The synthesis of D-asperlin

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The synthesis of the D-enantiomer of asperlin has been carried out. The stereochemistry of the epoxide ring has been assigned as 6*R*,7*S* for this D-enantiomer.

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On a réalisé la synthèse de l'énantiomère D de l'asperline. On a attribué la stéréochimie 6*R*,7*S* au cycle époxyde de cet énantiomère D.

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Introduction

Asperlin is an antibiotic (U-13393) isolated from *Aspergillus nidulans* (1). It was assigned (1) the structure indicated in formula **1** (see Scheme 2). The D-enantiomer of asperlin was later synthesized (2), confirming the gross structural features of **1** and assigning a *trans* stereochemistry to the epoxide ring. A synthesis of racemic asperlin has recently appeared (3). Despite these synthetic efforts, the absolute stereochemistry of the epoxide ring remained to be established. Spin-lattice relaxation and nuclear Overhauser enhancement (nOe) measurements were used to tentatively propose the configuration of natural asperlin (4) as 6*R*,7*S*.

We have carried out an enantioespecific synthesis of the D-enantiomer of asperlin, which permits an unequivocal assignment of the stereochemistry of the oxirane ring, which turned out to be 6*R*,7*S*, **1***a*.

Results and discussion

The synthesis was initiated with tri-*O*-acetyl-D-glucal **2**, which was transformed into **3** by standard methods. Inversion of the configuration at C-4 (5) and manipulation of the C-4 and C-6 functions allowed for the preparation of aldehyde **4** (see Scheme 1). Reaction of **4** with the phosphorane derived from chloroacetaldehyde gave the *trans*-olefin **5** almost exclusively. $NaBH_4$ reduction of **5** at −20°C in methanol afforded **6** (95%) and the corresponding dihydro derivative (5%).

Epoxidation of **6** with *m*CPBA (*m*-chloroperbenzoic acid) in dichloromethane yielded a 5:4 ratio of the two possible epoxides (86% overall yield of isolated products). The major component (higher R_f) corresponds to the only product obtained by epoxidation of **6** using Sharpless conditions (6) (titanium isopropoxide, L-(+)-diethyl tartrate, and *tert*-butylhydroperoxide (TBHP)).

The mixture of epoxides **7***a* and **7***b* was separated by flash chromatography and the next sequence of reactions (see Scheme 2) was carried out separately with each isomer.

Epoxide **7***a* (6*R*,7*S*) was mesylated under standard conditions and this derivative treated (7) with $NaBH_4$ in acetonitrile under reflux. The 8-desoxy derivative **8***a* was obtained with good yield (90%). The same result was obtained (8) using "Red-Al", but the yield was significantly lower (50%).

Treatment of **8***a* (6*R*,7*S*) with Jones reagent (9) at 0–5°C during 30 min led to the formation of the lactone **9***a* (30%) and the recovery of starting material (60%). Accounting for this possible turnover, the overall yield of this oxidation approaches the 60%. Attempts to improve the lactone yield by carrying out a controlled hydrolysis of **8***a*, followed by oxidation of the corresponding hemiacetal, were not successful.

The attempted removal of the *tert*-butyldimethylsilyl (*t*-BDMSi) group of **9***a*, using conditions (10) (tetra-*n*-butylammonium fluoride in THF) ordinarily successful with this protecting group, also failed. Apparently, the basicity of the fluoride salt was sufficient to open the lactone ring, leading to a complex mixture of products. Hydrolysis (AcOH–H_2O, 7:3) (10) was rather sluggish at room temperature and led to undesirable side products when forcing these conditions.

The removal of the *t*-BDMSi group took place smoothly when compound **8***a* was treated with tetra-*n*-butylammonium fluoride in THF solution. Compound **10***a* (6*R*,7*S*), obtained in this way, was easily acetylated using standard conditions (Ac_2O/pyridine), and afforded the corresponding acetyl derivative **11***a* (100%).

Jones oxidation of **11***a* at 0–5°C, during 2 h, led to the isolation of the D-enantiomer of asperlin **1***a* (30%) and the recovery of starting material (60%). The identity with asperlin was established by comparison of the ^1H nmr spectra of **1***a* in $CDCl_3$ and C_6D_6 with published data (1, 4) (see Experimental).

The reaction sequence depicted in Scheme 2 was also applied to **7***b* (6*S*,7*R*). Compounds **8***b*, **9***b*, **10***b*, **11***b*, and **1***b* were thus obtained, and their data can be found in the Experimental.

We can then conclude that if the Sharpless rule for the asymmetric epoxidation of allylic alcohols is applicable to compound **6**, this synthesis establishes the absolute stereochemistry of natural asperlin as 6*S*,7*R*.

Experimental

For general experimental details see the preceding paper (16).

Preparation of compound ***3***

Compound **3** was prepared following literature procedures (12, 13).

Partial hydrolysis of ***3***

To a cold solution (−20°C) of **3** (120 mg, 0.32 mmol) in methanol (1.5 mL), a small amount (3 mg) of solid KOH was added and the solution stirred at −20°C for 12 h. Aqueous 5% HCl was added to reach pH 7.0. The solvent was removed and the residue separated by flash chromatography to yield 60 mg (67.5%) of ethyl 6-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (14) and 6.0 mg each of starting material (4.9%) and ethyl 4-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (6.7%).

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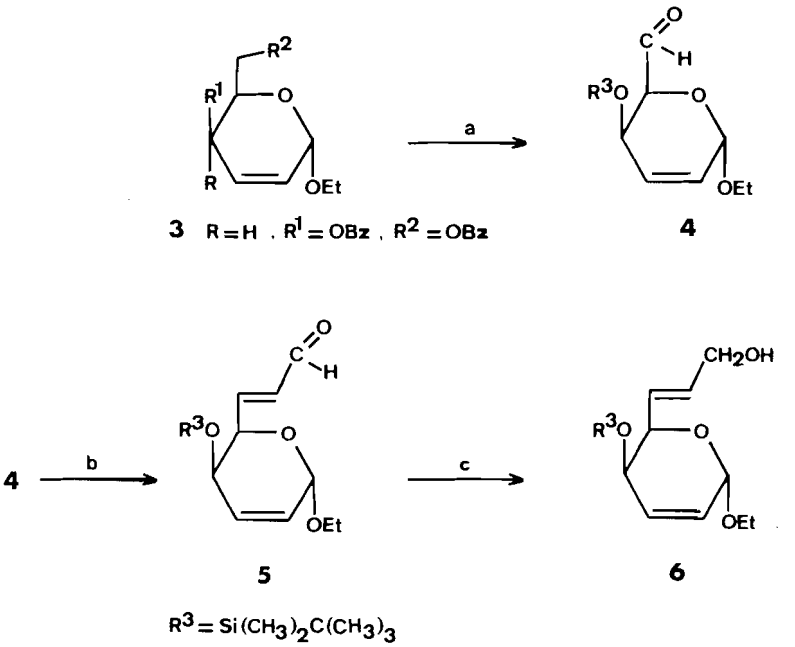
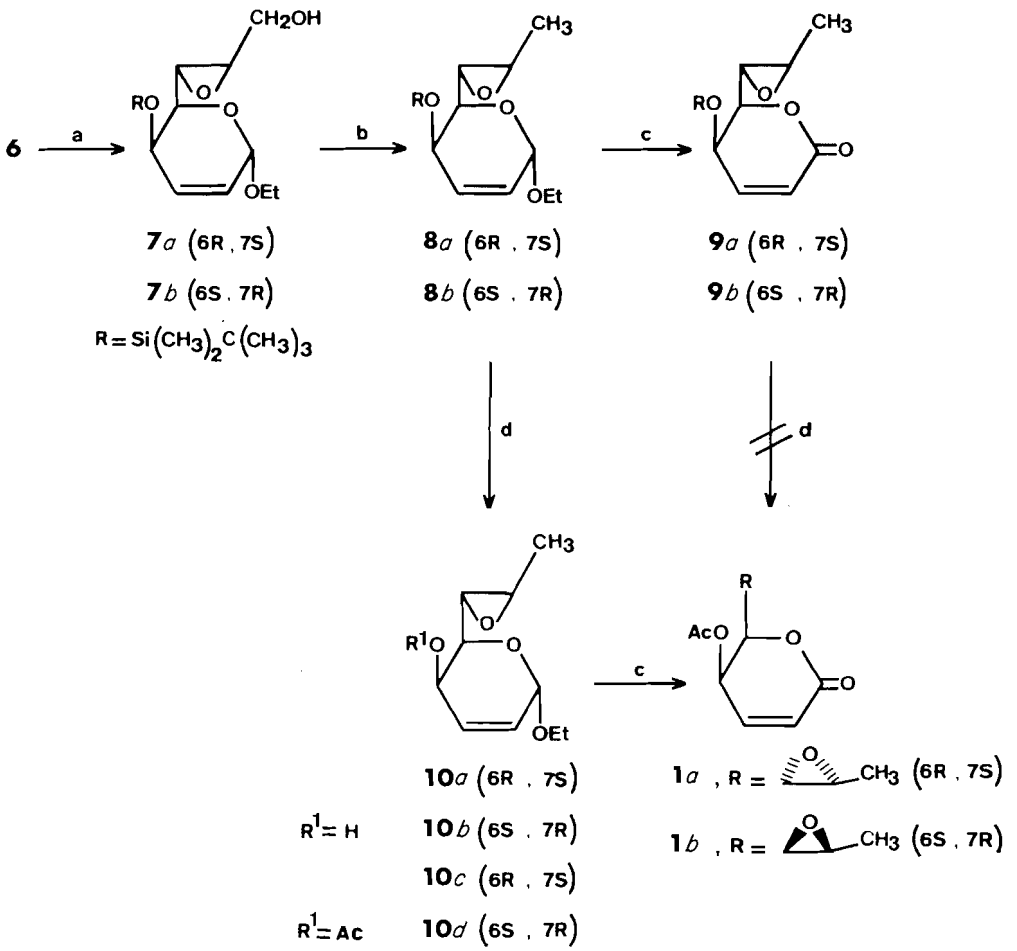


(a) MeOH, KOH, −20°C; DMAP, Et_3N, $(CH_3)_3CSi(CH_3)_2Cl$, CH_2Cl_2; MeOH, KOH, r.t.; PCC, molecular sieves, CH_2Cl_2; (b) $Ph_3P{=}CHCHO$, C_6H_6; (c) $NaBH_4$, MeOH, −5°C

SCHEME 1



(a) *m*-CPBA, CH_2Cl_2 or Ti(O—i-Pr)$_4$, L-(+)-diethyl tartrate, TBHP, CH_2Cl_2, −20°C; (b) MsCl, C_6H_5N, 0°C; $NaBH_4$, CH_3CN, molecular sieves; (c) CrO_3, H_2SO_4, CH_3COCH_3; (d) (*n*-Bu)$_4$NF, THF

SCHEME 2

Preparation of the tert-*butyldimethylsilyl derivative* ***4***

To a solution of **3***a*, ethyl 6-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (4.0 g, 14.3 mmol), in CH_2Cl_2 (20 mL), under argon, were sequentially added DMAP (4-dimethylamino pyridine) (610 mg, 4.7 mmol), Et_3N (1.53 g, 18 mmol), and *t*-BDMSiCl (2.416 g, 16 mmol). The mixture was stirred at room temperature overnight. The organic layer was washed with water, brine, and again with water.

The residue obtained was dissolved in methanol (20 mL) and a catalytic amount of KOH was added to this solution. After 3 h the solution was diluted with water and extracted with CH_2Cl_2. Column chromatography of the crude product gave pure ethyl 4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (2.7 g, 81%).

PCC (pyridinium chlorochromate) (6.45 g, 3 equiv.) was dissolved in anhydrous CH_2Cl_2 (50 mL) and molecular sieves (3Å, 10 g) were added to this solution. After stirring for 2 h, a CH_2Cl_2 solution of the alcohol prepared above (2.5 g, 1 equiv.) was added to the reaction mixture. The oxidation was complete after 2 h. The solids were eliminated by filtering through a Celite layer. Evaporation afforded crude aldehyde **4**, which was purified by column chromatography yielding 1.8 g of pure **4** (67%, aldehyde proton at δ 9.70).

Preparation of the aldehyde ***5***

A solution of formylmethylenetriphenylphosphorane (11) (5.0 g, 16.4 mmol) in dry benzene (125 mL) was mixed with the aldehyde **4** (2.87 g, 10 mmol) dissolved in benzene (10 mL). The mixture was heated in an oil bath at 110°C for 2 h. Evaporation of the solvent and chromatographic separation yielded **5** (2.7 g, 86%), mp 69–71°C; $[\alpha]_D$ −170° (*c* 0.642); ^{1}H nmr δ: 7.0 (dd, *J* = 3 and 15 Hz, H-6), 6.68 (ddd, *J* = 1.5, 7.0, and 15.0 Hz, H-7), 9.65 (d, *J* = 7 Hz, H-8).

$NaBH_4$ reduction of ***5***

A solution of **5** (1.4 g, 4.8 mmol) in methanol (50 mL) was reduced with excess $NaBH_4$ at −20°C. The methanol was poured over water and the aqueous solution extracted with CH_2Cl_2. The residue obtained by evaporation of the CH_2Cl_2 solution was purified by flash chromatography, yielding **6** (1.3 g, 95%) and its dihydro derivative (63 mg, 5%); **6**, mp 70°C, $[\alpha]_D$ −124° (*c* 1.07); ^{1}H nmr δ: 6.07 (m, 4H, olefinic protons), 4.32 (d, *J* = 5 Hz, H-8).

Epoxidation of ***6***

(a) With m*CPBA*

To a solution of **6** (800 mg, 2.5 mmol) in anhydrous CH_2Cl_2 (40 mL) was added *m*CPBA (600 mg, 3.3 mmol). The epoxidation was complete after 2 h. The organic solvent was washed with aqueous $NaHSO_3$, aqueous $NaHCO_3$, and water. Evaporation of the solvent yielded a mixture of **7***a* and **7***b*. Careful flash chromatography of the crude product (hexane – ethyl acetate 9:1) afforded **7***a* (400 mg, 48%) and **7***b* (320 mg, 38%); **7***a*, thick oil, $[\alpha]_D$ −123° (*c* 0.75); ^{1}H nmr (300 MHz) δ: 5.04 (dd, *J* = 1.0 and 2.9 Hz, H-1), 5.88 (dd, *J* = 2.9 and 10.2 Hz, H-2), 6.01 (ddd, *J* = 1.0, 5.3, and 10.2 Hz, H-3), 3.98 (dd, *J* = 2.5 and 5.3 Hz, H-4), 3.78 (dd, *J* = 2.5 and 5.7 Hz, H-5), 3.28 (dd, *J* = 2.3 and 5.7 Hz, H-6), 3.23 (m, H-7), 3.60 (m, H-8), 4.00 (m, H-8′); ^{13}C nmr (δ): 93.7 (C-1), 127.8 (C-2),[2] 129.1 (C-3),[2] 62.3 (C-4), 70.6 (C-5), 54.1 (C-6), 57.2 (C-7), 61.7 (C-8). *Anal.* calcd. for $C_{16}H_{30}O_5Si$: C 58.19, H 9.08; found: C 58.41, H 9.27.

7*b* mp 51°C, $[\alpha]_D$ −69° (0.68); ^{1}H nmr (300 MHz) δ: 5.09 (dd, *J* = 1.0 and 2.9 Hz, H-1), 5.90 (dd, *J* = 2.9 and 10.2 Hz, H-2), 5.98 (ddd, *J* = 1.0, 5.1, and 10.2 Hz, H-3), 3.93 (dd, *J* = 2.6 and 5.1 Hz, H-4), 3.63 (dd, *J* = 2.6 and 6.8 Hz, H-5), 3.35 (dd, *J* = 2.3 and 6.8 Hz, H-6), 3.10 (m, H-7), 3.60 (m, H-8), 4.00 (m, H-8′); ^{13}C nmr (δ): 93.7 (C-1), 127.8 (C-2),[2] 129.1 (C-3),[2] 62.3 (C-4), 70.6 (C-5), 54.1 (C-6), 57.2 (C-7), 61.7 (C-8). *Anal.* calcd. for $C_{16}H_{30}O_5Si$: C 58.19, H 9.08; found: C 58.20, H 9.15.

(b) With TBHP

To a cold (−20°C), serum-capped flask, containing anhydrous CH_2Cl_2 (15 mL), under argon, the following compounds were sequentially added: titanium isopropoxide (42 mg, 1.4 mmol), L-(+)-diethyl tartrate (0.25 mL), **6** (400 mg, 1.25 mmol), and a solution (15) of TBHP in toluene (0.84 mL, 2.8 mmol). The mixture was kept at −20°C overnight. Aqueous 10% tartaric acid (5 mL) was added with stirring, and the organic layer was washed with water and aqueous $NaHCO_3$. Chromatography of the residue afforded **7***a* (300 mg, 72%) (see above).

Preparation of compound ***8***

The following procedure was applied separately to **7***a* and **7***b*.

To a cold solution (0°C) of the alcohol (**7***a* or **7***b*) (330 mg, 1 mmol) in pyridine (5 mL) was added, dropwise, 0.18 mL of mesyl chloride. After 2 h, the solution was poured over cold, aqueous saturated $NaHCO_3$ (30 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL) and the organic solvent dried and evaporated, yielding the mesyl derivative, which was used in the next step without further purification.

The whole crude product, obtained as above (~1 mmol), was dissolved in acetonitrile (15 mL) and powdered molecular sieves (3Å) were added to this solution, which was heated under reflux for 1 h. $NaBH_4$ (150 mg) was added and the heating continued for 24 h. A single product was formed, which was chromatographically purified to give **8***a* or **8***b* in 90 and 70% yields, respectively.

8*a*, thick oil, $[\alpha]_D^{20}$ −124° (*c* 0.98); ^{1}H nmr (300 MHz) δ: 5.02 (d, *J* = 3.3 Hz, H-1), 5.84 (dd, *J* = 3.3 and 11.3 Hz, H-2), 6.00 (ddd, *J* = 1.3, 6.0, and 11.3 Hz, H-3), 3.95 (dd, *J* = 3.0 and 6.0 Hz, H-4), 3.63 (dd, *J* = 3.0 and 7.0 Hz, H-5), 2.96 (dd, *J* = 2.3 and 7.0 Hz, H-6), 3.03 (m, H-7), 1.35 (d, *J* = 6.0 Hz, H-8). *Anal.* calcd. for $C_{16}H_{30}O_4Si$: C 61.15, H 9.55; found: C 61.43, H 9.44.

8*b*, mp 68–70°C; $[\alpha]_D^{20}$ −87.5° (*c* 0.665); ^{1}H nmr (300 MHz) δ: 3.03 (dd, *J* = 2.3 and 8.0 Hz, H-6), 2.89 (m, H-7). *Anal.* calcd. for $C_{16}H_{30}O_4Si$: C 61.15, H 9.55; found: C 60.92, H 9.85.

Preparation of the lactone ***9***

The following procedure (9) was applied separately to epoxides **8***a* and **8***b*.

To a cold (0–5°C) solution of **8***a* (157 mg, 0.5 mmol) in acetone (10 mL), a large excess (1.5 mL, 0.07 mL required) of Jones reagent was added, followed by solid $MgSO_4$. The mixture was stirred for 30 min. A few drops of isopropyl alcohol were added, the pH of the solution made neutral by the addition of solid $NaHCO_3$, and the solids filtered off. The solution was diluted with water and most of the acetone eliminated under vacuum. Finally, it was extracted with CH_2Cl_2 and this solvent dried and evaporated to give a mixture that was purified by tlc yielding **9***a* (42 mg, 30%) and **8***a* (86 mg, 60%).

9*a*, thick oil, $[\alpha]_D^{20}$ −167° (*c* 0.862); ^{1}H nmr (300 MHz) δ: 6.08 (d, *J* = 10.6 Hz, H-2), 6.86 (dd, *J* = 6.0 and 10.6 Hz, H-3), 4.29 (d, *J* = 3.0 and 6.0 Hz, H-4), 3.83 (dd, *J* = 3.0 and 7.6 Hz, H-5), 3.05 (m, H-6 and H-7), 1.35 (d, *J* = 5.3 Hz, H-8); ^{13}C nmr (δ): 162.2 (C-1), 122.5 (C-2), 144.2 (C-3), 61.3 (C-4), 81.3 (C-5), 55.4 (C-6),[2] 54.6 (C-7),[2] 17.2 (C-8).

9*b*, mp 93–95°C; $[\alpha]_D^{20}$ −78° (*c* 0.329); ^{1}H nmr (300 MHz) δ: 5.99 (d, *J* = 10.6 Hz, H-2), 6.69 (dd, *J* = 4.3 and 10.6 Hz, H-3), 4.5 (dd, *J* = 4.3 and 5.3 Hz, H-4), 4.09 (dd, *J* = 5.3 and 5.6 Hz, H-5), 3.14 (dd, *J* = 2.6 and 5.6 Hz, H-6), 2.93 (m, H-7), 1.31 (d, *J* = 6.0 Hz, H-8); ^{13}C nmr (δ): 165.8 (C-1), 122.1 (C-2), 144.5 (C-3), 63.4 (C-4), 80.2 (C-5), 56.5 (C-6), 50.4 (C-7), 17.0 (C-8).

Preparation of compound ***10***

The following procedure was applied separately to epoxides **8***a* and **8***b*.

To a solution of **8***a* (157 mg, 0.5 mmol) in freshly distilled THF (7 mL) was added tetra-*n*-butylammonium fluoride (260 mg, 1 mmol). The mixture was stirred for 30 min at room temperature. The solvent, once washed with water, was evaporated under vacuum and the residue, **10***a*, was acetylated with Ac_2O/pyridine at room temperature during 4 h. The usual work-up yielded compound **11***a* (120 mg, 100%) as a thick oil; ^{1}H nmr (300 MHz) δ: 5.06 (d, partially overlapping with H-4, H-1), 6.02 (dd, *J* = 2.6 and 11.0 Hz, H-2), 6.15 (ddd, *J* = 1.3, 6.0, and 11.0 Hz, H-3), 5.08 (ddd, *J* = 0.6, 3.0, and 6.0 Hz, H-4), 3.96 (dd, *J* = 3.0 and 6.0 Hz, H-5), 2.90 (dd, *J* = 6.0 and 2.3 Hz, H-6), 3.09 (m, H-7), 1.36 (d, *J* = 5.2 Hz, H-8).

[2]These assignments can be reversed.

Preparation of compound **1**

The same procedure was applied to compounds **11***a* and **11***b* (this last one was not further characterized).

To a cold solution (0–5°C) of **11***a* (120 mg, 0.5 mmol) in acetone (10 mL), a large excess (1.5 mL, 0.07 mL required) of Jones reagent was added, followed by the addition of anhydrous $MgSO_4$ (140 mg). The mixture was stirred for 2 h. A few drops of isopropyl alcohol were then added and the solids filtered off. The solution was adjusted to pH 7.0 by the addition of solid $NaHCO_3$, diluted with water, and most of the acetone eliminated under vacuum. The solution was extracted with CH_2Cl_2 and this solvent dried and evaporated, affording a mixture of compounds that was separated by tlc. Compounds **1***a* (22 mg, 20%) and **11***a* (70 mg, 60%) were isolated; **1***a*, mp 69–71°C (lit. (1) mp 71–73°C), $[\alpha]_D^{30}$ −320° (*c* 0.951, $CHCl_3$); uv, λ_{max} (EtOH): 220 nm; ^{1}H nmr (300 MHz) ($CDCl_3$) δ: 6.22 (d, *J* = 9.6 Hz, H-2), 7.08 (dd, *J* = 5.7 and 9.6 Hz, H-3), 5.32 (dd, *J* = 3.0 and 5.7 Hz, H-4), 4.12 (dd, *J* = 3.0 and 7.2 Hz, H-5), 3.08 (m, H-6 and H-7), 1.39 (d, *J* = 5.1 Hz, H-8) (identical to published data, see ref. 1); (C_6D_6, 0.1 *M*) δ: 5.61 (d, *J* = 10.6 Hz, H-2), 6.19 (dd, *J* = 6.3 and 10.6 Hz, H-3), 4.76 (dd, *J* = 3.0 and 6.3 Hz, H-4), 3.23 (dd, *J* = 3.0 and 7.0 Hz, H-5), 2.69 (dd, *J* = 2.0 and 7.0 Hz, H-6), 2.48 (m, H-7), 0.82 (d, *J* = 5.6 Hz, H-8) (see ref. 4).

1*b* (prepared as above) (13 mg, 11%), mp 63–65°C; $[\alpha]_D^{30}$ −170° (*c* 0.355, $CHCl_3$); uv λ_{max} (EtOH): 220 nm; ^{1}H nmr (300 MHz) ($CDCl_3$) δ: 6.22 (d, *J* = 9.9 Hz, H-2), 6.87 (dd, *J* = 5.1 and 9.9 Hz, H-3), 5.51 (dd, *J* = 3.6 and 5.1 Hz, H-4), 4.36 (dd, *J* = 3.6 and 4.8 Hz, H-5), 3.02 (m, H-6 and H-7), 1.35 (d, *J* = 5.1 Hz, H-8); (C_6D_6) δ: 5.61 (d, *J* = 10.6 Hz, H-2), 5.81 (dd, *J* = 5.6 and 10.6 Hz, H-3), 4.73 (dd, *J* = 3.0 and 5.6 Hz, H-4), 3.41 (dd, *J* = 3.0 and 6.0 Hz, H-5), 2.53 (m, H-6), 2.46 (m, H-7), 0.80 (d, *J* = 5.6 Hz, H-8).

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