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Economical and Convenient Carbonyl Transposition Approach Toward a 2-Arylcycloheptanone Derivative

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Abstract: A convenient, straightforward, and easy access to 2(2,3-dimethoxy-phenyl)-cycloheptanone, which employs an heteroatom-facilitated *ortho*-lithiation coupled to a carbonyl transposition strategy, is reported. The synthetic approach avoids using very expensive reagents or difficult-to-prepare starting materials.

Keywords: 2-Arylcycloheptanone, carbonyl transposition, chemical synthesis, epoxide rearrangement, *ortho*-lithiation

INTRODUCTION

Derivatives of 2-substituted cycloheptanone have been employed as synthetic intermediates.^[1] However, they are not easily available, because the efficient synthesis of α -aryl alkanones and cycloalkanones is still a challenging problem. Reagents and reactions employed for their preparation include diaryliodonium salts,^[2a–c] organobismuths,^[2f,g] organoboron derivatives,^[2h] iron and chromium carbonyls,^[3a,b] copper reagents,^[3c–g] organoleads,^[4a–c] nickel,^[4d] and palladium^[4e–g] derivatives, as well as Grignard^[5a] and organocadmiums,^[5b] photostimulated reactions^[5c] with ketone enolates,^[5d] and arylation of enamines with highly reactive halides.^[5e] Additional alternatives

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involve arylmethylene insertion through aryldiazomethane,^[6a-c] β -oxido carbenoid,^[6d] and 1-arylmethylbenzotriazole chemistry,^[6e] as well as the rearrangement of halohydrins, derived from the addition of benzylmagnesium chloride to carbonyl compounds followed by α -bromination.^[7]

Methods employed for accessing 2-aryl-substituted cycloheptanones include ring expansion of cyclohexanone with aryldiazomethane^[8] and arylmethyl benzotriazole derivatives.^[6e]

Stephaxocanidine (**1**), shown in Figure 1, is a novel natural product isolated from *Stephania cepharantha*.^[9] We have synthesized AC- and ABC-ring analogs^[10] of this tetracyclic compound and demonstrated that certain tricyclic derivatives possess interesting acetylcholinesterase-inhibiting activity.^[10d,e]

For a project related to the total synthesis of stephaxocanidine and structural analogs incorporating the D-ring of the natural product, we required a simple, inexpensive, and reliable route to 2(2,3-dimethoxyphenyl) cycloheptanone (**2**). However, the available methods require either expensive, unstable, or highly toxic reagents; not easily available starting materials; or special equipment or are limited to aromatics carrying electron-withdrawing groups.

RESULTS AND DISCUSSION

Compound **2** was previously prepared by Gutsche^[8] employing the corresponding phenyldiazomethane, an unstable compound for the preparation of which the hazardous, highly toxic, and currently not readily available anhydrous hydrazine is required; in addition, the transformation demands important quantities of mercury(II) oxide, which is added in excess as oxidant.

We envisioned a new synthesis of **2** as the result from the 1,2-addition of *ortho*-metallated 1,2-dimethoxybenzene (**3**) to cycloheptanone (**4**), followed by a carbonyl transposition. For reviews on carbonyl transposition, see^[11]

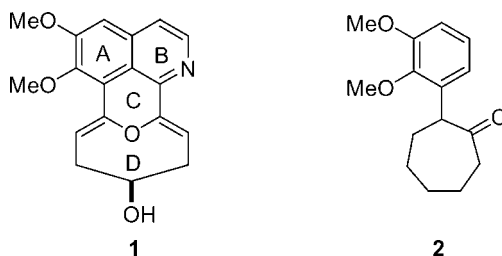


Figure 1. Stephaxocanidine (**1**) and target compound (**2**).

Thus, compound **3** was subjected to an heteroatom-facilitated *ortho* lithiation with *n*-butyllithium in dry Et₂O, and the resulting organometallic derivative was treated with cycloheptanone, resulting in 65% of alcohol **5**, which was easily dehydrated with catalytic amounts of oxalic acid in refluxing toluene,^[1c] furnishing aryl-cycloheptene **6**.

However, submission of **6** to hydroboration-oxidation with BH₃·SMe₂ gave mixtures of the expected secondary alcohol **7** and its epimer **8** (37%, combined yield)^[12] together with precursor **5**, the latter being the most abundant product.^[12b,c] Despite literature precedents regarding product distribution after hydroboration-oxidation of styrenes, the elevated proportion of **5** in the mixture was surprising, and consequently this approach was considered inefficient.

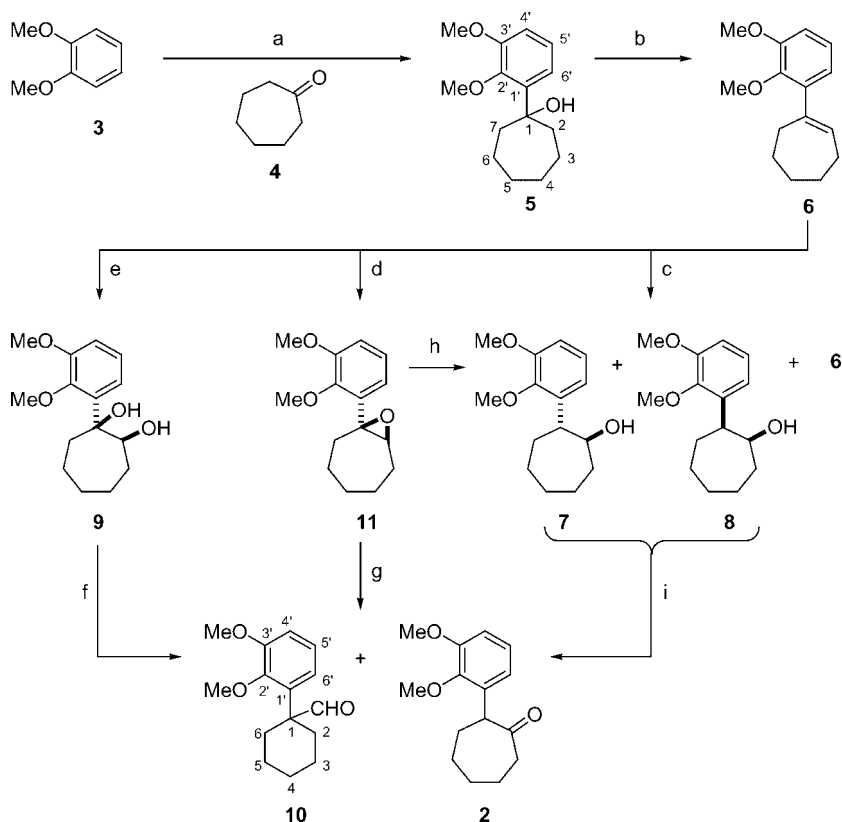
Therefore, cycloheptene **6** was catalytically dihydroxylated with osmium tetroxide, employing NMO as stoichiometric co-oxidant. However, the transformation proceeded sluggishly, and poor yields (30%) of diol **9** were realized after prolonged exposure to the reaction conditions. Moreover, when **9** was subjected to diol dehydration^[13] with TsOH in toluene at 80°C, the desired ketone **2** and the rearranged aldehyde **10** were obtained as an approximate 1:6 mixture in 77% combined yield.

An analogous result was observed when **6** was epoxidized with *m*-CPBA in chloroform and the resulting oxirane **11**, obtained in 97% yield, was rearranged with BF₃·Et₂O at –50°C or with ZnI₂ at room temperature in CH₂Cl₂ as solvent.^[13a] In the former case, only 11% of **2** was obtained, together with 57% of aldehyde **10**.

Scheme 1: Reagents and conditions: a) 1. *n*-BuLi, Et₂O, rt, overnight; 2. Cycloheptanone (**4**), 30 min, rt (65%); b) (COOH)₂ (cat.), PhMe, 110°C, 3 h (70%); c) 1. BH₃·SMe₂, THF, 0°C → rt, overnight; 2. H₂O₂, NaOH, 50°C (**7** + **8**, 37%); d) *m*-CPBA, Cl₂CH₂, NaHCO₃, 0°C, 1 h (97%); e) OsO₄, NMO, *t*-BuOH-H₂O (2 : 1), 96 h, rt (30%); f) TsOH, PhMe, 80°C, (77%); g) ZnI₂, CH₂Cl₂, rt, 2 h, (**2**, 27%; **10**, 25%) or BF₃Et₂O, CH₂Cl₂, –50°C, 3 h (**2**, 11%; **10**, 57%); h) H₂ (1 atm), 10% Pd/C (cat.), HCO₂NH₄, EtOH, rt, 1 h (78%); i) PCC/Al₂O₃, CH₂Cl₂, rt, overnight (88%).

The rearrangement of epoxides to carbonyl compounds is a useful reaction; however, constitution of the rearranged product is determined by the migratory aptitude of the substituents, as well as by the nature of the Lewis acid and solvent employed. The mechanisms of the rearrangements leading to both products are shown in Scheme 2. Coordination of the Lewis acid to the oxygen of the epoxide in **11** results in weakening of the C–O bond in intermediate **12**, followed by cleavage of one of the C–O bonds to give the most stable tertiary carbenium ion.

In this way, **12** can be rearranged through two alternative paths (*a* and *b*). In path *a*, the oxirane is rearranged by way of a hydride shift giving intermediate **14**, which provides ketone **2** after aqueous workup. However, when the transformation takes place through competing path *b* probably for steric reasons, a Meinwald rearrangement takes place, and alkyl migration to the



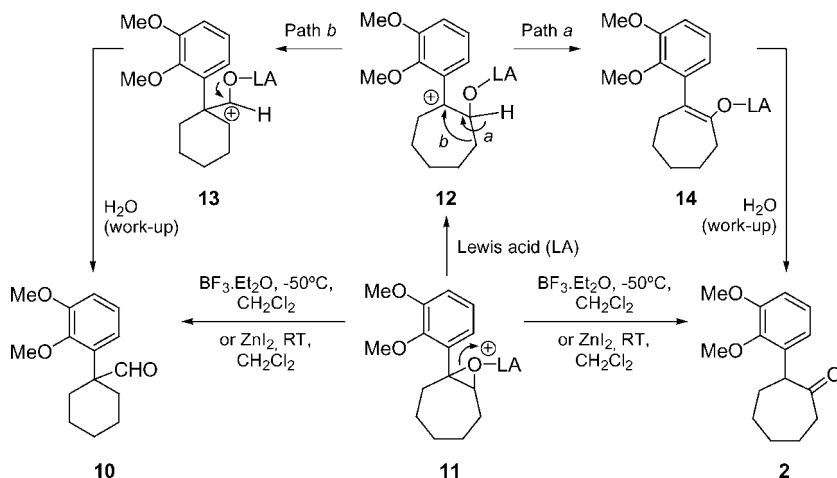
Scheme 1.

tertiary carbenium center with concomitant ring contraction gives way to cationic intermediate **13**, which finally yields aldehyde **10**.^[14]

In view of the outcome of these transformations, epoxide **11** was submitted to a catalytic hydrogenolysis in EtOH with 10% Pd/C and ammonium formate as additive, easily furnishing a mixture of diastereomeric alcohols **7** and **8** in combined 78% yield. Interestingly, the presence of ammonium formate^[15] was the key to avoid formation of undesirable side products.

Unexpectedly, however, the mixture of alcohols failed to oxidize under Swern conditions (trifluoroacetic anhydride (TFAA), dimethyl sulfoxide (DMSO), -60°C , then Et_3N); therefore, it was conveniently treated with pyridinium chlorochromate (PCC) supported on alumina, yielding 88% of the ketone **2**.

In conclusion, a simple and expedient synthesis of ketone **2** was developed, based on an heteroatom-facilitated lithiation coupled with a carbonyl transposition under conditions that avoid rearrangement to aldehyde **11**.



Scheme 2.

EXPERIMENTAL

General Procedures

Melting points were taken on an Ernst Leitz Wetzlar model 350 hot-stage microscope apparatus and are uncorrected. FT-IR spectra were determined with a Shimadzu IR Prestige 21 spectrophotometer as thin films held between NaCl cells or as dispersions in KBr disks. The ¹H and ¹³C NMR spectra were acquired in CDCl₃ employing TMS as internal standard with a Bruker AC200-E spectrometer operating at 200.13 and 50.33 MHz, respectively. Distortionless enhancement by polarization transfer (DEPT) 135 and DEPT 90 experiments aided the interpretation of the fully decoupled ¹³C NMR spectra. HRMS data were obtained from Kent Electronics (UK). The reactions were carried out under dry nitrogen or argon atmospheres, employing oven-dried glassware. Commercial reagents were used without further purification. Dry THF, Et₂O, and toluene were prepared by distillation from Na-benzophenone ketyl, and anhydrous CH₂Cl₂ was obtained by refluxing 4 h over P₂O₅, followed by distillation. Anhydrous solvents were stored in dry Schlenk bottles. All new compounds gave single spots on TLC plates run in different hexane–EtOAc solvent systems. Spots were visualized by exposure to UV light (254 and 365 nm), followed by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating. Standard workup procedures consisted of diluting the reaction with brine (5–10 mL) and extracting the products with EtOAc (4 × 20–30 mL); the combined organic extracts were washed once with brine, dried over Na₂SO₄, and concentrated under reduced pressure, and the respective residues were chromatographed. Flash column chromatographies were carried out with silica gel 60 H,

eluting with hexane–EtOAc mixtures under positive pressure and employing gradient techniques.

1-(2',3'-Dimethoxyphenyl) Cycloheptene (**6**)

A solution of *n*-BuLi in hexanes (6.95 mL, 8 mmol) was added dropwise to an ice-water-cooled solution of **3** (1000 mg, 7.25 mmol) in anhydrous Et₂O (10 mL). The reaction was stirred overnight at room temperature; then it was cooled again and treated with **4** (0.895 mL, 7.6 mmol). After a reaction period of 30 min, brine (10 mL) was added, and the reaction was submitted to the conventional workup and chromatography procedure, giving **5** (1185 mg, 65%) as an oil. IR (film, ν): 3515, 2925, 2857, 1581, 1473, 1385, 1298, 1168, 1075, and 746 cm⁻¹; ¹H NMR (δ): 1.15–2.35 (m, 13H, H-2, H-3, H-4, H-5, H-6, H-7, and OH), 3.86 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃) and 6.80–7.15 (m, 3H, ArH-4', ArH-5' and ArH-6'); ¹³C NMR (δ): 22.83 (C-3 and C-6), 29.83 (C-4 and C-5), 41.83 (C-2 and C-7), 55.65 (OCH₃-3'), 60.82 (OCH₃-2'), 77.59 (C-1), 111.30 (C-4'), 117.86 (C-5'), 123.42 (C-6'), 142.61 (C-1'), 146.60 (C-2'), and 152.61 (C-3'). Anal. calcd. for C₁₅H₂₂O₃: C, 71.97; H, 8.86. Found: C, 72.27; H, 8.68. Without further purification, oxalic acid dihydrate (48 mg, 0.38 mmol) was added to a solution of **5** (1185 mg, 4.74 mmol) in dry toluene (10 mL), and the reaction was heated at 110°C during 3 h until completed (TLC). Then most of the solvent was removed under reduced pressure, and the remaining oil was chromatographed, furnishing **6** (770 mg, 70%) as a solid; mp: 32–34°C (Hexane–EtOAc). IR (KBr, ν): 2931, 2838, 1590, 1470, 1306, 1267, 1093, 1011, and 788 cm⁻¹; ¹H NMR (δ): 1.50–1.90 (m, 6H, H-3 and H-6), 2.20–2.31 (m, 2H, H-7), 2.45–2.53 (m, 2H, H-3), 3.78 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 5.88 (t, 1H, *J* = 6.6, H-2), 6.72 (dd, 1H, *J* = 1.3 and 7.5, ArH-4'), 6.79 (dd, 1H, *J* = 1.3 and 8.2, ArH-6') and 6.95 (dd, 1H, *J* = 7.5 and 8.2, ArH-5'); ¹³C NMR (δ): 26.83 (C-5), 26.95 (C-4), 28.94 (C-6), 32.66 (C-3), 34.45 (C-7), 55.73 (OCH₃-3'), 60.22 (OCH₃-2'), 110.77 (C-4'), 121.49 (C-6'), 123.37 (C-5'), 131.36 (C-2), 140.98 (C-1'), 143.74 (C-1), 146.05 (C-2'), and 152.58 (C-3'). HRMS: Found: *m/z* = 232.14644; C₁₅H₂₀O₂ requires *m/z* = 232.14633. Anal. calcd. for C₁₅H₂₀O₂: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.71.

1-(2,3-Dimethoxyphenyl)-8-oxabicyclo [5.1.0] Octane (**11**)

A 0.5 M sodium hydrogen carbonate solution (2.05 mL, 1.025 mmol) was added to a solution of **6** (95 mg, 0.41 mmol) in CH₂Cl₂ (2.7 mL) cooled in an ice-water bath. The biphasic system was treated with a solution of *m*CPBA (72%, 147 mg, 0.614 mmol) in CH₂Cl₂ (1.45 mL), and the reaction was stirred 1 h at 0°C. The reaction was diluted with brine and submitted to conventional workup and chromatography procedure, furnishing **11** (99 mg, 97%), as a solid; mp: 58–62°C. IR (KBr, ν): 2929, 2849, 1683, 1464, 1302,

1268, 1069, 787, and 748 cm^{-1} ; $^1\text{H NMR}$ (δ): 1.17–1.32 (m, 1H, H-4), 1.46–1.75 and 2.00–2.12 (m, 8H, H-2, H-3, H-4, H-5, and H-6), 2.20–2.35 (m, 1H, H-2), 3.12 (t, 1H, $J = 4.4$, H-7), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.82 (dd, 1H, $J = 2.0$ and 7.6, ArH-4'), 6.92 (dd, 1H, $J = 2.0$ and 7.7, ArH-6') and 7.00 (dd, 1H, $J = 7.6$ and 7.7, ArH-5'); $^{13}\text{C NMR}$ (δ): 24.27 (C-4), 24.39 (C-5), 28.69 (C-3), 30.88 (C-6), 34.32 (C-2), 55.61 (OCH_3 -3'), 60.43 (OCH_3 -2'), 62.44 (C-7), 63.37 (C-1), 111.47 (C-4'), 119.01 (C-6'), 123.65 (C-5'), 137.97 (C-1'), 146.50 (C-2'), and 152.40 (C-3'). HRMS: Found: $m/z = 248.14093$; $\text{C}_{15}\text{H}_{20}\text{O}_3$ requires $m/z = 248.14125$. Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 8.15.

2-(2',3'-Dimethoxyphenyl) Cycloheptanone (**2**)

Ten percent Pd/C (26 mg) was added to a solution of oxirane **11** (74 mg, 0.166 mmol) and ammonium formate (56.4 mg, 0.895 mmol) in EtOH (5 mL), and the system was hydrogenated under atmospheric pressure until complete consumption of the starting material. Then the catalyst was filtered through a Celite pad, and the filtrate was concentrated in vacuo. Chromatography of the residue afforded **7** (38 mg, 51%) and **8** (20 mg, 27%). **Compound 7**: IR (film, ν): 3461, 2929, 2834, 1583, 1464, 1266, 1168, 1086, 785, and 747 cm^{-1} ; $^1\text{H NMR}$ (δ): 1.50–1.88 (m, 10H, H-3, H-4, H-5, H-6 and H-7), 1.91–2.06 (m, 1H, H-2), 3.04–3.15 (m, 1H, H-1), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.78 (dd, 1H, $J = 1.4$ and 6.7, ArH-4'), 6.82 (dd, 1H, $J = 1.4$ and 6.7, ArH-6') and 7.05 (t, 1H, $J = 8$, ArH-5'); $^{13}\text{C NMR}$ (δ): 21.83 (C-6), 27.37 (C-5), 27.72 (C-4), 31.92 (C-3), 35.76 (C-7), 47.56 (C-2), 55.54 (OCH_3 -3'), 60.73 (OCH_3 -2'), 76.83 (C-1), 110.20 (C-4'), 119.12 (C-6'), 124.40 (C-5'), 139.57 (C-1'), 146.70 (C-2'), and 152.72 (C-3'). **Compound 8**: IR (film, ν): 3482, 2927, 2857, 1583, 1476, 1275, 1072, 783, and 749 cm^{-1} ; $^1\text{H NMR}$ (δ): 1.45–1.91 (m, 10H, H-3, H-4, H-5, H-6, and H-7), 1.94–2.21 (m, 1H, H-2), 3.25 (dt, 1H, $J = 2.1$, 2.3, and 11.1, OH), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.80 (dd, 1H, $J = 1.6$ and 7.9, ArH-4'), 6.86 (dd, 1H, $J = 1.6$ and 7.9, ArH-6') and 7.02 (t, 1H, $J = 7.9$, ArH-5'); $^{13}\text{C NMR}$ (δ): 21.72 (C-6), 27.01 (C-5), 27.97 (C-4), 28.39 (C-3), 35.34 (C-7), 44.71 (C-2), 55.58 (OCH_3 -3'), 60.70 (OCH_3 -2'), 72.53 (C-1), 110.50 (C-4'), 120.80 (C-6'), 123.80 (C-5'), 139.27 (C-1'), and 152.61 (C-2' and C-3'). Without further purification, sodium acetate (12.2 mg, 0.15 mmol) and PCC/ Al_2O_3 (276 mg, 3 equiv.) were successively added to a mixture of **7** and **8** (19 mg) in CH_2Cl_2 (5 mL). The reaction was stirred overnight at room temperature until completion; the solids were separated by filtration through Celite, the filter was washed with CH_2Cl_2 , and the filtrate was concentrated under reduced pressure and chromatographed, affording **2** (10.7 mg, 88%) as an oil. IR (film, ν): 2931, 2855, 1696, 1585, 1453, 1276, 1169, 1084, and 747 cm^{-1} ; $^1\text{H NMR}$ (δ): 1.39–1.78, 1.89–2.02 and 2.59–2.85 (m, 10H, H-3, H-4, H-5, H-6, and H-7), 3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.89–3.99 (m, 1H, H-2), 6.77

(dd, 1H, $J = 1.5$ and 7.5 , ArH-4'), 6.81 (dd, 1H, $J = 1.5$ and 8.0 , ArH-6'), and 7.01 (dd, 1H, $J = 7.5$ and 8.0 , ArH-5'); ^{13}C NMR (δ): 24.41 (C-6), 29.63 (C-4), 29.79 (C-3), 31.86 (C-5), 43.73 (C-7), 53.16 (C-2), 55.54 (OCH₃-2'), 59.98 (OCH₃-3'), 110.96 (C-4'), 120.78 (C-6'), 123.74 (C-5'), 145.80 (C-2'), 152.34 (C-3'), and 214.35 (C-1). HRMS: Found: $m/z = 248.14115$; C₁₅H₂₀O₃ requires $m/z = 248.14125$. Anal. calcd. for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.67; H, 8.19.

Rearrangement of Epoxide **11** under Lewis Acid Assistance, Synthesis of 1-(2,3-Dimethoxyphenyl)-cyclohexanecarbaldehyde (**10**)

Method 1: A solution of oxirane **11** (20 mg, 0.08 mmol) in CH₂Cl₂ (1 mL) was cooled to -50°C and treated with a 0.76 M solution of BF₃ · Et₂O in CH₂Cl₂ (0.03 mL, 0.023 mmol). After stirring at -50°C for 3 h, the reaction was quenched with brine (5 mL), and after acquiring room temperature, the products were submitted to the conventional workup and chromatography procedure, furnishing aldehyde **10** (11.3 mg, 57%) as an oil. IR (film, ν): 2931, 2858, 1722, 1580, 1456, 1301, 1225, 1148, 1095, 786, and 746 cm⁻¹; ^1H NMR (δ): 1.50–1.83 (m, 8H, H-2_{ax}, H-3, H-4, H-5, and H-6_{ax}), 2.10–2.30 (m, 2H, H-2_{eq}, and H-6_{eq}), 3.76 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 6.84 (dd, 1H, $J = 1.8$ and 7.8 , ArH-4'), 6.94 (dd, 1H, $J = 1.8$ and 8.2 , ArH-6'), 7.02 (dd, 1H, $J = 7.8$, and 8.2 , H-5'), and 9.75 (s, 1H, CHO); ^{13}C NMR (δ): 22.69 (C3 and C-5), 25.43 (C-4), 32.35 (C-2 and C-6), 51.93 (C-1), 55.58 (OCH₃-3'), 60.02 (OCH₃-2'), 111.39 (C-4'), 118.91 (C-6'), 123.72 (C-5'), 138.34 (C-1'), 146.27 (C-2'), 152.54 (C-3'), and 204.07 (CHO); HRMS: Found: $m/z = 249.14914$; C₁₅H₂₁O₃ (M + 1) requires $m/z = 248.14125$. Anal. calcd. for C₁₆H₂₂O₃: C, 72.55; H, 8.12. Found: C, 72.72; H, 8.20. Increasing solvent polarity furnished ketone **2** (2.2 mg, 11%). Method 2: Zinc iodide (31 mg) was added to a solution of **11** (16 mg, 0.065 mmol) in CH₂Cl₂. After stirring 2 h at room temperature, the mixture was chromatographed, furnishing **10** (4.3 mg, 27%) and **2** (4.0 mg, 25%).

cis-1-(2,3-Dimethoxyphenyl)-cycloheptane-1,2-diol (**9**)

An OsO₄ solution in *t*-BuOH (0.15 mL, 0.007 mmol) was added to an ice-water-bath-cooled solution of olefin **6** (40 mg, 0.172 mmol) and NMO (28 mg, 0.234 mmol) in 2:1 *t*-BuOH-H₂O (3 mL). The reaction was left overnight at room temperature, and then more NMO (28 mg) was added; after 4 days the reaction was terminated by addition of 10% NaHSO₃ (5 mL). The organics were extracted with EtOAc (4 × 25 mL), and the combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), concentrated in vacuo, and chromatographed, furnishing diol **9** (13.5 mg, 30%) as a white solid; mp: 122–124°C (hexane–EtOAc). IR (KBr, ν): 3448, 3249, 2924, 2859, 1582, 1472, 1253, 1182, 1054, 963, 833, and 753 cm⁻¹; ^1H NMR (δ): 1.50–2.15 (m, 10H, H-3, H-4, H-5, H-6 and H-7),

3.36 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 4.18 (bd, 1H, $J = 10.8$, OH-2), 4.26 (s, 1H, OH-1), 6.85 (dd, 1H, $J = 1.8$ and 7.9, ArH-4'), 7.11 (dd, 1H, $J = 7.8$ and 8.0, ArH-5') and 7.14 (dd, 1H, $J = 1.8$ and 8.0, ArH-6'); ¹³C NMR (δ): 19.93 (C-4), 22.52 (C-6), 26.69 (C-5), 30.32 (C-3), 37.91 (C-7), 55.64 (OCH₃-3'), 60.64 (OCH₃-2'), 77.11 (C-2), 78.50 (C-1), 111.45 (C-4'), 118.77 (C-5'), 123.61 (C-6'), 140.14 (C-1'), 146.26 (C-3'), and 152.78 (C-2'). HRMS: Found: $m/z = 266.15206$; C₁₅H₂₂O₄ requires $m/z = 266.15181$. Anal. calcd. for C₁₅H₂₂O₄: C, 67.64; H, 8.33. Found: C, 67.77; H, 8.29.

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