

Use of 1,1'-Binaphthalene-8,8'-diol as a Chiral Auxiliary for Asymmetric Michael Addition. Application to the Syntheses of Turmeronol A and B

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Highly diastereoselective Michael addition of lithium diorganocuprates to the half-ester of 1,1'-binaphthalene-8,8'-diol gave β -substituted esters with high enantiomeric excess after methanolysis. The optically active phenolic sesquiterpenes turmeronol A (1) and B (2) have been synthesized using this reaction as a key step.

Key words asymmetric reaction; 8,8'-dihydroxy-1,1'-binaphthyl; Michael addition; sesquiterpenoid; diastereoselectivity

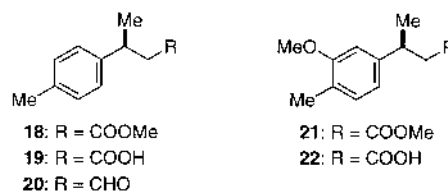
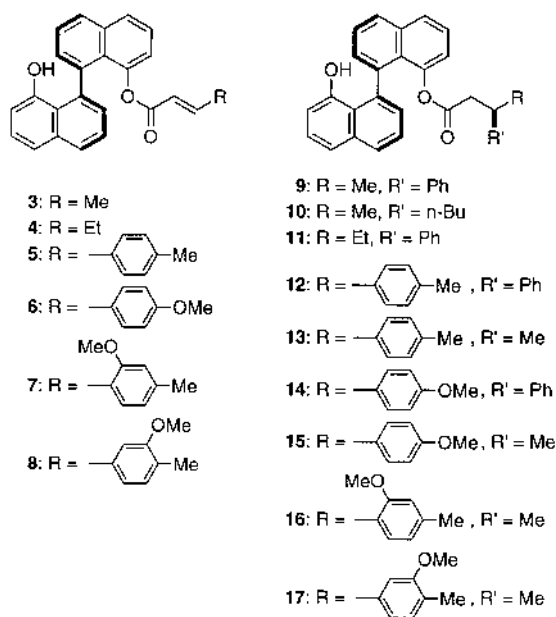
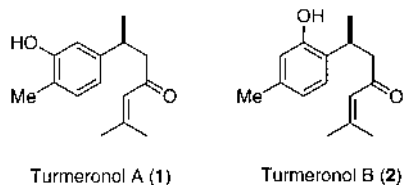
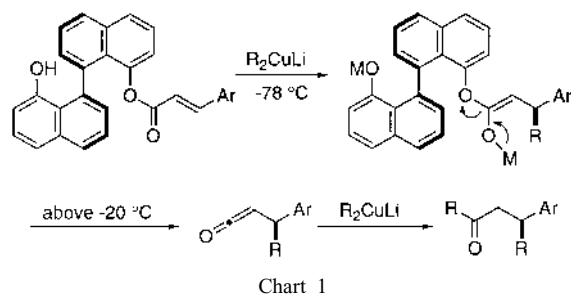
Since optically active 8,8'-disubstituted-1,1'-binaphthyl creates a highly dissymmetric microenvironment around the substituents at C-8 and C-8',^{1,2)} it has attracted increasing attention in the field of catalytic^{3,4)} and stoichiometric⁵⁾ asymmetric synthesis, as a chiral proton source,⁶⁾ and in recognition of chiral molecules.⁷⁾ We previously reported a one-step synthesis of the optically active β -substituted ketones *via* tandem 1,4- and 1,2-addition of lithium dialkylcuprates to a half-ester of 1,1'-binaphthalene-8,8'-diol (8,8'-BINOL).^{5a)} The reaction involves the Michael addition, followed by the formation of a ketene that undergoes the 1,2-addition and finally gives a β -substituted ketone with high enantiomeric excess (ee) (Chart 1). Temperature control was found to be crucial for the elimination of 8,8'-BINOL to yield an intermediate ketene. These findings suggested that it might be possible to obtain the 1,4-addition product by suppressing the elimination step under the reaction conditions. In this paper, we report this achievement and its application to the synthe-

sis of optically active turmeronol A (1) and turmeronol B (2).

α,β -Unsaturated half-esters 3—8 were prepared by the condensation of 8,8'-BINOL with the corresponding acids⁸⁾ in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (WSC) and 4-dimethylaminopyridine (DMAP). The half-esters were treated with lithium diorganocuprate in Et₂O while maintaining the temperature below -20 °C to afford the desired Michael addition product. The results are shown in Table 1. Excellent diastereoselectivity and fair to good chemical yields were observed, except for entry 8. In the case of entry 8, the half-ester 7 had low reactivity against Me₂CuLi due to the neighboring methoxy group. Increasing the reaction temperature and time did not improve the yield, and instead the product generated by 1,4-addition followed by 1,2-addition of the reagent was obtained.

Some of these products were easily converted to the chiral synthetic intermediates of aromatic bisabolane sesquiterpenes. Thus transesterification of optically active 13 and 17 using lithium methoxide gave the corresponding methyl esters 18 and 21 which were hydrolyzed to the acids 19 and 22 in high overall yield, respectively. Reduction of 18 with DIBAL afforded 20 in 91% yield. The optically active 19, 20, and 22 were previously transformed into a number of bisabolane sesquiterpenoids, as indicated in Chart 2.

To demonstrate the synthetic utility of the present asymmetric Michael addition, we synthesized optically active 1 and 2, inhibitors of soybean lipoxygenase isolated from the spice turmeric (*Curcuma longa* L.).¹⁷⁾ To the best of our knowledge, only one synthesis of optically active 1⁹⁾ and synthesis of racemic 2¹⁸⁾ have been reported. Chart 3 outlines the syntheses of 1 and 2. Demethylation of optically active



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Table 1. Michael Additions to 3–8

Entry	Ester	Reaction conditions			Product	Yield (%) ^{a)}	de (%) ^{b)}
		R ₂ CuLi (eq)	Temp (°C)	Time (h)			
1	(<i>dl</i>)-3	Ph ₂ CuLi (4)	-78	1	9	88	>99
2	(<i>dl</i>)-3	<i>n</i> -Bu ₂ CuLi (10)	-78 ^{c)}	2	10	72	98
3	(<i>R</i>)-4	Ph ₂ CuLi (8)	-78	2	11	97	>99
4	(<i>dl</i>)-5	Ph ₂ CuLi (8)	-20	5	12	47	>99
5	(<i>R</i>)-5	Me ₂ CuLi (10)	-20	2	13	87	>99
6	(<i>dl</i>)-6	Ph ₂ CuLi (8)	-20	5	14	75	>99
7	(<i>R</i>)-6	Me ₂ CuLi (10)	-20	2	15	59	92
8	(<i>R</i>)-7	Me ₂ CuLi (10)	-20	2	16	29	>99
9	(<i>R</i>)-8	Me ₂ CuLi (10)	-20	2	17	81	>99

a) Isolated yield. b) Determined by 200 or 400 MHz ¹H-NMR. c) Gradually increased to -20 °C.

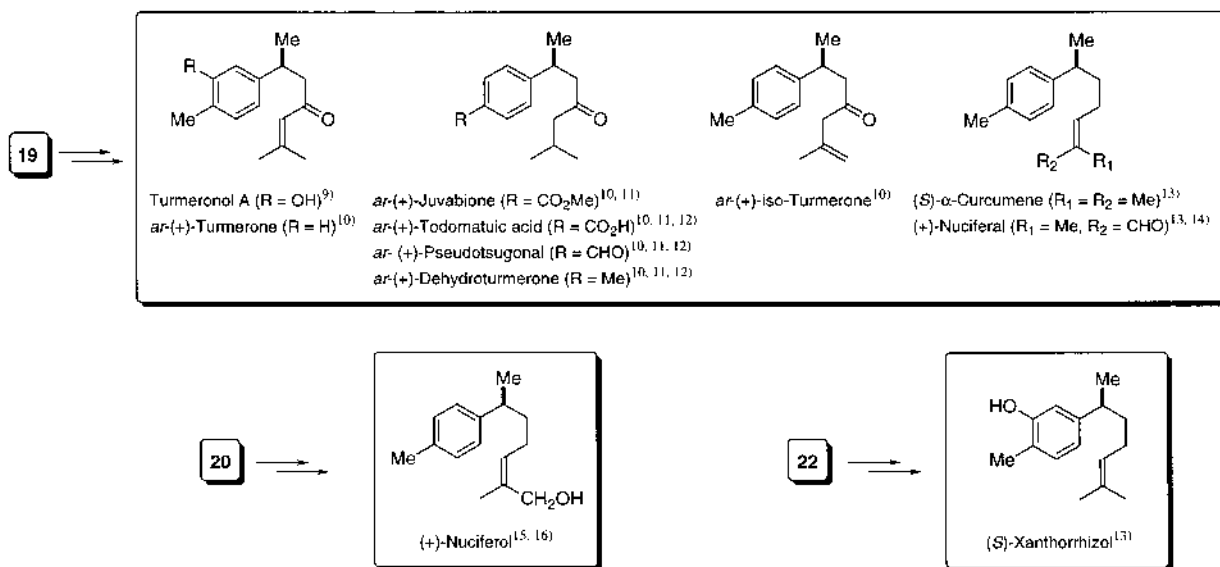


Chart 2. Bisabolane Sesquiterpenoids Previously Synthesized from 19, 20, and 22

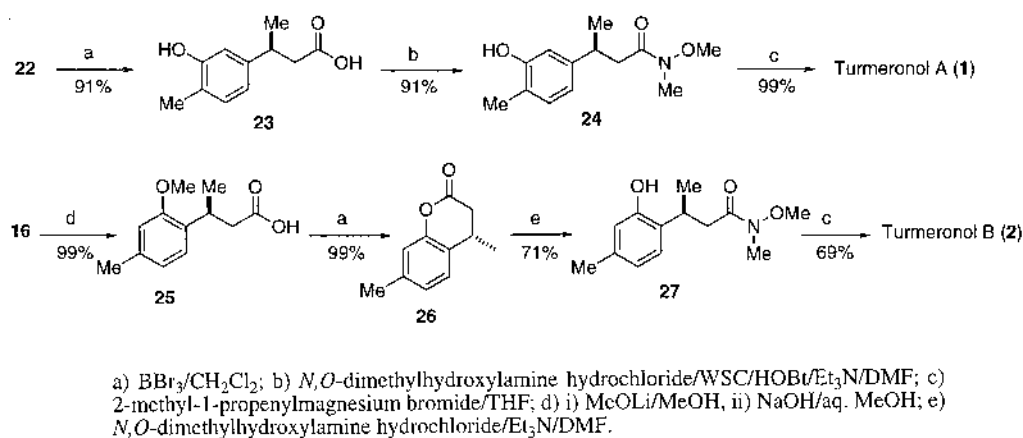


Chart 3. Syntheses of (+)-Turmeronol A (1) and (+)-Turmeronol B (2)

22 with boron tribromide gave **23** in good yield. The corresponding Weinreb amide **24** prepared by treatment with *N,O*-dimethylhydroxylamine hydrochloride¹⁹⁾ was reacted with 2-methyl-1-propenylmagnesium bromide to afford (+)-turmeronol A (**1**) in 90% overall yield from **23**. Demethylation of **25**, prepared from **16**, gave the lactone **26**, which was

transformed to (+)-**2** via the sequence similar to that for (+)-**1**. Physical data including ¹H-NMR spectra, IR spectra, and [α]_D values for synthetic (+)-turmeronol A (**1**) and B (**2**) were in satisfactory agreement with those of natural products.²⁰⁾

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- 20) Synthetic turmeronol A (**1**) and turmeronol B (**2**) show the following characterization data: turmeronol A (**1**): $[\alpha]_D^{21} = +62.3^\circ$ ($c=0.43$, CHCl₃) (lit.¹⁷) $[\alpha]_D^{23} = +63^\circ$; IR (CHCl₃) 3390, 1680, 1615 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃) δ 1.22 (d, 3H, $J=6.9$ Hz), 1.86 (d, 3H, $J=1.2$ Hz), 2.11 (d, 3H $J=1.2$ Hz), 2.20 (s, 3H), 2.59 (dd, 1H $J=15.6$, 8.3 Hz), 2.72 (dd, 1H $J=15.6$, 6.2 Hz), 3.15—3.25 (m, 1H), 5.55 (s, 1H, OH), 6.04 (t, 1H $J=1.2$ Hz), 6.67 (s, 1H), 6.70 (d, 1H $J=7.8$ Hz), 7.03 (d, 1H $J=7.8$ Hz); MS m/z (rel. intensity) 232 (M⁺, 70), 149 (100); HRMS. Calcd for C₁₅H₂₀O₂: 232.1463. Found: 232.1448. *Anal.* Calcd for C₁₅H₂₀O₂·0.1H₂O: C, 76.95; H, 8.70. Found: C, 76.98; H, 8.65. The optical purity was determined to be 99% ee by HPLC (Daicel Chiralcel OB column, 0.7 ml/min, hexane/2-propanol=96/4). Turmeronol B (**2**): $[\alpha]_D^{21} = +82.2^\circ$ ($c=0.45$, CHCl₃) (lit.¹⁷) $[\alpha]_D^{23} = +79^\circ$; IR (CHCl₃) 3280, 1675, 1615 cm⁻¹; ¹H-NMR (200 MHz, CDCl₃) δ 1.29 (d, 3H $J=7.1$ Hz), 1.85 (d, 3H $J=1.2$ Hz), 2.11 (d, 3H $J=1.2$ Hz), 2.25 (s, 3H), 2.80 (d, 2H $J=6.6$ Hz), 3.48—3.69 (m, 1H), 6.00 (m, 1H), 6.72 (d, 1H $J=7.6$ Hz), 6.74 (s, 1H), 7.02 (d, 1H $J=7.6$ Hz), 8.13 (s, 1H); MS m/z (rel. intensity) 232 (M⁺, 35), 135 (100); HR-MS. Calcd for C₁₅H₂₀O₂: 232.1463. Found: 232.1446. *Anal.* Calcd for C₁₅H₂₀O₂: C, 77.55; H, 8.68. Found: C, 77.50; H, 8.87. The optical purity was determined to be 99% ee by HPLC (Daicel Chiralcel OJ column, 1 ml/min, hexane/2-propanol=98/2).