Synthesis of Malabaricones, Diarylnonanoids Occurring in Myristiceaeous Plants

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Naturally occurring diarylnonanoids, malabaricones A, B, C, D, and 1-(2-hydroxy-6-methoxyphenyl)-9-(3,4-methylenedioxyphenyl)nonan-1-one were synthesized from a common intermediate, 6-benzyloxyhexyltriphenyl phosphonium bromide, by use of the Wittig reaction and crossed aldol reaction as key steps.

Keywords malabaricone; diarylnonanoid; Myristiceae; synthesis; 6-benzyloxyhexyltriphenyl phosphonium bromide; Wittig reaction; crossed aldol reaction; dehydroboration

The plants of Myristiceae characteristically contain a group of compounds classified as diarylnonanoids (Table I), all of which are derivatives of 2,6-dihydroxyacetophenone and are considered to be biosynthesized from a phenylpropanoid and six C₂ units. Malabaricones A–D are the typical examples,¹⁰ and one of them (malabaricone C) was recently suggested to have significant biological activities (such as nematocidal,¹⁵ bacteriocidal,³¹ and antioxidant³⁵ activities). So far, only one report on the synthesis of malabaricone A has appeared.⁴ This paper describes our synthesis of the above diarylnonanoids.

Our synthetic scheme is indicated in Chart 1. We chose a hexane unit differently substituted at the two termini, e.g., 6-benzyloxyhexyltriphenyl phosphonium salt, as a common intermediate. The C–C bond formations at ① and ② followed by additional manipulations were expected to lead to the desired diarylnonanoids.

Results and Discussion

Syntheses of the Common Intermediate 5 and 7-Arylheptanols ⁷ Based on the results of preliminary experiments, we chose a benzyl group for protection of one terminus of hexanediol. Acetals such as an ethoxyethyl or an acetyl group were not appropriate because of their susceptibility to bromination or low selectivity in mono-protection.

1,6-Hexanediol mono-benzyl ether ²⁵ was obtained in 46% yield on mono-benzylation of 1,6-hexanediol and converted to the bromide ³ in 88% yield by N-bromosuccinimide and triphenylphosphine according to a known procedure⁴⁵ with some modifications. Heating of ³ with triphenylphosphine at 140 °C without solvent gave the expected phosphonium salt ⁴ in 75% yield.

The phosphonium salt ⁴ was converted to the ylide with potassium tert-butoxide ( tert-BuOK) in tetrahydrofuran

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Name</th>
<th>Botanical sources</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>la</td>
<td>Malabaricone A</td>
<td>Myristica malabarica LAM.</td>
<td>1a)</td>
</tr>
<tr>
<td>lb</td>
<td>Malabaricone B</td>
<td>M. dactyloides GAERTN.</td>
<td>1b, c</td>
</tr>
<tr>
<td>lc</td>
<td>Malabaricone C</td>
<td>M. malabarica LAM.</td>
<td>1a)</td>
</tr>
<tr>
<td>ld</td>
<td>Malabaricone D</td>
<td>M. dactyloides GAERTN.</td>
<td>1b)</td>
</tr>
<tr>
<td>le</td>
<td>No name</td>
<td>M. fragrans HOUTT.</td>
<td>1d)</td>
</tr>
<tr>
<td>lf</td>
<td>No name</td>
<td>M. dactyloides GAERTN.</td>
<td>1b)</td>
</tr>
<tr>
<td>lg</td>
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<td>M. dactyloides GAERTN.</td>
<td>1c)</td>
</tr>
<tr>
<td>lh</td>
<td>No name</td>
<td>M. glabla BL.</td>
<td>1c)</td>
</tr>
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(Horsfieldia glabla WARB.)

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(THF)-dimethyl sulfoxide (DMSO) and allowed to react with various aromatic aldehydes to yield 7-arylheptanol benzyl ethers 5 in 50—75% yield (Table II). Sonication during the formation of the ylide increased the yields of 5. The configurations of the olefinic moiety in 5 are mainly Z as evidenced from the coupling constant of \( J = 11.5 \text{ Hz} \) for the two olefinic protons in the proton nuclear magnetic resonance (\(^1\)H-NMR) spectra.

Hydrogenation of 5 in ethanol over 10% Pd–C gave, with concomitant hydrogenolysis of the benzyl group, the 7-arylheptanals 6 in high yields.

**Synthesis of Malabaricones** The 7-arylheptanol 6d was subjected to Swern oxidation and the resulting aldehyde 7d was coupled with the tri-anion derived from 2,6-dihydroxyacetophenone and 3 mol eq of lithium diisopropylamide (LDA) in THF–hexamethylphosphortriamide (HMPA) to give the aldol product 8 in 38% yield. Without HMPA no aldol product was obtained.

Treatment of 8 with a catalytic amount of \( p \)-toluenesulfonic acid (TsOH) gave the chromanone derivative 10 (66% yield), instead of the expected conjugated ketone 9. Model experiments of this dehydration reaction on the 2-hydroxy and 2,6-dihydroxy derivatives, 14 and 11, revealed that the mono-phenolic compound 14 gave the expected conjugated ketone 15 smoothly, while the di-phenolic compound 11 gave the chromanone 13 exclusively on the same treatment. This indicated that one of the ortho-phenolic group is strongly hydrogen bonded to the carbonyl group, and therefore, although the conjugated ketones are formed by dehydration, the free phenolic hydroxyl group in the 2,6-dihydroxy compounds (e.g. 9’ and 12’) rapidly adds in a Michael fashion to the conjugated enone, while the hydroxyl group in 2-hydroxy compounds is masked by hydrogen bonding and does not add to the conjugated enone.

Therefore the 7-arylheptanals 7 prepared by Swern oxidation of 6 were subjected to aldol condensation with the di-anion derived from 2-benzylxylo-6-hydroxyacetophenone as described above. Addition of HMPA was again necessary to obtain the products in these reactions. The resulting aldol products 16 were smoothly dehydrated to the conjugated ketones 17 as expected.

Hydrogenation of 17 in acetonitrile (for preventing over-reduction of the carbonyl group) over 10% Pd–C gave, with concomitant hydrogenolysis of the benzyl group, the saturated 2,6-dihydroxyacetophenone derivatives 18. Compounds 18a, mp 78—80 °C, and 18d, mp 91—92 °C, were identical with malabaricone A (1a) and malabaricone D (1d), respectively.

Compounds 18b and 18c were demethylated with boron tribromide in dichloromethane to give the phenols of mp 102—104 °C and mp 119—121 °C, which were identical with malabaricone B (1b) and C (1c), respectively.

In a similar manner, 1-(2-hydroxy-6-methoxyphenyl)-9-(3,4-methylenedioxyphenyl)nonan-1-one 18e, mp 52—53 °C, was synthesized starting from 7d and 2-hydroxy-6-
TABLE III. Yields in the Conversion of 7→16→17→18 (see Chart 4)

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>7</td>
<td>16→17→18</td>
</tr>
<tr>
<td>a</td>
<td>71 86 89 (R'=H)</td>
</tr>
<tr>
<td>b</td>
<td>74 88 88 (R'=H)</td>
</tr>
<tr>
<td>c</td>
<td>73 91 88 (R'=H)</td>
</tr>
<tr>
<td>d</td>
<td>77 85 71 (R'=H)</td>
</tr>
<tr>
<td>e</td>
<td>100 90 91 (R'=Me)</td>
</tr>
</tbody>
</table>

methoxaceatophenone and was shown to be identical with a natural diarylanonanoid 1e found in Myristica dactyloides. 14)

The identities of the above synthesized diarylanonoids with the natural compounds were confirmed by comparisons of their physical and spectral data with those reported.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage melting point apparatus and are uncorrected. Infrared (IR) spectra were taken for the CHCl₃ solutions on a JASCO A-202 spectrometer and are given in cm⁻¹. ¹H-NMR spectra were taken for the CDC₁₃ solutions on a JOEL JNM-FX100 (FT-NMR; 100 MHz) spectrometer and are given in δ (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Aromatic protons indicated by ranges appeared as multiplets. Mass spectra (MS) were measured with a Hitachi H-80 mass spectrometer at an ionization voltage of 20 eV and major peaks are indicated by m/z (%). Ultraviolet (UV) spectra were measured in ethanol with a Hitachi 323 spectrometer and λ_max are given in nm (λ). Organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. Column chromatography was performed on silica gel (Fuji-Davison BW-820MH).

6-Benzylxoxethyl Bromide (3) N-Bromosuccinimide (9.9 g, 56 mmol) and PPh₃ (14.59 g, 56 mmol) were added to a stirred solution of 1,6-hexanediol mono-benzyl ether₂² (5.78 g, 28 mmol) in THF (200 ml) in several portions at room temperature. After 2 h, the reaction mixture was concentrated to half the initial volume and diluted with hexane. The precipitate was removed by filtration and the filtrate was concentrated to leave a residue, which was chromatographed to give 3 (6.63 g, 88%) as a colorless oil. ¹H-NMR: 1.20-2.00 (8H), 3.35 (2H, dd, J=15, 7Hz, -CH₂Br), 3.50 (2H, dd, J=15, 6Hz, -CH₂O), 4.49 (2H, s, PhCH₂O), 7.32 (2H, s, Ph-H). MS: 272 and 270 (1:1, each 1%) (M⁺ for ⁴¹Br and ⁷⁹Br), 92 (100).

6-Benzylxoxethyltriphenylphosphonium Bromide (4) Compound 3 (947 mg, 3.5 mmol) and PPh₃ (917 mg, 3.5 mmol) were heated at 140°C for 2 h. The mixture was crystallized from acetone-ether to give 4 (1.39 g, 75%) as colorless prisms, mp 125-127.5°C. ¹H-NMR: 1.24-1.80 (8H), 3.42 (2H, t, J=6.5Hz, -OCH₂-), 3.74 (2H, m, P=CH₂-), 4.44 (2H, s, -OCH₂Ph), 7.49 (5H, s, Ph-H), 7.60-7.96 (15H, Ph-H). MS: 453 (Ph₃P+) (C₂₅H₃₁O₇Ph), 262 (100). Anal. Calc. for C₃₅H₄₅BrO₇Ph: C, 69.54; H, 6.46. Found: C, 69.79; H, 6.42.

Chart 4

18a-d: R'=:H
18e: R'=Me
for a→e, see Table III

(2)-Benzylxoxethyl-7-arylhet-6-ene (5) (General Procedure) An aromatic aldehyde (10.5 mmol) in THF (2 ml) was added dropwise to a stirred solution of the ylide [9.5 mmol, prepared from tert-ButOK and 4 in THF-DMSO (25:1, 165 ml)] under an Ar atmosphere and the mixture was stirred for an additional 50 min with occasional sonication at room temperature. The reaction mixture was poured into ice-water, acidified with HCl and extracted with CHCl₃. Chromatography of the residue from the CHCl₃ extract gave the corresponding arylethenyl benzyl ether 5 in the yield indicated in Table II. The products were used directly for hydrogenation. The spectral data are as follows.

(2)-Benzylxoxethyl-7-(3-methoxyphenyl)het-6-ene (5b): This was prepared from 4 and 3-methoxybenzaldehyde as a yellow oil. ¹H-NMR: 1.20-1.80 (6H), 2.28 (2H, m, -CH₂CH₂-), 3.45 (2H, t, J=6.3Hz, -CH₂O), 3.78 (3H, s, OCH₃), 4.47 (2H, s, PhCH₂O), 5.55 (1H, dt, J=11.5, 7.5Hz, ArCH=CH₂), 6.38 (1H, d, J=11.5Hz, ArCH=CH₂), 7.08-7.38 (10H, Ph-H). MS: 280 (M⁺, 2), 91 (100).

(2)-Benzylxoxethyl-7-(4-methoxyphenyl)het-6-ene (5b): This was prepared from 4 and 4-methoxybenzaldehyde as a yellow oil. ¹H-NMR: 1.20-1.80 (6H), 2.28 (2H, m, -CH₂CH₂-), 3.45 (2H, t, J=6.3Hz, -CH₂O), 3.78 (3H, s, OCH₃), 4.47 (2H, s, PhCH₂O), 5.55 (1H, dt, J=11.5, 7.5Hz, ArCH=CH₂), 6.38 (1H, d, J=11.5Hz, ArCH=CH₂), 7.25 (3H, s, ArH), 7.31 (5H, br, Ph-H). MS: 310 (M⁺, 60), 151 (100).

(2)-Benzylxoxethyl-7-(3,4-dimethoxyphenyl)het-6-ene (5d): This was prepared from 4 and piperonal as a yellow oil. ¹H-NMR: 1.12-1.80 (6H), 1.92-2.45 (2H, m, =CH₂CH₂-), 3.45 (2H, t, J=6.3Hz, -CH₂O), 4.48 (2H, s, -OCH₂Ph), 5.52 (1H, dt, J=11.5, 6.5Hz, ArCH=CH₂), 5.93 (2H, s, PhCH₂O), 6.28 (6H, dt, J=11.5, 6Hz, ArCH=CH₂). MS: 340 (M⁺, 60), 180 (100).

7-Arylhetepantoct 6 (General Procedure) One of compounds 5 (6.5 mmol) in ethanol (50 ml) was hydrogenated over 10% Pd-C (0.8 g) at room temperature under hydrogen pressure of 4 kg/cm² for 24 h. Removal of the catalyst and the solvent from the mixtue left an oil which was purified by chromatography to give the corresponding arylethanol 6 in the yield indicated in Table II.

7-Phenylethanol (6a): Colorless oil. IR: 3620. ¹H-NMR: 1.18-1.76 (10H), 2.60 (2H, t, J=7.8Hz, PhCH₂-), 3.62 (2H, t, J=6.3Hz, -CH₂OH), 7.04-7.36 (5H, Ph-H). MS: 192 (M⁺, 26), 104 (100). High resolution mass spectra (HRMS) m/z (M⁺): Caled for C₁₇H₁₇OH: 192.1513. Found: 192.1522.

7-(4-Methoxyphenyl)ethanol (6b): Colorless solid, mp <30°C. IR: 3620. ¹H-NMR: 1.12-1.76 (10H), 2.54 (2H, t, J=7.8Hz, ArCH₂-), 3.60 (2H, brs, -CH₂OH), 6.75, 7.08 (each 2H, d, J=8.5Hz, ArH). MS: 222 (M⁺, 91), 121 (100). HRMS m/z (M⁺): Caled for C₁₉H₂₁O₂: 222.1619.
Found: 222.1610.

7-(3,4-Dimethoxyphenyl)heptan-6-one (6c): Colorless oil. IR: 3620. \( \text{C-H} \) stretching.

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Found: 252.1719.

7-(3,4-Methylenedioxyphenyl)heptan-6one (6d): Colorless oil. IR: 3620.

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Found: 236.1405.

7-Arylheptanals 7 (General Procedure) A 7-aryl-heptanone (0.79 mmol) in \( \text{CH}_2\text{Cl}_2 (3 \text{ ml}) \) was added to a stirred solution of DMSO (0.15 ml) and oxalyl chloride (0.16 ml) in \( \text{CH}_2\text{Cl}_2 (2 \text{ ml}) \) at \(-78 \text{ °C}. \) After 15 min, \( \text{BnNH} \) (0.45 ml) was added and stirring was continued at \(-78 \text{ °C} \) for 5 min, then at room temperature for 20 min. The reaction mixture was filtered and washed with \( \text{CH}_2\text{Cl}_2, \) washed with 1N HCl, and concentrated. Chromatography of the product gave the corresponding 7-aryl-7-aminopropyl in the yield indicated in Table II. These compounds gave the following spectral data, and were used for the next step without further characterization.

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Benzyl-2,6-Dihydroxyacetophenone 2,6-Dihydroxyacetophenone (0.5g, 3.3 mmol) and NaH (13 mg, 3.3 mmol) in DMSO (10 ml) was stirred at room temperature for 10 min. Benzyl bromide (0.46 mmol) was added and stirring continued for 1h. The reaction mixture was poured into cold 1N HCl and extracted with \( \text{CH}_2\text{Cl}_2. \) Chromatography of the product gave 2-benzyloxy-6-hydroxyacetophenone (610 mg, 76%). mp 109–110 °C, as yellow needles from benzene–ether.

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Condensation of 2,6-Dihydroxyacetophenone with Decanal and Dehydroacetone (7): Colorless oil. IR: 3722.

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Condensation of \( \alpha \)-Hydroxyacetophenone with Decanal and Dehydroacetone (1-2-[Hydroxy-2Hydroxy-2-Decanone-1(5)] \( \alpha \)-Hydroxyacetophenone (1.13 g, 8.3 mmol) in THF (5 ml) was added dropwise to a solution of LDA (10 mmol) in THF (5 ml) over 5 min at \(-78 \text{ °C} \) under an Ar atmosphere and the mixture was stirred for 15 min. A solution of n-decanal (0.66 ml, 3.5 mmol) and HMPA (1.8 ml, 10.0 mmol) in THF (6 ml) was added, and the reaction mixture was stirred at \(-78 \text{ °C} \) for 50 min, and at \( 0 \text{ °C} \) for 1 h, then poured into cold 10% HCl and extracted with AcOEt. Work-up of the reaction gave an oil of \( \alpha \)-H (263 mg). A solution of the aldol 11 and \( p \)-TOS (134 mg, 0.7 mmol) in benzene (10 ml) was heated under reflux for 45 min. The cooled mixture was washed with saturated aqueous NaHCO\(_3\), and concentrated. Chromatography of the residue gave the chromane 12 (270 mg, 28% from 2,6-dihydroxyacetophenone) as a yellow oil. IR: 1614, 1621, 1573.

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Condensation of \( \alpha \)-Hydroxyacetophenone with Decanal and Dehydroacetone (1-2-[Hydroxy-2Hydroxy-2-Decanone-1(5)] \( \alpha \)-Hydroxyacetophenone (1.13 g, 8.3 mmol) in THF (5 ml) was added dropwise to a solution of LDA (10 mmol) in THF (10 ml) over 5 min at \(-78 \text{ °C} \) under an Ar atmosphere and the mixture was stirred for 30 min. n-Decanal (1.7 ml, 9 mmol) and HMPA (8 mmol) in THF (10 ml) was added to this solution and the mixture was stirred for a further 1h. Work-up of the reaction mixture was then concentrated in vacuo and the residue was purified by column chromatography on silica gel.

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Dehydration of the Aldol The aldol 8 (90 mg, 0.23 mmol) and \( p \)-TOS
(5 mg, 0.02 mmol) in benzene (10 ml) were heated under reflux for 3.5 h, and the mixture was worked up as described below. The products were purified by chromatography to give 18 in the yield indicated in Table III.

1-(2,6-Dihydroxyphenyl)-9-(3,4-methylenedioxyphenyl)-1-nonanone (Malabaricone A) (18a) (21):
Pale yellow solids from hexane–ether, mp 78–80°C (lit. 81–82°C). ①③ 1H NMR: 3350, 1626, 1599. 13C NMR: 106.1–182.0 (12H), 2.52 (2H, t, J = 7.5 Hz, Ph–CH2–), 3.12 (2H, t, J = 7.5 Hz, CH2–CO–), 3.63 (2H, d, J = 8 Hz, Ar–CH2), 6.79–6.2 (6H, Ar–OH and Ph–H), 5.97 (1H, br, OH), MS: 326 (M+2, 21), 237 (100). Anal. Calcld. for C21H22O6: C, 72.7; H, 5.03. Found: C, 72.7; H, 5.07. The data were identical with those reported for malabaricone A. ①③

1-(2,6-Dihydroxyphenyl)-9-(4-methoxyphenyl)-1-nonanone (18b):
Yellowish solids from ether, mp 78–80°C. 1H NMR: 3300, 1626, 1605. 13C NMR: 108.0–180.0 (12H), 2.52 (2H, t, J = 7.5 Hz, Ar–CH2–), 3.10 (2H, t, J = 7.5 Hz, CH2–CO–), 3.76 (2H, d, J = 7.5 Hz, Ar–CH2), 6.79–6.2 (6H, Ar–OH and Ph–H), 5.97 (1H, br, OH), MS: 326 (M+2, 100). Anal. Calcld. for C21H22O6: C, 72.7; H, 5.03. Found: C, 72.7; H, 5.03. These data were identical with those reported for malabaricone B. ①③

References and Notes


2) Private communication from Prof. M. Hattori, Toyama Medical and Pharmaceutical University.

3) Private communication from Prof. N. Nakatani, Osaka City University.


