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Improved Synthesis of Racemic and Optically Active 4-Hydroxycyclohex-2-en-1-one†

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Abstract: A simple and inexpensive synthetic route which affords *S*-(-)-4-hydroxycyclohex-2-en-1-one (**1a**) with high stereoselectivity and moderate enantioselectivity is reported. A key step in this procedure involves baker's yeast promoted reduction of 1α,4α,4aα,6,7,8aα-hexahydro-1,4-methanonaphthalene-5,8-dione (**3**), which affords optically active 8-hydroxy-1α,4α,4aα,8β,8aα-tetrahydro-1,4-methanonaphthalen-5(1*H*)-one (**4a**, 80% de, 67% ee) in 32% yield. The absolute configuration of the 3,5-dinitrobenzoate ester of **4a** (i. e., **5a**) was established unequivocally via single crystal X-ray structural analysis.

During the past several years, there has been increasing interest in the biological and pharmacological properties of members of the compactin-mevinolin family of natural products.[1,2] Optically active 4-hydroxycyclohex-2-en-1-one (**1**) has been employed in several laboratories as a starting material for the synthesis of compounds of this type.[3-5] It is therefore of considerable interest to develop efficient methods for preparing optically active **1** which minimize the number of required synthetic steps and maximize the overall chemical and optical yield of this important intermediate.

Danishefsky and co-workers[3] developed a multistep procedure to prepare (*S*)-(-)-**1** by starting from quinic acid as a homochiral natural product. Solladié[4] prepared both (*R*)-(+)- and (*S*)-(-)-**1** by using a chiral sulfoxide as an auxillary which was eliminated in the final synthetic step to form the conjugated double bond. Subsequently, Winterfeldt[5] utilized a retro-Diels-Alder reaction to prepare (*S*)-(-)-**1** (i. e., **1a**) in which a configurationally well-defined, asymmetrically functionalized cyclopentadiene was used as a chiral template.

An Improved Synthesis of (*S*)-(-)-4-Hydroxycyclohex-2-en-1-one (1a). We now report a simple and inexpensive synthetic route which affords **1a** with high stereoselectivity and moderate enantioselectivity (Scheme 1). Thus, 1α,4α,4aα,8aα-tetrahydro-1,4-methanonaphthalene-5,8-dione (**2**), prepared via Diels-Alder reaction between cyclopentadiene and *p*-benzoquinone,[6] was subjected to ultrasound promoted Zn/HOAc reduction, thereby affording 1α,4α,4aα,6,7,8aα-hexahydro-1,4-methanonaphthalene-5,8-dione (**3**).[7] Subsequent

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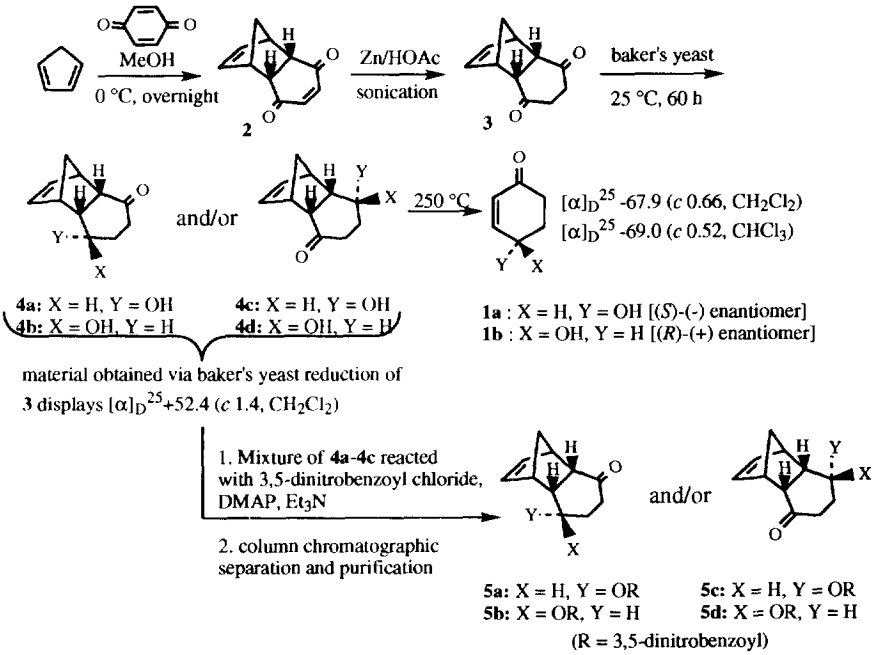
reaction of **3** with baker's yeast at room temperature for 60 hours produced **4a-4d** (mixture of isomers) as an oil, $[\alpha]_D^{25}$+52.4 (*c* 1.4, CH_2Cl_2). This is a key step in the synthesis of optically active **1**, since optical induction at the chiral *C*HOH center in **4** occurs therein. The mixture of optically active isomeric ketols **4a-4d** (obtained via baker's yeast promoted reduction of **3**, *vide supra*) was pyrolyzed in a Kugelrohr at 250 °C under reduced pressure (*ca.* 80 mm Hg). Thus, **4a-4d** suffered [4 + 2] cycloreversion (i. e., retro-Diels-Alder reaction), thereby affording optically active (*S*)-(-)-4-hydroxycyclohex-2-en-1-one (**1a**) as a colorless oil, $[\alpha]_D^{25}$ -67.9 (*c* 0.66, CH_2Cl_2); $[\alpha]_D^{25}$ -69.0 (*c* 0.52, $CHCl_3$).

Scheme 1

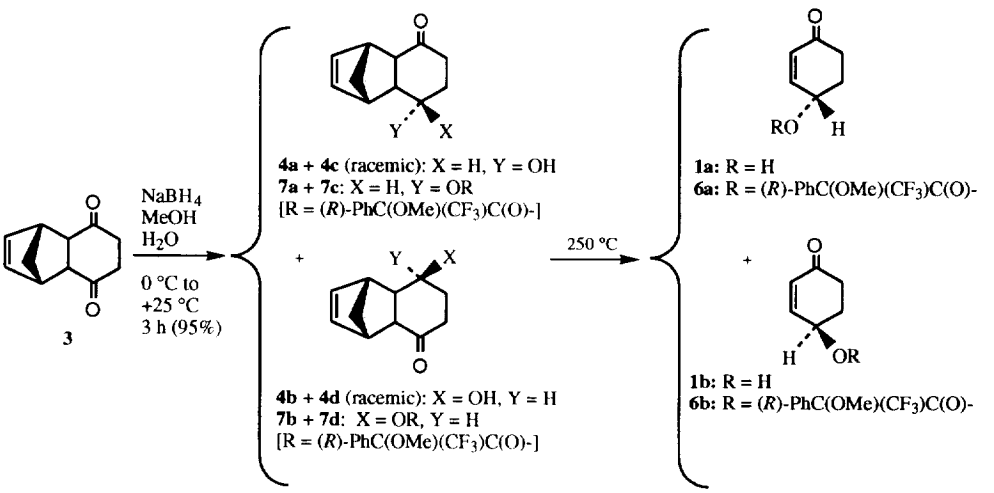


Determination of the Optical Purity of 1a. Several different values have been reported for the optical rotation of **1a** (i. e., $[\alpha]_D^{25}$ -119° (*c* 0.92, $CHCl_3$),[3] $[\alpha]_D^{25}$ -95° (*c* 0.06, $CHCl_3$),[4] and $[\alpha]_D^{25}$ -78° (*c* 0.45, $CHCl_3$).[5] For this reason, we deemed it worthwhile to determine independently the optical purity of **1a** which had been prepared by using the method described above. This determination was accomplished via application of Mosher's method.[9]

Thus, $NaBH_4$ promoted reduction of **3** afforded a diastereoisomeric mixture of racemic ketols, *rac*-**4a** (i. e., **4a** + **4c**, 94% de, (as determined by careful integration of the gated-decoupled, proton noise-decoupled ^{13}C NMR spectrum[8] of the product mixture) and *rac*-**4b** (i. e., **4b** + **4d**, minor product), in 95% yield (Scheme 2). The product mixture thereby obtained subsequently was pyrolyzed *in vacuo* by using the procedure described above, thereby affording *rac*-**1**. Subsequently, the corresponding Mosher's ester derivatives of *rac*-**1** (i. e., a mixture of diastereoisomeric esters **6a** and **6b**) and of a (racemic) mixture of **4a** + **4c** (i. e., **7a** + **7c**) were prepared, and their corresponding gated-decoupled, proton noise-decoupled ^{13}C NMR spectra[8] were obtained at 50 MHz. The resulting ^{13}C NMR spectrum of an equimolar mixture of **6a** + **6b** displays two well-

resolved signals for the diastereoisomeric C(3) carbon atoms at δ 145.12 and 145.46 (integrated ratio 1:1, as required). Similarly, the corresponding ^{13}C NMR spectrum of a mixture of diastereoisomers **7a** + **7c** displays two well-resolved signals at δ 37.11 and 37.35 (integrated ratio 1:1, as required). Thus, we elected to employ these two sets of ^{13}C NMR signals as a means to determine the optical purity of optically active **1a** and **4a** which were obtained by using the asymmetric synthesis route described previously.

Scheme 2



This same procedure was repeated for the Mosher's ester derivative of optically active **1** that had been obtained via pyrolysis of optically active ketols (i. e., **4a-4d**, which in turn had been prepared via baker's yeast promoted reduction of **3**, Scheme 1). Careful integration of the C(3) carbon atom signals at δ 145.12 (minor product) and δ 145.46 (major product) in the gated-decoupled, proton noise-decoupled ^{13}C NMR spectrum[8] of **6a** + **6b** thereby obtained revealed the presence of 64% ee of **6a** (and, hence, of (*S*)-(-)-**1**).

Determination of the Optical Purity of 4a. Integration of the *C*HOH and *C*=O resonance signals in the gated-decoupled, proton noise-decoupled ^{13}C NMR spectrum[8] of the mixture of **4a-4d** thereby obtained indicated the presence of 80% de of **4a**. In order to confirm the absolute configuration of **4a**, the mixture of isomeric ketoalcohols **4a-4d** was allowed to react with excess 3,5-dinitrobenzoyl chloride in the presence of base. The major product of this reaction, i. e., ketoester **5a**, was isolated via column chromatography (see the Experimental Section). The chiral carbon atom C(8) in **5a** was shown unequivocally to possess (*S*)-(-) absolute configuration via single crystal X-ray structural analysis.

A mixture of **5a** and **5c** could be separated from the gross mixture of **5a-5d** by careful column chromatography. Subsequently, the mixture of **5a** and **5c** thereby obtained was hydrolyzed under basic conditions to afford a mixture of **4a** and **4c**. The corresponding Mosher's esters of **4a** + **4c** (i. e., **7a** and **7c**) were prepared, and the gated-decoupled, proton noise-decoupled ^{13}C NMR spectrum[8] of this mixture of esters was obtained. Careful integration of the resonance signals at δ 37.11 and 37.35 (*vide supra*) of **7a** + **7c** revealed the presence of 67% ee of **7a** (and, hence, of **4a**).

Summary and Conclusions. A new synthetic method which affords (*S*)-(-)-4-hydroxy-2-cyclohex-2-en-1-one (**1a**) with high stereoselectivity and moderate enantioselectivity is reported herein. The Diels-Alder cycloadduct, **2**, formed via thermal reaction of cyclopentadiene with *p*-benzoquinone, was selectively reduced by Zn-HOAc, thereby affording 1α,4α,4aα,6,7,8aα-hexahydro-1,4-methanonaphthalene-5,8-dione (**3**),[7] a readily available a prochiral tricyclic diketone which serves as a key precursor to **1a**. Baker's yeast promoted reduction of **3** afforded **4a** as the major product (80% de, 67% ee). Finally, Diels-Alder cycloreversion of **4a** thereby obtained produced **1a** (64% ee). The absolute configuration of **5a**, a solid 3,5-dinitrobenzoate derivative of the major ketol formed via baker's yeast promoted reduction of **3**, was established unequivocally *via* single crystal X-ray structural analysis. The convenient synthetic route described herein is shorter than other existing routes to **1a** and utilizes inexpensive starting materials and reagents.

Experimental Section

Melting points are uncorrected. 1α,4α,4aα,6,7,8aα-Hexahydro-1,4-methanonaphthalene-5,8-dione (**3**) was synthesized via a literature procedure.[7] α–Methoxy-α-(trifluoromethyl)phenylacetic acid [i. e., (*R*)-(+)-Mosher's acid, (+)-MTPA] was used as obtained from Aldrich Chemical Co. High-resolution mass spectra were obtained by the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, NE. Elemental microanalyses were performed by M-H-W Laboratories, Phoenix, AZ.

Baker's Yeast Promoted Reduction of 3. To an aqueous solution of sucrose (7.36 g, 21.5 mmol) and Na_2HPO_4 (50 mg, 0.35 mmol) in H_2O (27 mL) at 30-35 °C was added baker's yeast (1.6 g). The resulting suspension was stirred at 30-35 °C for 30 minutes, at which time **3** (480 mg, 2.72 mmol) was added. The resulting mixture was stirred at room temperature for 60 h. Celite (1.6 g) was added, and the resulting mixture was filtered. The residue was washed sequentially with water (30 mL) and Et_2O (2 x 20 mL), and the filtrate was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residual oil thereby obtained was purified *via* column chromatography on silica gel by eluting with 25% EtOAc-hexane. The first chromatography fractions afforded recovered **3** (326 mg, 68%) followed by **4a-4d** [obtained as a mixture of diastereoisomeric ketoalcohols, $[\alpha]_D^{25}$ +52.4 (*c* 1.4, CH_2Cl_2), 155 mg, 32%] as a colorless oil; IR (neat) 3430 (s), 2958 (s), 2901 (m), 1690 (s), 1330 (w), 1246 (w), 1182 (w), 1077 (m), 1048 (m), 738 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.25 (*AB*, J_{AB} = 8.4 Hz, 1 H), 1.38 (*AB*, J_{AB} = 8.3 Hz, 1 H), 1.65-1.94 (m, 2 H), 2.10-2.24 (m, 2 H), 2.27 (s, 1 H), 2.72-2.90 (m, 2 H), 3.03 (s, 1 H), 3.22 (s, 1 H), 4.20-4.34 (m, 1 H), 5.98-6.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.59 (t). 30.47 (t), 35.86 (t), 30.06 (t), 44.04 (d), 44.98 (d), 45.57 (d), 45.71 (d), 48.04 (t), 48.91 (d), 49.74 (d), 49.84 (t), 51.35 (d), 51.86 (d), 67.42 (d), 71.14 (d), 134.7 (d), 135.1 (d), 136.5 (d), 137.6 (d), 213.5 (s), 214.1 (s); MS (70 eV) *m/z* (relative intensity) 178 (molecular ion, 3.7), 113 (15.0), 95 (14), 91 (15.3), 66 (100). HRMS Calcd for $C_{11}H_{14}O_2$: M_r^+, 178.0994. Found: M_r^+, 178.0990. Integration of the gated-decoupled ^{13}C NMR spectrum of this material indicates that it contains **4a** + **4c**. (80% de). This material was used as obtained in the next step.

(*S*)-(-)-**4-Hydroxycyclohex-2-en-1-one** (**1a**) The material which was obtained above via baker's yeast promoted reduction of **3** (160 mg, 0.90 mmol) was pyrolyzed *in vacuo* (*ca.* 80 mm Hg) at 250 °C in a Kugelrohr during 2.5 h. The distilled product was collected and purified *via* flash column chromatography on silica gel by eluting with 40% EtOAc-hexanes to afford (*S*)-**1** as an oil (50 mg, 50%): IR (neat) 3412 (br vs), 2949 (m), 2871 (w), 1670 (s), 1664 (s), 1377 (m), 1253 (m), 1207 (w), 1063 (m), 972 (w), 946 (w), 861 (w), 757 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.80-2.02 (m, 1 H), 2.18-2.58 (m, 3 H), 3.74 (br s, 1 H), 4.43-4.56 (m, 1 H), 5.87 (*AB*, J_{AB} = 10.3 Hz, 1 H), 6.90 (*AB*, J_{AB} = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 32.15 (t), 35.26 (t), 65.94 (d), 128.7 (d), 153.7 (d), 199.5 (s); $[\alpha]_D$ -67.9 (*c* 0.66, CH_2Cl_2); $[\alpha]_D$ -69.0 (*c* 0.52, $CHCl_3$). The enantiomeric excess of (*S*)-(-)-**1** was determined *via* Mosher's method.[7] Integration of the gated-decoupled ^{13}C NMR spectrum of the corresponding Mosher's esters of (*S*)-**1** thereby obtained indicates the enantiomeric excess of (*S*)-(-)-**1** to be 67% ee.

(1*R*, 4*S*, 4a*S*, 8*S*, 8a*R*)-8-(3',5'-Dinitrobenzoyloxy)-1α,4α,4aα,8β,8aα-tetrahydro-1,4-methanonaphthalen-5(1*H*)-one (**5a**). To a solution of the mixture of **4a-4d** obtained previously via baker's yeast reduction of **3** (110 mg, 0.61 mmol, *vide supra*), in CH_2Cl_2 (10 mL) was added Et_3N (1.5 mL) under argon at

room temperature. To the resulting solution were added 3,5-dinitrobenzoyl chloride (356 mg, 1.54 mmol) and 4-dimethylaminopyridine (DMAP, 10 mg), and the reaction mixture then was allowed to stir continuously overnight at ambient temperature. Methylene chloride (100 mL) was added, and the resulting mixture was washed sequentially with cold 3% aqueous HCl (20 mL) and water (2 x 40 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*., and the residue thereby obtained was purified *via* column chromatography on silica gel (400 mesh) by eluting with 20% EtOAc-hexane. Diastereoisomerically pure 8-(3',5'-dinitrobenzoyloxy)-1α,4α,4aα,8α,8aα-tetrahydro-1,4-methanonaphthalen-5(1*H*)-one (i. e., tricyclic keto-ester **5a** which contains an *exo*-8-OC(O)Ar group where Ar = 3,5-dinitrophenyl, 20 mg, 9%), $[\alpha]_D^{25}$ -69.9 (*c* 1.0, CH_2Cl_2), was thereby obtained as a colorless microcrystalline solid: mp 168-169 °C; IR (nujol) 2922 (vs), 2856 (vs), 1724 (w), 1698 (w), 1538 (w), 1458 (s), 1378 (m), 1272 (w), 1165 (w), 720 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.35 (*AB*, J_{AB} = 8.6 Hz, 1 H), 1.53 (*AB*, J_{AB} = 8.6 Hz, 1 H), 2.00-2.30 (m, 3 H), 2.38-2.62 (m, 1 H), 2.88-3.10 (m, 3 H), 3.35 (br s, 1 H), 4.70-4.83 (m, 1 H), 6.18 (*AB*, J_{AB} = 5.5 Hz, 1 H), 6,25 (*AB*, J_{AB} = 5.5 Hz, 1 H), 9.15-9.20 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 27.35 (t), 36.96 (t), 44.77 (d), 45.66 (d), 46.11 (d), 48.10 (t), 52.37 (d), 76.72 (d), 122.5 (d), 129.4 (d), 133.9 (s), 135.0 (d), 138.5 (d), 148.7 (s), 211.1(s); Anal. Calcd for $C_{18}H_{16}N_2O_7$: C, 58.07; H, 4.33. Found: C, 57.89, H, 4.13.

Continued elution of the chromatography column afforded diastereoisomerically pure 8-(3',5'-dinitrobenzoyloxy)-1α,4α,4aα,8β,8aα-tetrahydro-1,4-methanonaphthalen-5(1*H*)-one (**5a** + **5c**, 130 mg, 57%), $[\alpha]_D^{25}$ +13.8 (*c* 1.0, CH_2Cl_2), as a colorless microcrystalline solid: mp 130-131 °C; IR (nujol) 2922 (vs), 2856 (vs), 1724 (w), 1698 (w), 1545 (w), 1458 (s), 1378 (m), 1345 (w), 720 cm^{-1} (w) ; ^1H NMR ($CDCl_3$) δ 1.35 (*AB*, J_{AB} = 8.6 Hz, 1 H), 1.48 (*AB*, J_{AB} = 8.6 Hz, 1 H), 1.95-2.45 (m, 4 H), 2.98-3.22 (m, 3 H), 3.38 (br s, 1 H), 5.60-5.73 (m, 1 H), 6.06 (*AB*, J_{AB} = 5.5 Hz, 1 H), 6.28 (*AB*, J_{AB} = 5.6 Hz, 1 H), 9.07-9.12 (m, 2 H), 9.20-9.24 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.06 (t), 36.23 (t), 43.17 (d), 45.62 (d), 45.96 (d), 49.88 (t), 51.68 (d), 73.57 (d), 122.5 (d), 129.4 (d), 133.8 (s), 135.0 (d), 137.0 (d), 148.8 (s), 161.7 (s), 210.1 (s); Anal. Calcd for $C_{18}H_{16}N_2O_7$: C, 58.07; H, 4.33. Found: C, 58.11, H, 4.43. The absolute configuration of the chiral center at C(8) in the major product, i.e., enantiomer **5a**, was established unequivocally to be (8*S*-)via single crystal X-ray structural analysis (*vide infra*).

Sodium Borohydride Promoted Reduction of 3. A solution of **3** (750 mg, 4.3 mmol) in a mixture of MeOH (12 mL) and H_2O (2 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled mixture was added $NaBH_4$ (45 mg, 4.7 mmol). After the addition of the reducing agent had been completed, the external cold bath was removed, and the resulting mixture was allowed to warm to room temperature during 1 h and then stirred continuously at room temperature for 2 h. Acetic acid (0.1 mL) was added followed sequentially by addition of ice-water (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with water (30 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* to afford a yellow oil, which subsequently was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. In this manner, a 1:1 mixture of **4a** and **4c**, 730 mg, 95%) was obtained as a pale yellow oil); IR (neat) 3428 (br s), 2962 (s), 2902 (s), 1698 (s), 1458 (w), 1418 (w), 1332 (m), 1245 (m), 1179 (m), 1072 (m), 1052 (m), 946 (w), 906 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.16 (*AB*, J_{AB} = 8.4 Hz, 1 H), 1.27 (*AB*, J_{AB} = 8.4 Hz, 1 H), 1.58-1.78 (m, 2 H), 1.97-2.14 (m, 2 H), 2.73 (s, 2 H), 2.95-3.18 (m, 3 H), 4.11-4.28 (m, 1 H), 5.85-6.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.30 (t), 35.99 (t), 44.85 (d), 45.39 (d), 45.61 (d), 49.65 (t), 51.21 (d), 67.23 (d), 135.3 (d), 135.9 (d), 213.7 (s).

Racemic 4-hydroxy-2-cyclohexen-1-one (1). Racemic *endo*-**4** (720 mg, 4.04 mmol), the product obtained via $NaBH_4$ promoted reduction of **3** (*vide supra*), was pyrolyzed *in vacuo* (*ca.* 80 mm Hg) in a Kugelrohr at 250 °C for 3 h. The distillate was collected and subsequently was purified via flash column chromatography on silica gel by eluting with 50% EtOAc-hexane. Racemic *endo*-**1** (226 mg, 50%) was thereby obtained as a colorless oil; IR (neat) 3414 (s), 2949 (m), 2862 (w), 1678 (s), 1372 (m), 1059 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.72-1.95 (m, 1 H), 2.10-2.34 (m, 2 H), 2.34-2.50 (m, 1 H), 4.27 (s, 1H), 4.42 (br s, 1 H for OH), 5.79 (*AB*, J_{AB} = 9.0 Hz, 1 H), 6.85 (*AB*, J_{AB} = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.91 (t), 35.11 (t), 65.64 (d), 128.4 (d), 154.0 (d), 199.6 (s).

X-ray Structure of 5a. X-ray structure data for **5a** is presented in Table 1. All data were collected on an Enraf-Nonius CAD-4 diffractometer by using the ω scan technique, Mo Kα radiation (λ = 0.71073 Å), and a graphite monochromator. Standard procedures used in our laboratory have been described previously.[10] Data were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods (SIR[11]), and the model was refined by using full-matrix least squares techniques. All hydrogen atoms were refined anisotropically. Hydrogen atoms were located on difference maps and then included in the model

in idealized positions [U(H) = 1.3 B_{eq}(C)]. After the refinement had been completed, the atomic coordinates were inverted through the origin, and the model was refined from the isotropic stage. Although few differences were observed, these were sufficient to enable assignment of the structure as the (8*S*-) enantiomer. All computations other than those specified were performed by using MolEN.[12] Scattering factors were taken from the usual sources.[13]

Table 1. X-ray structure data for **5a**

Formula	$C_{18}H_{16}N_2O_7$	$2\theta_{max}$	44
Size (mm)	0.21 x 0.25 x 0.32	Total reflections	2398
Space Group	$P2_12_12_1$	Unique reflections	2033
a (Å)	10.617 (1)	R_{int}	0.012
b (Å)	11.1950 (8)	$I \geq 3\sigma(I)$	1689
c (Å)	13.8569 (9)	Parameters	244
V (Å^3)	1647.0 (2)	Residuals: R, R_W	0.0322, 0.0335
Z-value	4	$(\Delta/\sigma)_{max}$	<0.01
D_{calc} (g-cm^{-3})	1.502	ρmin; ρmax	0.22, -0.26
μ (cm^{-1})	1.10		

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