** offers an interesting possibility for a fragmentation approach to morphine *via* a further cycloaddition as shown. The morphinan skeleton **42** could, in principle, be obtained by fragmentation and dehydration of adduct **41**. One can further imagine subjecting compound **42** to recently described microbial oxidation for the direct conversion of an aromatic ring to catechol²⁵. These somewhat speculative endeavors form the focus of our current research and will be reported in due course.



SCHEME 8
Projections for future research

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REFERENCES AND NOTES

1. Hudlický T., Gonzales D., Gibson David T.: *Aldrichim. Acta* **1999**, 32, 35.
2. a) Gibson D. T., Koch J. R., Schuld C. L., Kallio R. E.: *Biochemistry* **1968**, 7, 3795; b) Gibson D. T., Koch J. R., Kallio R. E.: *Biochemistry* **1968**, 7, 2653.
3. For recent reviews, see: a) Widdowson D. A., Ribbons D. W., Thomas S. D.: *Janssen Chim. Acta* **1990**, 8; b) Carless H. A.: *Tetrahedron: Asymmetry* **1992**, 3, 795; c) Sheldrake G. N. in: *Chirality and Industry* (A. N. Collins, G. N. Sheldrake and J. Crosby, Eds), p. 127. John Wiley and Sons, Ltd., Chichester, U.K. 1992; d) Brown S. M., Hudlický T. in: *Organic Synthesis: Theory and Applications* (T. Hudlický, Ed.), Vol. 2, p. 113. JAI Press, Greenwich, CT 1993; e) Hudlický T., Reed J. W. in: *Advances in Asymmetric Synthesis* (A. Hassner, Ed.), p. 271. JAI Press, Greenwich, CT 1995; f) Grund A. D.: *SIM News* **1995**, 45, 59; g) Hudlický T., Thorpe A.: *J. Chem. Commun.* **1996**, 1993; h) Hudlický T.: *Chem. Rev. (Washington, D. C.)* **1996**, 96, 3; i) Hudlický T.: *ACS Symp. Ser.* **1996**, 626, 180; j) Hudlický T. in: *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes* (P. T. Anastas and T. C. Williamson, Eds), Chap. 10, p. 166. Oxford University Press, Oxford, U.K. 1998; k) Boyd D. R., Sheldrake G. N.: *Nat. Prod. Rep.* **1998**, 309.
4. a) Hudlický T., Price J. D., Rulin F., Tsunoda T.: *J. Am. Chem. Soc.* **1990**, 112, 9439; b) Mandel M., Hudlický T., Kwart L. D., Whited G. M.: *J. Org. Chem.* **1993**, 58, 2331; c) Hudlický T., Mandel M., Rouden J., Lee R. S., Bachmann B., Dudding T., Yost K. J., Merola J. S.: *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553; d) Mandel M., Hudlický T.: *J. Chem. Soc., Perkin Trans. 1* **1993**, 741; e) Hudlický T., Abboud K. A., Entwistle D. A., Fan R., Maurya R., Thorpe A. J., Bolonick J., Myers B.: *Synthesis* **1996**, 897.
5. For review see: Hudlický T., Entwistle D. A., Pitzer K. K., Thorpe A. J.: *Chem. Rev. (Washington, D. C.)* **1996**, 96, 1195.
6. a) Gonzales D., Martinot T., Hudlický T.: *Tetrahedron Lett.* **1999**, 40, 3077; b) Akgün H., Hudlický T.: *Tetrahedron Lett.* **1999**, 40, 3081; c) Hudlický T., Tian X., Königsberger K., Maurya R., Rouden J., Fan B.: *J. Am. Chem. Soc.* **1996**, 118, 10752; d) Hudlický T., Olivo H.: *J. Am. Chem. Soc.* **1992**, 114, 9694; e) Polt R.: *Organic Synthesis: Theory and Applications*, Vol. 3, p. 109. JAI Press, Greenwich (CT) 1996; f) Hudlický T.: *J. Heterocycl. Chem.* **2000**, 37, 535.
7. The following dienediols are commercially available from Aldrich Chemical Company: (1S,2R)-(cis)-3-Bromocyclohexa-3,5-diene-1,2-diol 35 \$/g, (1S,2R)-(cis)-3-Chlorocyclohexa-3,5-diene-1,2-diol 31 \$/g, (1S,2R)-(cis)-3-Phenylcyclohexa-3,5-diene-1,2-diol 75 \$/g, (1S,2R)-(cis)-1,2-Dihydronaphthalene-1,2-diol 75 \$/g.
8. For latest reports of new metabolites, see: a) Bui V., Hansen T. V., Stenstrom Y., Ribbons D. W., Hudlický T.: *J. Chem. Soc., Perkin Trans. 1* **2000**, 1669; b) Boyd D. R., Sharma N. D., Bowers N. I., Duffy J., Harrison J. S., Dalton H.: *J. Chem. Soc., Perkin Trans. 1* **2000**, 1345.
9. Banwell M. G., Dupuche J. R., Gable R. W.: *Aust. J. Chem.* **1996**, 49, 639.
10. Hudlický T., McKibben B. P.: *J. Chem. Soc., Perkin Trans. 1* **1994**, 485.
11. Hudlický T., Olivo H., McKibben B. P.: *J. Am. Chem. Soc.* **1994**, 116, 5108.
12. a) Banwell M. G., Dupuche J. R.: *Chem. Commun.* **1996**, 869; Singlet oxygen cycloadditions: b) Hudlický T., Rulin F., Tsunoda T., Luna H., Andersen C., Price J. D.: *Isr. J. Chem.* **1991**, 31, 229; c) Hudlický T., Luna H., Olivo H., Andersen C., Nugent T., Price J. D.: *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907; d) Carless H. A. J., Oak O. Z.: *Tetrahedron Lett.* **1989**, 30, 1719; e) Hudlický T., Luna H., Barbieri G., Kwart L. D.: *J. Am. Chem. Soc.* **1988**, 110, 4735; Acylnitroso additions: f) Braun H., Burger W., Kresze G.,

- Schmidtchen F. P., Vaerman J. L., Viehe H. G.: *Tetrahedron: Asymmetry* **1990**, *1*, 403; g) Hudlický T., Olivo H. F.: *J. Am. Chem. Soc.* **1992**, *114*, 9694; h) Hudlický T., Gonzales D., Martinot T.: *Tetrahedron Lett.* **1999**, 3077.
13. Banwell M. G., Hockless D. C. R., Holman J. W., Longmore R. W., McRae K. J., Pham H. T. T.: *Synlett* **1999**, 1491.
14. a) Banwell M. G., Damos P., McLeod M. D., Hockless D. C. R.: *Synlett* **1998**, 897; b) Banwell M. G., McLeod M. D.: *Chem. Commun.* **1998**, 1851.
15. a) Hudlický T., Boros C. H., Boros E. E.: *Synthesis* **1992**, 174; b) Butora G., Gum A. G., Hudlický T., Abboud K. A.: *Synthesis* **1998**, 275.
16. Hudlický T., Seoane G., Pettus T. J.: *J. Org. Chem.* **1989**, *54*, 4239.
17. a) Hudlický T., Endoma M. A. A., Butora G. J.: *J. Chem. Soc., Perkin Trans. 1* **1996**, 2187; b) Hudlický T., Stabile M., Gibson D. T., Whited G. M.: *Org. Synth.* **1999**, *76*, 77.
18. First reported by Staudinger H., Meyer J.: *Helv. Chim. Acta* **1919**, *2*, 635. For review on azide reductions see: Scriven E. F. V., Turnbull K.: *Chem. Rev. (Washington, D. C.)* **1988**, *88*, 297.
19. Zylstra G. J., Gibson D. T.: *J. Biol. Chem.* **1989**, *264*, 14940.
20. Stabile M. R., Hudlický T., Meisels M. L.: *Tetrahedron: Asymmetry* **1995**, *6*, 537.
21. Stabile M. R., Hudlický T., Meisels M. L., Butora G. J., Gum A. G., Fearnley S. P., Thorpe A. J., Ellis M. R.: *Chirality* **1995**, *7*, 556.
22. a) Butora G. J., Hudlický T., Fearnley S. P., Stabile M. R., Gum A. G., Gonzales D.: *Synthesis* **1998**, 665; b) Novak B. H., Hudlický T., Reed J. W., Mulzer J., Trauner D.: *Curr. Org. Chem.* **2000**, 343.
23. Frey D. A., Duan C., Ghiviriga I., Hudlický T.: *Collect. Czech. Chem. Commun.* **2000**, *65*, 561.
24. a) Hudlický T., Boros E. E., Olivo H. F., Merola J. S.: *J. Org. Chem.* **1992**, *57*, 1026; b) Pittol C. A., Pryce R. J., Roberts S. M., Ryback G., Sik V., Williams J. O.: *J. Chem. Soc., Perkin Trans. 1* **1989**, 1160; c) Ley S. V., Redgrave A. J., Taylor S. C., Ahmed S., Ribbons D. W.: *Synlett* **1991**, 741; d) Hudlický T., Boros C. H.: *Tetrahedron Lett.* **1993**, *34*, 2557.
25. Bui V. P., Hansen T. V., Stenstrom Y., Hudlický T.: *Green Chem.* **2000**, 263.



Tomáš Hudlický was born in 1949 in Prague, Czechoslovakia, where he received his elementary and middle school education. After several years of working as a process chemist apprentice and in other odd jobs in pharmaceutical chemistry, it became apparent that higher education opportunities were closed to him. In 1968, he emigrated to the U.S. with his parents and sister. Hudlický's educational experience continued at Blacksburg High School, from which he dropped out in the spring of 1969. Accepted as a probational student at Virginia Tech the following autumn, he received his B.S. in chemistry in 1973, and went on to pursue graduate studies at Rice University under the direction of Professor Ernest Wenkert in the field of indole alkaloid total synthesis, earning his Ph.D. in 1977. He then spent a year at the University of Geneva working under the late Professor Wolfgang Oppolzer on the

synthesis of isocomene. In 1978, he joined the faculty at the Illinois Institute of Technology as an Assistant Professor, and began the first phase of his research career in the field of general methods of synthesis for triquinane terpenes and other natural products containing five-membered rings by

[4+1] cyclopentene, pyrroline, and dihydrofuran annulation methodologies. He returned to his alma mater, Virginia Tech, in 1982, and rose to the rank of Professor in 1988. One year later, at the 20-year class reunion of the Blacksburg High School class of 1969, he received his High School Diploma. The next phase of his research involved the investigation of cis-cyclohexadienediols in enantioselective synthesis. In 1995, he moved to his present position at the University of Florida in Gainesville. His current research interests include the development of enantioselective synthetic methods, bacterial dioxygenase-mediated degradation of aromatics, design and synthesis of fluorinated inhalation anesthetic agents, synthesis of morphine and amaryllidaceae alkaloids, and design of unnatural oligo-saccharide conjugates with new molecular properties. His hobbies include skiing, hockey, martial arts, and music.



Josef Zezula was born in Jihlava, Czechoslovakia in 1976. He attended elementary school in Polná and high school in Jihlava. After graduation, he was accepted at the Institute of Chemical Technology, Prague, where he worked in Professor Ivan Stibor's research group on the synthesis of calixarene-based macromolecules. He received his MSc. degree in 1999, and went on to pursue graduate studies at the University of Florida, where he is currently a second year graduate student in Professor Tomáš Hudlický's group. His research interests include the use of products from microbial biotransformations in organic synthesis.