Transition-Metal-Catalyzed Oxidations. 11.[1] Total Synthesis of (±)-Lacinilene C Methyl Ether by β-Naphthol to α-Ketol Oxidation

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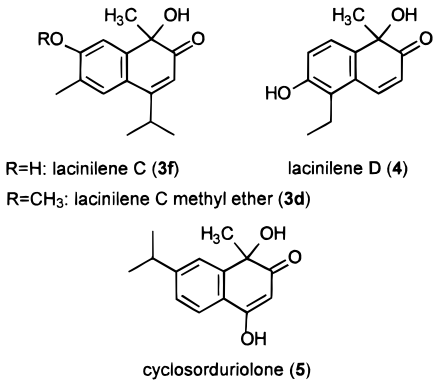
Introduction

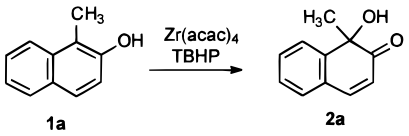
The lacinilenes belong to a group of phytoalexines produced by the cotton plant *Gossypium hirsutum* upon infection with bacteria such as *Xanthomonas campestris* or *malvacearum*.[2] The growth of the bacteria is stopped by this cocktail of different phytoalexins. The goal of the present study was to test the convenient naphthol to ketol oxidation previously discovered by our group[3] in the synthesis of lacinilene C methyl ether (**3d**) and to make related compounds available for biological testing. The 1,4-additions to ketols of type **2** with organometallic reagents was also investigated in a broader context since relatively little is known about the reactivity of α,β-unsaturated ketols with these reagents.[4] The six-membered α-ketol structural element, now easily accessible by our oxidation method,[3,5] is also present in a number of other interesting natural products such as in the anthracyclinones aranciamycinone[6] and steffimycinone[7] or the more closely related targets lacinilene C (**3f**)[8,9] and its methyl ether **3d**,[9,10] lacinilene D (**4**),[11] and cyclosorduriolone (**5**)[12] (Chart 1).

The interesting biological properties of the lacinilenes have promoted the interest of synthetic chemists, and two syntheses of **3d** are known relying essentially on Friedel−Crafts chemistry to construct the highly functionalized bicyclic system. De Pascual Terera et al.[13] transformed carvone to the substituted 2-naphthol **23d,** which can be oxidized to **3d** by phenylselenic acid anhydride (Barton reagent).[14] Key steps in the synthesis of McCormick et al. were the oxidation of a dihydronaphthalene with osmium tetroxide followed by DDQ-mediated desaturation of a saturated ketol of type **17**[15] (vide infra, Scheme 3).

Chart 1



Scheme 1



In our synthetic plans we anticipated the oxidation of simple 2-naphthols **1** to the ketols **2** (Scheme 1) followed by conjugate addition of cuprates to yield the alkylated systems of type **17** followed by DDQ desaturation. Previously,[3] we employed *tert*-butyl hydroperoxide (TBHP) in the presence of titanium or zirconium alkoxides or the Mimoun molybdenum oxodiperoxo complex.[16] $Zr(acac)_4$ was used as the catalyst in the present study because it was less moisture sensitive and the yields of the oxidation step of **1** to **2** were generally higher (80−90%).

Results and Discussion

A series of differently substituted 1-methyl-2-naphthols **1a**−**e** were prepared as outlined in Scheme 2 to test the generality of the oxidation and the metallo-organic reactions (α-tetralone **10b** and β-tetralone **13a** are commercially available). Conventional tetralone synthesis using Friedel−Crafts chemistry starting from **6c**−**e** and succinic anhydride **7** via the keto acids **8c**−**e**[17] and the phenylbutyric acids **9c**−**e**[17] afforded the 1-tetralones **10c**−**e**. The 1-tetralones **10c**−**e** were converted to the corresponding 1-methyl-2-tetralones **13a**−**e** by a sequence of reactions involving methylmagnesium iodide addition to the tertiary alcohols **11a**−**e** (not isolated), acid-catalyzed water elimination to the olefins **12a**−**e**, oxidation of the olefins **12a**−**e** to *cis*-diols, and treatment with hydrochloric acid. Thermal dehydrogenation by heating of the 2-tetralons **13a**−**e** with palladium on charcoal then afforded the required substituted 1-methyl-2-naphthols **1a**−**e**. Oxygenation of the 2-naphthols with

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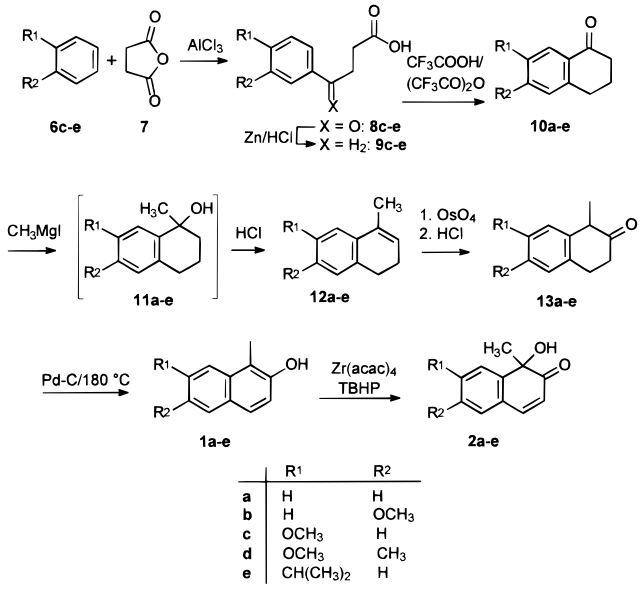
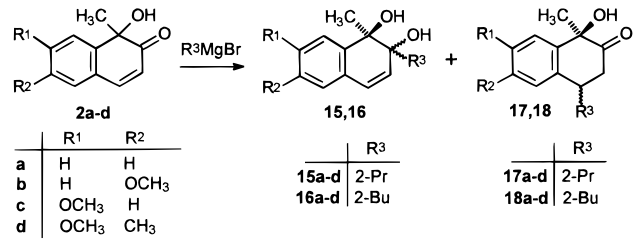
Scheme 2



	R1	R2
a	H	H
b	H	OCH_3
c	OCH_3	H
d	OCH_3	CH_3
e	$CH(CH_3)_2$	H

Scheme 3



	R1	R2
a	H	H
b	H	OCH_3
c	OCH_3	H
d	OCH_3	CH_3

	R3
15a-d	2-Pr
16a-d	2-Bu

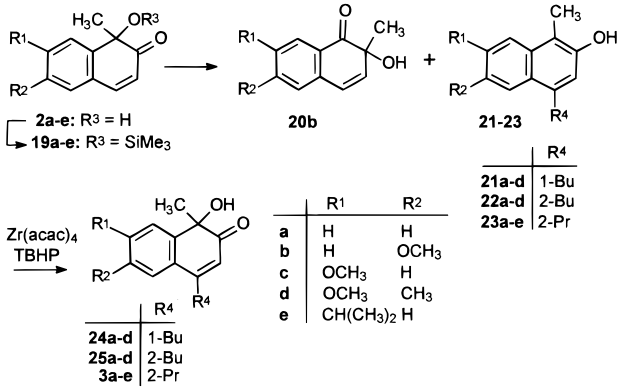
	R3
17a-d	2-Pr
18a-d	2-Bu

TBHP using the stable zirconium tetraacetylacetate as the catalyst produced the key intermediates **2a**−**e** in 75−90% yield within 12−15 h of reaction time.

We first tested the reaction of **2a**−**d** with the Grignard reagents derived from 2-bromopropane and 2-bromobutane to evaluate the reactivity of the ketols with organometallic reagents particularly with respect to the 1,2- or 1,4-addition mode. Not unexpectedly, a mixture of the 1,2- and 1,4-addition products **15/16** and **17/18** in a ratio of ca. 1:1.1 (by ^{1}H NMR) was formed. Both product families were mixtures of stereoisomers. (The isomers originating from the exocyclic stereogenic center formed by the addition of the 2-butyl anion were not separated.) The *trans*-diols from **15/16** (identified by their failure to form cyclic boronic esters) predominated (ca. 2.5:1). Neither isomeric pair was separated since the diols were not the compounds of interest, and the stereogenic center at C-4 of **17**/**18** was destroyed in the subsequent dehydrogenation step leading to lacinilene C methyl ether (**3d**). Thus, a first synthesis of the racemic natural product **3d** was achieved by DDQ dehydrogenation of **17d** according to the method of McCormick et al.[15] However, before extending the procedure to the analogues, we investigated the addition of cuprates to avoid the 1,2-addition and improve the yields of the conjugate addition products to the α,*β*-unsaturated ketol systems.

Surprisingly, the unsaturated ketol **2b** did not react with the cuprate derived from *n*-butyllithium and CuBr. To increase the reactivity of **2b**, 1 equiv of boron trifluoride etherate was added prior to the reaction with the cuprate as suggested by House and Lee.[18] However, only mixtures of the rearranged ketol **20b** (ca. 40%), the starting naphthol **2b** (ca. 40%), and the alkylated naphthol **21b** (ca. 20%) were isolated. The relatively easy rearrangement of these "allylic" ketols was known from our previous investigations.[3] Also, in addition to the Lewis acid-catalyzed dehydration, a reduction of the α-ketol system by the organometallic reagent had occurred. To prevent the rearrangement, the α-ketols **2a**−**e** were converted to the corresponding silyl ethers **19a**−**e** prior to the Lewis acid-mediated cuprate addition. After some experimentation, it was found that the "higher-order" cuprates, prepared according to the method of Lipshutz et al.[19] by addition of copper(I) cyanide to the lithium compounds, gave better yields of the alkylation products. The addition of boron trifluoride etherate was also required under these conditions and the adducts **21a**−**d**, **22a**−**d**, and **23a**−**e** were isolated in 56−66% yields in addition to smaller amouts of the starting 2-naphthols **1a**−**e** (27−37%). The less polar alkylation products were easily separated from the 2-naphthols **1a**−**e** and no rearrangement to ketols of type **20** was observed under these conditions. It is worth noting that these conditions induced aromatization of the α-ketols **2** and that the overall process allows the alkylation of 2-naphthols in the meta-position to the hydroxy group in contrast to traditional Friedel−Crafts type chemistry. In addition, the mild conditions of this nucleophilic cuprate addition are compatible with many functional groups.

Scheme 4



	R1	R2
a	H	H
b	H	OCH_3
c	OCH_3	H
d	OCH_3	CH_3
e	$CH(CH_3)_2$	H

	R4
21a-d	1-Bu
22a-d	2-Bu
23a-e	2-Pr

	R4
24a-d	1-Bu
25a-d	2-Bu
3a-e	2-Pr

The final step in the synthesis of the racemic natural product lacinilene C methyl ether (**3d**) and the analogues required a second oxygenation step of the naphthols **21a**−**d**, **22a**−**d**, and **23a**−**e** (Scheme 4). This was performed using the same $Zr(acac)_4$/TBHP system as described for the oxygenation of the starting 2-naphthols **1a**−**e** to afford the 4-alkylated α-ketols **24a**−**d**, **25a**−**d**, and **3a**−**e** in 67−74% yield.

Experimental Section

For instumentation and general methods see ref 21. The 1-tetralones were prepared according to the procedure of Zubaida et al.[17] The assignment in the NMR spectra was based on DEPT and two-dimensional techniques.

General Procedure I for the Conversion of the 1-Tetralones 10a−e to the 2-Naphthols 1a−e. A solution of the 1-tetralones **10b**−**e** (0.1 mol) in dry diethyl ether (150 mL) was treated portionwise under nitrogen at 20 °C with a 1 M solution

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(250 mL) of methylmagnesium iodide in dry diethyl ether, and the mixture was refluxed for 4 h. The cold solution was then hydrolyzed by the addition of saturated aqueous ammonium chloride (400 mL). The phases were separated, the aqueous phase was extracted twice with diethyl ether (200 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was redissolved in dichloromethane and stirred vigorously for 30 min with 10% hydrochloric acid. Usual workup and bulb to bulb distillation afforded the 4-methyl-1,2-dihydronaphthalenes (ca. 90%).

A solution of the olefins **12a**−**e** (ca. 90 mmol) and *N*-methylmorpholine *N*-oxide (14.9 g, 108 mmol) in acetone (100 mL) was then treated with a solution of osmium tetroxide in *tert*-butyl alcohol (4.5 mL, 0.2 mmol/L), and the mixture was stirred for 2 d. Sodium dithionite (9.5 g, 54 mmol) and Florisil (4.5 g) were added, and the suspension was stirred for 1 h, filtered, diluted with water (450 mL), and extracted twice with dichloromethane (100 mL). The combined organic phases were vigorously stirred with 6 N hydrochloric acid, and the organic phase was separated, dried ($MgSO_4$), evaporated to dryness under reduced pressure, and distilled by bulb to bulb distillation to yield the 2-tetralones **13b**−**e** (ca. 75%).

The tetralones **13a**−**e** (**13a** is commercially available) were mixed with palladium on charcoal (10%, 2.5 g) and refluxed in dry mesitylene (25 mL) under nitrogen for 3 h. The hot solution was filtered and rinsed with hot mesitylene (120 mL). The bulk part of the 2-naphthol crystallized from the cold mesitylene solution. A second crop was obtained from chromatography of the mother liquor on silica gel to yield ca. 50−70% (based on the 1-tetralones) of the 2-naphthols **1a**−**e**.

General Procedure II for the Oxygenation of the 2-Naphthols 1a−e to the α-Ketols 2a−e. A solution of the 2-naphthols **1a**−**e** (10 mmol) in dry dichloromethane (10 mL) was treated with $Zr(acac)_4$ (1 mmol) and powdered activated molecular sieves (0.3 nm, 0.5 g), and the mixture was stirred for 30 min. A solution of *tert*-butyl hydroperoxide (TBHP) (22 mmol) in dry dichloromethane (25 mL) was then added, and the suspension was stirred for 12−15 h at 20 °C (TLC control). Sulfuric acid (10 mL, 10%) was then added under stirring (30 min). The mixture was filtered, water (100 mL) was added, the organic phase was separated, and the aqueous phase was extracted twice with dichloromethane (100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness under reduced pressure, and the crude products were purified by crystallization (yields 75−90%).

General Procedure III for the Silylation of the α-Ketols 2a−e to the Silyl Ethers 19a−e. A solution of the α-ketols **2a**−**e** (10 mmol) in dry dichloromethane (50 mL) and pyridine (0.85 mL, 11 mmol) was treated with trimethylsilyl chloride (TMSCl) (1.6 mL, 12.5 mmol), and the mixture was stirred for 18 h at 20 °C. The solution was diluted by addition of *n*-pentane (200 mL), the pyridinium hydrochloride was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The crude silyl ethers **19a**−**e** were purified by bulb to bulb distillation (yield >95%).

General Procedure IV for the Reaction of the α-Ketols 2a−e with Grignard Reagents. The solution of the ca. 1 M Grignard reagents were prepared from magnesium turnings (2.4 g, 0.1 mmol) and 2-bromopropane or 2-bromobutane (0.1 mmol) in dry diethyl ether (10 mL) and dilution to 100 mL. A solution of the ketols **2a**−**d** (1 mmol) in dry diethyl ether (15 mL) was then treated portionwise with the Grignard solution (2.5 mL) and the mixtures were refluxed for 4 h. Alternatively, the mixtures were stirred for 8 h at 20 °C. The mixtures were then hydrolyzed by addition of aqueous ammonium chloride (10 mL), the organic phase was separated, and the aqueous phase extracted with diethyl ether (15 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The mixtures were separated by thin-layer chromatography.

General Procedure V for the Reaction of the Silyl Ethers 19a−e with Cuprates. A suspension of copper(I) cyanide (358 mg, 4.0 mmol) in THF (3 mL) and diethyl ether (3 mL) was treated under argon at −50 °C with a solution of the alkyllithium (8 mmol). The solution was cooled to −78 °C, and boron trifluoride etherate (0.5 mL) and the silyl ethers **19a**−**e** (1 mmol) were added. The mixture was allowed to warm to 20 °C within 8 h and was then hydrolyzed by addition of saturated aqueous ammonium chloride (10 mL). The organic phase was separated, the aqueous phase extracted twice with diethyl ether, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was separated by column or preparative thin-layer chromatography on silica gel.

7-Methoxy-1,6-dimethylnaphthalene-2-ol (1d) was prepared from **13d** (19.0 g, 0.1 mol) according to the general procedure I: yield 11.1 g (55%); mp 170 °C; IR (KBr) ν 3250, 3005, 2956, 2912, 2842, 1874, 1770, 1645, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3/CD_3OD$ 1:0.01) δ 2.33 (s, 3 H, 1-CH_3), 2.48 (s, 3 H, 6-CH_3), 2.85 (s, 1 H, 2-OH), 3.95 (s, 3 H, OCH_3), 6.87 (d, J = 8.7 Hz, 1 H, 3-H), 7.06 (s, 1 H, 8-H), 7.45 (d, J = 8.7 Hz, 1 H, 4-H), 7.47 (s, 1 H, 5-H); ^{13}C NMR (50 MHz, $CDCl_3/CD_3OD$ 1:0.01) δ 14.91 (q, 1-CH_3), 20.66 (q, 6-CH_3), 59.42 (q, OCH_3), 104.72 (d, 8-C), 118.81 (s, 1-C), 119.26 (d, 3-C), 128.29 (s, 6-C), 129.04 (s, 10-C), 130.13 (d, 5-C), 133.54 (d, 4-C), 138.23 (s, 9-C), 155.38 (s, 2-C), 161.48 (s, 7-C); MS (80 eV); m/z 202 (100) [M^+], 187 (3), 171 (3), 159 (7). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.42; H, 7.20.

1-Hydroxy-7-methoxy-1,6-dimethyl-1*H*-naphthalene-2-one (2d) was prepared from **1d** (2.0 g, 10 mmol) according to the general procedure II: yield 1.9 g (89%), yellow crystals; mp 104 °C; IR (KBr) ν 3452, 2988, 2924, 2864, 2826, 2353, 2325, 1671 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.56 (s, 3 H, 1-CH_3), 2.22 (s, 3 H, 6-CH_3), 3.94 (s, 3 H, OCH_3), 3.95 (s, 1 H, 1-OH), 6.06 (d, J = 9.8 Hz, 1 H, 3-H), 7.07 (s, 1 H, 8-H), 7.21 (s, 1 H, 5-H), 7.38 (d, J = 9.8 Hz, 1 H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.20 (q, 6-CH_3), 34.03 (q, 1-CH_3), 56.09 (q, OCH_3), 77.70 (s, 1-C), 107.76 (d, 8-C), 119.85 (d, 3-C), 121.19 (s, 6-C), 126.31 (s, 10-C), 132.27 (d, 5-C), 145.78 (s, 9-C), 146.47 (d, 4-C), 160.44 (s, 7-C), 206.05 (s, 2-C); MS (80 eV) m/z 217 (7) [$M^+ - H$], 200 (17), 190 (3). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.68; H, 6.64.

7-Methoxy-1,6-dimethyl-1-trimethylsilanyloxy-1*H*-naphthalene-2-one (19d) was prepared from **2d** (2.2 g, 10 mmol) according to the general procedure III: yield 2.8 g (98%), yellow oil; bp 170−180 °C/0.7 Torr; IR (film) ν 3462, 2978, 2934, 2874, 2836, 2363, 2330, 1677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 9 H, OTMS), 1.54 (s, 3 H, 1-CH_3), 2.24 (s, 3 H, 6-CH_3), 3.92 (s, 3 H, OCH_3), 6.03 (d, $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 7.07 (s, 1 H, 5-H), 7.19 (s, 1 H, 8-H), 7.31 (d, $J_{3,4}$ = 9.8 Hz, 1 H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 2.14 (q, OTMS), 16.19 (q, 6-CH_3), 34.20 (q, 1-CH_3), 55.85 (q, OCH_3), 80.61 (s, 1-C), 108.08 (d, 8-C), 121.45 (s, 6-C), 121.83 (d, 3-C), 126.23 (s, 10-C), 132.01 (d, 5-C), 145.01 (d, 4-C), 148.37 (s, 9-C), 160.18 (s, 7-C), 204.49 (s, 2-C); MS (80 eV) m/z 291 (3) [$M^+ + H$], 275 (100), 260 (28), 231 (9), 201 (12), 173 (3), 141 (1), 129 (3), 115 (8), 103 (2). Anal. Calcd for $C_{16}H_{22}O_3Si$: C, 66.17; H, 7.64. Found: C, 64.86; H, 6.96.

7-Methoxy-1,6-dimethyl-4-(2-propyl)-naphthalene-2-ol (23d) was prepared from **19d** (290 mg, 1.0 mmol) according to the general procedure V: yield 161 mg (66%), colorless crystals; mp 168 °C (ref[8] mp 169−172 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (d, J = 6.7 Hz, 6 H, CH(CH_3)$_2$), 2.42 (s, 3 H, 1-CH_3), 2.52 (s, 3 H, 6-CH_3), 3.70 (m, J = 6.8 Hz, 1 H, CH(CH_3)$_2$), 4.01 (s, 3 H, OCH_3), 4.81 (s, 1 H, 1-OH), 6.88 (s, 1 H, 3-H), 7.15 (s, 1 H, 8-H), 7.83 (s, 1 H, 5-H).

1-Hydroxy-7-methoxy-1,6-dimethyl-4-(2-propyl)-1*H*-naphthalene-2-one (*rac*-lacinilene C methyl ether, 3d) was prepared from **23d** (244 mg, 10 mmol) according to the general procedure II: yield 190 mg (73%), yellow crystals; mp 101−103 °C (lit.[15] mp 100 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J = 6.7 Hz, 3 H, CH(CH_3)$_2$), 1.31 (d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$), 1.56 (s, 3 H, 1-CH_3), 2.27 (s, 3 H, 6-CH_3), 3.25 (m, J = 6.8 Hz, 1 H, CH(CH_3)$_2$), 3.95 (s, 3 H, OCH_3), 3.96 (s, 1 H, 1-OH), 6.05 (s, 1 H, 3-H), 7.25 (s, 1 H, 8-H), 7.38 (s, 1 H, 5-H).

Supporting Information Available: Detailed experimental procedures and spectral data for compounds **1a**−**e**, **2a**−**e, 3a**−**e, 19a**−**e, 21a**−**c, 22a**−**c,** and **23a**−**e** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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