mg (62%) of hydrocarbons. Analysis by GLC: 57% diphenylacetylene; 3% stilbene; 21% 1,2-diphenylethane. Starting material (21%) was recovered.

With Sodium in Liquid Ammonia. To a three-necked 50-mL round-bottomed flask was added bis(diethoxyphosphinyl)stilbene (402 mg, 0.8 mmol) dissolved in THF (15 mL). The flask was then equipped with a dry ice condenser and stopcock and cooled to −78 °C. Ammonia (15 mL), distilled from Na metal, was admitted to the flask, and Na metal (38 mg, 1.7 mmol) was added in small pieces (under Ar) until the blue color just persisted, at which time the solution was quenched with an excess of *tert*-butyl alcohol. The NH_3 was allowed to evaporate and the material was added to H_2O (50 mL) and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$), filtered ($MgSO_4$), concentrated in vacuo, and chromatographed (gravity column, silica gel 60, 27 g, ethyl acetate as the eluent) to give 110 mg (74%) of hydrocarbons. Analysis by GLC: 40% diphenylacetylene; 34% stilbene; 0% 1,2-diphenylethane. Starting material (24%) was recovered.

With Lithium in Liquid Ammonia. To a three-necked 50-mL round-bottomed flask was added bis(diethoxyphosphinyl)-stilbene (312 mg, 0.6 mmol) dissolved in THF (10 mL). The flask was then equipped with a dry ice condenser and stopcock and cooled to −78 °C (dry ice, acetone). Ammonia (15 mL), distilled from Na metal, was admitted to the flask and Li metal (10 mg, 1.4 mmol) was added under vigorous Ar flow, turning the solution a deep blue. The color persisted for approximately 1 min, and additonal small amounts of Li (ca. 1 mg) were added until the color just persisted at which time the solution was quenched with an excess of *tert*-butyl alcohol. The NH_3 was allowed to evaporate and the material was added to H_2O (40 mL) and extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo, to give 108 mg (100%) of hydrocarbons. Analysis by GLC: 39% diphenylacetylene; 44% stilbene; 17% 1,2-diphenylethane.

With Sodium Naphthalenide. To a two-necked 50-mL round-bottomed flask was added freshly distilled HMPA (7 mL) and freshly sublimed naphthalene (161 mg, 1.3 mmol) followed by Na metal (26 mg, 1.1 mmol). To this mixture was added bis(diethoxyphosphinyl)stilbene (144 mg, 0.3 mmol) dissolved in THF (4 mL), and the resulting green mixture was stirred under Ar for 12 h. The mixture was added to H_2O (50 mL) and extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were washed with H_2O (3 × 30 mL), dried ($MgSO_4$), filtered ($MgSO_4$), concentrated in vacuo, and chromatographed (gravity column, silica gel 60, 33 g, 100% hexane as the eluent) to give 37 mg (68%) of hydrocarbons by GLC: 39% diphenylacetylene; 29% stilbene; 0% 1,2-diphenylethane. Starting material (32%) was recovered.

With Lithium Naphthalenide. To a two-necked 50-mL round-bottomed flask was added freshly distilled HMPA (7 mL), freshly sublimed naphthalene (5 mg, 0.04 mmol), and Li metal, (5 mg, 0.7 mmol). To this mixture was added bis(diethoxyphosphinyl)stilbene (155 mg, 0.3 mmol) dissolved in THF (2.4 mL), and the resulting green mixture was stirred under Ar for 12 h. The mixture was added to H_2O (50 mL) and extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were washed with H_2O (3 × 3 mL), dried ($MgSO_4$), filtered ($MgSO_4$), concentrated in vacuo, and chromatographed (gravity column, silica gel 60, 33 g, 100% hexane as the eluent) to give 43 mg (79%) of hydrocarbons. Analysis by GLC: 49% diphenylacetylene; 24% stilbene; 6% 1,2-diphenylethane. Starting material (21%) was recovered.

With Hydrogen. To a 250-mL high-pressure Parr flask was added 100% ethanol (20 mL), PtO_2 (29 mg, 0.1 mmol), and bis(diethoxyphosphinyl)stilbene (184 mg, 0.4 mmol). The container was stoppered, flushed with H_2 (4×), charged with H_2 (40 psi), and allowed to stir at this pressure for 72 h. The mixture was filtered, added to saturated $NaHCO_3$ (50 mL), and extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were dried ($MgSO_4$), filtered ($MgSO_4$), concentrated in vacuo to a volume of a few milliliters, and injected directly into a liquid chromatograph (MPLC). The material was purified with a 1.5 × 25 cm silica gel 60 column (300 g), using ethyl acetate as the eluent, at a pressure of 25 psi, collecting 100-mL-sized fractions. Removal of the solvent from the appropriate fractions gave 62 mg (85%) of hydrocarbons. Analysis by GLC: 0% diphenylacetylene; 0% stilbene; 85% 1,2-diphenylethane. Starting material (10%) was recovered.

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Registry No. 2, 93304-54-2; benzoin, 119-53-9; diethyl chlorophosphate, 814-49-3; diphenylacetylene, 501-65-5; 1,2-diphenylethane, 103-29-7; stilbene, 588-59-0.

Studies in Anthracycline Synthesis: Simple Diels–Alder Routes to Pachybasin, ω-Hydroxypachybasin, Aloe-emodin, and Fallacinol

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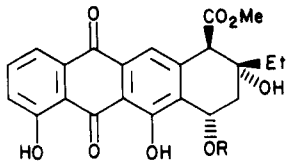
In connection with our interest in developing new synthetic routes to the aglycons of the anticancer anthracycline aclacinomycin A (1) and related structures,[1] we required a simple and practical approach to various 1-hydroxy-3-methylanthraquinones as well as the corresponding ω-hydroxy compounds. The natural products pachybasin (2)[2] and ω-hydroxypachybasin (3)[3] are prototypes of these structures. Using Diels–Alder based methodology, we now report a simple, one-pot synthesis of pachybasin, as well as new syntheses of ω-hydroxypachybasin, aloe-emodin (4), and fallacinol (5).



1, R = rhodosamine, 2-deoxyfucose, and cinerulose A residues

Brassard has shown that the Diels–Alder additions of naphthoquinones to mixed trimethylsilyl vinylketene acetals affords a versatile route to substituted hydroxyanthraquinones.[4] This methodology has been adopted more recently by others in synthetic approaches to anthracyclinone systems.[5]

We felt that pachybasin (2) could be prepared most efficiently by the reaction of 2-bromonaphthoquinone (6)[6] with the readily prepared vinylketene acetal 7 derived from methyl senecioate (8).[7] Indeed, diene 7 reacted rapidly with quinone 5 in methylene chloride at room temperature in the presence of potassium carbonate as HBr scavanger. Heating the reaction mixture with sodium acetate completed the aromatization process, and following acidification pachybasin (2) was isolated cleanly by direct crys-

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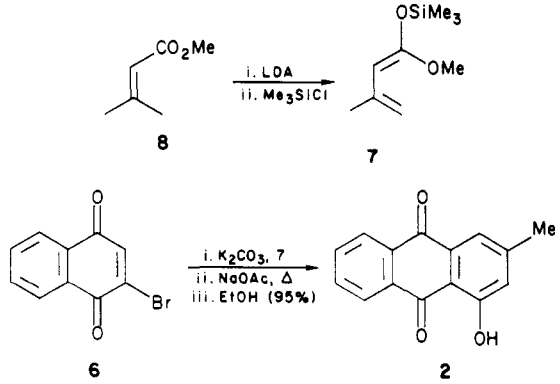
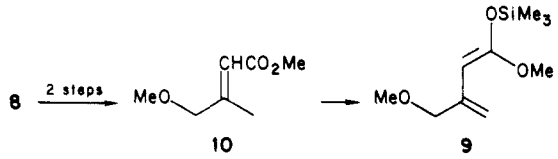


tallization. Quantities (100 g) were readily prepared in this manner. An alternate Diels–Alder route to **2**, reported several years ago, involved the addition of naphthoquinone to 4-methyl-6-methoxy-α-pyrone, followed by thermal elimination of CO_2, silver oxide oxidation, and HBr demethylation.[8] More recent syntheses of **2** involve reaction sequences starting with the Michael addition of substituted phthalide anions to 5-methylcyclohexenone.[9]

A number of naturally occurring 1-hydroxy-3-(hydroxymethyl)anthraquinones are known, as illustrated in Table I.[10] An appropriate synthon for the synthesis of anthraquinones of this type appeared to be the methoxy-substituted vinylketene acetal **9**. The latter was readily



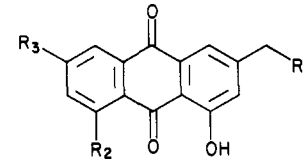
prepared in good yield by lithiation and subsequent silylation of methoxy ester *cis/trans*-**10**, available from methyl senecioate (**8**) by the known step of NBS bromination.[11]

Although slightly less reactive than **7**, diene **9** combined smoothly with 2-bromonaphthoquinone (**6**) in the presence of an acid scavenger to give, in good yield, ω-methoxypachybasin (**11**). Treatment of **11** with 48% HBr in acetic acid gave the bromide **12**, which was converted by sodium acetate in acetic acid to the corresponding acetate **13**. Alkaline hydrolysis of the latter afforded, after neutralization, ω-hydroxypachybasin (**3**), the properties of which coincided with those reported for the natural product.[3]

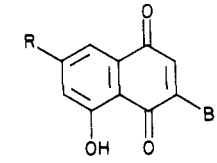
Analogous reaction sequences employing diene **9** led to a new synthesis of aloe-emodin (**4**) and to the synthesis of the more complex fallacinol (**5**). Thus, diene **9** and 3-bromojuglone (**14**)[12] afforded aloe-emodin ω-methyl ether (**15**), which was transformed into aloe-emodin via bromide **16**[13] and acetate **17**. In a similar manner, diene **9** and 3-bromo-7-methoxyjuglone (**18**) afforded the dimethyl ether **19**, which was selectively demethylated and converted into bromide **20** by HBr in acetic acid; bromide **20** was then hydrolyzed to fallacinol (**5**) via the acetate **21**.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared (KBr) and low-resolution and



3, R_1 = OH; R_2 = R_3 = H
4, R_1 = R_2 = OH; R_3 = H
5, R_1 = R_2 = OH; R_3 = OMe
11, R_1 = OMe; R_2 = R_3 = H
12, R_1 = Br; R_2 = R_3 = H
13, R_1 = OAc; R_2 = R_3 = H
15, R_1 = OMe; R_2 = OH; R_3 = H
16, R_1 = Br; R_2 = OH; R_3 = H
17, R_1 = OAc; R_2 = OH; R_3 = H
19, R_1 = R_3 = OMe; R_2 = OH
20, R_1 = Br; R_2 = OH; R_3 = OMe
21, R_1 = OAc; R_2 = OH; R_3 = OMe



14, R = H
18, R = OMe

high-resolution mass spectra were determined by using Perkin-Elmer 137, RMH2, and VG 7070H spectrometers, respectively. NMR spectra were recorded on a Bruker 250FT machine with $CDCl_3$ solutions containing Me_4Si as an internal standard and are reported in δ values (J values are in hertz). Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed with water and dried over anhydrous Na_2SO_4 prior to filtration and evaporation. All solvents were dried by standard procedure prior to use.

Synthesis of Pachybasin (2). A solution of the diene (**7**)[7] (41.0 g, 0.22 mol) in CH_2Cl_2 (40 mL) was added over 30 min to a rapidly stirred solution of 2-bromonaphthoquinone (**6**)[6] (47.4 g, 0.20 mol) and K_2CO_3 (anhydrous) (8.3 g, 0.60 mol) in CH_2Cl_2 (600 mL) at 0 °C. The reaction was stirred overnight at room temperature, then heated with NaOAc (8.0 g, 0.10 mol) for 10 min, cooled, and filtered. Acidification with HOAc (5 mL) followed by standard workup gave after evaporation of the solvent a brown yellow solid which upon treatment with EtOH gave after filtration **2** as bright yellow crystals (38 g, 93%): mp 179–180 °C (lit.[2] mp 176–177 °C); ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3 H), 7.10 (s, 1 H), 7.65 (s, 1 H), 7.80 (m, 2 H), 8.25 (m, 2 H), 12.52 (s, 1 H).

***cis/trans*-Methyl ω-Methoxysenecioate (10).** To a solution of KOMe (prepared from KO*t*-Bu (17.4 g, 15.5 mmol) and MeOH (200 mL)) at 0 °C was added a solution of *cis/trans*-methyl ω-bromosenecioate[11] (30 g, 15.5 mmol) in MeOH (50 mL) over 1 h. The reaction was stirred for an additional hour at 0 °C and then at room temperature overnight. The MeOH was evaporated in vacuo at 30 °C and the residue was extracted with ether and water. Evaporation of the ether at 30 °C in vacuo followed by vacuum distillation of the crude product gave 19 g 85%) of the ester **10** as a mixture of isomers: bp 114–130 °C (30 mm) (lit.[14] bp 64–65 °C (1 mm) trans; ^{1}H NMR ($CDCl_3$) (trans) δ 2.10 (s, 3 H), 3.26 (s, 3 H), 3.70 (s, 3 H), 3.90 (d, 2 H, J = 3 Hz), 5.94 (d, 1 H, J = 3 Hz); (cis) 1.94 (s, 3 H), 3.24 (s, 3 H), 3.68 (s, 3 H), 4.44 (d, 2 H, J = 2.5 Hz), 5.78 (d, 1 H, J = 2.5 Hz).

1-Methoxy-3-(methoxymethyl)-1-(trimethylsiloxy)-1,3-butadiene (9). A solution of **10** (17.4 g, 0.12 mol) in dry THF (73 mL) was added dropwise over 20 min to a solution of LDA (0.13 mol) in THF (145 mL) at −78 °C under N_2. Stirring was continued for 1.5 h and freshly distilled Me_3SiCl (18.4 mL, 0.15 mol) was then added. After 30 min the solution was allowed to warm to ambient temperature, pentane was added to the concentrated solution, and filtration of the solution through Celite followed by evaporation of the solvent gave crude **9**. Distillation gave pure **9** as a colorless liquid (23.0 g, 89%) which rapidly yellows on exposure to air: bp 60–64 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 3.27 (s, 3 H), 3.56 (s, 3 H), 4.00 (s, 1 H), 4.89 (d, 1 H, J = 3 Hz), 5.14 (d, 1 H, J = 3 Hz); MS, m/e (relative intensity) 216 (M^+, 100), 201 (23), 185 (16).

ω-Methoxypachybasin (11). A solution of the diene **9** (4.5 g, 21 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 20 min to a rapidly stirred solution of 2-bromonaphthoquinone[6] (**6**) (4.7 g, 20 mmol) in CH_2Cl_2 (50 mL) containing K_2CO_3 (anhydrous) (8.3 g, 60 mmol). After 2 h, NaOAc (8.2 g, 60 mmol) was added and the reaction mixture was refluxed for 10 min, cooled, filtered,

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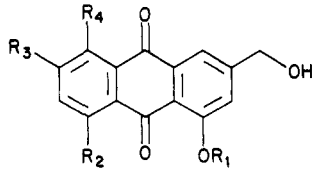
Table I. Some Naturally Occurring 1-Hydroxy-3-(hydroxymethyl)anthraquinones



R_1	R_2	R_3	R_4	compounds
H	OH	H	H	aloe-emodin (4)
H	OMe	OH	H	ω-hydroxyquestin
H	OH	OH	H	citreorosein
H	OH	OMe	H	fallacinol (5)
H	H	H	H	ω-hydroxypachybasin (3)[3]
Me	OH	H	H	carviolin

and acidified with HOAc (5 mL). Following workup as described, the crude product was crystallized from EtOH to afford pure **11** as yellow crystals (4.2 g, 79%): mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3 H), 4.54 (s, 2 H), 7.33 (s, 1 H), 7.76 (m, 3 H), 8.32 (m, 2 H), 12.65 (s, 1 H). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.53; H, 4.53.

3-(Bromomethyl)-1-hydroxyanthraquinone (12). A suspension of **11** (1.0 g, 3.7 mmol) in 30% HBr in HOAc (13 mL) was refluxed for 45 min. After cooling, the yellow crystals were filtered off and washed with cold water to give **12** (1.0 g, 85%): mp 202–203.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.50 (s, 2 H), 7.33 (s, 1 H), 7.75 (m, 3 H), 8.35 (m, 2 H), 12.55 (s, 1 H). Anal. Calcd for $C_{15}H_9BrO_3$: C, 56.81; H, 2.86. Found: C, 57.01; H, 3.00.

3-(Acetoxymethyl)-1-hydroxyanthraquinone (13). The bromide **12** (0.88 g, 2.7 mmol) was refluxed with NaOAc (1.14 g, 13.8 mmol) in HOAc (8.8 mL) for 30 min under N_2. After cooling, the solid mass was poured onto ice and the yellow crystals were filtered off and washed with water to give the acetate **13** (0.81 g, 2.7 mmol): mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 5.20 (s, 2 H), 7.33 (s, 1 H), 7.78 (m, 3 H), 8.66 (m, 2 H), 12.98 (s, 1 H); high-resolution mass spectrum, *m/e* 296.0675 (calcd for $C_{17}H_{12}O_5$ 296.0685).

ω-Hydroxypachybasin (3). A solution of the acetate **13** (0.8 g, 2.7 mmol) was refluxed under N_2 with 2% KOH in EtOH for 10 min. The cooled solution was then poured into 1 N HCl (25 mL). Extraction followed by evaporation of the solvent gave **3** as yellow needles (0.65 g, 100%): mp 208–209 °C (lit.[3] mp 211–212 °C); ^{1}H NMR ($CDCl_3$) δ 4.78 (s, 2 H), 7.34 (s, 1 H), 7.80 (m, 3 H), 8.34 (m, 2 H), 12.60 (s, 1 H).

3-Bromo-5-hydroxy-7-methoxynaphthoquinone (18): Prepared by the general method of Brassard[7a] from 2,6-dibromobenzoquinone and 1,3-dimethoxy-1-(trimethylsiloxy)-1,3-butadiene in 67% yield: mp 176–177 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3 H), 6.68 (d, 1 H, *J* = 3 Hz), 7.20 (d, 1 H, *J* = 3 Hz), 7.46 (s, 1 H), 9.28 (s, 1 H). Anal. Calcd for $C_{11}H_7BrO_4$: C, 46.67; H, 2.49. Found: C, 46.47; H, 2.64.

Aloe-emodin ω-Methyl Ether (15). A solution of **9** (0.13 g, 0.60 mmol) and 3-bromojuglone[12] (**14**) (0.10 g, 0.40 mmol) in CH_2Cl_2 (4 mL) containing K_2CO_3 (0.16 g, 1.2 mmol) was stirred and heated in a sealed tube under N_2 at 75 °C for 1 h. NaOAc (0.1 g, 1.2 mmol) was then added and heating was continued for an additional 0.5 h. Standard workup gave orange crystals of **15** (0.10 g, 63%): mp 147.5–148 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3 H), 4.55 (s, 2 H), 7.32 (m, 2 H), 7.80 (m, 3 H), 12.10 (s, 1 H), 12.16 (s, 1 H); high-resolution mass spectrum *m/e* 284.0689 (calcd for $C_{16}H_{12}O_5$ 284.0685).

Aloe-emodin ω-Acetate (17). The ether **15** was converted into aloe-emodin ω-acetate in 93% yield by using the same procedure as for the synthesis of **13** from **11** without isolation of the bromide: mp 194.5–195.5 °C. Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.39; H, 4.33. Found: C, 65.15; H, 4.11.

Aloe-emodin (4). The acetate **17** was hydrolyzed under the same conditions used for **13** to give aloe-emodin (**4**) in 100% yield: mp 222–223 °C (lit.[10] mp 223–224 °C).

Fallacinol ω-Methyl Ether (19). A solution of the diene **9** (0.61 g, 2.8 mmol) in CH_2Cl_2 (5 mL) was added to a rapidly stirred solution of **18** (0.36 g, 1.3 mmol) in CH_2Cl_2 (10 mL) at −25 °C over 10 min. After 2 h at this temperature, K_2CO_3 (anhydrous) (0.53 g, 3.8 mmol) was added and the reaction stirred at room temperature for 10 h. The filtered solution was chromatographed, the solvent evaporated, and the residue treated with EtOH to afford **19** as yellow crystals (1.88 g, 83%): mp 174.5–175.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3 H), 4.00 (s, 3 H), 4.60 (s, 2 H), 6.63 (d, 1 H, *J* = 2 Hz), 7.26 (d, 1 H, *J* = 2 Hz), 7.36 (d, 1 H, *J* = 2 Hz), 7.74 (d, 1 H, *J* = 2 Hz), 12.14 (s, 1 H), 12.26 (s, 1 H); high-resolution mass spectrum, *m/e* 314.0782 (calcd for $C_{17}H_{14}O_6$ 314.0790).

Fallacinol ω-Acetate (21). Ether **19** was converted into fallacinol ω-acetate in93% yield by using the same procedure as for the synthesis of **3** from **11** without isolation of the bromide: mp 19–191 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 3.98 (s, 3 H), 5.23 (s, 2 H), 7.23 (d, 1 H, *J* = 2 Hz), 7.30 (d, 1 H, *J* = 2 Hz), 7.38 (d, 1 H, *J* = 2 Hz), 7.83 (d, 1 H, *J* = 2 Hz), 12.21 (s, 1 H), 12.30 (s, 1 H); high-resolution mass spectrum, *e/e* 342.0736 (clacd for $C_{18}H_{14}O_7$ 342.0739).

Fallacinol (5). The acetate **21** was hydrolyzed under the same conditions used for **11** to give fallacinol (**5**) in 100% yield: mp 239–240 °C (lit.[10] mp 238–239 °C); high-resolution mass spectrum, *m/e* 300.0630 (calcd for $C_{16}H_{12}O_6$ 300.0630).

Acknowledgment. This work was supported by a grant from the National Institutes of Health, CA 30377.

Registry No. **2**, 2549-78-2; **3**, 51995-90-5; **4**, 481-72-1; **5**, 569-05-1; **6**, 2065-37-4; **7**, 73311-51-0; **9**, 93564-92-2; (*E*)-**10**, 88806-83-1; (*Z*)-**10**, 88806-84-2; **11**, 93564-93-3; **12**, 93564-94-4; **13**, 93564-95-5; **14**, 52431-65-9; **15**, 93564-96-6; **17**, 65615-58-9; **18**, 93564-97-7; **19**, 93564-98-8; **21**, 20194-61-0; methyl *cis*-ω-bromosenecioate, 27652-13-7; methyl *trans*-ω-bromosenecioate, 19041-17-9; 2,6-dibromobenzoquinone, 19643-45-9; 1,3-dimethoxy-1-(trimethylsiloxy)-1,3-butadiene, 74272-66-5.

Sulfur-Directed Diels–Alder Reactions. Synthesis of 1,5-Disubstituted Cyclohexene Derivatives

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We recently required a 1,5-disubstituted cyclohexene derivative of general structure **1**. Preparation of **1** using the Diels–Alder reaction appeared attractive (Scheme I); however, this substitution pattern is opposite that obtained from thermal or Lewis acid catalyzed Diels–Alder reactions of isoprene and typical electron-poor dienophiles.[1] Others have approached closely related problems by the temporary introduction of a powerful directly group in either the dienophile (nitro,[2] phenylsulfonyl[3]) or the diene. The latter solution was more appropriate to the case at hand, and consequently the powerfully directing phenylthio group was chosen. To our surprise, inspection of the literature turned up no examples of the Diels–Alder reaction of simple dienes like **2a** with unsymmetrical dienophiles.[4] The parent diene **2b** has been studied by Cohen, who found that the sulfur serves admirably as a regiocontrol element.[5] Should this be the case with **2a**, the resulting Diels–Alder adduct **3** would be expected to undergo desulfurization to provide the desired 1,5-disubstituted cyclohexene **1**. We now describe an operationally simple and inexpensive synthesis of diene **2a** and report that it does indeed serve as a synthetic equivalent of isoprene, having

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