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Tandem reactions in organic synthesis

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Tandem reactions in organic synthesis

by

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has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

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For the Major Program

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GENERAL INTRODUCTION

For one hundred years, organic synthesis has been one of the central parts of chemistry. New synthetic methodologies and strategies are coming out and these are being used in industry. With the increased concern about our environment, more efficient and environmentally benign procedures for valuable target molecules are needed. In that sense, multiple transformations in a single step suits those demands well. Chapter One introduces the direct synthesis of 5-substituted naphthoquinones and provides extensive information about peri-metalation on naphthalene derivatives. Chapters Two and Three describe a new synthetic strategy to construct bridged complex molecules using Diels-Alder/Radical Cyclization (DARC). This new strategy could be applied in the synthesis of the cumbiasin A skeleton and other biologically active natural products in a highly efficient manner. The numbering of the compounds, schemes and references used are independent in each section.

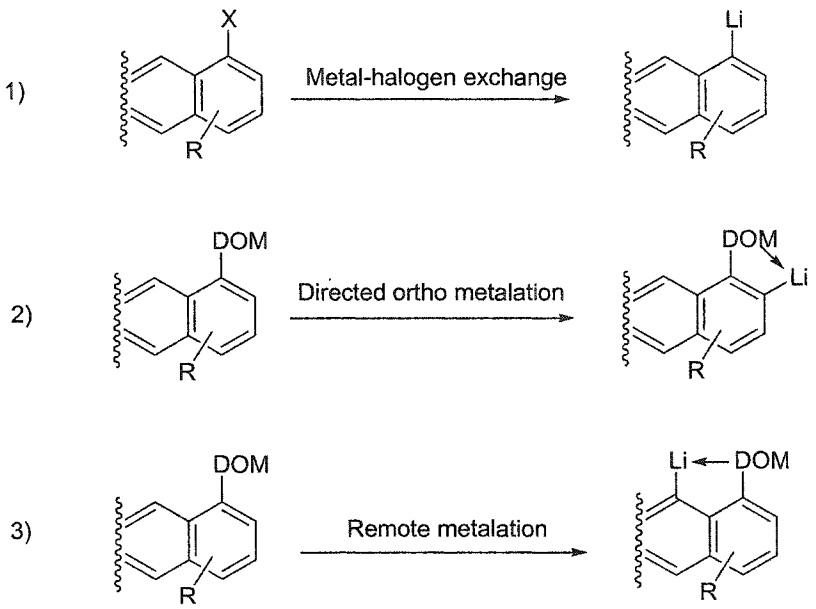
CHAPTER 1. DIRECT SYNTHESIS OF 5-SUBSTITUTED NAPHTHOQUINONES

Introduction

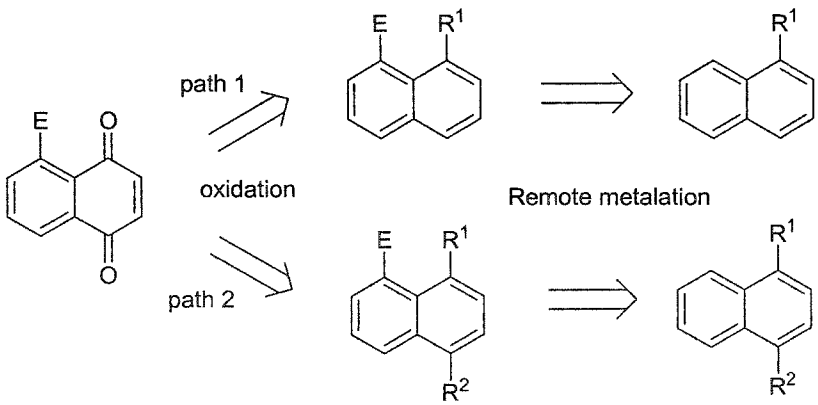
There are many biologically active natural products which contain a naphthoquinone moiety in their structures. To access those substances, we continued our study on the regioselective Diels-Alder reactions of substituted naphthoquinones.[1] Even though there is a wealth of procedures for the synthesis of 2-substituted or 2,3-disubstituted naphthoquinones, there are only limited examples for the synthesis of 5-substituted naphthoquinones.[2] During our investigation towards 5-substituted naphthoquinones, we evaluated peri-metalation as a strategy for constructing 5-substituted naphthoquinones. This novel methodoloy could be applied in the synthesis of perylene analogs and other naphthoquinone natural products.

Results and Discussion

Retrosynthetic analysis for the synthesis of 5-substituted naphthoquinones is shown below. Lithiated aromatic compounds could be accessible via metal-halogen exchange,[3] direct ortho lithiation,[4] and remote metalation.[5] Among these methods, remote metalation will be a choice of the strategies to functionalize naphthalene derivatives.

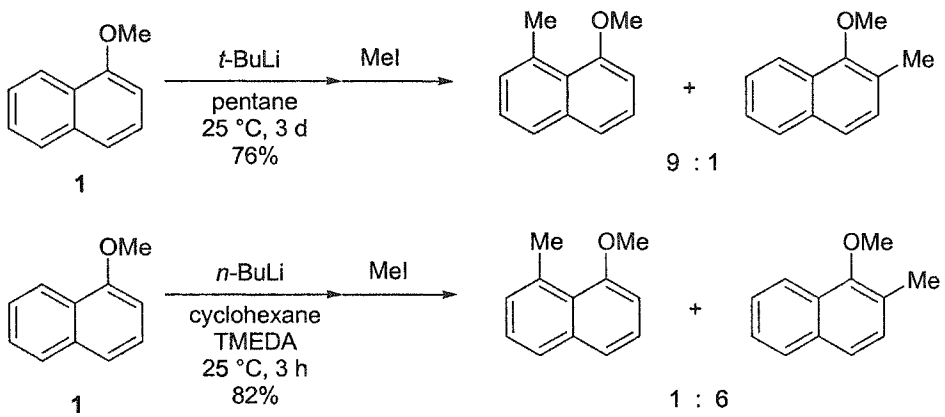


Clearly, two different starting materials might be used in remote metalation to introduce a substituent at the 8-position. A subsequent oxidation step would convert intermediates into 1,4-naphthoquinone derivatives.

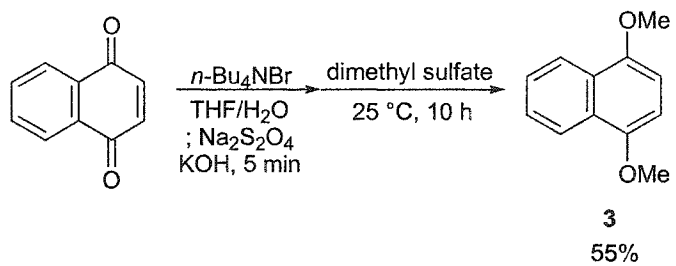


First, we tested the regioselective metalation on 1-substituted naphthoquinones according to the reported procedure and results showed the dramatic changes in regioselectivities depending on the reaction conditions.[6] In case of 1-methoxynaphthalene (**1**), metalation gave a 9:1 ratio of remote:ortho metalation products in 76% yield when compound **1** was treated

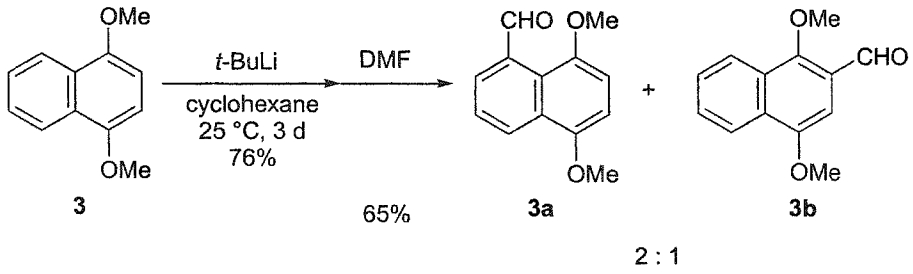
with *t*-BuLi in cyclohexane at 25 °C. Surprisingly, this regioselectivity was reversed to a 1:6 ratio of remote:ortho metalation products in 82% yield when one equivalent of TMEDA was added during the metalation step.



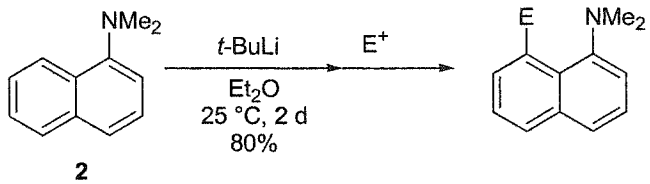
After we observed these promising results, we decided to use these optimized conditions for 1,4-dimethoxynaphthalene, since there are ample examples of oxidative demethylation for 1,4-dimethoxynaphthalene derivatives into 1,4-naphthoquinones.[7] 1,4-Dimethoxynaphthalene (**3**) was prepared from 1,4-naphtoquinone via the reductive methylation.[8]



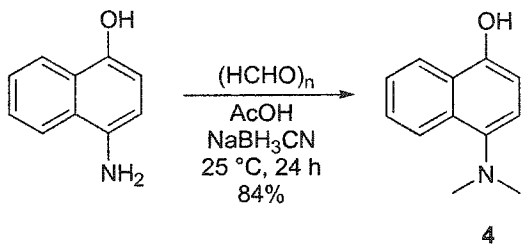
Unfortunately, when 1,4-dimethoxynaphthalene was treated with *t*-BuLi in cyclohexane for 3 days at 25 °C, the ratio of remote to ortho metalated product dropped from 9:1 to 2:1.



We figured that the methoxy group in the para-position increased the acidity of the hydrogens in the ortho position, which resulted in the lower regioselectivity in metalation step. Based on this speculation, we decided to attach an electron-donating substituent in the 4-position to increase the regioselectivity which later could be converted into a 1,4-naphthoquinone moiety. After searching for suitable candidates, we found that the *N,N*-dimethylamino group could act as a directing group for remote metalation.[9]

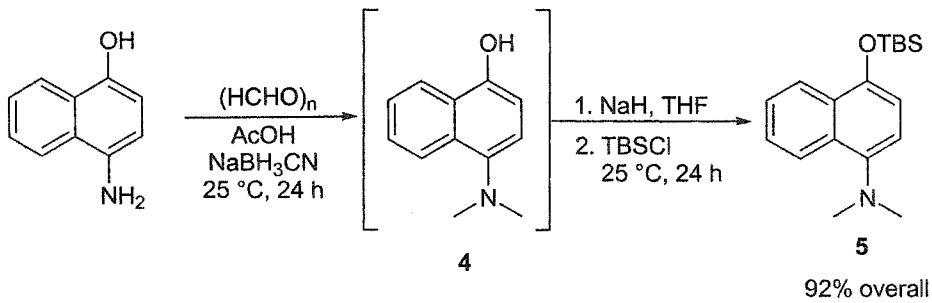


This result encouraged us to prepare 4-dimethylaminonaphthalen-1-ol (**4**) as our next candidate. 4-Dimethylaminonaphthalen-1-ol (**4**) was generated from 4-aminonaphthalen-1-ol using reductive amination with sodium cyanoborohydride in the presence of paraformaldehyde in acetic acid.[10]

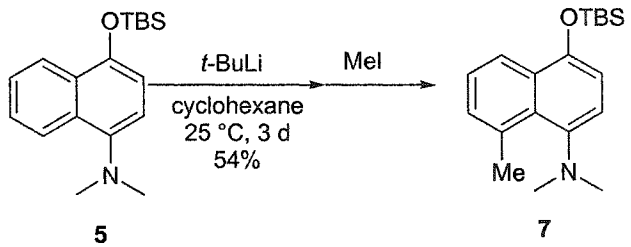


The product **4** was rather unstable in prolonged contact with air and purification using flash column chromatography. It is desirable to protect the free hydroxy group immediately

after extraction. After protection as the TBS ether, the resulting compound **5** is considerably more stable than was phenol **4** and could be directly prepared in a one-pot procedure.

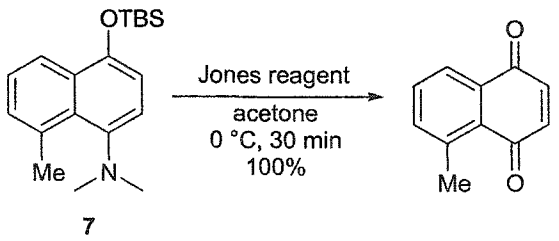


With compound **5** in hand, the optimized remote metalation was conducted. To our delight, metalation of **5** using *tert*-butyllithium in cyclohexane for 72 h at ambient temperature, followed by trapping with methyl iodide led to a 54% yield of **6**, plus recovered starting material. Metalation of **5** using *n*-butyllithium afforded lower yields.



Several points should be addressed for the exclusive formation of the remote metalated product. First, the *N,N*-dimethylamino group is now the directing group instead of the methoxy group. Second, the bulky TBS group is crucial to block the undesired metalation as well as enhance the stability of the compound **5**.

After this preliminary regioselective metalation, we tested the suitability of compound **7** as a precursor to naphthoquinone. When compound **5** was treated with Jones' reagent in acetone at 0 °C for 30 min, 1,4-naphthoquinone was generated in quantitative yield. In this step, the TBS ether group was deprotected by the acidic nature of the Jones's reagent.



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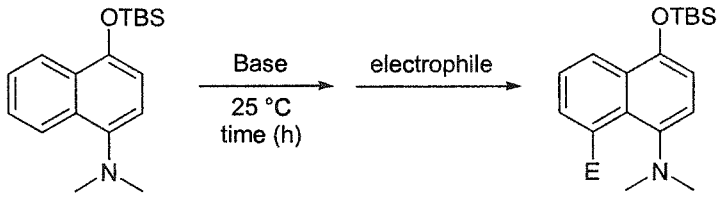
The successful oxidation of **5** prompted us to react the anion of **5** with a variety of electrophiles. The results are collated in Table 1.



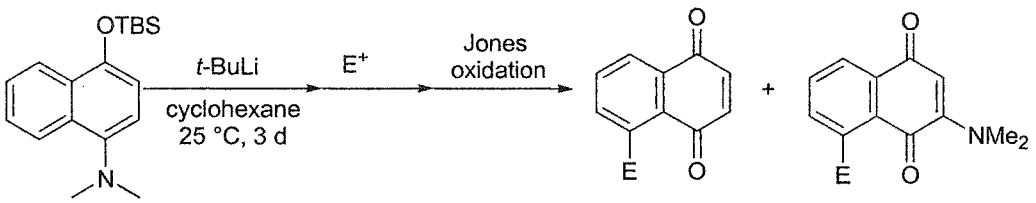
5 **6**

Base	Solvent	Time (h)	Electrophile	E	Yield (%)	Conversion (%)
n-BuLi 1.2 equiv	Et_2O	48	MeI	Me	26	41 **7**
		72	MeI	Me	34	51
	cyclohexane	72	MeI	Me	6	37
t-BuLi 1.2 equiv	cyclohexane	72	MeI	Me	54	94 **7**
			DMF	CHO	30	- **8**
			$(PhS)_2$	SPh	46	- **9**
			CO_2 (g)	CO_2H	45	95 **10**
t-BuLi 2.0 equiv	cyclohexane	72	CO_2 (g)	CO_2H	41	53 **10**
t-BuLi 1.2 equiv	cyclohexane	72	PhCHO	PhCHOH	35	44 **11**
			propylene oxide	$CH_2CHMeOH$	17	54 **12**
			BnBr	Bn	27	47 **13**
			n-Bu_3SnCl	$SnBu_3$	50	83 **14**

Table 1. Remote metalation

The anion of **5** reacted successfully with various electrophiles. Quenching the anion solution with D_2O afforded an 87% yield of deuterium incorporation. The anion did not react well with propylene oxide, benzyl chloride, or benzyl bromide. Attempts to trap the alkoxide intermediate from propylene oxide did not lead to improved yields.

We next tried a sequence of reactions involving metalation, trapping with an electrophile, and oxidation without purification of intermediates. The results are shown in Table 2.



E+	E	Yield (%)			
CO_2	CO_2H	42	**16**	0	
DMF	CHO	55	**17**	0	
I_2	I	40	**18**	20	**19**
I_2	I	44	**18**	3*	**19**

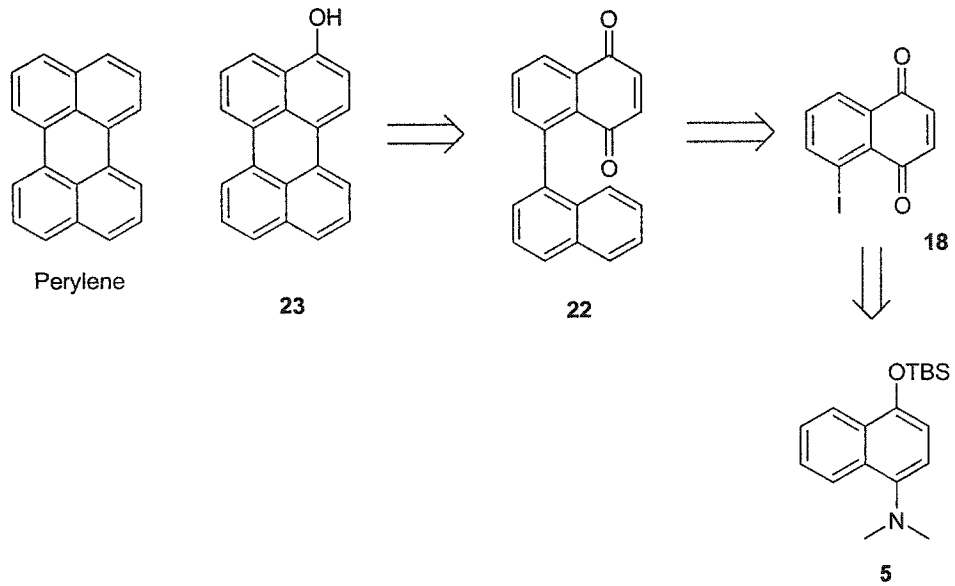
* An extra equiv of sulfuric acid was used.

Table 2. Remote metalation and in situ Jones oxidation

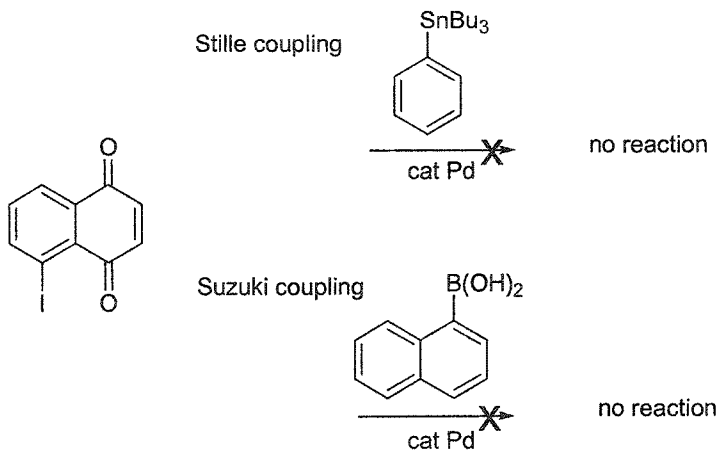
The reaction with iodine generated two products; **18** and **19**. The formation of **19** could be minimized by adding one equivalent of sulfuric acid before the oxidation and conducting the reaction at -78 °C. By this modification, a 44% yield of **18** and a 3% yield of **19** were obtained. The metalation of **5**, followed by trapping with alkyl halides, carbonyl groups, and stannyl halides and subsequent oxidation produces naphthoquinones in good overall yields.

With this efficient way to access 5-substituted naphthoquinones in hand, we applied this methodology for the synthesis of perylene analogs. Perylene quinones are known to have

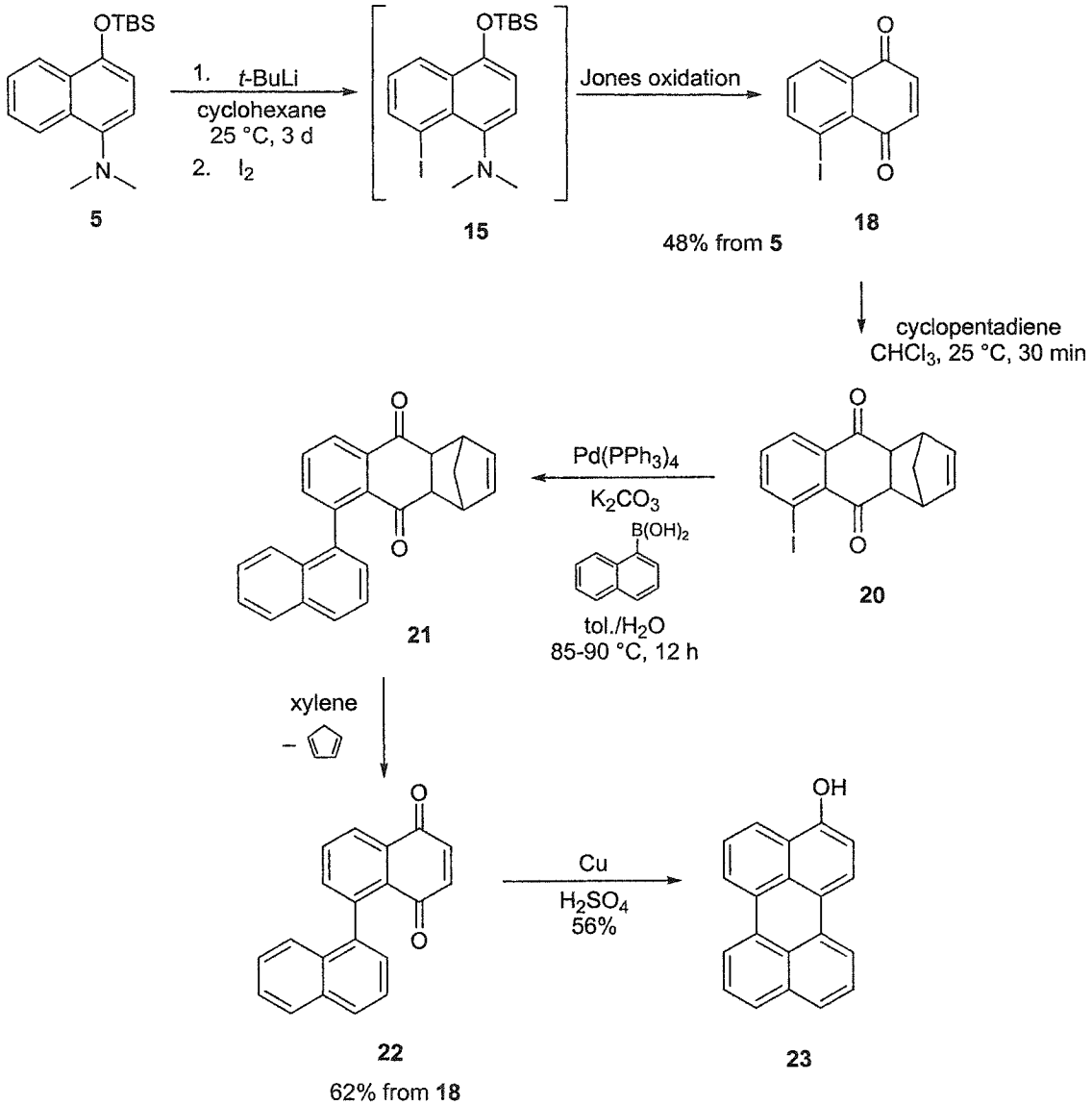
antitumor and antivirial activity.[11] As shown in the retrosynthetic analysis, we envisioned that two naphthalene moieties could be coupled involving a Pd-mediated cross coupling reaction, followed by acid-catalyzed aromatization. Precursor **18** for the cross coupling reaction could be derived from remote metalation.



5-Iodo-1,4-naphthoquinone was prepared by our direct method from compound **5** in 48 % overall yield in two steps. With compound **18** in hand, we carried out various palladium-catalyzed coupling reactions. However, all the attempts to make a C-C bond between 5-iodo-1,4-naphthoquinone and an aryl tin/boron compound were unsuccessful.



We speculated that the naphthoquinone moiety might inhibit the catalytic cycle by converting reactive Pd(0) into unreactive Pd(II) for cross coupling reaction. Therefore, we decided to temporarily protect the benzoquinone moiety using a Diels-Alder reaction with cyclopentadiene.[12] The Diels-Alder reaction between 5-iodo-1,4-naphthoquinone and freshly distilled cyclopentadiene proceeded smoothly at ambient temperature in 30 min to give Diels-Alder adduct **20** in a quantitative yield. After masking the benzoquinone moiety, we set the stage for the crucial C-C bond formation. Gratifyingly, Diels-Alder adduct **20** smoothly underwent Suzuki cross coupling[13] with 1-naphthaleneboronic acid in the presence of $Pd(PPh_3)_4$ to afford the cross coupled product **21** and an inseparable trace amount of reduced compound. The product was then subjected to a retro-Diels-Alder reaction in boiling xylene to give unmasked product **22** in 62% yield over 3 steps from compound **18**. Finally, acid catalyzed cyclization was performed with concentrated sulfuric acid in the presence of copper powder to give perylene analog **23** in 56% yield.



In conclusion, we successfully developed the methodology for the preparation of 5-substituted naphthoquinones in a concise manner. Synthetically valuable 5-substituted naphthoquinones could be prepared in 4 steps from a commercially available starting material. This new synthetic method was applied to a biologically active perylene analog and could be explored to access other naphthoquinone-containing natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, cyclohexane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

1,4-Dimethoxynaphthalene (3)

To a stirred mixture of 1,4-naphthoquinone hydrate (317 mg, 2 mmol) and tetrabuthylammonium bromide (75 mg, 0.23 mmol) in THF (5 mL) and water (2 mL) was added a solution of sodium hydrosulfite (2.09 g, 12 mmol) in water (2 mL). After 15 min at 25 °C, aqueous potassium hydroxide (2.58 g, 46 mmol, in 2 mL of water) was added. After 5 min, dimethyl sulfate (4 mL, 42.4 mmol) was added and the mixture was stirred for 10 h at 25 °C. The aqueous phase was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give 1,4-dimethoxynaphthalene (207 mg, 55%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.23-8.19 (m, 2H), 7.52-7.49 (m, 2H), 6.71 (s, 2H), 3.97 (s, 6H).

Compound 3a and 3b

To a solution of **3** (357 mg, 1.89 mmol) in dry cyclohexane (3.4 mL) under argon was added *tert*-butyllithium (1.34 mL, 1.7 M in pentane, 2.28 mmol) at 0 °C. The solution was stirred at room temperature for 3 days. The resulting red solution was cooled to 0 °C, and DMF (220 μL, 2.85 mmol) and THF (2 mL) were added. After 1 h, the reaction was warmed to 25 °C, and then stirred overnight. The reaction was quenched by the addition of aqueous 1N HCl (4 mL). The aqueous phase was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified via flash column chromatography to give **3a** (179 mg, 44%) and **3b** (89 mg, 22%): **3a** R_f (hexane-EtOAc 2:1) = 0.47; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.43 (dd, J = 8.4, 1.2 Hz, 1H), 7.93 (dd, J = 7.2, 1.2 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H); **3b** R_f (hexane-EtOAc 2:1) = 0.61; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.28-8.25 (m, 1H), 8.20-8.17 (m, 1H), 7.64-7.59 (m, 2H), 7.11 (s, 1H), 4.08 (s, 3H), 4.01 (s, 3H).

4-Dimethylamino-1-(*tert*-butyldimethylsilyloxy)naphthalene (5).

To a stirred suspension of 4-amino-1-naphthol (1.0 g, 4.60 mmol) and paraformaldehyde (1.38 g, 46.0 mmol) in AcOH (30 mL) at 25 °C under argon was added in one portion sodium cyanoborohydride (1.45 g, 23.0 mmol) and dry THF (6 mL). The resulting mixture was stirred at room temperature for 24 h. The pale pink suspension was then quenched slowly with saturated aqueous Na_2CO_3 (40 mL) at 0 °C and extracted. The organic layer was dried over $MgSO_4$ and concentrated under vacuum (overnight) to give compound **4** as a red, oily residue. The residue was dissolved in dry THF (10 mL) under argon, cooled to 0 °C, and treated with sodium hydride (221 mg, 9.2 mmol). The reaction mixture was stirred for 2 h at

0 °C, and then TBDMSCl (832 mg, 5.52 mmol) was added. The reaction was warmed to room temperature and stirred for 8 h before being quenched with MeOH. The residue was adsorbed on silica gel and then purified by flash column chromatography (hexane-ether 40:1), to give compound **5** (1.27 g, 92%) as a off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J = 18.0, 7.6 Hz, 2H), 7.50 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 2.86 (s, 6H), 1.12 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 144.8, 130.4, 128.9, 125.8, 125.2, 124.0, 123.2, 114.3, 112.1, 45.8, 26.1, 18.6, -4.0; R_f (hexane-EtOAc 2:1) = 0.96.

Representative Procedure for *in situ* Oxidation.

To a solution of **5** (294 mg, 0.98 mmol) in dry cyclohexane (3 mL) under argon was added *tert*-butyllithium (690 μL, 1.7 M in pentane) at 0 °C. The solution was stirred at room temperature for 3 days. The resulting red solution was cooled to 0 °C, and DMF (113 μL, 1.46 mmol) was added. After 1 h at 0 °C, the reaction mixture was warmed to room temperature [the addition of THF (1 mL) is necessary for MeI, Bu_3SnCl, propylene oxide, iodine, benzyl bromide, and diphenyl disulfide] and then quenched with MeOH. After removal of the volatiles in vacuo, the residue was dissolved in acetone (10 mL), cooled to 0 °C, and treated with Jones' reagent (1.1 mL, 2.7 M). The solution was stirred at 0 °C for 30 min and then quenched with 2-propanol (1 mL). The organic layer was extracted with $CHCl_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified via flash column chromatography to give the 5-substituted naphthoquinones.

Compound 7

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 6.4 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.02 (s, 3H), 2.71 (s, 6H), 1.14 (s, 9H), 0.32 (s, 6H); IR (KBr) 3057, 2957, 2928, 1592 cm^{-1}; HRMS *m/e* (EI) for $C_{19}H_{29}ONSi$ $(M)^+$ calcd 315.2018, measured 315.2022; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 146.5, 135.2, 130.8, 130.2, 129.9, 124.8, 121.4, 117.0, 112.0, 46.2, 26.2, 23.8, 18.6, -4.0. R_f (hexane-EtOAc 8:1) = 0.87.

Compound 9

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 8.0, 1.6 Hz, 2H), 7.44 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.75 (s, 6H), 1.10 (s, 9 H), 0.29 (s, 6H); HRMS *m/e* (EI) for $C_{24}H_{31}ONSSi$ $(M)^+$ calcd 409.1896, measured 409.1903; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 145.3, 138.1, 136.4, 136.2, 129.9, 129.7, 129.3, 128.6, 125.0, 124.4, 119.3, 119.0, 112.7, 46.1, 26.1, 18.6, -4.0; R_f (hexane-EtOAc 8:1) = 0.77.

Compound 10

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (dd, J = 7.2, 1.5 Hz, 1H), 8.49 (dd, J = 8.4, 1.5 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 2.92 (s, 6H), 1.09 (s, 9H), 0.31 (s, 6H); HRMS *m/e* (EI) for $C_{19}H_{27}O_3NSi$ $(M)^+$ calcd 345.1760, measured 345.1766; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 152.5, 136.9, 136.5, 130.1, 130.1, 127.9, 127.8, 125.4, 120.5, 111.9, 46.0, 26.0, 18.6, -4.1; R_f (hexane-EtOAc 1:2) = 0.17.

Compound 11

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 8.0, 1.6 Hz, 1H), 8.26 (bs, 1H), 7.39-7.27 (m, 8H), 6.86 (d, J = 8.4 Hz, 1H), 6.28 (s, 1H), 2.70 (s, 3H), 2.22 (s, 3H), 1.10 (s, 9H), 0.29 (s, 6H); IR (KBr) 3395, 2929, 1595 cm^{-1}; HRMS *m/e* (EI) for $C_{25}H_{33}O_2NSi$ $(M)^+$ calcd 407.2281, measured 407.2288; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 145.4, 143.2, 139.1, 130.7, 130.5, 130.2, 128.1,127.2, 126.7, 124.5, 123.8, 120.9, 112.3, 77.1, 48.5, 46.7, 26.1, 18.6, -4.0, -4.1; R_f (hexane-EtOAc 2:1) = 0.27.

Compound 12

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.4, 1.6 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.98 (m, 1H), 3.76 (dd, J = 13.2, 3.6 Hz, 1H), 3.23 (dd, J = 13.6, 7.6 Hz, 1H), 2.84 (bs, 1H), 2.75 (s, 3H), 2.67 (s, 3H), 1.19 (d, J = 6.0 Hz, 3H), 1.11 (s, 9H), 0.30 (s, 6H); IR (KBr) 3415, 2928, 2778, 1593 cm^{-1}; HRMS *m/e* (EI) for $C_{21}H_{33}O_2NSi$ $(M)^+$ calcd 359.2281, measured 359.2285; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 145.1, 135.2, 131.5, 130.6, 129.6, 124.8, 122.9, 117.7, 111.9, 69.9, 47.1, 46.9, 45.8, 26.1, 23.3, 18.6, -4.0; R_f (hexane-EtOAc 3:1) = 0.36.

Compound 13

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.19 (t, J = 7.2 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 6.81 (d, J = 8.4 Hz, 1H), 4.85 (s, 2H), 2.48 (s, 6H), 1.13 (s, 9H), 0.31 (s, 6H); HRMS *m/e* (EI) for $C_{25}H_{33}ONSi$ $(M)^+$ calcd 391.2331, measured 391.2338; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 146.1, 143.9, 136.8, 131.2, 130.4, 130.2, 128.4, 128.1, 125.1, 124.8, 122.3, 118.3, 112.1, 46.2, 42.4, 26.1, 18.6, -4.0;. R_f (hexane-EtOAc 8:1) = 0.80.

Compound 14

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.4, 1.2 Hz, 1H), 7.72 (dd, J = 6.4, 1.2 Hz, 1H), 7.43 (dd, J = 8.0, 6.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 2.61 (s, 6H), 1.51-1.42 (m, 6H), 1.34-1.25 (m, 6H), 1.1 (s, 9H), 1.04-0.99 (m, 6H), 0.84 (t, J = 7.2 Hz, 9H), 0.28 (s, 6H); HRMS *m/e* (EI) for $C_{30}H_{53}ONSiSn$ $(M)^+$ calcd 591.2918, measured 591.2925; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 146.6, 138.3, 136.6, 136.1, 128.9, 124.9, 123.1, 115.3, 111.9, 47.9, 29.5, 27.9, 26.2, 18.7, 14.0, 11.9, -4.0;. R_f (hexane-EtOAc 30:1) = 0.79.

Compound 15

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 2.67 (s, 6H), 1.13 (s, 9H), 0.31 (s, 6H); IR (KBr) 2925, 2855, 1589 cm^{-1}; HRMS *m/e* (EI) for $C_{18}H_{26}ONISi$ $(M)^+$ calcd 427.0829, measured 427.0834; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.2, 142.1, 130.1, 128.7, 125.9, 124.0, 118.9, 113.0, 88.1, 45.7, 26.1, 18.6, -4.0;. R_f (hexane-EtOAc 2:1) = 0.89.

Compound 16

^{1}H NMR (400 MHz, CD_3CN/CD_3OD) δ 8.85 (dd, J = 8.0, 1.2 Hz, 1H), 8.58 (t, J = 7.6 Hz, 1H), 8.47 (dd, J = 7.6, 1.2 Hz, 1H), 7.74 (s, 2H); IR (KBr) 3327, 2930, 1695, 1671 cm^{-1}; HRMS *m/e* (EI) for $C_{11}H_6O_4$ $(M)^+$ calcd 202.0266, measured 202.0269; ^{13}C NMR (100 MHz, CD_3CN/CD_3OD) δ 185.7, 185.6, 172.1, 140.1, 139.6, 136.1, 135.2, 133.6, 133.3, 129.7, 128.3. R_f (hexane-EtOAc 1:1) = 0.07.

Compound 17

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.30 (dd, J = 7.6, 1.2 Hz, 1H), 8.06 (dd, J = 7.6, 1.2 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.04 (s, 2H); IR (KBr) 3081, 2887, 1694, 1669, 1659 cm^{-1}; HRMS *m/e* (EI) for $C_{11}H_6O_3$ $(M)^+$ calcd 186.0317, measured 186.0320; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 186.6, 184.0, 139.4, 138.4, 137.9, 134.2, 133.5, 132.7, 131.5, 130.9; R_f (hexane-EtOAc 1:1) = 0.37.

Compound 18

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, J = 7.8, 1.2 Hz, 1H), 8.17 (dd, J = 7.5, 1.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 10.5 Hz, 1H), 6.96 (d, J = 10.2 Hz, 1H); IR (KBr) 3055, 1669 cm^{-1}; HRMS *m/e* (EI) for $C_{10}H_5O_2I$ $(M)^+$ calcd 283.9334, measured 283.9338; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 183,4, 148.4, 139.9, 137.3, 134.5, 133.9, 130.9, 127.8, 92.9; R_f (hexane-EtOAc 5:1) = 0.31.

Compound 19

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, J = 8.1, 1.5 Hz, 1H), 8.04 (dd, J = 7.8, 1.5 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 5.87 (s, 1H), 3.19 (s, 6H); HRMS *m/e* (EI) for $C_{12}H_{10}O_2NI$ $(M)^+$ calcd 326.9756, measured 326.9761; ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8, 181.0, 151.7, 148.1, 135.3, 132.3, 131.1, 127.8, 107.9, 91.3, 42.4. R_f (hexane-EtOAc 2:1) = 0.38.

Compound 20

To a 0 °C solution of 5-iodo-1,4-naphthoquinone (500 mg, 1.76 mmol) in $CHCl_3$ (15 mL)

was added freshly distilled cyclopentadiene (530 μL). After 30 min at 0 °C, the reaction mixture was warmed to room temperature and further stirred for 1 h. The reaction mixture was concentrated in vacuo to give Diel-Alder adduct **20** as a pale yellow oil. The residue was used in the next step without purification.

The residue was diluted with toluene (15 mL) and then treated with $Pd(PPh_3)_4$ (203 mg, 0.18 mmol), 1-naphthaleneboronic acid (333 mg, 1.94 mmol), K_2CO_3 (365 mg, 2.64 mmol) and H_2O (1.2 mL). The reaction was refluxed for 12 h at 85-90 °C. After cooling the reaction mixture, it was partitioned with ethyl acetate and sat. Na_2CO_3. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give an inseparable mixture of cross coupled product **21** and reduced starting material. This mixture was diluted with xylene and distilled twice to remove cyclopentadiene. The solution was concentrated under reduced pressure and the residue was purified via flash column chromatography to give compound **22** (316 mg, 62%) as an orange solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 7.6, 1.2 Hz, 1H), 7.64 (dd, J = 8.4, 2.8 Hz, 2H), 7.84 (t, J = 8.0 Hz, 1H), 7.65 (dd, J = 7.6, 1.2 Hz, 1H), 7.56 (dd, J = 8.4, 8.0 Hz, 1H), 7.50-7.46 (m, 1H), 7.36-7.27 (m, 3H), 6.97 (d, J = 10.0 Hz, 1H), 6.73 (d, J = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 184.8, 141.8, 140.2, 139.2, 138.2, 137.3, 133.5, 133.3, 131.9, 130.3, 128.7, 128.0, 127.0, 126.3, 126.0, 125.6, 125.14, 125.11; R_f (hexane-Et_2O 1:1) = 0.55.

Compound 23

To a 0 °C solution of compound **22** (30 mg, 0.11 mmol) in sulfuric acid (18 M, 3 mL) was added copper powder (from Aldrich, 20 mg, 0.32 mmol). After 2 h at 0 °C, the reaction

mixture was warmed to 10 °C and further stirred for 3 h. The reaction was quenched by the addition of ice-water (10 mL), then extracted extensively with $CHCl_3$ (4 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give perylene analog **23** (16 mg, 56%) as a yellow greenish solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.34 (d, J = 7.6 Hz, 1 H), 8.28 (d, J = 7.6 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.50 -7.44 (m, 3H), 6.95 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 134.5, 131.4, 130.9, 130.4, 127.6, 126.9, 126.7, 125.9, 125.6, 125.2, 122.2, 121.9, 121.2, 120.1, 118.6, 109.6; HR MS *m/e* (EI) for $C_{20}H_{12}O$ $(M)^+$ calcd 268.0888, measured 268.0893; R_f (hexane-Et_2O 1:1) = 0.39.

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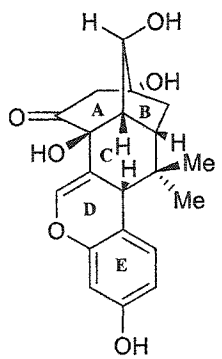
CHAPTER 2. DIELS-ALDER/RADICAL CYCLIZATIONS (DARC) FOR THE RAPID CONSTRUCTION OF BRIDGED RING SYSTEMS

Introduction

Carbon-carbon bond formation is a crucial part of organic chemistry. Among the numerous methods, one efficient way is the Diels-Alder reaction. Known for more than 100 years, it has been reviewed thoroughly[1] and has been actively used in academic and industrial laboratories. Along with its high stereo- and regioselectivity, one of the advantages of this transformation is that it can be combined with other reactions in following step without the isolation of intermediates, which has been termed a tandem or domino reaction.[2]

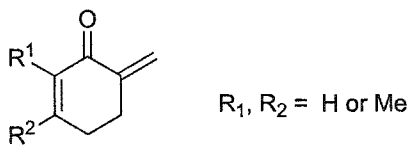
This concept has gained its popularity in the synthetic community because the highest possible efficiency of synthetic operations must be obtained. To devise these types of reactions, it is necessary to arrange the sequence of each reaction carefully even though each individual step in multiple reaction process has been well studied.

In the course of our synthetic studies towards developing new strategy to construct the bridged tricyclic system for the total synthesis of miroestrol,[3] we devised an interesting combination between Diels-Alder and radical cyclizations in tandem fashion.



miroestrol

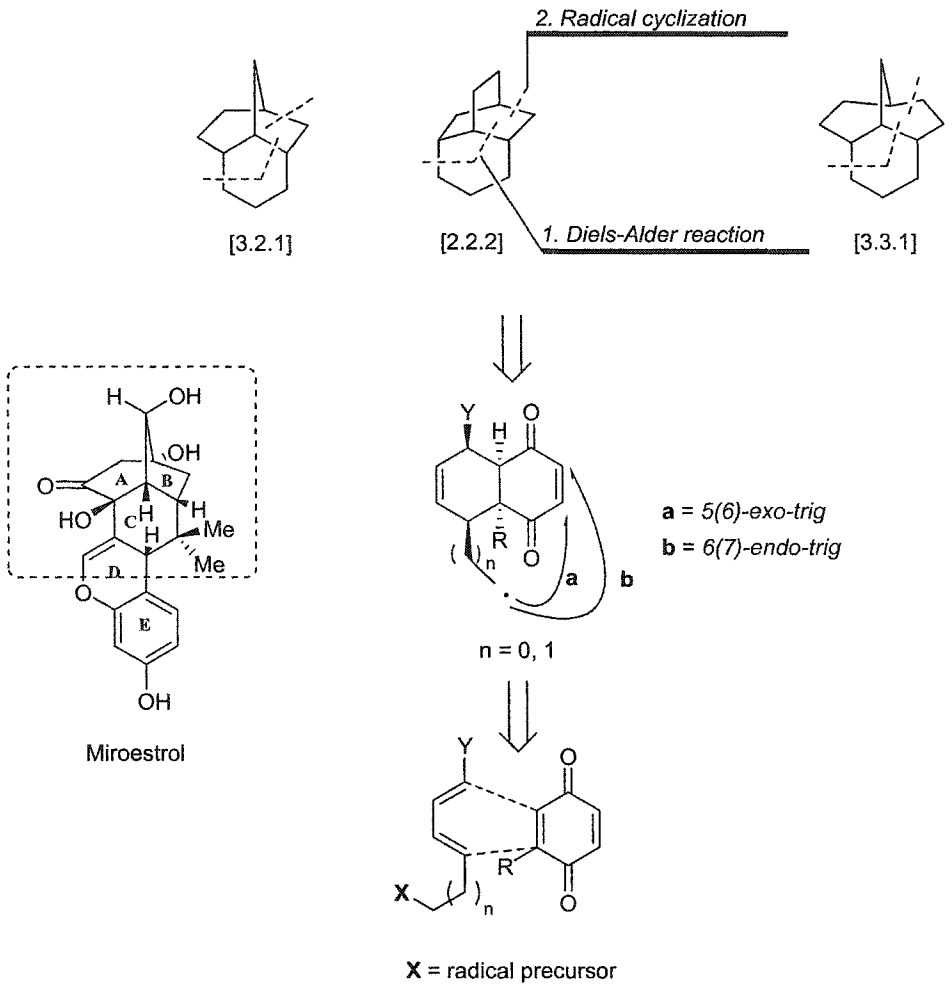
While there are many applications of tandem reactions to fused polycyclic molecules,[4] there are few examples of tandem reactions to bridged ring systems. Nevertheless, tandem processes utilizing Diels-Alder/radical cyclizations have never been explored. During our investigation, we also developed a new method to synthesize 6-methylenecyclohex-2-en-1-one derivatives.



6-methylenecyclohex-2-en-1-one derivatives

Results and Discussion

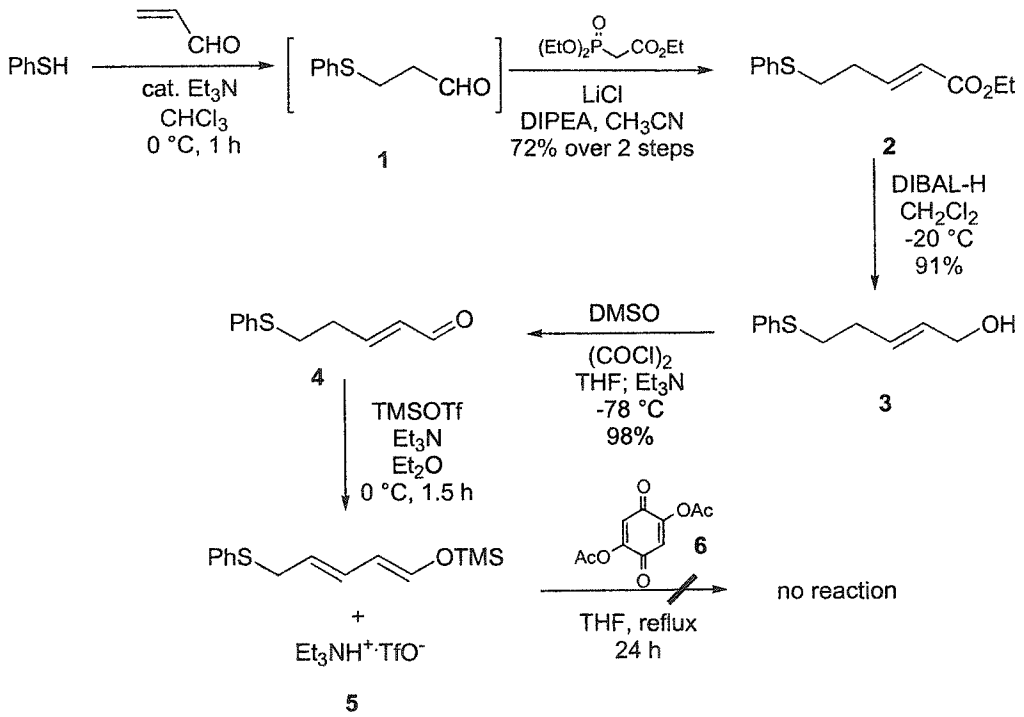
As illustrated in the retrosynthetic scheme, the bridged tricyclic skeleton would be accessible from a Diels-Alder reaction between a substituted 1,4-benzoquinone as a dienophile and a diene precursor for the radical cyclizations.



The choice of substituents in the 1,4-benzoquinone is crucial for the control of the regiochemistry of the intermolecular Diels-Alder reaction and to accelerate the reaction rate at lower temperature. Another important factor that should be considered is that the type of precursor for the intramolecular radical reaction in the following step should be compatible with the Diels-Alder reaction.

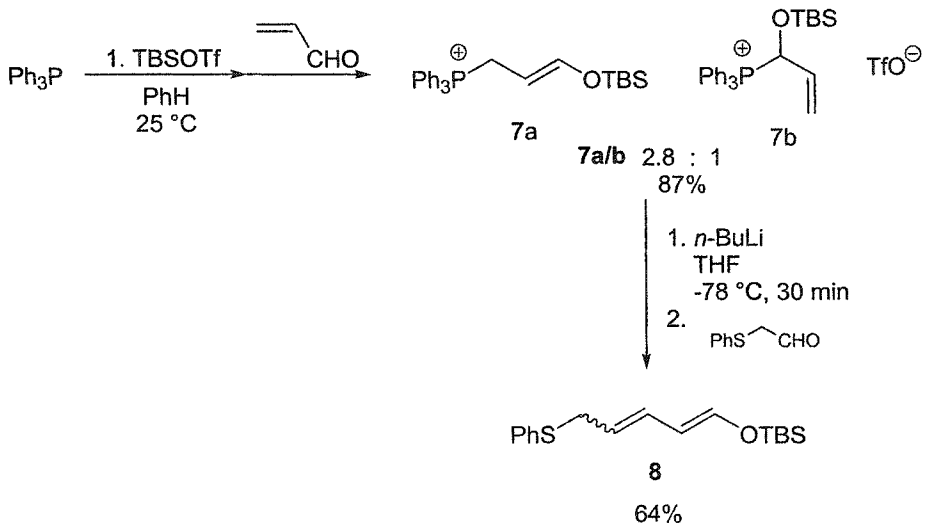
We began our study with diene **5** containing a thioether as a precursor for the second radical cyclization step. Thiophenol was treated with acrolein in the presence of a catalytic amount of triethylamine to provide 1,4-addition product **1**. It was subjected to a Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate in Roush-Masamune conditions

to give α,β-unsaturated ester **2** in 72% yield over 2 steps.[5] Unsaturated ester **2** was reduced to the corresponding allylic alcohol **3** with DIBAL in a 91% yield. The alcohol **3** was oxidized to an α,β-unsaturated aldehyde **4** via Swern oxidation.[6] With aldehyde **4** in hand, we tried to generate the silyl enol ether with TMSOTf/Et_3N. However, the isolation of the silyl enol ether **5** from the by-product was unsuccessful. When crude diene **5** was subjected to a Diels-Alder reaction with 2,5-diacetoxy-1,4-benzoquinone **6**, it was unsuccessful and only 80% of compound **4** was recovered.

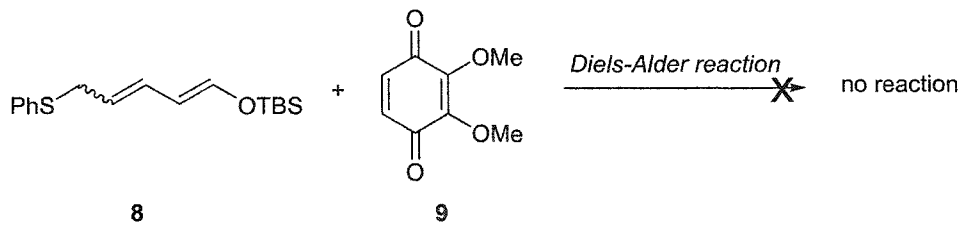


After we learned the difficulties the purification of diene in a small scale, we turned our attention to more stable diene **8** bearing a TBS group instead of a TMS group. TBS-protected silyl enol ether **8** was prepared from triphenylphosphine in a 64% overall yield in 2 steps. Indeed, TBS-protected diene **8** was stable enough to be purified via flash column

chromatography.



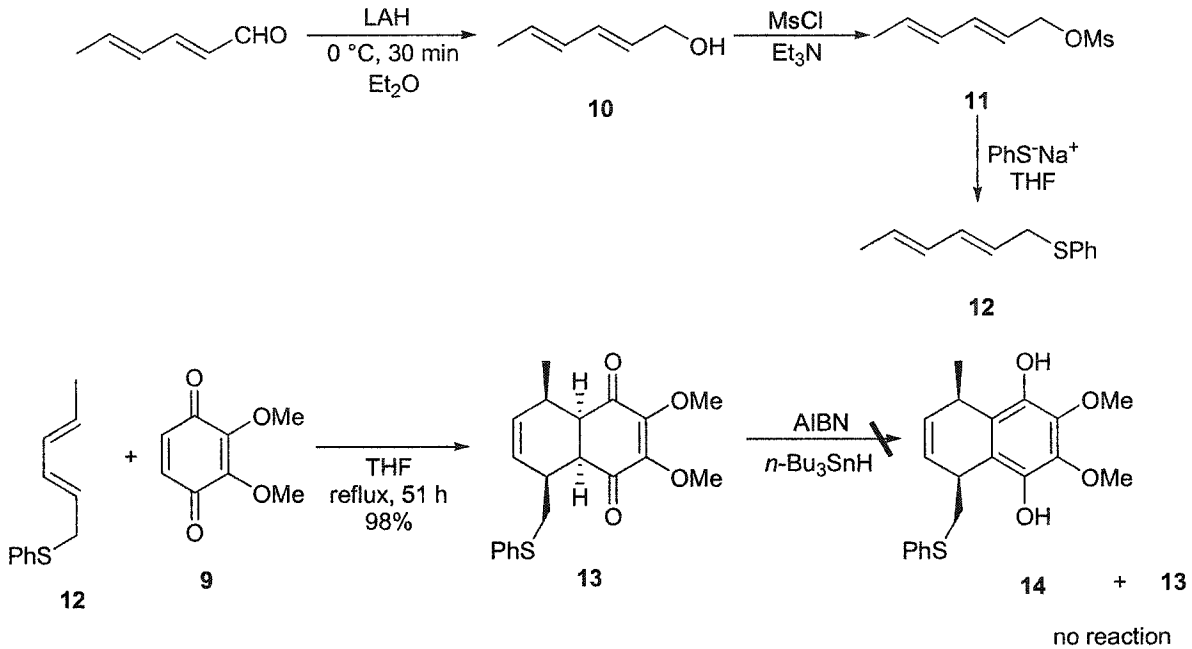
With diene **8** in hand, we undertook the Diels-Alder reaction with 2,3-dimethoxy-1,4-benzoquinone **9**, which was made from 1,2,3-trimethoxybenzene.[7] An advantage of this dienophile **9** is that we could put aside problems related with the regioselectivity of the Diels-Alder reaction compared to 2,5-disubstitued 1,4-benzoquinone derivatives. Unfortunately, all of our attempts to effect the Diels-Alder reaction failed to give the desired products.



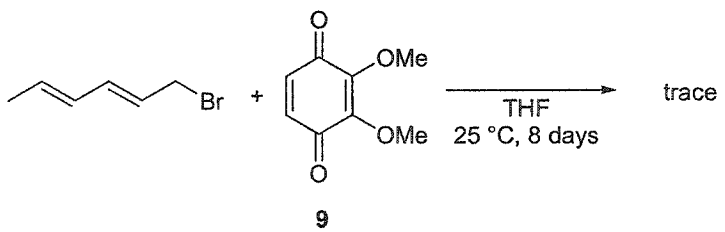
8 **9**

In spite of the high reactivity of dienes like **5** and **8**, they were not compatible with 1,4-benzoquinone derivatives. When the silyl enol ether moiety was removed, diene **12** underwent a Diels-Alder reaction smoothly to provide product **13** in a 98% yield. Due to its tendency to aromatize, we directly subjected crude Diels-Alder adduct **13** to the radical cyclization using *n*-Bu_3SnH/AIBN conditions. Unfortunately, the only products we could isolate were aromatized starting material **14** and unreacted starting material **13**. Even though

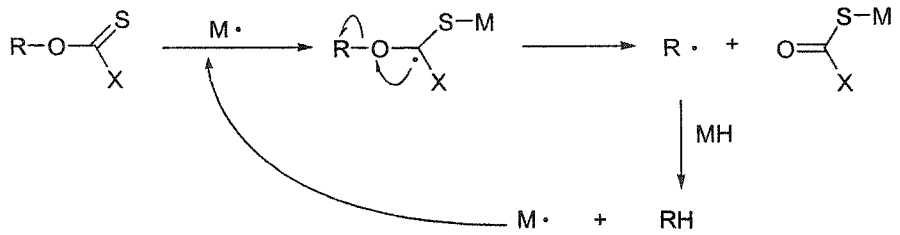
the thiophenyl group has been used as a radical precursor,[8] it did not work for our system.



After we failed to generate a radical from the thiophenyl group, we modified the radical precursor in the diene. Reductive removal of bromide and iodine atoms by *n*-Bu_3SnH is a well established procedure.[9] Sorbyl bromide was prepared by the reported procedure[10] and then subjected to Diels-Alder reaction with dienophile **9**. This reaction was too sluggish to give any desired adduct in reasonable yield.

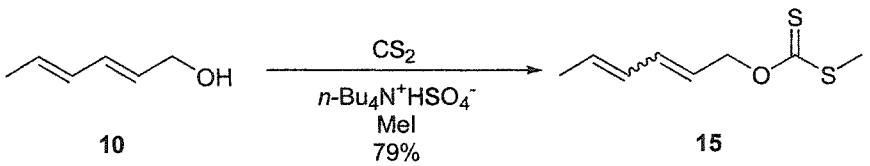


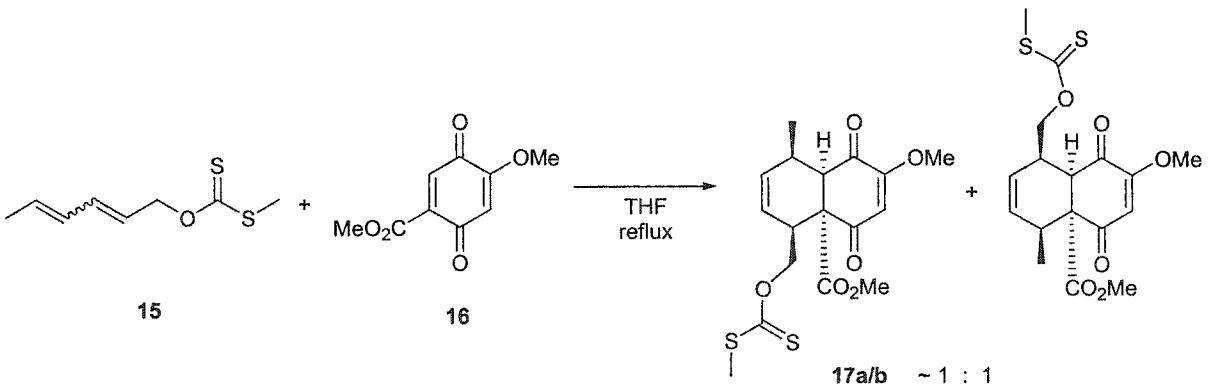
In the literature, there are many examples of radical deoxygenation. Barton's group has reported the reductive removal of hydroxy group via thiono esters.[11] The driving force for this method is the formation of the strong carbonyl bond at the expense of a weak thiocarbonyl moiety.



M = R_3Sn
X = Ph, Im, SMe

To test the feasibility of radical deoxygenation, we prepared the xanthate ester **15** from hexa-2,4-dien-1-ol in 79% yield. When the diene **15** was treated with dienophile **16**[12], the product was unstable during the purification via flash column chromatography. The crude mixture itself showed almost equal amounts of regioisomers.



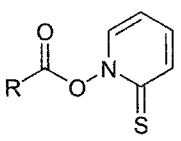


With the results from the previous attempts, we came to a conclusion for the modification for our diene and dienophiles to avoid problems. First, it would be better to use the terminal *E*-diene to enhance the regioselectivity in the Diels-Alder reaction. Second, the radical precursor should be installed in the diene from the beginning of our sequence due to the instability of the Diels-Alder adduct. Third, it would be helpful to have an activating group in

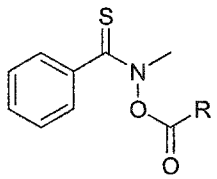
the dienophile because it would allow the reaction to occur under milder conditions and the resulting adduct could avoid aromatization during the purification.

A carboxylic acid could be used as a precursor to a radical. Various methods have been developed to generate radical intermediates from carboxylic acids.[13] *O*-acyl thiohydroxamates which are known as Barton esters have been investigated thoroughly by Barton and co-workers and developed as one of the most convenient and versatile sources of carbon-centered radicals.[14]

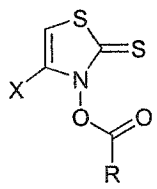
This facile radical generation process resulted from the weak N-O bond, which could be cleaved thermally or photochemically. A considerable variety of O-acyl derivatives have been synthesized and their conditions for the initiation are well studied.[15]



Thermal 110 °C
Photochemical Tungsten lamp

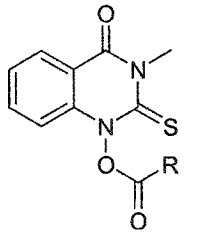


Thermal stable to 130 °C
Photochemical Hg (medium)



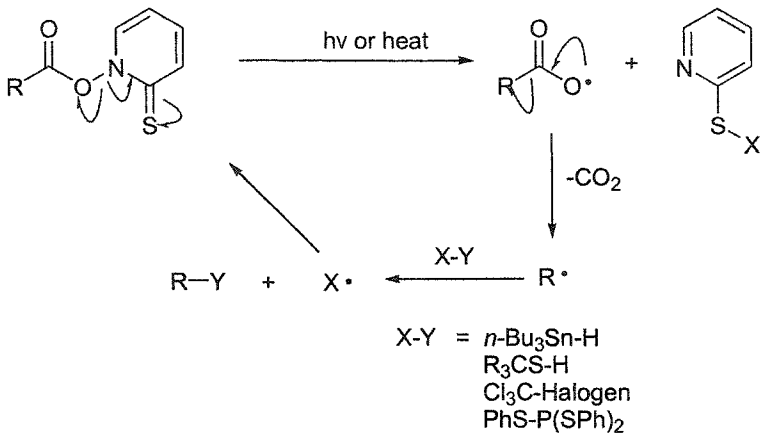
X = Ph
Thermal 110 °C
Photochemical Tungsten lamp

X = Me
Thermal 110 °C
Photochemical Hg (medium)

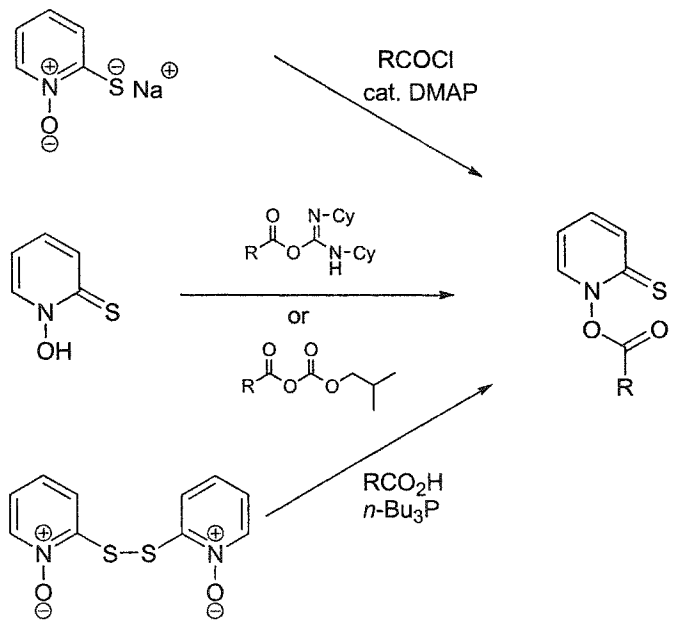


Thermal stable to 130 °C
Photochemical Hg (medium)

The mechanism of decarboxylation using Barton ester similar to the Barton-McCombie reductive deoxygenation of xanthates. Formation of the strong carbonyl bond, instead of a thiocarbonyl bond, is one of the driving forces for this process. In this process, the aromatization of the pyridine and the release of carbon dioxide make this reaction more thermodynamically favorable than deoxygenation.

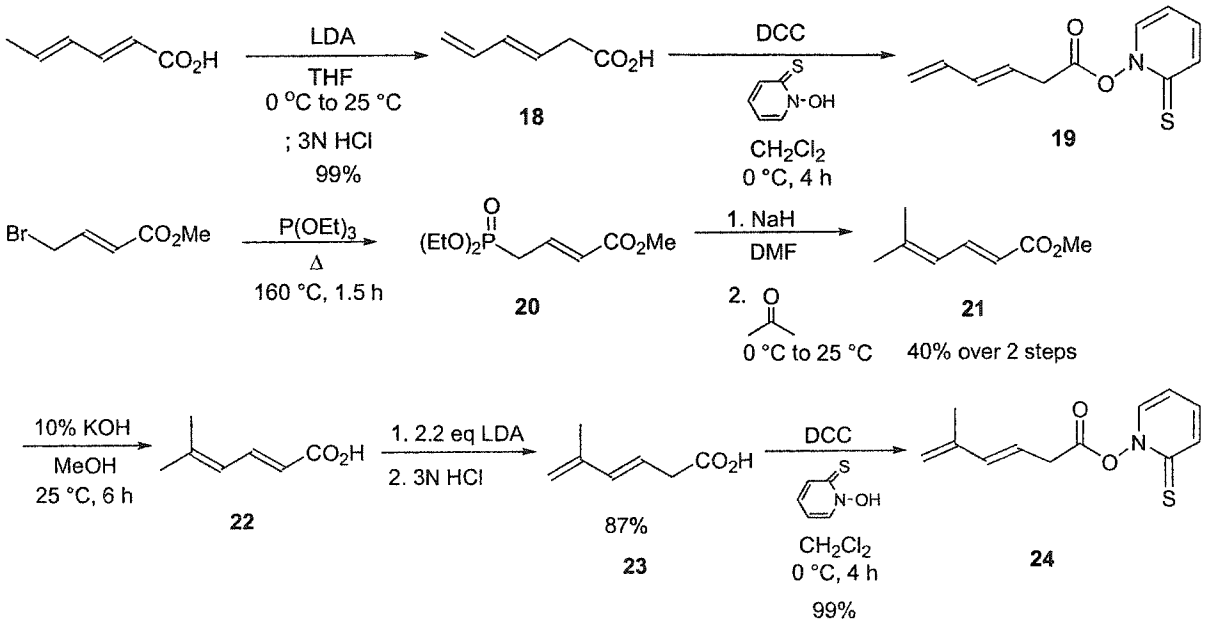


Typical procedures for preparation of *O*-acyl thiohydroxamates based on 2-mercaptopyridine *N*-oxide are shown below.[15,16]

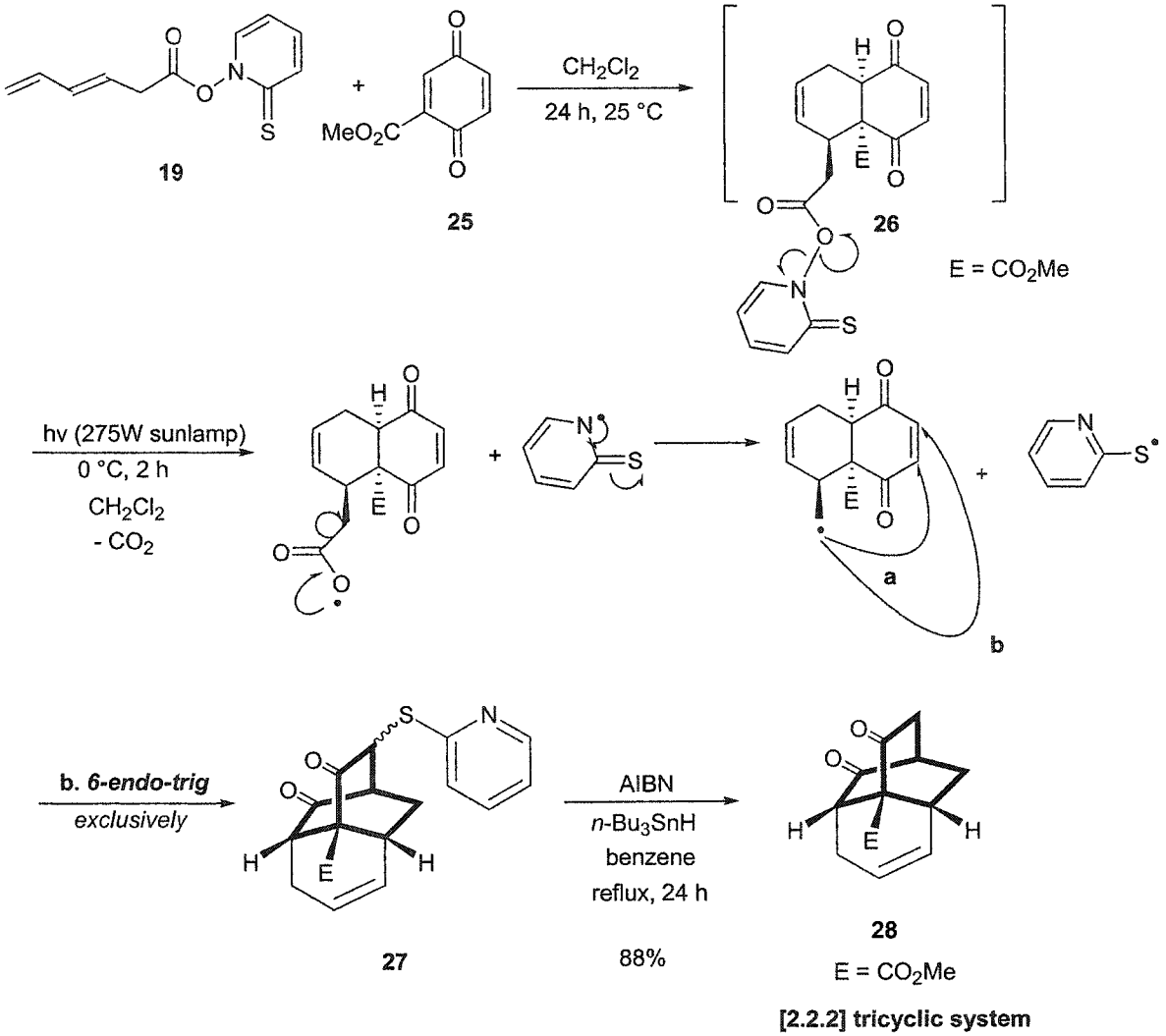


Before we started our new approach, we were concerned about the thermal stability of the Barton ester in the Diels-Alder reaction. Because of its thermal instability, it might be unsuitable as a diene in the thermal Diels-Alder reaction. In the previous reports, the Barton ester was prepared immediately before the decarboxylation step. However, it could be useful if it underwent the Diels-Alder reaction at a reasonably low temperature. We commenced the

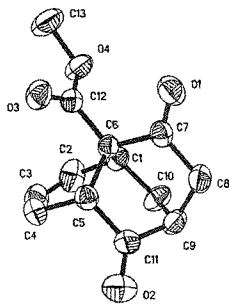
preparation of diene **19** from sorbic acid. The deconjugated diene was prepared from sorbic acid via deconjugation, followed by rapid quenching with 3N HCl. This rather unstable terminal diene **18** was converted to a Barton ester using DCC at 0 °C for 4 h in 99% yield. During the purification, all experiments were conducted with minimal exposure to light. Using a similar manner, diene **24** was synthesized from methyl 4-bromobut-2-enoate via Arbuzov reaction,[17] Horner-Wadsworth-Emmons reaction, hydrolysis, deconjugation, and activation to the Barton ester.



With compounds **19** and **24** in hand, we conducted the Diels-Alder reaction with 2-carbomethoxy-1,4-benzoquinone **25** in CH_2Cl_2 at ambient temperature. To our delight, the Diels-Alder reaction proceeded smoothly to give only one regioisomer **26** in quantitative yield. Adduct **26** was then subjected to radical cyclization with a 275 W tungsten light at 0 °C without purification. After 2 h at 0 °C, we isolated the cyclized product **27** in 73% yield.



Based on the facile 5-*exo*-trig cyclization compared to a 6-*endo*-trig cyclization,[18] we anticipated the [3.2.1] tricyclic compound as our isolated product. Surprisingly, the product we obtained was the [2.2.2] tricyclic compound. The structure of the product **28** was determined unambiguously by x-ray crystallography after desulfurization with AIBN/*n*-Bu_3SnH.[19]



The successful tandem Diels-Alder/radical cyclization prompted us to react diene **19** and **24** with a variety of dienophiles. The results are collated in Table 1.

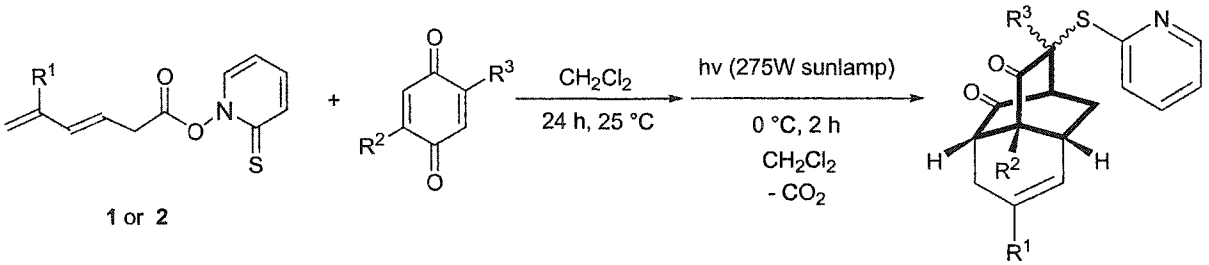


Table 1. Tandem Diels-Alder/radical cyclization for [2.2.2] tricyclic system

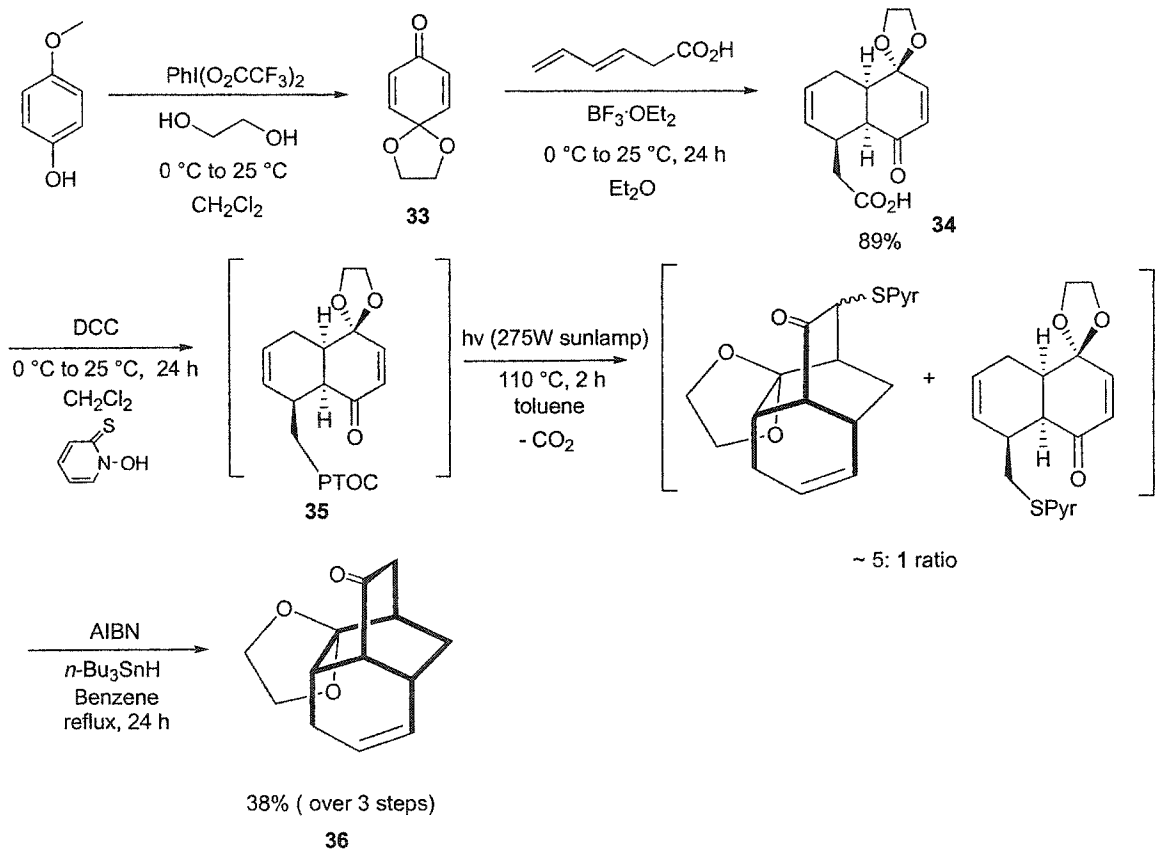
Entry	R^1	R^2	R^3	Yield (%)	Product
1	H	CO_2Me	H	73(76)*	**27**
2	H	COMe	H	55	**29**
3	H	CO_2Me	Me	71	**30**
4	H	CHO	H	No reaction**	
5	H	CN	H	No reaction**	
6	H	H	H	No reaction**	
7	Me	CO_2Me	H	57	**31**
8	Me	COMe	H	75	**32**

** no reaction : Diels-Alder reaction failed

* radical cyclization in CH_3CN

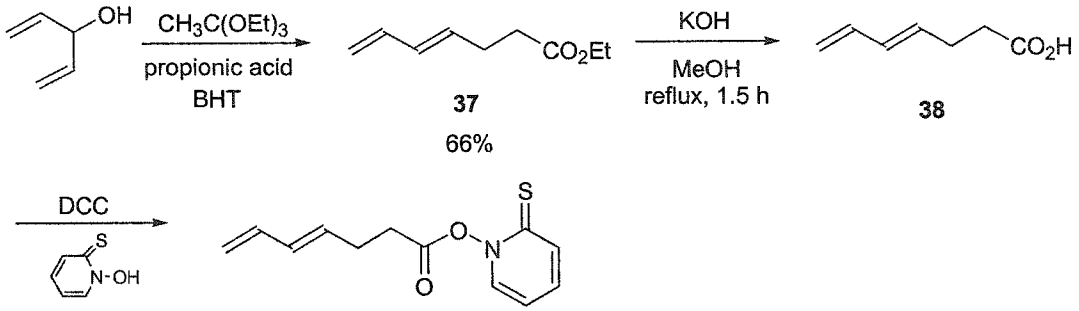
In the case of dienophiles with electron withdrawing groups, the Diels-Alder/radical

cyclization underwent smoothly to give [2.2.2] cyclized products. However, formyl or nitrile groups are not compatible with Barton ester in entries 3, 4 and 5. When a dienophile has no electron-withdrawing group, it is possible to conduct this tandem Diels-Alder/radical cyclization in a sequential manner. For example, monoketal 1,4-benzoquinone **33**[20] underwent a Lewis acid catalyzed Diels-Alder reaction with diene **18** in 89% yield. After converting the carboxylic acid moiety in **34** into a Barton ester, the crude product **35** was subjected to radical cyclization and desulfurization to give tricyclic compound **36** in 38% yield over 3 steps. In this manner, Diels-Alder/radical cyclization strategy could be used with unactivated dienophiles, as well as activated dienophiles.

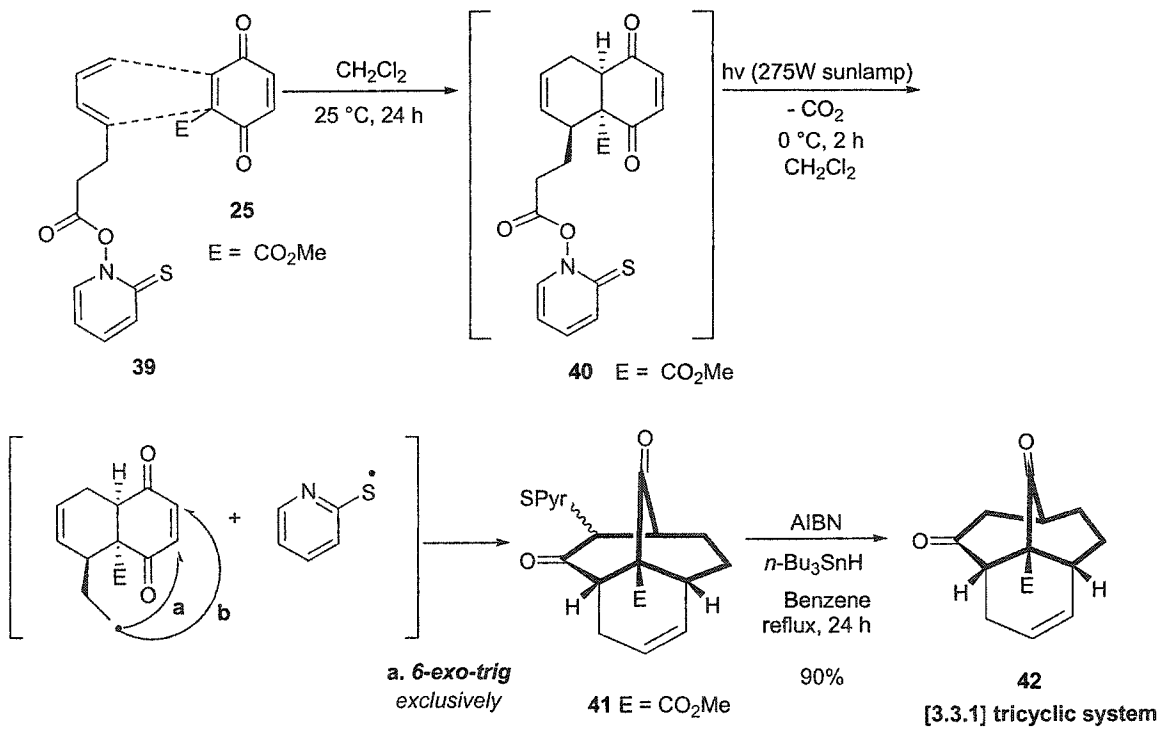


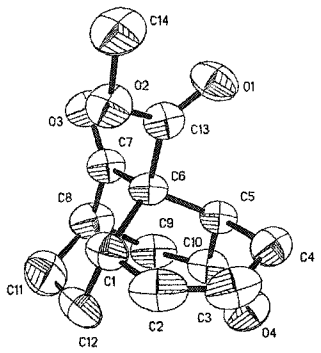
After we observed the unusual preference for 6-*endo*-trig cyclization, we decided to test the preference of radical cyclization for 6-*exo*-trig versus 7-*endo*-trig. To answer the question,

we prepared diene **39** from penta-1,4-dien-3-ol[21] via Johnson orthoester Claisen rearrangement,[22] hydrolysis, and activation to the Barton ester in good overall yield.

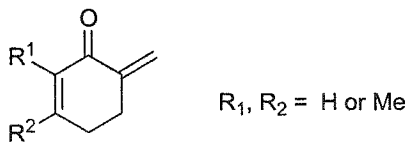


With diene **39** in hand, we performed the Diels-Alder/radical cyclization with 2-carbomethoxy-1,4-benzoquinone (**25**) in the same manner to give [3.3.1] tricyclic compound **41** in 61% yield. Its x-ray structure was obtained after desulfurization. Clearly, the radical intermediate generated from **40** followed the general preference for 6-*exo*-trig over 7-*endo*-trig in the radical cyclization step.



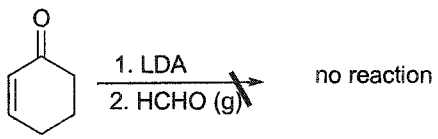


In the course of exploring the feasibility of the Diels-Alder/radical cyclization to other substrates, we decided to prepare the cyclohexenone derivatives containing exo methylene groups. To our surprise, there is almost no direct preparation for these molecules. The only reported procedures for these compounds are synthetically not quite easy to perform on a large scale.[23] Although there are several methods developed to access exo methylene carbonyl compounds, the generation of 6-methylenecyclohex-2-en-1-one derivatives could be difficult by the conventional methods because of their tendency to aromatize to give phenol derivatives.



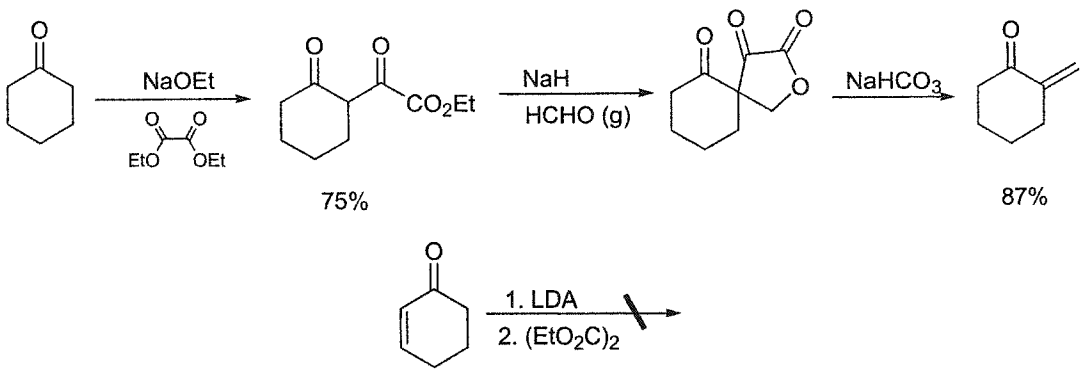
6-methylenecyclohex-2-en-1-one derivatives

We began our approach to these molecules via α-hydroxymethylation and subsequent elimination procedures. When 2-cyclohexenone was deprotonated with LDA and then quenched with paraformaldehyde gas,[24] it only gave polymeric mixtures.

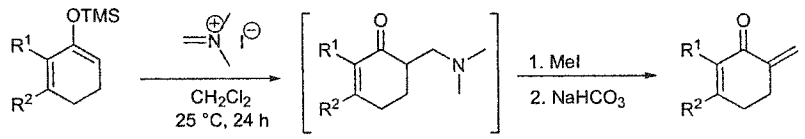


McMurry and co-workers reported the synthesis of unsaturated carbonyl compounds via

a three step procedure involving the formation of an ethyloxalyl derivative, reaction with an aldehyde to give a diketolactone, and base cleavage to product.[25] Although this method was quite efficient in preparing α-methylenecyclohexanone, α-methylenebutyrolactone, and α-methylenevalerolactone, we found this procedure did not work well because of the difficulty in the reliable preparation of ethyloxalyl derivatives from cyclohexenone.



The introduction of a methylene group α to a ketone also could be achieved via base catalyzed Mannich reaction with Eschenmoser's salt.[26] There are a wealth of examples which utilize this transformation.[27] In general, the preparation is conducted in a three-step sequence: the generation of an α-aminomethyl group, quaternization, and β-elimination of the dialkylamino group. Cyclohexenone was deprotonated with LDA at -78 °C to generate the kinetic enolate, and then the enolate was treated with Eschenmoser's salt. However, we could not isolate our desired product from the reaction mixture. We postulated that the enolate might be too reactive for Eschenmoser's salt even at low temperature. The silyl enol ether is one of the synthetic equivalents for enolates. Indeed, the silyl enol ether of cyclohexenones[28] underwent aminomethylation at 25 °C cleanly to give compound **2** in a good yield. Crude products were directly converted to ammonium salts with excess MeI. The ammonium salts were subjected to β-elimination with $NaHCO_3$ to give our desired α-methylene cyclohexenone derivatives. The results are summarized in Table 2.



1 2 3

Table 2. Preparation of α-methylene cyclohexenone derivatives

Entry	R^1	R^2	**2** Yield (%)	**3** Yield (%)*
1	H	H	98	66 **43**
2	H	Me	99	49 **44**
3	Me	H	81	67 **45**

*After flash column chromatography (SiO_2)

We found that these products could be purified via flash column chromatography without any serious aromatization. During our preparation sequence for α-methylene cyclohexenone derivatives, we conducted only one chromatographic separation for the last step.

In conclusion, we successfully developed a new strategy to construct the bridged tricyclic systems via tandem Diels-Alder/radical cyclization process. During this tandem process, we observed the unusual preference for 6-*endo*-trig over 5-*exo*-trig in the radical cyclization step. In our effort to expand this strategy to other molecules, we found a concise preparation of α-methylene cyclohexenones, which would be useful to construct spirocyclic systems. We are currently investigating the application of the Diels-Alder/radical cyclization (DARC) to different types of polycyclic natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used

without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

3-(Phenylthio)propanal (1)

To a 0 °C solution of acrolein (2 mL, 26.94 mmol) and thiophenol (2.72 mL, 26.52 mmol) in $CHCl_3$ (4.4 mL) was added triethylamine (100 μL, 0.72 mmol). After 1 h at 0 °C, the reaction mixture was diluted with ether (30 mL). The organic layer was washed with 5% NaOH (2 × 10 mL), water (10 mL), and brine (10 mL) The extract was dried over $MgSO_4$, filtered, and concentrated in vacuo to give compound **1** (5.33 g, >99%) as a oil. The crude product was used in the following step without purification: ^1H NMR (400 MHz, $CDCl_3$) δ 9.72-9.71 (m, 1H), 7.34-7.18 (m, 5H), 3.17-3.13 (m, 2H), 2.75-2.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 135.2, 130.0, 129.2, 126.7, 43.3, 26.4; R_f(hexane-Et_2O 2:1) = 0.43.

5-Phenylthio-2-pentenoic acid ethyl ester (2)

To a solution of LiCl (2.62 g, 61.9 mmol), diisopropylethylamine (9.06 mL, 52.0 mmol),

and triethyl phosphonoacetate (12.3 mL, 61.9 mmol) in dry CH_3CN (120 mL) under argon was added a solution of aldehyde 2 (8.64 g, 52.0 mmol) in CH_3CN (12 mL plus 3 mL rinse) at 25 °C. After 10 h at 25 °C, the reaction was quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography to give α,β-unsaturated ester **2** (8.9 g, 72%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 4H), 7.17 (t, J = 7.2 Hz, 1H), 6.94 (dt, J = 16.0, 6.8 Hz, 1H), 5.85 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 2.51-2.46 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 146.1, 135.6, 129.6, 129.0, 126.3, 122.8, 60.2, 32.0, 31.7, 14.2; R_f (hexane-Et_2O 2:1) = 0.59.

5-(Phenylthio)pent-2-en-1-ol (3)

To a –40 °C solution of α,β-unsaturated ester **2** (1.57 g, 6.64 mmol) in CH_2Cl_2 (30 mL) was added DIBAL-H (13.8 mL, 1 M solution in THF, 13.8 mmol) dropwise. After 2 h at -20 °C, the reaction was warm to 25 °C for 2 h. The reaction was quenched with saturated NH_4Cl (5 mL), and stirred for 5 min. The mixture was diluted with Et_2O (100 mL) and treated with $MgSO_4$ (1.7 g). The heterogeneous mixture was then filtered through a pad of Celite in a fritted glass funnel, and the residue was rinsed thoroughly with CH_2Cl_2. The filtrate was concentrated in vacuo and the crude residue was purified via flash column chromatography to give allylic alcohol **3** (1.2 g, 91%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (m, 4H), 7.16 (t, J = 7.2 Hz, 1H), 5.68-5.65 (m, 2H), 4.05 (d, J = 3.2 Hz, 2H), 2.94 (t, J = 7.6 Hz, 2H), 2.38-2.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 131.0, 129.9, 129.3, 128.9, 126.0, 63.2, 33.2, 31.9; R_f (hexane-EtOAc 2:1) = 0.38.

5-(Phenylthio)pent-2-enal (4)

To a –78 °C solution of oxalyl chloride (882 μL, 10.1 mmol.) in dry CH_2Cl_2 (20 mL) under argon was added DMSO (1.44 mL, 20.2 mmol.) dropwise via syringe. After stirring for 30 min at – 78 °C, a solution of **3** (1.16 g, 5.95 mmol) in CH_2Cl_2 (8 mL plus 2 mL rinse) was added dropwise via cannula. The solution was then stirred for 30 min at –78 °C, followed by the addition of triethylamine (4.64 mL, 33.3 mmol.). After stirring for 80 min at –78 °C, the reaction mixture was poured into a separatory funnel containing hexane (320 mL) and 1 M $NaHSO_4$ (80 mL). The hexane layer was washed with brine (80 mL), then the combined aqueous layers were extracted with hexane-CH_2Cl_2 (100:10 × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (hexane-Et_2O from 10:1 to 1:1) to give α,β-unsaturated aldehyde **4** (1.1 g, 98 %) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (d, J = 7.8 Hz, 1H), 7.35-7.25 (m, 4H), 7.21-7.16 (m, 1H), 6.79 (dt, J = 15.0, 6.0, 6.9 Hz, 1H), 6.10 (ddt, J = 15.6, 7.8, 1.5 Hz, 1H), 3.03 (t, J = 7.2 Hz, 2H), 2.60 (dq, J = 6.9, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 155.2, 135.2, 133.7, 129.8, 128.9, 126.5, 32.0, 31.8; R_f (hexane-EtOAc 2:1) = 0.67.

2,5-Diacetoxy-1,4-benzoquinone (6)

A solution of 2,5-dihydroxy-1,4-benzoquinone (5.0 g, 35.7 mmol) in acetic anhydride (80 mL) was heated at 95 °C for 5 h. After cooling the reaction mixture, the mixture was concentrated in vacuo, followed by washing the dark brown solid with Et_2O-pentane (1:1) several times. The product was dried thoroughly under vacuum overnight to give 2,5-

diacetoxy-1,4-benzoquinone (**6**) (7.7 g, 96%) as a dark brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 167.6, 152.6, 122.5, 20.7; R_f (hexane-Et_2O 1:1) = 0.39.

Phosphonium salt 7a/b

To a solution of triphenylphosphine (245 mg, 0.93 mmol) in benzene (3 mL) under argon was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (214 μL, 0.93 mmol) slowly. The reaction mixture in a test tube was treated with acrolein (70 μL, 0.93 mmol) dropwise. After stirring at 25 °C for 5 min, the reaction mixture was kept without stirring to form two layers. The upper layer was removed using pipette, the lower layer was concentrated in vacuo to give phosphonium salt (471 mg, 87%) as a white foam. The salt was the mixture of 1,4-addition and 1,2-addition in a 2.75 to 1 ratio. It was used in the following step without any purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.62 (m, 15H), 6.59 (dd, J = 11.6, 5.2 Hz, 1H), 4.75-4.67 (m, 1H), 4.12 (dd, J = 13.2, 7.6 Hz, 2H), 0.82 (s, 9H), 0.05 (s, 6H).

2,3-Dimethoxy-1,4-benzoquinone (9)

To a solution of 1,2,3-trimethoxybenzene (5.0 g, 29.7 mmol), $K_3Fe(CN)_6$ (1.2 g, 3.6 mmol) in acetic acid (30 mL) was added a solution of H_2O_2 (7.4 mL, 30% in water) at 25 °C. After stirring for 24 h, the reaction mixture was diluted with CH_2Cl_2 and was successively washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified via flash column chromatography to give 2,3-dimethoxy-1,4-benzoquinone (1.3 g, 27%) as a red solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 2H), 4.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1,

145.1, 134.7, 61.3; R_f (hexane-EtOAc 3:1) = 0.40.

Hexa-2,4-dien-1-ol (10)

To a 0 °C suspension of LAH (3.44 g, 90.6 mmol) in Et_2O (200 mL) was added a solution of 2,4-hexadienal (10 mL, 90.6 mmol) in Et_2O (50 mL) dropwise. After 1 h at 0 °C, the reaction mixture was quenched by the successive addition of H_2O (5 mL), 1N NaOH (5 mL), and H_2O (15 mL) at 0 °C. The heterogeneous mixture was filtered through Celite and rinsed with Et_2O. The filtrate was concentrated in vacuo to give allylic alcohol **10** (9.1 g, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22-6.16 (m, 1H), 6.09-6.02 (m, 1H), 5.73-5.65 (m, 2H), 4.12 (bs, 2H), 1.76 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 130.9, 130.1, 129.4, 63.4, 18.2; R_f (hexane-Et_2O 5:1) = 0.23.

Hexa-2,4-dienylsulfanyl-benzene (12)

To a 0 °C solution of alcohol **10** (500 mg, 5.09 mmol) and triethylamine (746 μL, 5.35 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (414 μL, 5.35 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with the addition of water,. The product was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo without heating the bath. The crude compound **11** (589 mg, 66%) was subjected to the next step directly.

To a 0 °C solution of thiophenol (312 μL, 3.04 mmol) in THF (3 mL) under argon was added with NaH (81 mg, 3.34 mmol). After 30 min at 0 °C, the reaction mixture was treated with a solution of compound **11** (589 mg, 3.34 mmol) in THF (3 mL plus 2 mL rinse). The reaction mixture was warmed to room temperature and stirred overnight. The reaction

mixture was concentrated in vacuo and then the crude residue was purified via flash column chromatography to give diene **12** (291 mg, 50%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.12 (m, 5H), 6.10-5.94 (m, 2H), 5.67-5.53 (m, 2H), 3.55 (d, J = 7.5 Hz, 2H), 1.71 (d, J = 7.5 Hz, 3H); R_f (hexane-Et_2O 15:1) = 0.72.

Diels-Alder adduct 13

A mixture of diene 12 (222 mg, 1.17 mmol) and 2,3-dimethoxy-1,4-benzoquinone (140 mg, 0.83 mmol) in THF (1.7 mL) was heated to reflux for 51 h. The reaction was cooled to room temperature and then concentrated in vacuo to give crude Diels-Alder adduct **13** (98% by ^{1}H NMR): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.14 (m, 5H), 5.70 (d, J = 9.6 Hz, 1H), 5.62-5.57 (m, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 3.60-3.54 (m, 1H), 3.41-3.34 (m, 2H), 3.13 (t, J = 7.2 Hz, 1H), 2.65 (bm, 1H), 2.48 (bm, 1H), 0.83 (d, J = 7.2 Hz, 3H).

Hexa-3,5-dienoic acid (18)

To a 0 °C solution of diisopropylamine (5.5 mL, 39.2 mmol) in THF (40 mL) was added *n*-BuLi (15.7 mL, 2.5 M in hexane, 39.2 mmol) via syringe. After 30 min at 0 °C, a solution of sorbic acid (2.0 g, 17.8 mmol) in THF (10 mL plus 1 mL rinse) was added dropwise via cannula. The reaction was warmed to room temperature and further stirred 1 h. The reaction was recooled to 0 °C and quenched by the rapid addition of 3N HCl (40 mL) and extracted with Et_2O (3 × 60 mL). The combined organic layers was washed with brine (2 × 60 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give deconjugated acid **18** in a quantitative yield. The acid **18** could be purified via flash column chromatography without any isomerization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (dt, J = 16.8, 10.2 Hz, 1H), 5.77 (dt, J

= 15.0, 7.2 Hz, 1H), 5.19 (d, J = 16.2 Hz, 1H), 5.09 (d, J = 9.3 Hz, 1H), 3.17 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 136.4, 135.1, 124.7, 117.6, 37.8; R_f(hexane-Et_2O 2:1) = 0.35.

Diene 19

To a stirred solution of 2-mercaptopyridine *N*-oxide (252 mg, 1.98 mmol) and DCC (417 mg, 2.02 mmol) in CH_2Cl_2 (5 mL) at 0 °C in the dark (aluminum foil) under argon was added a solution of 3,5-hexadienoic acid **18** (222 mg, 1.98 mmol) in CH_2Cl_2 (4 mL plus 1 mL rinse) via cannula. After 4 h at 0 °C, the resultant orange-yellow suspension was filtered through a short pad (*ca* 4 cm) of silica gel (prepacked with CH_2Cl_2) to remove insoluble 1,3-dicyclohexylurea and washed with CH_2Cl_2 (300 mL). The filtrate was concentrated at 25 °C to give the diene **19** (440 mg, 99 %) as a red oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (ddd, J = 8.8, 2.0, 0.8 Hz, 1H), 7.60 (ddd, J = 6.8, 1.6, 0.4 Hz, 1H), 7.21 (ddd, J = 15.6, 7.2, 1.6 Hz, 1H), 6.64 (dt, J = 7.2, 2.0 Hz, 1H), 6.41-6.26 (m, 2 H), 5.88-5.81 (m, 1 H), 5.24 (dd, J = 16.8, 2.0 Hz, 1H), 5.14 (dd, J = 10.4, 2.0 Hz, 1H), 3.55 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 167.1, 137.7, 137.3, 136.3, 135.9, 133.8, 112.5, 118.4, 112.9, 35.3.

Compound 20

A mixture of triethyl phosphite (9.1 mL, 52.3 mmol) and methyl 4-bromobut-2-enoate (6.4 mL, 43.6 mmol) was heated at 160 °C for 1.5 h. The excess triethyl phosphite was removed via vacuum distillation (100 °C, 2 mmHg). The residue was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92-6.87 (m, 1H), 5.97 (dd, J = 15.2, 4.8 Hz, 1H), 4.17-4.09 (m, 4H), 3.75 (s, 3H), 2.75 (ddd, J = 22.8, 8.0, 1.6 Hz, 2H),

1.33 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 138.1, 138.0, 125.6, 125.5, 62.5, 62.4, 51.8, 31.5, 30.2, 16.6, 16.5.

Compound 21

To a 0 °C suspension of NaH (1.18 g, 49.05 mmol; prewashed with pentane) in DMF (50 mL) under argon was added dropwise a solution of phosphonate **20** (10.53 g, 44.59 mmol) in DMF (20 mL plus 4 mL rinse). The reaction was stirred 10 min at 0 °C, and then warmed to 25 °C. After 1 h at 25 °C, the reaction mixture was treated with acetone (3.6 mL, 49.05 mmol) and further stirred 24 h at 25 °C. The reaction was quenched by the addition of 1 N HCl (90 mL), and then extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with H_2O (2 × 80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo at 25 °C. The residue was purified via flash column chromatography (hexane-Et_2O = 10:1) to give compound **21** (2.51 g, 40 %) as a rather volatile colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 15.2, 11.6 Hz, 1H), 5.99 (dd, J = 11.6, 0.8 Hz, 1H), 5.77 (d, J = 15.2 Hz, 1H), 3.74 (s, 3H), 1.90 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 146.7, 141.5, 123.9, 118.3, 51.6, 26.8, 19.2; R_f (hexane-Et_2O 5:1) = 0.54.

Compound 22

To a solution of ester **21** (503 mg, 3.58 mmol) in MeOH (9 mL) was added 10 % KOH (36 mL), then stirred 6 h at 25 °C (monitored the disappearance of ester using tlc). The reaction mixture was carefully acidified with 3N HCl (40 mL) at 0 °C, then extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give carboxylic acid **22** (428 mg, 95 %) as

a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 15.2, 11.6 Hz, 1H), 6.03 (d, J = 12.0 Hz, 1H), 5.77 (d, J = 15.2 Hz, 1H), 1.91 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 148.2, 143.5, 123.9, 117.9, 26.9, 19.3; R_f (hexane/ EtOAc 2:1) = 0.49.

Compound 23

To a 0 °C solution of diisopropylamine (868 μL, 6.19 mmol) in THF (5 mL) was added *n*-BuLi (2.47 mL, 2.5 M in hexane, 6.19 mmol) via syringe. After 30 min at 0 °C, a solution of acid **22** (355 mg, 2.81 mmol) in THF (3 mL plus 1 mL rinse) was added dropwise via cannula. The reaction was warmed to room temperature and further stirred 1 h. The reaction was recooled to 0 °C and quenched by the rapid addition of 3 N HCl (8 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexane-Et_2O = 10:1 to 3:1) to give the deconjugated acid **23** (308 mg, 87 %) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J = 15.6 Hz, 1H), 5.72 (dt, J = 15.6, 7.6 Hz, 1H), 4.98 (s, 1H), 4.96 (s, 1H), 3.20 (dd, J = 7.2, 1.2 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 141.5, 137.1, 120.9, 116.8, 38.0, 18.7; R_f (hexane-Et_2O 2:1) = 0.32; HRMS *m/e* (EI) for $C_7H_{10}O_2$ $(M)^+$ calcd 126.0681, measured 126.0600.

Compound 24

The same procedure for **19** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H), 7.24-7.19 (m, 1H), 6.66 (dt, J = 6.8, 2.0 Hz, 1H), 6.37 (d, J = 15.6 Hz, 1H), 5.79 (dt, J = 15.6, 7.2 Hz, 1H), 5.00 (d, J = 6.8 Hz, 2H), 3.56 (d, J = 7.2 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 167.2, 141.0,138.1, 137.7, 137.0, 133.8, 118.6, 117.3, 112.8,

35.3, 18.4.

Compound 25

To a mixture of methyl 2,5-dihydroxybenzoate (1.0 g, 5.95 mmol) , anhydrous $MgSO_4$ (2.1 g, 17.25 mmol), and Et_2O (20 mL) was added silver (I) oxide (4.7 g, 20.22 mmol) at 25 °C. After stirred 3 h at 25 °C, the heterogeneous mixture was filtered through a pad of Celite, rinsed with Et_2O. The filtrate was concentrate in vacuo to give 2-methoxycarbonyl-1,4-benzoquinone (888 mg, 90%) as an orange solid. This compound was used in the following steps without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 1.5 Hz, 1H), 6.85 (bs, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 183.1, 163.2, 137.04, 137.00, 136.6, 136.2, 53.2.

Compounds 26 and 27

A solution of diene **19** (474 mg, 2.14 mmol) and 2-methoxycarbonyl-1,4-benzoquinone **25** (391 mg, 2.35 mmol) in dry CH_2Cl_2 (10 mL) was placed in a flask protected from the light with aluminum foil at 25 °C. After stirred for 24 h at 25 °C, the solution was diluted with CH_2Cl_2 (10 mL) and degassed with argon for 10 min. The reaction mixture was subsequently exposed to light using a 275 W sunlamp from a distance of 15 cm, while maintaining the temperature at 0 °C. After 2 h at 0 °C, the reaction mixture was concentrated in vacuo and the crude residue was purified via flash column chromatography (hexane-Et_2O = 10:1 to 1:1) to give tricyclic diketone **27** (538 mg, 73 %) as a yellow foamy oil. Compound **26**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 6.6 Hz, 1H), 7.61 (dd, J = 9.0, 1.5 Hz, 1H), 7.30-7.24 (m, 1H), 6.84-6.70 (m, 2H), 6.60 (dd, J = 10.5, 1.2 Hz, 1H), 5.85-5.81 (m, 1H), 5.71-5.68 (m,

1H), 3.94-3.85 (m, 1H), 3.77 (s, 3H), 3.61 (dd, J = 9.3, 6.9 Hz, 1H), 3.35-3.20 (m, 2H), 2.27-2.40 (m, 1H), 2.24-2.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 193.6, 175.0, 170.2, 168.1, 140.1, 137.7, 137.4, 136.5, 133.9, 127.4, 123.6, 112.8, 61.3, 53.4, 50.2, 35.5, 32.7, 25.6. Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39-8.35 (m, 2H), 7.50 (bt, J = 7.8 Hz, 2H), 7.16 (dd, J = 11.4, 8.1 Hz, 2H), 7.06-6.99 (m, 2H), 5.85-5.78 (m, 2H), 5.58 (bdd, J = 10.2, 2.7 Hz, 2H), 5.29 (t, J = 2.1 Hz, 1H), 4.97 (d, J = 3.3 Hz, 1H), 3.76 (s, 6H), 3.32-3.24 (m, 3H), 3.13 (bd, J = 6.3 Hz, 1H), 3.07-3.04 (m, 1H), 2.93-2.92 (m, 1H), 2.69-2.67 (m, 1H), 2.62-2.60 (m, 1H), 2.51-2.27 (m, 4H), 1.95 (ddd, J = 13.8, 4.5, 1.5 Hz, 1H), 1.78 (btd, J = 13.8, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.92, 211.73, 205.73, 205.40, 169.10, 169.01, 155.04, 154.71, 149.68, 149.58, 136.76, 136.64, 129.83, 129.58, 124.79, 124.57, 123.09, 122.56, 120.94, 120.64, 61.75, 61.46, 52.80, 50.20, 50.14, 49.19, 49.13, 44.46, 44.20, 33.25, 31.65, 30.17, 29.48, 25.29, 25.27; R_f (hexane-EtOAc 2:1) = 0.45; HRMS *m/e* (EI) for $C_{18}H_{17}NO_4S$ $(M)^+$ calcd 343.0878, measured 343.0885.

Compound 28

A solution of tricyclic diketone **27** (158 mg, 0.46 mmol), AIBN (8.2 mg, 0.05 mmol) and *n*-Bu_3SnH (493 μL, 1.83 mmol) in dry benzene (8 mL) was degassed with Ar for 10 min at 25 °C and then heated at 80 °C for 24 h. The solution was concentrated to remove benzene and the residue was dissolved in CH_3CN (30 mL). The CH_3CN layer was washed with hexane (4 × 20 mL) to remove organotin by-products. The CH_3CN layer was concentrated and purified via flash column chromatography (hexane-Et_2O = 10:1 to 1:1) to give desulfurized product **28** (94 mg, 88 %) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.82 (m, 1H), 5.59 (dd, J = 9.6, 2 Hz, 1H), 3.79 (s, 3H), 3.24 (t, J = 9.2 Hz, 1H), 3.04 (d,

J = 6.0 Hz, 1H), 2.82 (bs, 1H), 2.68-2.54 (m, 3H), 2.35 (bd, J = 18.8 Hz, 1H), 2.14 (t, J = 12.8 Hz, 1H), 1.88 (bd, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 207.2, 169.4, 129.7, 124.5, 61.4, 52.7, 44.1, 43.5, 40.9, 30.3, 30.4, 25.3; R_f (hexane-EtOAc 2:1) = 0.36; HRMS *m/e* (EI) for $C_{13}H_{14}O_4$ $(M)^+$ calcd 234.0892, measured 234.0897.

Compound 29

The same procedure for **26** and **27** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43-8.41 (m, 1H), 8.39-8.37 (m, 1H), 7.55-7.50 (m, 2H), 7.22-7.19 (m, 1H), 7.18-7.16 (m, 1H), 7.09-7.03 (m, 2H), 5.90-5.84 (m, 2H), 5.63-5.58 (m, 2H), 5.29 (t, J = 2.4 Hz, 1H), 4.98 (d, J = 3.2 Hz, 1H), 3.30-3.19 (m, 4H), 3.09-3.06 (m, 1H), 2.96-2.94 (m, 1H), 2.68-2.66 (m, 1H), 2.63-2.61 (m, 2H), 2.57-2.39 (m, 3H), 2.25 (s, 3H), 2.24 (s, 3H), 1.99 (ddd, J = 13.6, 4.4, 1.6 Hz, 1H), 1.84-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.29, 212.10, 208.16, 207.71, 204.40, 204.12, 154.93, 154.57, 149.69, 149.58, 136.84, 136.71, 129.27, 129.04, 125.66, 125.55, 123.22, 122.60, 121.06, 120.72, 65.01, 64.75, 50.53, 50.26, 49.37, 49.07, 43.89, 43.63, 33.72, 31.81, 30.17, 29.99, 27.50, 27.35, 25.17, 25.13; R_f (hexane-EtOAc 2:1) = 0.22; HRMS *m/e* (EI) for $C_{18}H_{17}NO_3S$ $(M)^+$ calcd 327.0929, measured 327.0934.

Compound 30

The same procedure for **26** and **27** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) Major isomer δ 8.42-8.41 (m, 1H), 7.54-7.49 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.07-7.04 (m, 1H), 5.84-5.80 (m, 1H), 5.60 (dd, J = 9.6, 3.2 Hz, 1H), 5.13 (s, 1H), 3.773 (s, 3H), 3.30-3.24 (m, 2H), 2.73-2.67 (m, 1H), 2.43-2.29 (m, 2H), 1.79 (dd, J = 13.6, 1.6 Hz, 1H), 1.17 (s, 3H); Minor isomer δ 8.33-8.32 (m, 1H), 7.54-7.49 (m, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.04-7.02 (m,

1H), 5.84-5.80 (m, 1H), 5.60 (dd, J = 9.6, 3.2 Hz, 1H), 5.36 (d, J = 2.8 Hz, 1H), 3.778 (s, 3H), 3.18-3.16 (m, 2H), 2.73-2.67 (m, 1H), 2.43-2.29 (m, 2H), 1.50-1.45 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) Major δ 212.25, 205.68, 169.12, 154.72, 149.25, 136.79, 129.69, 124.92, 122.95, 121.00, 61.21, 52.92, 52.74, 49.75, 43.85, 40.79, 30.63, 25.64, 17.20; Minor δ 213.04, 205.98, 169.38, 155.36, 149.13, 136.66, 130.11. 124.55, 122.37, 120.64, 60.90, 54.08, 52.74, 50l.19, 44.16, 37.70, 31.10, 25.83, 17.36; R_f (hexane-Et_2O 2:1) = 0.15; HRMS *m/e* (EI) for $C_{19}H_{19}NO_4S$ $(M)^+$ calcd 357.1035, measured 357.1040.

Compound 31

The same procedure for **26** and **27** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.39 (m, 1H), 8.34-8.36 (m, 1H), 7.62-7.61 (m, 1H), 7.54-7.49 (m, 1H), 7.20 (td, J = 8.0, 0.8 Hz, 1H), 7.16 (td, J = 8.0, 0.8 Hz, 1H), 7.07-7.05 (m, 2H), 5.53 (bdt, J = 6.4, 1.6 Hz, 2H), 5.30 (t, J = 2.0 Hz, 1H), 4.98 (d, J = 3.6 Hz, 1H), 3.78 (bs, 6H), 3.28-3.24 (m, 3H), 3.14 (dt, J = 6.4, 2.0 Hz, 1H), 3.06 (m, 1H), 2.94-2.92 (m, 1H), 2.55 (bs, 1H), 2.51 (bs, 1H), 2.45 (ddd, J = 14.0, 10.4, 1.6 Hz, 1H), 2.38-2.25 (m, 3H), 1.95 (ddd, J = 14.0, 5.2, 2.0 Hz, 1H), 1.77 (bd, J = 15.6 Hz, 1H), 1.63 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.94, 211.75, 206.26, 205.98, 169.17, 169.08, 155.01, 154.68, 149.62, 149.53, 136.72, 136.60, 132.39, 132.19, 124.05, 123.02, 122.50, 120.89, 120.56, 61.73, 61.41, 53.73, 50.32, 50.11, 49.24, 49.15, 44.73, 44.49, 33.72, 31.92, 30.42, 29.99, 29.61, 23.13; R_f (hexane-EtOAc 2:1) = 0.49; HRMS *m/e* (EI) for $C_{19}H_{19}NO_4S$ $(M)^+$ calcd 357.1035, measured 357.1039.

Compound 32

The same procedure for **26** and **27** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.39

(m, 1H), 8.37-8.36 (m, 1H), 7.54-7.49 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.07-7.01 (m, 2H), 5.57 (bt, J = 5.2 Hz, 2H), 5.27 (t, J = 2.0 Hz, 1H), 4.97 (d, J = 3.2 Hz, 1H), 3.06-3.04 (m, 1H), 2.93-2.92 (m, 1H), 2.55-2.36 (m, 4H), 2.24 (s, 3H), 2.22 (s, 3H), 2.22-2.15 (m, 2H), 1.96 (ddd, J = 14.0, 4.8, 2.0 Hz, 1H), 1.81-1.76 (m, 1H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.14, 211.97, 208.50, 208.09, 204.52, 204.24, 154.89, 154.52, 149.53, 149.42, 136.68, 136.56, 133.37, 133.23, 123.42, 123.17, 123.00, 122.42, 120.87, 120.55, 64.84, 64.57, 50.38, 50.29, 49.25, 49.17, 44.05, 43.80, 34.16, 30.41, 29.46, 29.40, 27.45, 27.30, 22.98; R_f (hexane-EtOAc 2:1) = 0.38; HRMS *m/e* (EI) for $C_{19}H_{19}NO_3S$ $(M)^+$ calcd 341.1086, measured 341.1092.

Monoketal 1,4-benzoquinone (33)

To a 0 °C solution of PIFA (13.5 g, 31.4 mmol) in CH_2Cl_2 (180 mL) was added slowly a solution of *p*-methoxyphenol (3.0 g, 24.2 mmol) and ethylene glycol (2.23 g, 36.0 mmol) in CH_2Cl_2 (24 mL plus 4 mL rinse). After stirring 1 h at 0 °C, the reaction mixture was warmed to room temperature and further stirred for 4 h. The reaction was quenched by the addition of saturated aqueous Na_2CO_3 (100 mL) and the CH_2Cl_2 layer was decanted. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (hexane-Et_2O = 10:1 to 1:1) afforded monoketal benzoquinone (3.1 g, 83 %) as a pale yellow solid. The product could be further purified via recrystallization in Et_2O-hexane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 10.0 Hz, 2H), 6.18 (d, J = 10.0 H, 2H), 4.15 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 143.4, 129.1, 98.3, 66.0; R_f (hexane-EtOAc 2:1) = 0.36.

Diels-Alder Adduct 34

To a 0 °C solution of 1,4-benzoquinone monoketal **33** (331 mg, 2.18 mmol) in Et_2O (4 mL) was added $BF_3{\cdot}OEt_2$ (331 μL, 2.61 mmol) and stirred for 15 min at 0 °C. To the resulting yellow solution was added via cannula a solution of 3,5-hexadienoic acid **18** (269 mg, 2.40 mmol) in Et_2O (4 mL plus 1 mL rinse). After 3 h at 0 °C, the reaction was warmed room temperature and further stirred for 21 h. The reaction was quenched by the addition of H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude Diels-Alder adduct **34** (513 mg, 89 %) as a yellow oil. Diels-Alder adduct **34** was used in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (dd, J = 10.4, 2.4 Hz, 1H), 5.90 (d, J = 10.4 Hz, 1H), 5.58 (s, 2H), 4.12-3.93 (m, 5H), 3.33 (t, J = 3.6 Hz, 1H), 2.99 (d, J = 7.6 Hz, 2H), 2.814-2.806 (m, 1H), 2.57-2.51 (m, 1H), 2.29-2.24 (m, 1H), 2.02-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 179.3, 141.9, 130.3, 129.1, 125.3, 106.7, 65.4, 64.8, 47.0, 45.0, 36.9, 34.5, 24.6; R_f (hexane-EtOAc 2:1) = 0.16; HRMS *m/e* (EI) for $C_{14}H_{16}O_5$ $(M)^+$ calcd 264.0998, measured 264.0999.

Compound 35

To a 0 °C solution of 2-mercaptopyridine *N*-oxide (138 mg, 1.08 mmol) and DCC (228 mg, 1.10 mmol) in CH_2Cl_2 (3 mL) in the dark (aluminum foil) under Ar was added a solution of Diels-Alder adduct **34** (286 mg, 1.08 mmol) in CH_2Cl_2 (2 mL plus 1 mL rinse). After 4 h at 0 °C, the reaction was warmed room temperature and stirred further for 20 h. The resulting orange-yellow suspension was diluted with CH_2Cl_2-hexane (1:1, 15 mL) and then filtered through a pad of Celite (prepacked with CH_2Cl_2-hexane 1:1) to remove insoluble 1,3-

dicyclohexylurea and washed with CH_2Cl_2-hexane (1:1, 70 mL). The filtrate was concentrated at 25 °C to give crude Barton's ester (455 mg, 99 %) as a red oil. The compound **35** was used directly for the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dt, J = 8.8, 1.6 Hz, 2H), 7.22 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 6.66 (dt, J = 6.8, 1.6 Hz, 1H), 6.37 (dd, J = 10.0, 2.4 Hz, 1H), 5.91 (d, J = 10 Hz, 1H), 5.70-5.62 (m, 2H), 4.07-3.94 (m, 4H), 3.48 (t, J = 4.0 Hz, 1H), 3.42-3.28 (m, 2H), 3.04-3.03 (m, 1H), 2.59-2.53 (m, 1H), 2.31-2.25 (m, 1H) 2.04-1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 175.8, 168.6, 142.4, 137.9, 137.2, 133.8, 130.2, 128.4, 125.8, 112.8, 106.6, 65.5, 64.8, 46.6, 44.6, 34.6, 34.3, 24.6.

Compound 36

The above Barton's ester **35** (455 mg) was diluted with toluene (11 mL), then degassed with argon for 10 min; until this point, all flasks were protected from the light with aluminum foil. The reaction mixture was heated at 110 °C, while the flask was subsequently exposed to light using 275 W sunlamp from a distance of 15 cm. After 2 h at 110 °C, the reaction mixture was concentrated in vacuo to give 5:1 ratio of cyclized product to recombination product and a trace amount of bipyridyl compound (based on ^{1}H NMR), which was directly subjected to desulfurization (the same procedure for compound **28**) with AIBN/*n*-Bu_3SnH to yield the desulfurized compound of ketone **36** (90 mg, 38 %) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.85 (m, 1H), 5.72 (ddd, J = 9.6, 4.8, 2.0 Hz, 1H), 4.02-3.96 (m, 2H), 3.93-3.84 (m, 2H), 2.62 (bd, J = 18.4 Hz, 1H), 2.43-2.41 (m, 2H), 2.34 (t, J = 2.8 Hz, 1H), 2.22 (ddt, J = 18.0, 3.2, 1.6 Hz, 1H), 2.16-2.11 (m, 2H), 2.06-2.00 (m, 1H), 1.76 (dt, J = 6.4, 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 129.8, 125.0, 111.1, 66.2, 63.6, 49.9, 40.8, 38.7, 35.2, 29.0, 26.8, 24.8; R_f (CH_2Cl_2-EtOAc 10:1) = 0.57; HRMS *m/e* (EI) for

$C_{14}H_{20}O_3$ $(M)^+$ calcd 220.1099, measured 220.1103.

Compound 37

A solution of penta-1,4-dien-3-ol (**1**) (5.46 g, 64.98 mmol) and propionic acid (436 μl, 5.85 mmol) in triethyl orthoacetate (60 mL) was heated to reflux for 1 h (set oil bath 120 °C). The mixture was cooled and ethanol was removed by distillation [bp 68 °C (760 mmHg)]. The mixture was heated to reflux for 2 h, cooled and ethanol was again removed by distillation. 2,6-Di-*tert*-butyl-4-methylphenol (215 mg, 0.97 mmol) was added and triethyl orthoacetate was removed in vacuo [bp 45-50 °C (18 mmHg)]. The crude residue was purified via flash column chromatography to give compound **37** (6.64 g, 66%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (dt, J = 17.2, 10.2 Hz, 1H), 6.09 (ddd, J = 15.0, 10.8, 0.3 Hz, 1H), 5.74-5.64 (m, 1H), 5.11 (d, J = 16.8 Hz, 1H), 4.99 (bd, J = 10.8 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.41-2.40 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 137.0, 132.8, 132.1, 115.9, 60.5, 34.0, 28.0, 14.4; R_f (hexane-Et_2OAc 5:1) = 0.51.

Compound 38

A solution of ethyl-(*E,E*)-hepta-4,6-dienoate (**37**) (748 mg, 4.85 mmol) and KOH (1.22 g, 21.8 mmol) in dry MeOH (25 mL) was heated to reflux for 1.5 h. MeOH was removed in vacuo and the residue partitioned between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was separated, acidified to pH 3 with 3N aqueous hydrochloric acid (3 mL) and extracted into Et_2O. The extracts were washed with brine, dried over $MgSO_4$ and concentrated to give compound **38** (488 mg, 80 %) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (dt, J = 17.2, 10.0 Hz, 1H), 6.09 (dd, J = 15.2, 10.4 Hz, 1H), 5.68 (dt, J = 14.8,

6.8 Hz, 1H), 5.11 (d, J = 17.2 Hz, 1H), 4.99 (d, J = 10.4 H, 1H), 2.47-2.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 136.9, 132.3, 132.2, 115.9, 33.7, 27.5; R_f (hexane- Et_2O 2:1) = 0.08.

Compound 39

The same procedure for **19** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 6.30 (dt, J = 16.8, 10 Hz, 1H), 6.15 (dd, J = 14.8, 10.8 Hz, 1H), 5.75 (dt, J = 15.2, 6.4 Hz, 1H), 5.14 (d, J = 16.8 Hz, 1H), 5.02 (d, J = 10.0 Hz, 1H), 2.81 (t, J = 7.2 Hz, 2H), 2.57 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 167.9, 137.7, 136.6, 136.3, 133.7, 132.3, 131.0, 116.1, 112.6, 30.9, 26.8.

Compound 42

The same procedure for **27** and **28** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.76 (m, 1H), 5.60 (dt, J = 10.0, 3.6 Hz, 1H), 3.79 (s, 3H), 3.43 (d, J = 7.6 Hz, 1H), 3.19-3.14 (m, 1H), 3.02-3.01 (m, 1H), 2.97-2.91 (m, 2H), 2.76 (dd, J = 18.8, 3.6 Hz, 1H), 2.12-2.10 (m, 1H), 2.06-2.02 (m, 2H), 1.98-1.91 (m, 1H), 1.51-1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 205.9, 170.4, 128.9, 124.9, 61.8, 52.9, 48.9, 46.4, 45.9, 40.3, 32.7, 26.1, 21.7; R_f (hexane-EtOAc 2:1) = 0.43; HRMS *m/e* (EI) for $C_{14}H_{16}O_4(M)^+$ calcd 248.1049, measured 248.1051.

Preparation of 6-methylenecyclohex-2-en-1-one derivatives; General experimental procedure

To a 0 °C solution of Eschenmoser's salt (1.3 mmol) in CH_2Cl_2 (0.4 M solution) was added the silyl enol ether (1 mmol). After stirring for 24 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and 1N HCl (6 mL). After 10 min, a 2N solution of NaOH was slowly added to the aqueous phase (until pH 14). The aqueous phase was extracted with CH_2Cl_2 (4 × 10mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the amine compound **2**, which was dissolved in dry MeOH (1M solution). Methyl iodide (1.75 mmol) was added slowly with stirring at 0 °C. The resulting solution was warmed to 25 °C and stirred for 1 h to give the ammonium salt as a colorless white precipitate. After volatiles were removed under reduced pressure, the crude salt was dissolved with H_2O (10 mL) and Et_2O (10 mL). To a solution of salt was added $NaHCO_3$ (4.5 mmol) and the reaction was stirred vigorously for 2 h at 25 °C. The aqueous layer was extracted with Et_2O (3 × 20mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified via flash column chromatography (Hexane-Et_2O = 10:1 to 5:1) to give compound **3** as a colorless volatile oil.

Compound 43

The general procedure was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dt, J = 10.0, 4.0 Hz, 1H), 6.15 (d, J = 10.0 Hz, 1H), 5.96 (d, J = 1.2 Hz, 1H), 5.29 (d, J = 1.2 Hz, 1H), 2.75 (t, J = 6.4 Hz, 2H), 2.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 150.7, 142.9, 130.5, 120.1, 31.0, 26.4; R_f (hexane-Et_2O 2:1) = 0.35; HRMS *m/e* (EI) for C_7H_8O $(M)^+$ calcd 108.0575, measured 108.0577.

Compound 44

The general procedure was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (bs, 1H), 5.96 (d, J = 1.6 Hz, 1H), 5.27 (d, J = 1.2 Hz, 1H), 2.73 (tt, J = 6.4, 1.6 Hz, 2H), 2.38 (t, J = 6.0 Hz, 2H), 2.00 (d, J = 0.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 163.0, 142.3, 127.5, 119.1, 31.6, 31.0, 24.8; R_f (hexane-Et_2O 2:1) = 0.31; HRMS *m/e* (EI) for $C_8H_{10}O$ $(M)^+$ calcd 122.0732, measured 122.0773.

Compound 45

The general procedure was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (bs, 1H), 5.95 (s, 1H), 5.25 (d, J = 1.6 Hz, 1H), 2.71 (t, J = 6.4 Hz, 2H), 2.40 (dd, J = 4.4, 2 Hz, 2H), 1.85 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 145.8, 143.5, 136.9, 119.7, 31.7, 26.3, 16.4; R_f (hexane-Et_2O 2:1) = 0.62; HRMS *m/e* (EI) for $C_8H_{10}O$ $(M)^+$ calcd 122.0732, measured 122.0773.

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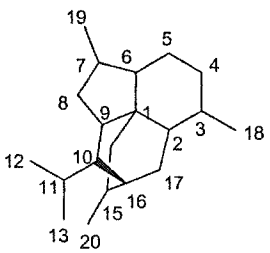
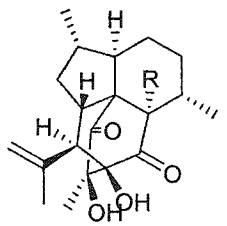
CHAPTER 3. SYNTHETIC STUDY TOWARDS CUMBIASIN A

Introduction

Cumbiasin A and other structurally related diterpenes were isolated from the hexane extract of the West Indian gorgonian *Pseudopterogorgia elisabethae* in 1996.[1] The structures of these marine metabolites were elucidated by extensive studies and showed unprecedented carbocyclic skeletons that contain a tetracyclic carbon frame named cumbiane. Cumbiasins A and B exhibit mild in vitro antituberculosis activity.



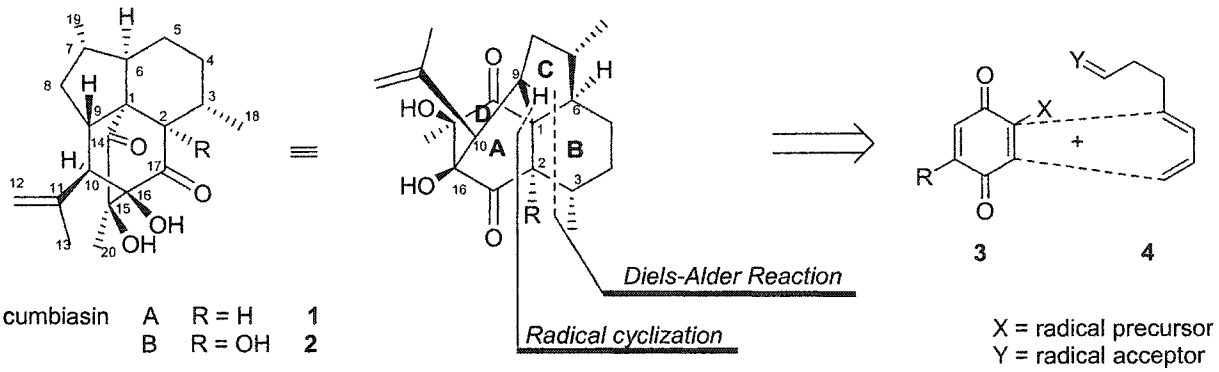


1 R = H cumbiasin A
2 R = OH cumbiasin B

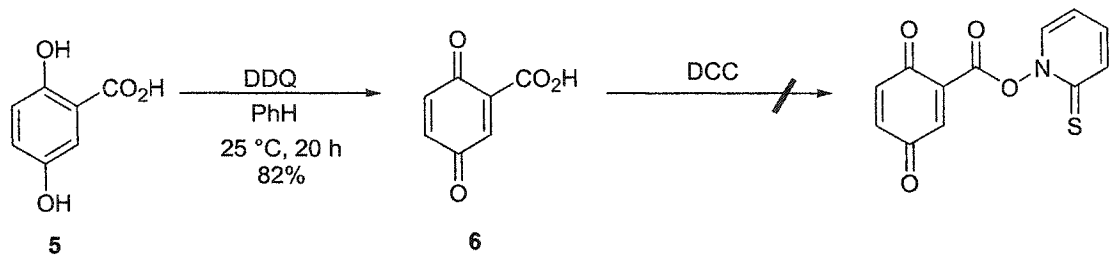
Despite their interesting biological activities, as well as their intriguing carbon framework, no synthetic approaches toward these targets have been reported. In the course of our effort to explore the Diels-Alder/Radical Cyclization strategy, cumbiasins A and B emerged as promising target molecules. With our strategy, the cumbiasin A skeleton could be accessible in a highly convergent and efficient manner. In this chapter, we discuss a direct approach to cumbiasin A via the Diels-Alder/Radical Cyclization strategy.

Results and Discussion

As illustrated in the retrosynthetic analysis, the skeletons of cumbiasin A would be accessible from benzoquinone **3** via intermolecular Diels-Alder reaction with diene **4**, followed by radical cyclization. The stereochemistry at C-1 in ring C is cis to C-6, which requires the inversion of the stereogenic center before the first 5-*exo*-trig cyclization. After the addition of radical to radical acceptor Y, the resulting radical could add to the enone part of the ring A system to form ring D simultaneously.



With our successful example in the tandem Diels-Alder/Radical Cyclization,[2] we decided to install a Barton ester in dienophile **3**. The precursor **3** for the Barton ester was prepared from 2,5-dihydroxybenzoic acid via DDQ oxidation at 25 °C in 82 % yield. Surprisingly, this compound **6** was not soluble in many organic solvents and subsequent treatment of the crude solution after oxidation gave only complicated results. Although generation of the radical using a Barton ester is convenient and mild, the preparation of the dienophile bearing a radical precursor had to be redesigned.



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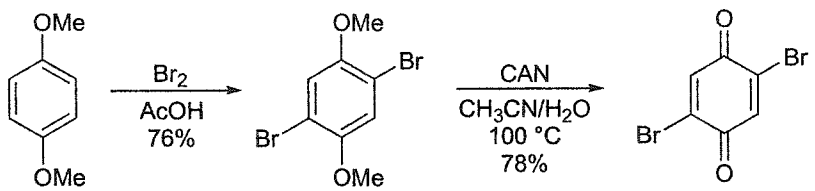
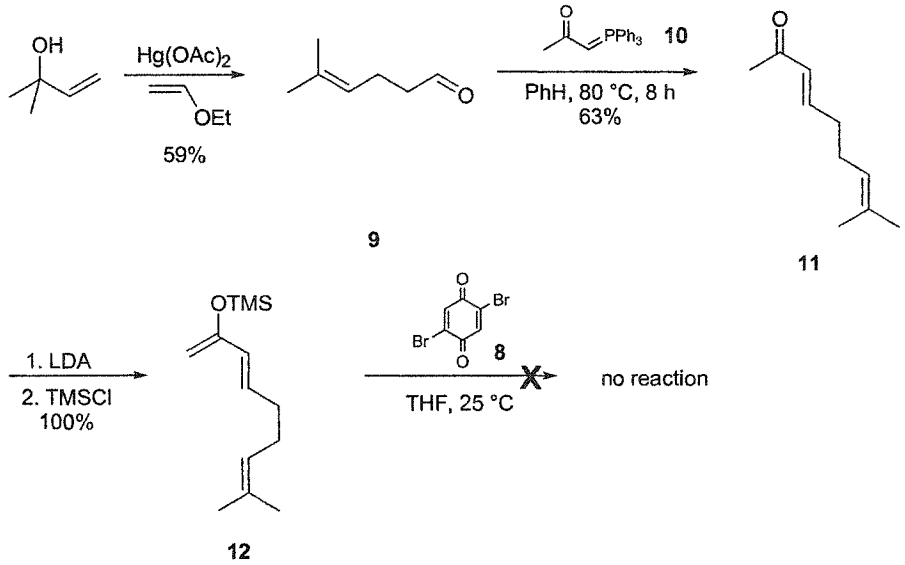
In the literature, Sha has developed the formation of the radical α to the carbonyl and used this strategy in the synthesis of (-)-pinguisenol and (-)-α-pinguisene.[3] Based on these previous results, we prepared 2,4-dibromo-1,4-benzoquinone by bromination of 1,4-dimethoxybenzene followed by oxidation using ceric ammonium nitrate.[4]

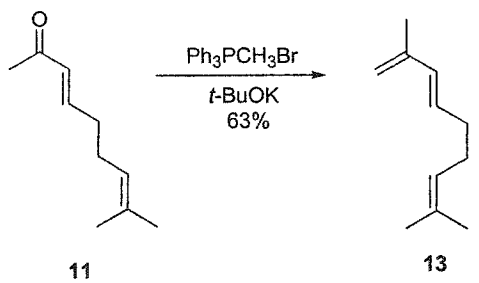


7 8

With 2,5-dibromo-1,4-benzoquinone in hand, we undertook the Diels-Alder reaction with diene **12**. Diene **12** was prepared from 2-methylbut-3-en-2-ol in 3 steps. Claisen rearrangement of 2-methylbut-3-en-2-ol at 140 °C for 7 h in a sealed tube gave the γ,δ-unsaturated aldehyde. Aldehyde **9** was then treated with ylide **10** in boiling benzene to afford enone **11** in 63% yield. Deprotonation of enone with LDA and treatment with TMSCl generated silyl enol ether **12**, which was directly subjected to the Diels-Alder reaction with dienophile **8** at 25 °C. Unfortunately, silyl enol ether **12** was too reactive to give the desired adduct even at room temperature.

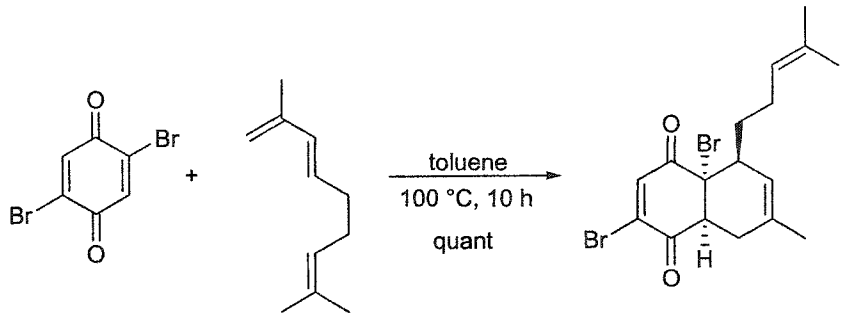


We then turned our attention to a more stable diene, which could tolerate the reaction conditions without decomposition. Compound **13**, our next diene, was prepared from enone **11**. Wittig reaction of enone **11** with methyltriphenylphosphonium bromide and potassium *tert*-butoxide at room temperature for 24 h afforded triene **13** in 63% yield. We conducted the crucial Diels-Alder reaction between diene **13** and dienophile **8**.



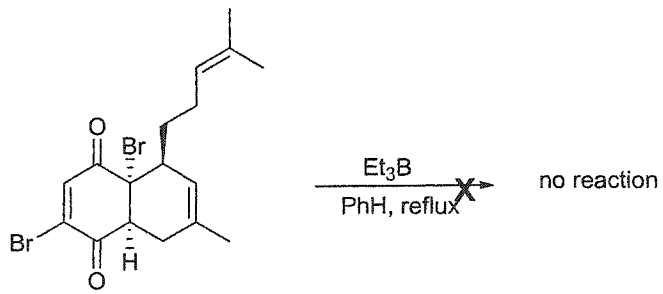
Although 2,5-dibromo-1,4-benzoquinone has been used as a dienophile, none of the examples gave the information about the regioselectivity. To our delight, the regioselectivity was controlled exclusively to give only one Diels-Alder adduct **14** in a quantitative yield. As we expected, the adduct **14** was not stable during chromatographic separation and a substantial amount (~20%) of product was aromatized via elimination and oxidation. This rather unstable Diels-Alder adduct was subjected to the radical cyclization step without

purification.



8 13 14

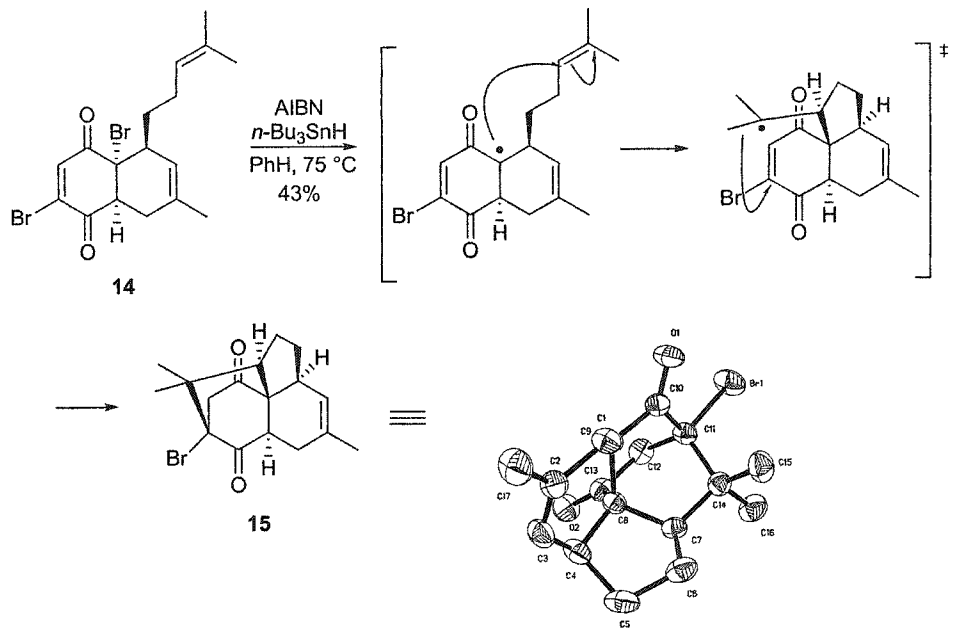
An atom transfer reaction has been utilized in radical chemistry.[5-7] Initiation of this process could occur thermally in the presence of AIBN,[8] BEt_3/O_2[9] or photochemically.[10] It would be beneficial if we could obtain more highly functionalized products. Based on the previous report, we conducted bromine atom transfer with Diels-Alder adduct **14** in the presence of catalytic amount of Et_3B in boiling benzene. However, we were unable to isolate any cyclized product from the reaction. Only the unreacted starting material was recovered after the reaction.



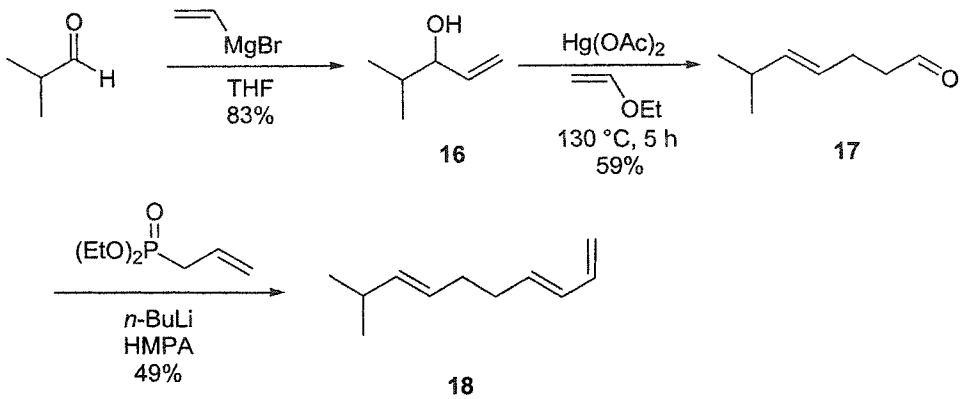
14

AIBN/*n*-Bu_3SnH conditions have been developed to generate a radical α to a ketone and used in the synthesis of various natural products.[3] In general, an α-iodo ketone was prepared as a precursor. When Diels-Alder adduct **14** was subjected to radical cyclization in benzene using AIBN/*n*-Bu_3SnH at 76 °C, it was smoothly cyclized in a 5-*exo*-trig fashion to form the

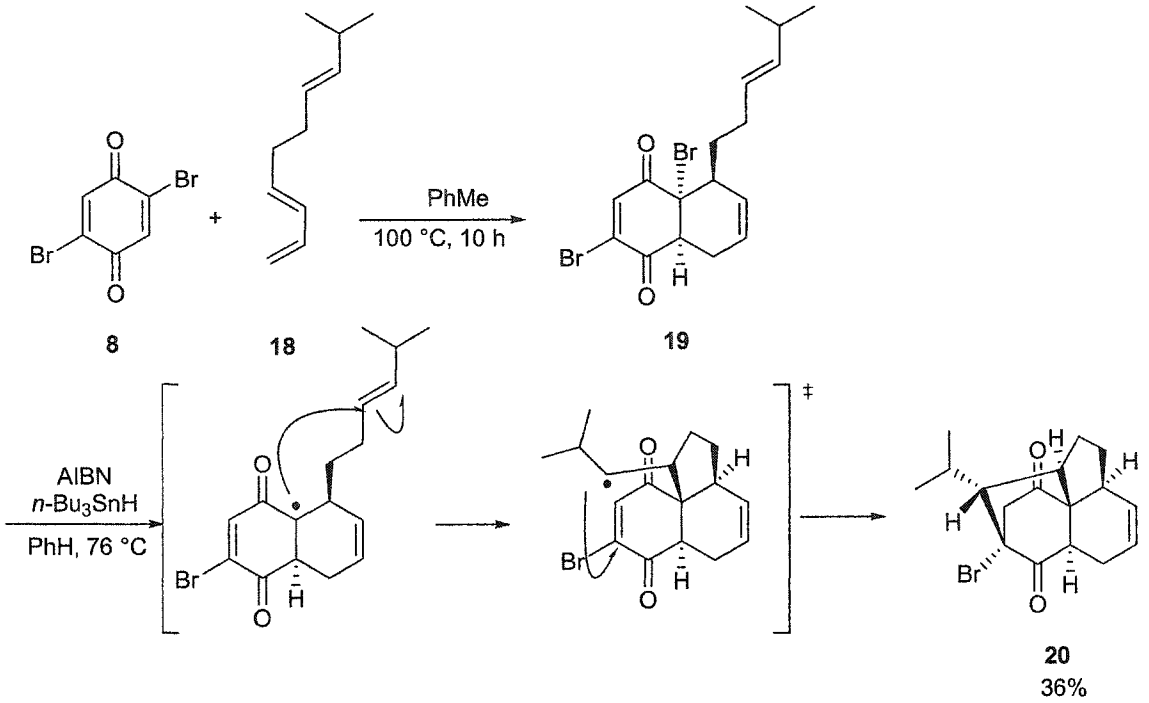
C ring and furthermore, the resulting intermediate was reacted with quinone moiety in ring A to construct ring D in the cumbiasins A skeleton. The stereochemistry of the cyclized product was unambiguously confirmed by x-ray crystallography. Indeed, the α-keto radical was inverted to form the cis ring juncture between rings B and C during this process.

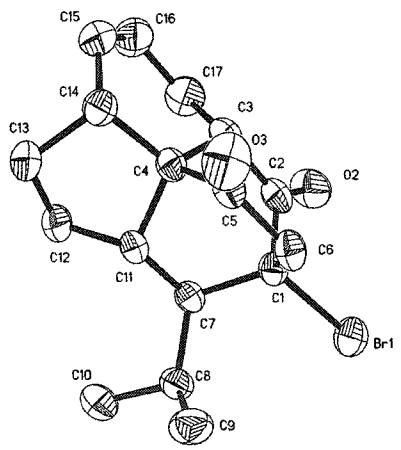


Encouraged by this fascinating result, we undertook the preparation of another diene bearing an isopropyl group. Diene **18** was obtained from isobutyraldehyde in 3 steps. Vinylmagnesium bromide addition to the aldehyde took place to provide allylic alcohol **16**. The alcohol **16** was subjected to Claisen rearrangement in the presence of freshly recrystallized $Hg(OAc)_2$ to provide γ,δ-unsaturated aldehyde **17** in 59% yield. The aldehyde **17** was converted into a terminal diene via Horner-Wadsworth-Emmons reaction with diethyl allylphosphonate in 49% yield.[11]



With diene **18** in hand, we performed the Diels-Alder /Radical Cyclization sequence in the same manner as for diene **13**. Treatment of diene **18** with 2,5-dibromo-1,4-benzoquinone in toluene at 100 °C for 10 h provided Diels-Alder adduct **19**. Subsequent radical cyclization of adduct **19** with AIBN/*n*-Bu_3SnH generated cyclized product **20** in 36% yield. The structure of compound **20** was confirmed by x-ray crystallography. The relative stereochemistry of six stereogenic centers was confirmed by x-ray crystallography. The ring c and b became cis ring juncture during the radical cyclization and the trans relationship of the isopropyl group was maintained to form ring A. However, the stereogenic centers at C-9 and C-10 were opposite to the ones in cumbiasin A. Clearly the conformation of the tether part of Diels-Alder adduct is crucial to control the resulting stereochemistry of radical cyclization step.





In conclusion, our Diels-Alder/Radical Cyclization strategy provided an efficient way to construct the carbon skeleton of cumbiasin A. During our synthetic approach, four carbon-carbon bonds and six stereogenic centers were formed in two steps. Currently we are investigating the total synthesis of cumbiasin A.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 A, 32-63 μm) was used for a flash column chromatography.

Compound 6

To a solution of 2.5-dihydroxybenzoic acid (200 mg, 1.30 mmol) in benzene (7 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (295 mg, 1.30 mmol) at room temperature under argon. The reaction mixture was stirred in the dark for 20 h at 25 °C. The heterogeneous mixture was filtered through a pad of Celite and washed with hexane. The filtrate was concentrated in vacuo to give compound **6** (160 mg, 81%) as a yellow solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 6.99 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 186.4, 169.8, 161.9, 141.4, 138.5, 136.3, 131.0, 127.5.

2,5-Dibromo-1,4-dimethoxybenzene (7)

To a solution of 1,4-dimethoxybenzene (10.78 g, 78.06 mmol) in acetic acid (22 mL) was

dropwise added Br_2 (8 mL, 156.12 mmol) in acetic acid (7 mL plus 2 mL rinse) at room temperature. After stirring for 2 h, the solution was cooled and the fine, white precipitate (17.61 g, 76%) of 2,5-dibromo-1,4-dimethoxybenzene was filtered and washed with water. The filtrate was diluted with water (20 mL) and extracted with $CHCl_3$, which was washed with 10% aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated, yielding an additional amount of product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 2H), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 117.3, 110.6, 57.2.

2,5-Dibromo-1,4-benzoquinone (8)

Compound **7** (15 g, 50.7 mmol) was dissolved in CH_3CN (150 mL) in an oil bath at 100 °C. A solution of ceric ammonium nitrate (75.0 g, 136.8 mmol) in water (300 mL) was added to the boiling CH_3CN solution. After completion of the addition, the reaction mixture was left to cool to room temperature with stirring over 30 min. The precipitate that formed was filtered and washed with water (50 mL), yielding 11.5 g (87% overall) of 2,5-dibromo-1,4-benzoquinone, as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 2H).

Compound 9

2-Methylbut-3-en-2-ol (4.85 mL, 46.4 mmol), ethyl vinyl ether (13.3 mL, 139.3 mmol), and freshly recrystallized $Hg(OAc)_2$ (2.96 g, 9.29 mmol) were heated in a sealed tube for 5 h at 130 °C (*extended reaction time will increase the amount of inseparable side product*). The reaction mixture was concentrated to remove volatiles and then purified via flash column chromatography (hexane: EtOAc = 50:1 to 30:1) to give rather volatile γ,δ-unsaturated aldehyde **9** (3.05 g, 59%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 1.5

Hz 1H), 5.12-5.09 (m, 1H), 2.50-2.32 (m, 4H), 1.61 (s, 3H), 1.56 (s, 3H) ; R_f(hexane-Et_2O 5:1) = 0.51.

Compound 11

To a solution of aldehyde **9** (1.87 g, 16.66 mmol) in benzene (40 mL) was added 1-triphenylphsphoranylidene-2-propanone (3.54 g, 11.10 mmol) at room temperature. The reaction mixture was boiled for 8 h. After cooling, the reaction mixture was concentrated to remove benzene and then the residue was washed with Et_2O. The triphenylphosphine oxide was filtered and the filtrate was concentrated in vacuo. The residue was purified via flash column chromatography to give the enone **11** (1.06 g, 63%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dt, J = 16.0, 6.4 Hz, 1H), 6.08 (d, J = 16.0 Hz, 1H), 5.10 (t, J = 6.8 Hz, 1H), 2.29-2.24 (m, 5H), 2.18-2.13 (m, 2H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 148.3, 133.1, 131.7, 122.9, 32.9, 27.0, 26.8, 25.9, 17.9; R_f(hexane-Et_2O 5:1) = 0.27.

Compound 12

To a 0 °C solution of diisopropylamine (426 μL, 3.04 mmol) in THF (7 mL) was added dropwise 1.22 mL of *n*-BuLi (2.5 M in hexanes, 3.04 mmol). After 30 min at 0 °C, the reaction mixture was cooled to –78 °C and treated dropwise with a solution of enone **11** (421 mg, 2.76 mmol) in THF (1 mL plus 1 mL rinse). The reaction was stirred for 30 min at –78 °C and quenched with the rapid addition of chlorotrimethylsilane (701 μL, 5.53 mmol). The reaction was warmed to room temperature and stirred further for 30 min. The reaction mixture was concentrated to remove volatiles and the residue was diluted with dry hexane (5

mL) and filtered. The filtrate was concentrated in vacuo to give silyl enol ether **12** (647 mg, 100%) as a pale yellow oil. The residue was used in the next step without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96-5.86 (m, 2H), 5.13-5.12 (m, 1H), 4.24 (bs, 2H), 2.14-2.08 (m, 4H), 1.69 (s, 3H), 1.61 (s, 3H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 132.1, 131.8, 127.9, 124.1, 94.4, 32.5, 27.9, 25.9, 17.9, 0.24.

Compound 13

To a suspension of Ph_3PCH_3Br (4.40 g, 12.3 mmol) in benzene (35 mL) was treated with *t*-BuOK (1.20 g, 10.7 mmol) at room temperature under argon and heated at 60 °C for 4 h, cooled to room temperature, and then a solution of enone **11** (1.25 g, 8.21 mmol) in benzene (5 mL plus 1 mL rinse). The mixture was stirred for 18 h at 25 °C and Ph_3PO was filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue was purified via flash column chromatography (silica gel: hexane-Et_2O 20:1) to give compound **13** (772 mg , 63%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, J = 15.6 Hz, 1H), 5.69 (dt, J = 15.6, 6.3 Hz, 1H), 5.19-5.14 (m, 1H), 4.89 (bs, 2H), 2.19-2.11 (m, 4H), 1.86 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 133.1, 132.0, 130.8, 124.1, 114.4, 33.2, 28.3, 25.9, 18.9, 17.9; R_f (hexane-Et_2O 5:1) = 0.88.

Compound 14

A mixture of diene **13** (156 mg, 1.04 mmol) and 2,5-dibromo-1,4-benzoquinone (260 mg, 0.99 mmol) in toluene (4.9 mL) was heated at 100 °C for 10 h. The reaction was cooled to room temperature and then concentrated in vacuo to give crude Diels-Alder adduct **14** (100% by ^{1}H NMR). The residue was used in the following step without purification: ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.13 (s, 1H), 5.39 (s, 1H), 5.09-5.07 (m, 1H), 3.78 (dd, J = 10.0, 7.2 Hz, 1H), 2.63-2.57 (m, 1H), 2.37-2.19 (m, 2H), 2.17-2.08 (m, 1H), 1.96-1.83 (m, 3H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 188.3, 139.6, 137.6, 132.8, 130.7, 123.6, 123.4, 68.5, 57.1, 46.3, 33.0, 31.2, 26.9, 25.9, 22.7, 18.0; R_f (hexane-Et_2O 2:1) = 0.61.

Compound 15

To a solution of Diels-Alder adduct **14** above in degassed benzene (24 mL) was added a solution of AIBN (16.2 mg, 0.10 mmol) and *n*-Bu_3SnH (330 μL, 1.25 mmol) in degassed benzene (8 mL) with a syringe pump during for 2 h at 76 °C. The reaction mixture was heated at reflux further 2 h and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and then the residue was dissolved in Et_2O (5 mL) and saturated aqueous KF (5 mL). The mixture was stirred for 12 h at 25 °C. The heterogeneous mixture was filtered through a sintered glass funnel and rinsed with CH_2Cl_2. The filtrate was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give cyclized product **15** (145 mg, 43%) as a white solid. The product was recrystallized in CH_2Cl_2-hexane: ^1H NMR (400 MHz, $CDCl_3$) δ 5.56-5.51 (m, 1H), 3.44 (d, J = 19.2 Hz, 1H), 3.25 (bt, J = 7.6 Hz, 1H), 2.90 (d, J = 19.2 Hz, 1H), 2.55 (dd, J = 16.0, 5.6 Hz, 1H), 2.36 (dd, J = 11.6, 5.6 Hz, 1H), 2.21-2.14 (m, 1H), 1.99 (dd, J = 13.6, 5.6 Hz, 1H), 1.86-1.81 (m, 1H), 1.80-1.68 (m, 4H), 1.65-1.59 (m, 1H), 1.43-1.33 (m, 1H), 1.27 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 204.0, 131.2, 127.3, 78.5, 55.8, 55.0, 46.8, 45.1, 39.8, 36.4, 32.5, 31.1, 29.1, 27.6, 23.7, 22.6; R_f (hexane-Et_2O 5:1) = 0.36; HRMS *m/e* (EI) for $C_{17}H_{21}BrO_2$ $(M)^+$ calcd 336.0745, measured 336.0732.

Compound 16

To a 0 °C solution of vinylmagnesium bromide (120 mL, 1 M in THF, 120 mmol) was added a solution of isobutyraldehyde (10.4 mL, 114.3 mmol) in THF (30 mL). The reaction mixture was warmed room temperature and stirred for overnight. The reaction was quenched by the addition of saturated NH_4Cl (50 mL) and extracted with Et_2O (200 mL). The organic layer was washed with water (50 mL), brine (50 mL) and dried over $MgSO_4$, filtered, concentrated in vacuo. The residue was distilled (120 °C, 760 mmHg) to give alcohol **16** (9.43 g, 82%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.2, 10.4, 6.4 Hz, 1H), 5.25 (bd, J = 17.2 Hz, 1H), 5.17 (bd, J = 10.4 Hz, 1H), 3.87 (t, J = 6.0 Hz, 1H), 1.77-1.72 (m, 1H), 1.48 (s, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 115.8, 78.5, 33.8, 18.4, 18.0; R_f (hexane-Et_2O 5:1) = 0.25.

Compound 17

Allylic alcohol **16** (1.06 g, 10.53 mmol), freshly distilled ethyl vinyl ether (3 mL, 31.60 mmol), and freshly recrystallized $Hg(OAc)_2$ (671 mg, 2.11 mmol) were heated in a sealed tube for 5 h at 130 °C under argon. The reaction mixture was concentrated to remove volatiles and then directly purified via flash column chromatography to give rather volatile γ,δ-unsaturated aldehyde **17** (782 mg, 59%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 2.0 Hz, 1H), 5.49-5.33 (m, 2H), 2.53-2.47 (m, 2H), 2.37-2.30 (m, 2H), 2.27-2.20 (m, 1H), 0.96 (d, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 139.3, 124.8, 43.8, 31.2, 25.4, 22.7; R_f (hexane-Et_2O 5:1) = 0.53.

Compound 18

To a –78 °C solution of diethyl allylphosphonate (428 μL, 2.45 mmol) in THF (7 mL) was added dropwise *n*-BuLi (981 μL, 2.5 M in hexanes, 2.45 mmol). After stirring for 15 min, a solution of the aldehyde **17** (258 mg, 2.04 mmol) in HMPA (854 μL, 4.91 mmol plus 1 mL THF rinse) was added dropwise via cannula. The resulting solution was stirred for 2 h at –78 °C, and then allowed to warm to 25 °C. After 12 h at 25 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give diene **18** (147.4 mg, 49%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (dt, J = 16.8, 10.2 Hz, 1H), 6.07 (dd, J = 15.3, 10.5 Hz, 1H), 5.71 (dt, J = 15.0, 6.3 Hz, 1H), 5.40-5.36 (m, 2H), 5.13-5.07 (m, 1H), 4.97-4.95 (m, 1H), 2.27-2.19 (m, 1H), 2.16-2.04 (m, 4H), 0.97 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 137.5, 135.1, 131.3, 126.4, 115.0, 32.9, 32.4, 31.2, 22.9; R_f (hexane-Et_2O 5:1) = 0.93.

Compound 19

The same procedure for **14** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 5.66-5.59 (m, 2H), 5.38 (dd, J = 15.2, 3.6 Hz, 1H), 5.31-5.25 (m, 1H), 3.76 (dd, J = 9.6, 7.6 Hz, 1H), 2.64 (bs, 1H), 2.49-2.44 (m, 1H), 2.35-2.29 (m, 1H), 2.22-2.15 (m, 2H), 1.93-1.84 (m, 3H), 0.91 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 188.2, 139.2, 137.6, 128.8, 125.6, 122.9, 68.3, 56.7, 45.7, 31.3, 31.1, 30.5, 28.7, 22.8, 22.7; R_f (hexane-Et_2O 2:1) = 0.63.

Compound 20

The same procedure for **15** was applied: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.79 (m, 2H), 3.50 (d, J = 19.6 Hz, 1H), 3.26 (bt, J = 7.2 Hz, 1H), 2.85 (d, J = 19.6 Hz, 1H), 2.74 (dt, J = 16.8, 5.6 Hz, 1H), 2.58-2.54 (m, 1H), 2.34 (dd, J = 12.0, 5.2 Hz, 1H), 2.24-2.15 (m, 2H), 2.12-2.04 (m, 1H), 2.01-1.93 (m, 1H), 1.90-1.84 (m, 1H), 1.67 (dd, J = 17.6, 5.2 Hz, 1H), 1.42-1.32 (m, 1H), 1.04 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 202.8, 133.9, 123.5, 72.2, 57.9, 48.4, 47.0, 45.7, 44.8, 36.7, 32.3, 32.1, 31.7, 27.2, 23.0, 16.8; R_f (hexane-Et_2O 5:1) = 0.36; HRMS *m/e* (EI) for $C_{17}H_{21}BrO_2$ $(M)^+$ calcd 336.0745, measured 336.0731.

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GENERAL CONCLUSIONS

In this dissertation, we have investigated direct and concise strategies for natural products.

Chapter 1 describes the efficient method for the preparation of 5-substituted naphthoquinones. Synthetically valuable 5-substituted naphthoquinones were prepared in 4 steps from commercially available starting material involving remote metalation strategy as a key step. This new method was applied to a biologically active perylene analog.

Chapter 2 describes the new tandem strategy to construct the bridged tricyclic system via Diels-Alder/Radical Cyclization process. During this tandem process, we found the unusual preference for 6-*endo*-trig over 5-*exo*-trig in the radical cyclization step. In addition, we developed a concise preparation of α-methylene cyclohexenones, which would be useful to construct spirocyclic systems.

Chapter 3 describes the application of our Diels-Alder/Radical Cyclization strategy to construct the carbon skeleton of cumbiasin A. During our synthetic approach, four carbon-carbon bonds and six stereogenic centers were formed in two steps.

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