Total Synthesis of (±)-Zeylena

Seiichiro OGAWA* and Tohei TAKAGAKI
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223
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Synopsis. Zeylena, isolated from the roots of *Uvaria zeylanica* L. (Annonaceae), has been synthesized as a racemic modification by an intramolecular cyclo-addition reaction of DL-*trans*-2,3-dihydroxy-1-(benzoyloxymethyl)cyclohexa-4,6-diene 3-(*E*)-cinnamate or its acetate.

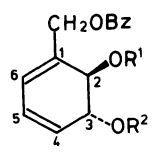
Zeylena (**7**) was isolated from the methanol extract of the roots of *Uvaria zeylanica* L. (Annonaceae).[1] Although it was found to lack tumor inhibitory activity, its biogenetic relationship to other biologically active *Uvaria* constituents has stimulated much interest.[2]

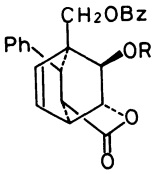
In continuation to our study for highly-oxygenated cyclohexane compounds,[3] we now describe a synthesis of racemic zeylena starting from DL-*trans*-2,3-diacetoxy-1-(benzoyloxymethyl)-4,6-cyclohexadiene (**1**).[4]

Selective *O*-deacetylation of **1** with *p*-toluenesulfonic acid in methanol gave the 2-acetate (**2**) and the dihydroxy compound (**3**) in 29 and 51% yeild, respectively. The structures were assigned on the basis of the ^{1}H NMR spectra.[3]

The monoacetate **2** was treated with (*E*)-cinnamoyl chloride in dichloromethane and pyridine to give the 3-(*E*)-cinnamate (**4**) in 62% yield. Intramolecular Diels-Alder reaction of **4** was carried out in toluene in a sealed tube at 70 °C for 4 d to afford a 91% yield of crystalline (±)-zeylena acetate (**6**),[1] which was readily convertible into racemic **7** in 40% yield[5] by treatment with *p*-toluenesulfonic acid in methanol–dichloromethane. The ^{1}H NMR spectra data of **7** were shown to be superposable on those of an authentic sample.[1,6]

Alternatively, selective esterification of **3** with the acid chloride was attempted in dichloromethane and pyridine at −60 °C. A mixture of the products was separated on a silica-gel column to afford the desired 3-(*E*)-cinnmate (**5**) in 27% yield, the structure of which was confirmed by the ^{1}H NMR spectrum. The ester **5** was then subjected to similar cyclo-addition reaction conditions to afford racemic **7** in 98% yield.





1 $R^1 = R^2 = Ac$
2 $R^1 = Ac$, $R^2 = H$
3 $R^1 = R^2 = H$
4 $R^1 = Ac$, $R^2 = COCH{=}CHPh$
5 $R^1 = H$, $R^2 = COCH{=}CHPh$

6 R = Ac
7 R = H

Fig. 1. The formulas depict only one of the respective enantiomers.

Experimental

Melting points were determined in a capillary in a MELTEMP melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM-390 (90 MHz) spectrometer in chloroform-*d* solution with tetramethylsilane as an internal standard. Mass spectra were measured with a Hitachi M 80B spectrometer. The silica gel used for column chromatography was Wakogel C-300 (Wako Co., 300 mesh).

Selective *O*-Deacetylation of DL-*trans*-2,3-Diacetoxy-1-(benzoyloxymethyl)-4,6-cyclohexadiene (1).[4] Compound **1** (100 mg, 0.30 mmol) was treated with *p*-toluenesulfonic acid (25 mg) in methanol (5 ml) as described in the reaction of the optically active **1**.[3] The products were separated on a silica-gel column to give 25 mg (29%) of DL-*trans*-2-acetoxy-1-benzoyloxymethyl-4,6-cyclohexadien-3-ol (**2**) as a syrup and 38 mg (51%) of DL-*trans*-1-benzoyloxymethyl-4,6-cyclohexadiene-2,3-diol (**3**) as a syrup. Both compounds were assigned by comparison of their ^{1}H NMR spectra with those of the corresponding optically active compounds.[3] MS (70 eV) *m/z* (rel intensity), data for **2**, 288 (M^+; 2.8), 228 (12), 124 (8), and 105 (100); data for **3**, 246 (M^+; 2.7), 228 (11), 124 (86), and 105 (100).

DL-*trans*-2-Acetoxy-1-benzoyloxymethyl-3-[(*E*)-cinnamoyloxy]-4,6-cyclohexadiene (4). To a solution of **2** (67 mg, 0.23 mmol), dichloromethane (1.0 ml), and pyridine (0.2 ml) was added a solution of (*E*)-cinnamoyl chloride (83 mg, 0.50 mmol) in dichloromethane (0.5 ml) dropwise at −50 °C, and then the mixture was stirred at the same temperature for 10 min. The mixture was diluted with ethyl acetate (10 ml) and washed with 1 M† hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. Removal of the solvent gave a syrup, which was chromatographed on a silica-gel column (8 g) with ethyl acetate–hexane (1:4) as an eluant to give mainly 60 mg (62%) of **4** as a syrup. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.02 (3H, s, OAc), 4.93 (2H, s, CH_2OBz), 5.63 (1H, dd, $J_{2,3}$=6.2 Hz, $J_{3,4}$=3.3 Hz, H-3), 5.93 (1H, d, H-2), 6.00—6.33 (3H, m, H-4, 5, and 6), 6.37 (1H, d, *J*=15.5 Hz, COCH=CHPh), 7.33—7.57 (8H, m) and 7.80—8.03 (2H, m) (OBz and COCH=CHPh), 7.68 (1H, d, COCH=CHPh); MS (70 eV) *m/z* (rel intensity) 418 (M^+; 4.4), 376 (2.6), 228 (19), 131 (100), and 105 (60).

(±)-Zeylena Acetate (6). A solution of **4** (23 mg, 0.05 mmol) and toluene (1.0 ml) was heated in a sealed tube at 70 °C for 4 d. The mixture was concentrated and the residue was eluted from a column of silica gel (1 g) with ethyl acetate–hexane (2:5) to give 21 mg (91%) of **6** as plates; mp 150 °C (recrystallized from methanol–dichloromethane). ^{1}H NMR data ($CDCl_3$, 90 MHz) was identical with those reported for an optically active compound.[1]

Found: C, 71.60; H, 5.48%. Calcd for $C_{25}H_{22}O_6$: C, 71.77; H, 5.26%.

(±)-Zeylena (7). To a solution of **6** (39 mg, 0.09 mmol) in dichloromethane–methanol (1:6) (7 ml) was added *p*-toluenesulfonic acid (80 mg, 0.42 mmol) and the mixture was stirred at room temperature for 3 d. The mixture was then neutralized with sodium hydrogencarbonate and an insoluble material was removed by filtration. The filtrate was concentrated and the residue was chromatographed on a silica-gel column (2 g) with ethyl acetate–hexane (1:2) to give 14 mg (40%) of **7**; mp 173—174 °C (recrystallized from

† 1 M = 1 mol dm^{-3}.

dichloromethane–methanol). The ^{1}H NMR spectrum was superposable on that of an authentic sample.[1)]

Found: C, 73.22; H, 5.51%. Calcd for $C_{23}H_{20}O_5$: C, 73.40; H, 5.32%.

DL-*trans*-1-Benzoyloxymethyl-3-[(*E*)-cinnamoyloxy]-4,6-cyclohexadien-2-ol (5). To a solution of **3** (193 mg, 0.78 mmol) in dichloromethane (2.0 ml) and pyridine (0.8 ml) was added at −60 °C a solution of (*E*)-cinnamoyl chloride (133 mg, 0.80 mmol) in dichloromethane (0.8 ml), and the mixture was stirred at 0 °C for 0.5 h. TLC [ethyl acetate–hexane (1:2)] showed three componets (R_f=0.53, 0.34, and 0.26) and a trace of **3**. The mixture was diluted with ethanol and the solution was concentrated. The residual products were processed as described in the preparation of **4**. Fractionation of the products on a silica-gel column with ethyl acetate–hexane (1:3) gave mainly 81 mg (27%) of **5**; mp 87—88 °C (recrystallized from ether). TLC, R_f=0.34. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=3.09 (1H, br s, OH), 4.45 (1H, d, $J_{2,3}$=7 Hz, H-2), 5.04 (2H, narrow m, C$\underline{H}_2$OBz), 5.67 (1H, dd, $J_{3,4}$=3 Hz, H-3), 5.82—6.14 (3H, m, $\underline{H}$-4, 5, and 6), 6.41 (1H, d, J=15.5 Hz, CHC$\underline{H}$=CHPh), 7.31—7.54 (8H, m) and 8.01—8.12 (2H, m) (OBz and COCH=C$\underline{H}$Ph), 7.70 (1H, d, COCH=C$\underline{H}$Ph).

Found: C, 73.54; H, 5.54%. Calcd for $C_{23}H_{20}O_5$: C, 73.40; H, 5.32%.

Intramolecular Diels-Alder Reaction of 5. A solution of **5** (60 mg, 0.16 mmol) and toluene (2.0 ml) was heated in a sealed tube at 70 °C for 4 d. The mixture was concentrated and the residue was purified on a silica-gel column to give 59 mg (98%) of **7**, mp 173—174 °C, identical with the compound obtained from **6** in all respects.

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References

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5) The reaction is not optimized. A considerable amount of the methyl ester has been shown to be formed under these conditions.

6) Comparison of the ^{1}H NMR spectrum with that of an authentic sample was kindly carried out by Professor Robert B. Bates (University of Arizona), to whom our thanks are due.