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Polycondensed Heterocycles. Part 11: Preparation and Regioselective Reductions of 5-Phenyl-4*H*-pyrrolo[1,2-*a*][1]benzazepin-4-one

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Abstract—The Wadsworth–Emmons olefination between 2-(1*H*-pyrrol-1-yl)benzaldehyde and methyl α-(diethylphosphonyl)phenylacetate leads exclusively to the *cis*-isomer of methyl 2-(1*H*-pyrrol-1-yl)-α-phenylcinnamate, which, after transformation into the corresponding acid chloride, was easily cyclised to the title enone. This latter was regioselectively reduced to the corresponding saturated ketone or unsaturated alcohol, under different experimental conditions. An improved preparation of starting 2-(1*H*-pyrrol-1-yl)benzaldehyde is also reported.

Introduction

The interest in the chemistry of heterocyclic systems with general formulas **I**–**III** arises from the biological activity showed by several of their derivatives. Our recent work in this area has concentrated on the production of enolizable 6-arylpyrrolo[2,1-*d*][1,5]benzo*hetero*azepin-7(6*H*)ones **I**, as synthetic precursors of ligands **II**, specific for the peripheral-type benzodiazepine receptor (PBR),[1] and the corresponding 6-alkyl-6-aryl derivatives **III**, as inhibitors of HIV-reverse transcriptase (Fig. 1).[2]

For both classes of compounds, results of biological testing seemed to prove that the nature of the atom at position 5 was not crucial for the interaction with receptors. As a proof of such a hypothesis, we planned to prepare and test analogues with a methylene group replacing the heteroatom in position 5, as bioisosteres of the above compounds. Accordingly, we herein report the synthesis of 5-phenyl-4*H*-pyrrolo[1,2-*a*]-[1]benzazepin-4-one **1**, which, after selective 1,4-reduction of the enone moiety, furnishes the corresponding saturated ketone **2**, the common key intermediate for the preparation of both classes of isosteres (Scheme 1). Selective enone 1,2-reduction of compound **1** produces allylic alcohol **3**, which allows the preparation of new PBR ligands with a fairly unchanged overall conformation of the tricyclic system, but a different electronic arrangement due to the retaining of the double bond in the original 5,6-position. Furthermore, the corresponding saturated alcohol **4** was obtained when exposing enone **1** to less selective reduction conditions.

Results and Discussion

An exhaustive literature survey led to only two procedures for the preparation of pyrrolo[1,2-*a*][1]benzazepine derivatives,[3,4] the more adaptable being the one described by Plummer et al.,[3] who performed a polyphosphoric acid-catalysed cyclisation of a preformed 3-[2-(1*H*-pyrrol-1-yl)phenyl]propionic acid, as the key step. In our case, the

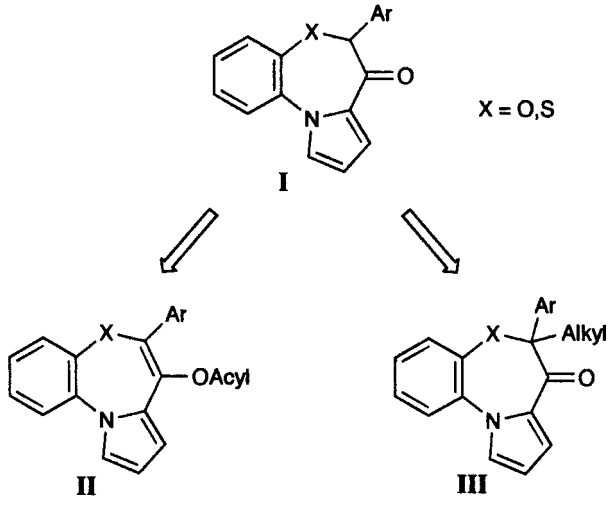

Figure 1.

Keywords: benzazepines; cyclisation; olefination; reduction.
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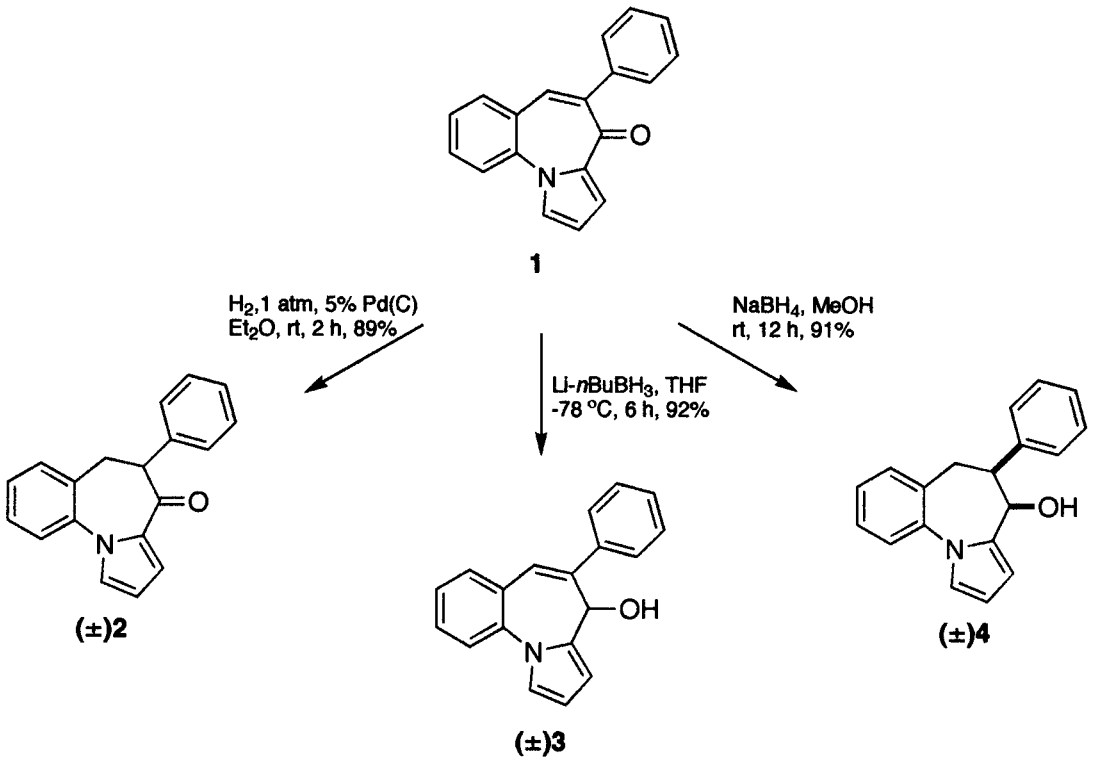
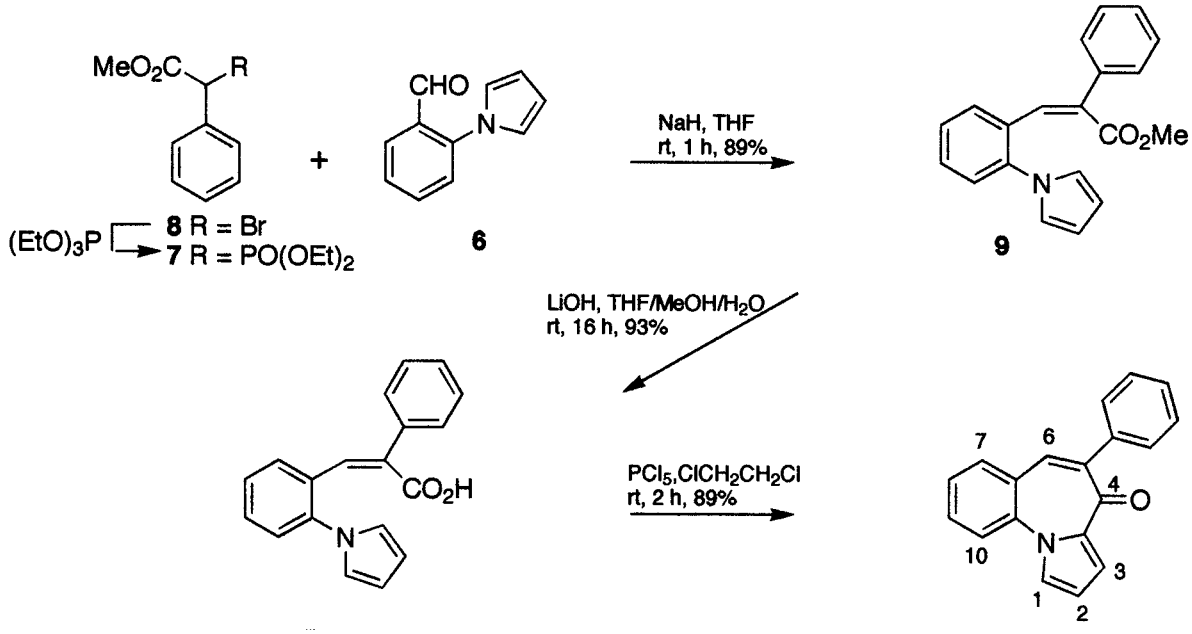


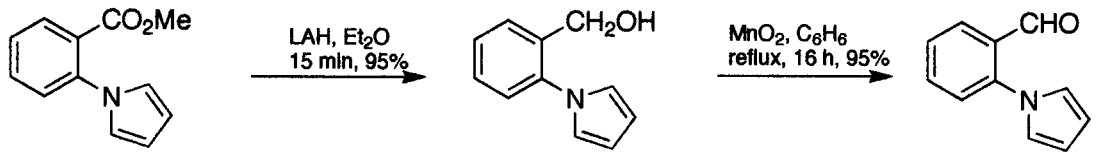
Scheme 1.

synthesis of a 2-(1*H*-pyrrol-1-yl)-α-phenylcinnamic acid **5** with which to subject to cyclisation had to be set up and 2-(1*H*-pyrrol-1-yl)benzaldehyde **6** was accordingly selected as the starting material.

Hence, the Wadsworth–Emmons olefination between the ylide generated by sodium hydride on crude methyl α-(diethylphosphonyl)phenylacetate **7**, (in turn obtained by action of triethyl phosphite on methyl α-bromophenylacetate **8**) and aldehyde **6** afforded the expected methyl 2-(1*H*-pyrrol-1-yl)-α-phenylcinnamate **9** exclusively as the *cis*-isomer (Scheme 2). No formation of any *trans*-isomer was actually detected after this reaction. Alkaline hydrolysis of ester **9** smoothly gave the desired acid **5** in very good yield. Our attempts to carry out the cyclisation to the title compound **1** after the procedure of Plummer et al. (polyphosphoric acid, 120°C) resulted in failure. Better results were achieved when using an uncatalysed Friedel–Crafts reaction with PCl_5, following a method already applied to similar compounds.[5] The choice of methyl ester **8**, a



Scheme 2.



Scheme 3.

strong lachrymatory compound, which requires accurate precautions during manipulation, was justified by the fact that its little encumbering methyl group should correctly drive the reaction towards a product with the desired geometry.

The starting aldehyde **6** had previously been prepared by Raines et al.,[6] after a McFadyen–Stevens reduction of methyl 2-(1*H*-pyrrol-1-yl)benzoate **10**, but such a method proved rather unsatisfactory owing to the low overall yield (~30%). Therefore, we found a new and more efficient two-step procedure, consisting of LAH reduction of the same starting ester **10** to 2-(1*H*-pyrrol-1-yl)benzenemethanol **11**[7] which swiftly was subjected to MnO_2 oxidation. In this way, aldehyde **6** was obtained in a 90% yield (Scheme 3).

The enone **1** was then selectively reduced to the racemic saturated ketone **2** by 5% Pd(C) catalysed hydrogenation under atmospheric pressure, the reaction interrupted after absorption of 1 equiv. of hydrogen. In fact, the corresponding saturated racemic *cis*-alcohol **4** was obtained at higher pressure of hydrogen and/or prolonged reaction time (Scheme 1). The relative configuration of alcohol **4** was assigned on the basis of ^{1}H NMR experiments, in comparison to the results previously obtained for related compounds,[8] reflecting the preferred approach of a second equivalent of hydrogen from the less hindered face of tricyclic system of intermediate ketone **2**. More straightforwardly, *cis*-alcohol **4** was obtained by action of $NaBH_4$ on enone **1**, very likely via an initial carbonyl reduction (without the possibility of isolating the intermediate unsaturated alcohol **3**) followed by stereospecific double bond saturation.

The regioselective carbonyl reduction of compound **1** was successfully carried out by use of lithium *n*-butylborohydride, following a procedure described by Kim et al.,[9] to give unsaturated alcohol **3** in a 92% yield. On the other hand, no such reaction occurred when attempted under different conditions (i.e.: Meerwein–Ponndorf reduction, DIBAH).

Conclusions

In conclusion, we have herein described a convenient reaction sequence, which allows the preparation of a precursor of numerous 5-phenylpyrrolo[1,2-*a*][1]benzazepine derivatives to submit to biological evaluation. Further possibilities for the reported synthetic method can be envisaged in the use, as starting materials, of derivatives of **6** and **8** bearing substituents on aromatic rings,[10] thereby obtaining a variety of substituted analogues.

Experimental

Where necessary, solvents were dried and purified according to the recommended procedures.[11] Extracts were dried over Na_2SO_4 and solvents were removed under reduced pressure. Melting points were determined using an Electrothermal 8103 capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 398 spectrophotometer using KBr discs and nuclear magnetic resonance spectra were taken on a Bruker 200 instrument. The chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectral data were determined by direct insertion at 70 eV with a VG70 spectrometer. Flash chromatography separations were performed using Merck 230–400 mesh silica gel as the solid phase. Elemental analyses were performed on a Perkin–Elmer 240C elemental analyzer. All reactions were carried out in an argon atmosphere.

2-(1*H*-Pyrrol-1-yl)benzaldehyde (6). To a cooled (0°C) and stirred solution of methyl 2-(pyrrol-1-yl)benzoate **10** (0.72 g, 3.6 mmol) in dry diethyl ether (15 mL) was added dropwise a slurry of LAH (0.28 g, 7.3 mmol) in the same solvent (10 mL). After 15 min, the unreacted LAH was cautiously quenched with ethyl acetate and a few drops of 15% sulfuric acid. The mixture was then extracted with ethyl acetate and the organic layer was evaporated to dryness to give almost pure 2-(1*H*-pyrrol-1-yl)benzenemethanol **11** (0.59 g, 95%) as an oil,[7] which was used without purification in the subsequent step. A solution of alcohol **11** (0.59 g, 3.4 mmol) in benzene (4 mL) was slowly added to a suspension of activated manganese dioxide (1.2 g, 13.8 mmol) in benzene (20 mL) then heated to reflux under a Dean–Stark apparatus for 16 h. After filtration, the solvent was evaporated and the residue was chromatographed (dichloromethane/light petroleum, 1:1) to afford pure **6** as a colourless oil (0.55 g, 95%), with physical and chemical data identical to those reported in ref. 5; bp 72°C/0.05 mmg, Lit.[6] bp 70–72°C/0.05 mmHg; δ_H (200 MHz, $CDCl_3$) 9.25 (s, 1H), 7.95 (m, 1H), 7.63 (m, 1H), 7.41 (m, 2H), 6.90 (m, 2H), 6.38 (m, 2H).

Methyl *cis*-2-(1*H*-pyrrol-1-yl)-α-phenylcinnamate (9). A mixture of (±)-methyl α-bromophenylacetate **8** (0.92 g, 4 mmol) and triethyl phosphite (8.3 g, 5 mmol) was heated at 160°C. After 1 h, a further portion of triethyl phosphite (8.3 g, 5 mmol) was added and heating continued for 1 h. The excess triethyl phosphite was distilled under vacuum at 60°C and the residue, essentially constituting phosphonyl ester **7** was dissolved in dry THF (10 mL). This solution was added dropwise into a cooled (0°C) suspension of sodium hydride (60% oil dispersion, 160 mg, 4 mmol) and dry THF (5 mL). Stirring was then maintained for 10 min at room temperature, then a solution of aldehyde **6** (0.7 g,

4 mmol) was added dropwise while cooling and left for 1 h at room temperature. The solvent was evaporated and the residue partitioned between water and ethyl acetate. The organic layer was separated, dried and concentrated to give a residue which was chromatographed (toluene/cyclohexane, 4:1) to give pure compound **9** as a thick oil (1.1 g, 89%); [Found: C, 79.34; H, 5.77; N, 4.55. $C_{20}H_{17}NO_2$ requires C, 79.19; H, 5.65; N, 4.62%]; IR (neat): ν_{max} 1720 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.58 (s, 1H), 7.17–7.32 (m, 7H), 6.81–6.98 (m, 4H), 6.38 (t, 2H, J=1.8 Hz), 3.75 (s, 3H); δ_C (50.3 MHz, $CDCl_3$) 165.4, 138.7, 137.2, 135.3, 130.7, 129.6, 129.4, 129.0, 127.9, 127.5, 127.1, 126.4, 126.0, 122.1, 109.4, 51.0; *m/z* [EI] 303 (14 M^+), 273 (12), 244 (100), 168 (31), 127 (15%).

***cis*-2-(1*H*-Pyrrol-1-yl)-α-phenylcinnamic acid (5).** A solution of lithium hydroxide monohydrate (84 mg, 2 mmol) in water (2 mL) was added dropwise to a cooled (0°C) solution of ester **9** (0.5 g, 1.65 mmol) in methanol (3 mL), THF (6 mL) and water (3 mL). The mixture was stirred for 16 h at room temperature, then concentrated to a small volume, and acidified (pH 4–5), with cooling, by dropwise addition of 1 M hydrochloric acid. The solid formed was extracted into ethyl acetate and the resulting solution was washed with water to neutrality and dried. The organic layer was evaporated to dryness to give acid **5** as white prisms (0.44 g, 93%); mp 97–99°C (hexanes); [Found: C, 79.03; H, 5.36; N, 4.68. $C_{19}H_{15}NO_2$ requires C, 78.87; H, 5.23; N, 4.84%]; IR (Nujol): ν_{max} 2980 (b), 1705 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.58 (bs, 1H, exchangeable), 7.54 (d, 1H, J=7.1 Hz), 7.28–7.44 (m, 8H), 6.92 (t, 2H, J=1.9 Hz), 6.83 (s, 1H), 6.28 (t, 2H, J=1.9 Hz); δ_C (50.3 MHz, $CDCl_3$) 171.3, 136.5, 137.3, 135.1, 134.0, 129.4, 129.1, 128.8, 127.5, 127.2, 126.8, 126.2, 126.0, 121.4, 109.1; *m/z* [EI] 289 (8 M^+), 244 (100), 154 (44), 127 (18%).

5-Phenyl-4*H*-pyrrolo[1,2-*a*][1]benzazepin-4-one (1). To a well-stirred solution of acid **5** (60 mg, 0.21 mmol) in dry 1,2-dichloroethane (2 mL) freshly sublimed phosphorus pentachloride (44 mg, 0.21 mmol) was added portionwise. The resulting mixture was stirred for 2 h at room temperature. The solvent was removed under vacuum and the residue was taken up in dichloromethane. The organic solution was shaken with aqueous sodium bicarbonate, then dried and concentrated. The resulting residue was chromatographed (dichloromethane) to give pure **1** as a colourless solid (50 mg, 89%); mp 186–188°C (hexanes); [Found: C, 84.30; H, 4.95; N, 5.10. $C_{19}H_{13}NO$ requires C, 84.11; H, 4.83; N, 5.16%]; IR (Nujol): ν_{max} 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.21–7.65 (m, 12H), 6.61 (t, 1H, J=3.4 Hz); δ_C (50.3 MHz, $CDCl_3$) 177.4, 140.5, 137.4, 135.3, 132.9, 129.8, 129.5, 129.1, 128.8, 128.2, 127.8, 127.1, 126.4, 126.2, 122.3, 117.0, 111.1; *m/z* [EI] 271 (15 M^+), 243 (100), 168 (18), 154 (7%).

(±)5,6-Dihydro-5-phenyl-4*H*-pyrrolo[1,2-*a*][1]benzazepin-4-one (2). A mixture of compound **1** (0.27 g, 1 mmol), ethyl acetate (20 mL) and 5% palladium on charcoal (50 mg) was stirred under a hydrogen blanket at atmospheric pressure for 2 h at room temperature. The catalyst was then removed by filtration through Celite and the clear solution concentrated to give a residue which was chromatographed (ethyl acetate/hexanes, 1:8). Compound **2** was obtained as a white solid (0.24 g, 88%); mp 157–158°C (hexanes); [Found: C, 83.71; H, 5.62; N, 5.16. $C_{19}H_{15}NO$ requires C, 83.49; H, 5.53; N, 5.12%]; IR (Nujol): ν_{max} 1705 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.23–7.35 (m, 11H), 6.45 (t, 1H, J=3.3 Hz), 3.96 (dd, 1H, J=9.5, 2.6 Hz), 3.35 (ddd, 2H, J=13.9, 9.5, 2.6 Hz); δ_C (50.3 MHz, $CDCl_3$) 190.2, 140.0, 138.7, 132.9, 132.5, 129.8, 129.0, 128.3, 127.8, 127.5, 127.0, 125.7, 122.4, 117.3, 111.4, 50.1, 32.7; *m/z* [EI] 273 (60 M^+), 244 (54), 168 (100), 154 (13), 127 (8%).

(±)4-Hydroxy-5-phenyl-4*H*-pyrrolo[1,2-*a*][1]benzazepine (3). To a solution of enone **1** (0.27 g, 1 mmol) in dry THF (6 mL), a suspension of lithium *n*-butylborohydride in THF–*n*-hexane [4 mL of a 0.25 M solution (prepared from borane–dimethyl sulfide complex and *n*-butyllithium, as described by Kim et al.), 1 mmol][9] was added dropwise over 5 min in a dry ice–acetone bath. After 6 h of being stirred at −78°C, the reaction mixture was hydrolysed with water (0.5 mL) and then allowed to warm to room temperature. The reaction mixture was oxidised with 10% NaOH (3 mL) and 30% H_2O_2 (2 mL) by stirring overnight at room temperature. After ethyl acetate (15 mL) was added, the aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with $NaHSO_3$ solution, then dried and concentrated to give a residue which was purified by chromatography (ethyl acetate/hexanes, 1:3) to give unsaturated alcohol **3** as a colourless oil (0.25 g, 92%); [Found: C, 83.33; H, 5.45; N, 5.19. $C_{19}H_{15}NO$ requires C, 83.49; H, 5.53; N, 5.12%]; IR (neat): ν_{max} 3350 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.00–7.51 (m, 11H), 6.45 (s, 1H), 6.35 (t, 1H, J=3.0 Hz), 6.18 (m, 1H), 1.70 (bs, 1H, exchangeable); δ_C (50.3 MHz, $CDCl_3$) 139.9, 137.6, 135.5, 133.8, 130.0, 129.4, 128.9, 128.3, 127.9, 126.4, 126.1, 122.5, 119.7, 116.9, 108.8, 106.2, 69.7; *m/z* [EI] 273 (5 M^+), 256 (52), 244 (100), 154 (15), 127 (13%).

(±)*cis*-5,6-Dihydro-4-hydroxy-5-phenyl-4*H*-pyrrolo[1,2-*a*][1]benzazepine (4). (a) A mixture of compound **1** (0.27 g, 1 mmol), ethyl acetate (20 mL) and 5% palladium on charcoal (50 mg) was hydrogenated for 24 h at atmospheric pressure (or, alternatively, for 1 h at 45 psi). The catalyst was then removed by filtration through Celite and the clear solution was concentrated to give a residue which was chromatographed (ethyl acetate/hexanes, 1:3). Compound **4** was obtained as a white solid (0.24 g, 88%); mp 137–138°C (hexanes); [Found: C, 83.03; H, 6.35; N, 5.21. $C_{19}H_{17}NO$ requires C, 82.88; H, 6.22; N, 5.09%]; IR (Nujol): ν_{max} 3360 (b) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.24–7.39 (m, 9H), 7.01 (m, 1H), 6.35 (t, 1H, J=3.0 Hz), 6.17 (m, 1H), 4.84 (d, 1H, J=6.8 Hz), 3.80 (dt, 1H, J=11.4, 6.8 Hz), 2.86 (ddd, 2H, J=13.6, 11.4, 6.8 Hz), 1.60 (bs, 1H, exchangeable); δ_C (50.3 MHz, $CDCl_3$) 139.7, 139.4, 133.8, 132.8, 130.0, 129.2, 128.5, 128.0, 127.6, 126.3, 122.4, 119.7, 108.8, 106.3, 68.7, 54.7, 37.5; *m/z* [EI] 275 (59 M^+), 258 (100), 246 (22), 180 (32), 168 (21), 154 (17%).

(b) To a stirred suspension of $NaBH_4$ (38 mg, 1 mmol) in dry methanol (10 mL) was added dropwise a solution of enone **1** (0.27 g, 1 mmol) in the same solvent (2 mL). The mixture was stirred overnight at room temperature. Removal of the solvent gave a white semisolid which was

stirred in water (20 mL) for 15 min, then extracted with ethyl acetate. The organic layer was evaporated to dryness and the resulting residue was chromatographed as above to give pure alcohol **4** (0.25 g, 91%).

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