Synthetic Communications®, 36: 299–310, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500377149

Taylor & Francis
Taylor & Francis Group

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

Andrea B. J. Bracca and Teodoro S. Kaufman
Instituto de Química Orgánica de Síntesis, IQUIOS (CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Argentina

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–e] 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

Received in the USA July 28, 2005
Address correspondence to Teodoro S. Kaufman, Instituto de Química Orgánica de Síntesis, IQUIOS (CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK, Rosario, Argentina. Tel./Fax: +54-341-4370477; E-mail: tkaufman@fbioyf.unr.edu.ar

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]

Stephaoxocanidine (**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 stephaoxocanidine 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]

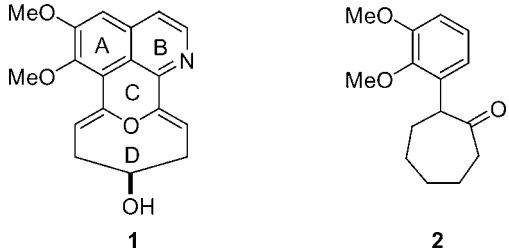


Figure 1. Stephaoxocanidine (**1**) and target compound (**2**).

Thus, compound **3** was subjected to an heteroatom-facilitated *ortho* lithiation with *n*-butyllithium in dry Et_2O, 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 $BH_3 \cdot SMe_2$ 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.

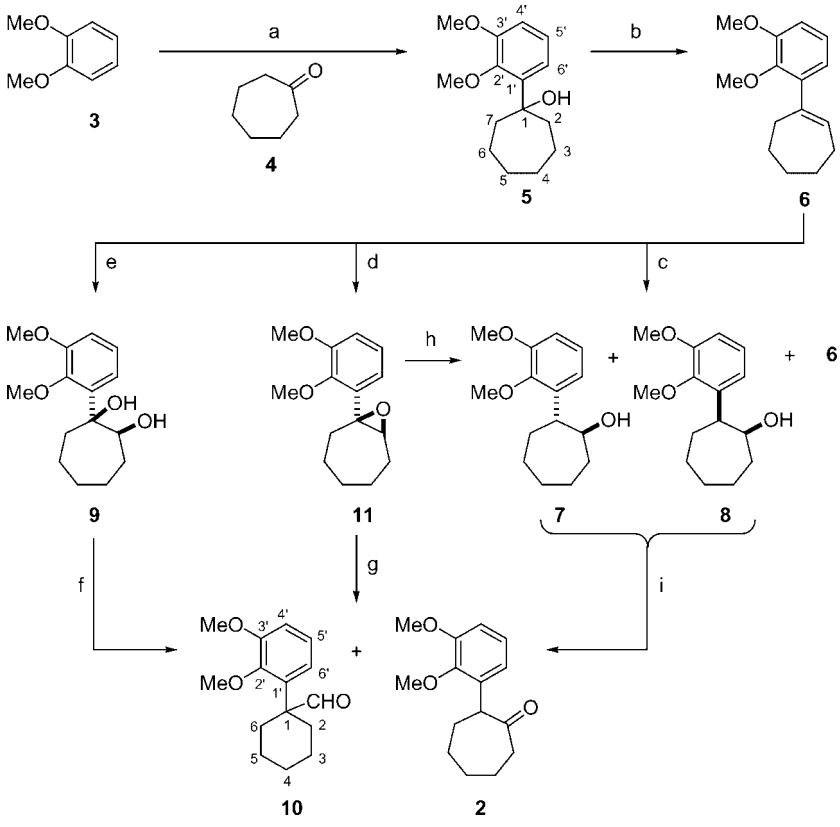
Therefore, cycloheptene **6** was catalytically dihydroxylated with osmium tetraoxide, employing NMO as stoichiometric co-oxidant. However, the transformation proceeded sluggishly, and poor yields (30%) of diol **9** were realized after prolonged exposure to the reaction conditions. Moreover, when **9** 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 $BF_3 \cdot Et_2O$ at −50°C or with ZnI_2 at room temperature in CH_2Cl_2 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, Et_2O, rt, overnight; 2. Cycloheptanone (**4**), 30 min, rt (65%); b) $(COOH)_2$ (cat.), PhMe, 110°C, 3 h (70%); c) 1. $BH_3 \cdot SMe_2$, THF, 0°C → rt, overnight; 2. H_2O_2, NaOH, 50°C (**7** + **8**, 37%); d) *m*-CPBA, Cl_2CH_2, $NaHCO_3$, 0°C, 1 h (97%); e) OsO_4, NMO, *t*-*B*uOH-H_2O (2 : 1), 96 h, rt (30%); f) TsOH, PhMe, 80°C, (77%); g) ZnI_2, CH_2Cl_2, rt, 2 h, (**2**, 27%; **10**, 25%) or BF_3Et_2O, CH_2Cl_2, −50°C, 3 h (**2**, 11%; **10**, 57%); h) H_2 (1 atm), 10% Pd/C (cat.), HCO_2NH_4, EtOH, rt, 1 h (78%); i) PCC/Al_2O_3, CH_2Cl_2, 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



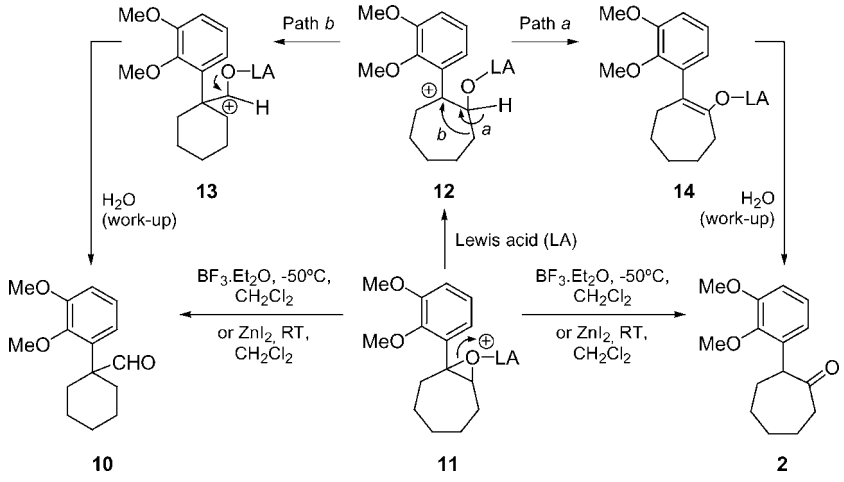
Scheme 1.

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), $-60^{\circ}C$, 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 ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ 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 ^{13}C 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, Et_2O, and toluene were prepared by distillation from Na-benzophenone ketyl, and anhydrous CH_2Cl_2 was obtained by refluxing 4 h over P_2O_5, 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 Na_2SO_4, 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 Et_2O (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, OCH_3), 3.96 (s, 3H, OCH_3) and 6.80–7.15 (m, 3H, ArH-4′, ArH-5′ and ArH-6′); ^{13}C 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 (OCH_3-3′), 60.82 (OCH_3-2′), 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 $C_{15}H_{22}O_3$: 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, OCH_3), 3.85 (s, 3H, OCH_3), 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′); ^{13}C NMR (δ): 26.83 (C-5), 26.95 (C-4), 28.94 (C-6), 32.66 (C-3), 34.45 (C-7), 55.73 (OCH_3-3′), 60.22 (OCH_3-2′), 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: $m/z = 232.14644$; $C_{15}H_{20}O_2$ requires $m/z = 232.14633$. Anal. calcd. for $C_{15}H_{20}O_2$: 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 CH_2Cl_2 (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 CH_2Cl_2 (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}; ^1H 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}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: $m/z = 248.14093$; $C_{15}H_{20}O_3$ requires $m/z = 248.14125$. Anal. calcd. for $C_{15}H_{20}O_3$: 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}; ^1H 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}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}; ^1H 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}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}; ^1H 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 (OCH_3-2′), 59.98 (OCH_3-3′), 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: $m/z = 248.14115$; $C_{15}H_{20}O_3$ requires $m/z = 248.14125$. Anal. calcd. for $C_{15}H_{20}O_3$: 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 CH_2Cl_2 (1 mL) was cooled to -50°C and treated with a 0.76 M solution of $BF_3 \cdot Et_2O$ in CH_2Cl_2 (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}; ^{1}H 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, OCH_3), 3.94 (s, 3H, OCH_3), 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 (OCH_3-3′), 60.02 (OCH_3-2′), 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: $m/z = 249.14914$; $C_{15}H_{21}O_3$ (M + 1) requires $m/z = 248.14125$. Anal. calcd. for $C_{16}H_{22}O_3$: 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 CH_2Cl_2. 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 OsO_4 solution in *t-B*uOH (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-B*uOH-H_2O (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% $NaHSO_3$ (5 mL). The organics were extracted with EtOAc (4 × 25 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), 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}; ^{1}H NMR (δ): 1.50–2.15 (m, 10H, H-3, H-4, H-5, H-6 and H-7),

3.36 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 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′); ^{13}C NMR (δ): 19.93 (C-4), 22.52 (C-6), 26.69 (C-5), 30.32 (C-3), 37.91 (C-7), 55.64 (OCH_3-3′), 60.64 (OCH_3-2′), 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: $m/z = 266.15206$; $C_{15}H_{22}O_4$ requires $m/z = 266.15181$. Anal. calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.77; H, 8.29.

ACKNOWLEDGMENT

The authors gratefully acknowledge financial support provided by CONICET, Fundación Antorchas, and ANPCyT (Project 06-12532) and also thank SECyT-UNR. A. B. J. B. especially acknowledges ANPCyT and CONICET for her fellowship.

REFERENCES

1. (a) Walker, G. N. Synthesis of methoxyhydrophenanthrenes and methoxyhydrocyclohepta[*a*]-naphthalenes by acylation of ketones with homoveratric anhydride. *J. Am. Chem. Soc.* **1957**, *79*, 3508–3514; (b) Cope, A. C.; Mehta, A. S. Molecular asymmetry of olefins. II. The absolute configuration of *trans*-cyclooctene. *J. Am. Chem. Soc.* **1964**, *86*, 5626–5630; (c) Ginsburg, D.; Pappo, R. Colchicine studies. I. Synthesis and reactions of 2-arylcyclohept-2-enones. *J. Am. Chem. Soc.* **1953**, *75*, 1094–1097.
2. (a) Varvoglis, A. Polyvalent iodine compounds in organic synthesis. *Synthesis* **1984**, 709–726, and references cited therein; (b) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. Regiocontrolled synthesis of carbocycle-fused indoles *via* arylation of silyl enol ethers with *o*-nitrophenylphenyliodonium fluoride. *Org. Lett.* **1999**, *1*, 673–676; (c) Chen, K.; Koser, G. F. Direct and regiocontrolled synthesis of.α-phenyl ketones from silyl enol ethers and diphenyliodonium fluoride. *J. Org. Chem.* **1991**, *56*, 5764–5767; (d) Ryan, J. H.; Stang, P. J. Direct α-arylation of ketones: The reaction of cyclic ketone enolates with diphenyliodonium triflate. *Tetrahedron Lett.* **1997**, *38*, 5061–5064; (e) Beringer, F. M.; Forgione, P. S.; Yudis, M. D. Diaryliodonium salts—XII: The phenylation of dimedone, dibenzoylmethane and tribenzoylmethane. *Tetrahedron* **1980**, *8*, 49–63; (f) Finet, J.-P. Arylation reactions with organobismuth reagents. *Chem. Rev.* **1989**, *89*, 1487–1501, and references cited therein; (g) Abramovitch, R. A.; Barton, D. H.R.; Finet, J.-P. Newer methods of arylation. *Tetrahedron* **1988**, *44*, 3039–3071and references cited therein; (h) Brown, H. C.; Nambu, H.; Rogic, M. M. Reaction of organoboranes with bromoacetone under the influence of potassium 2, 6-di-*tert*-butylphenoxide. A convenient procedure for the conversion of olefins into methyl ketones *via* hydroboration. *J. Am. Chem. Soc.* **1969**, *91*, 6852–6854, and references cited therein.

3. (a) Kelly, L. F.; Narula, A. S.; Birch, A. J. Organometallic compounds in organic synthesis. An equivalent of aromatic nucleophilic substitution by reactions of tricarbonyl cyclohexadienyliumiron salts with *O*-silylated enolates: A novel arylation in the 2-position of carbonyl compounds. *Tetrahedron Lett.* **1980**, *21*, 2455–2458; (b) Mino, T.; Matsuda, T.; Maruhashi, K.; Yamashita, M. Arylation of ketone *N,N*-dimethylhydrazones with (π-chlorobenzene)chromium tricarbonyl. *Organometallics* **1997**, *16*, 3241–3142; (c) Rathke, M. W.; Vogiazoglou, D. α-Phenylation of ketones. Reaction of bromo enamines with phenylcopper reagents. *J. Org. Chem.* **1987**, *52*, 3697–3698; (d) Marino, J. P.; Jaén, J. C. Stereospecific umpolung α-substitution of ketones via reactions of organocuprates with enol ethers of α, β-epoxycyclohexanones. *J. Am. Chem. Soc.* **1982**, *104*, 3165–3172, and references cited therein; (e) Sacks, C. E.; Fuchs, P. L. α-Arylation of carbonyl groups. Utilization of the *p*-toluenesulfonylazo olefin functional group as an enolonium synthon. *J. Am. Chem. Soc.* **1975**, *97*, 7372–7374; (f) Sakurai, H.; Shirahata, A.; Araki, Y.; Hosomi, A. Alkylation and arylation of 2-trimethylsiloxyallyl halides. A new regiospecific route to silyl enol ethers. *Tetrahedron Lett.* **1980**, *21*, 2325–2328; (g) Al Adel, I.; Adeoti Salami, B.; Levisalles, J.; Rudler, H. Organometallic chemistry. 5. Meerwein reaction. Arylation of ketones and of their derivatives. *Bull. Soc. Chim. Fr.* **1976**, 930–933.
4. (a) Pinhey, J. T. In *Comprehensive Organometallic Chemistry II*; McKillop, A., Ed.; Pergamon: Oxford, 1995; Vol. 11, Chapter 11, and references cited therein; (b) Pinhey, J. T. Organolead(IV) triacetates in organic synthesis. *Pure Appl. Chem.* **1996**, *68*, 819–824 and references cited therein; (c) Morgan, J.; Pinhey, J. T.; Rowe, B. A. α-Arylation of ketones by aryllead triacetates. Effect of methyl and phenyl substitution at the α-position. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1005–1008; (d) Hegedus, L. S.; Stiverson, R. K. π-(2-Methoxyallyl)nickel bromide, a reagent for the introduction of the acetonyl functional group into organic substrates. *J. Am. Chem. Soc.* **1974**, *96*, 3250–3254; (e) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. Highly active and selective catalysts for the formation of α-aryl ketones. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370; (f) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. Catalyzed asymmetric arylation reactions. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308; (g) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. Asymmetric arylation of ketone enolates. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919.
5. (a) Newman, M. S.; Farbman, M. The synthesis of hydroaromatic compounds containing angular groups. I. Hydrophenanthrene series. *J. Am. Chem. Soc.* **1944**, *66*, 1550–1552; (b) Jones, P. R.; Young, J. R. Organocadmium reagents. V. Reaction with α-halo esters and ketones. *J. Org. Chem.* **1968**, *33*, 1675–1576; (c) Bunnett, J. F.; Sundberg, J. E. Photostimulated arylation of ketone enolate ions by the SRN_1 mechanism. *J. Org. Chem.* **1976**, *41*, 1702–1706; (d) Caubere, P.; Lalloz, L. Arynic and SN_{Ar} reactions of polyhalogenobenzenes. IV. Condensation of ketone enolates. *J. Org. Chem.* **1975**, *40*, 2853–2858; (e) Kuehne, M. E. J. The arylation of enamines. *J. Am. Chem. Soc.* **1962**, *84*, 837–847.
6. (a) Loeschorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, J.-P. Lithium bromide catalyzed homologation of aldehydes with aryldiazomethanes. *J. Org. Chem.* **1983**, *48*, 4407–4410; (b) Gutsche, C. D.; Johnson, H. E. Ring enlargements. III. Ring enlargement of cyclohexanone with ethyl *N*-nitroso-*N*-benzylcarbamates carrying methyl and methoxyl substituents on the phenyl nucleus. *J. Am. Chem. Soc.* **1955**, *77*, 109–112; (c) Gutsche, C. D. 2-Phenylcyclopentanone.

Org. Synth. **1951**, *35*, 91–94; (d) Villieras, J.; Perriot, P.; Normant, J. F. Conversion of aldehydes to ketones and homologation of ketones *via* the lithium salts of 2-hydroxycarbenoids. *Synthesis* **1979**, 968–969; (e) Katritzky, A. R.; Toader, D.; Xie, L. General and efficient insertions of carbons carrying aryl and heteroaryl groups: Synthesis of α-aryl- and α-heteroaryl-substituted ketones. *J. Org. Chem.* **1996**, *61*, 7571–7577.

7. (a) Sisti, A. J. A new ring enlargement procedure. II. The reaction of the magnesium salt of 2-(α-bromobenzyl)-2-norbornanol. *Tetrahedron Lett.* **1967**, 5327–5329; (b) Sisti, A. J. Ring enlargement procedure. IV. Decomposition of the magnesium salts of various 1-(1-bromethyl)-1-cycloalkanols. *J. Org. Chem.* **1970**, *35*, 2670–2673; (c) Sisti, A. J.; Rusch, G. M.; Sukhon, H. K. Spontaneous ring enlargement during the free-radical bromination of 2-benzyl-1,3,3-trimethyl- and 2-benzyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol. *J. Org. Chem.* **1971**, *36*, 2030–2033.
8. Gutsche, C. D.; Jason, E. F. Ring enlargements. V. The preparation of 2-arylcycloheptanones and 2-aryl-2-cycloheptenones. *J. Am. Chem. Soc.* **1956**, *78*, 1184–1187.
9. (a) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M. Stephaoxocanine, a novel dihydroisoquinoline alkaloid from *Stephania cepharantha*. *J. Nat. Prod.* **1996**, *59*, 803–805; (b) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. Stephaoxocanidine, a new isoquinoline alkaloid from *Stephania cepharantha*. *Nat. Prod. Lett.* **1997**, *9*, 177–180; (c) Deng, J.-Z.; Zhao, S.-X.; Miao, Z.-Ch. An alkaloid with a novel skeleton from the roots of *Stephania excentrica*. *Nat. Prod. Lett.* **1993**, *2*, 283–286; (d) Deng, J.-Z.; Zhao, S.-X. 2-*N*-Methylexcentricine, a new alkaloid from roots of *Stephania excentrica*. *J. Nat. Prod.* **1997**, *60*, 294–295; (e) da-Cunha, E. V. L.; Cornélio, M. L.; Barbosa-Filho, J. M.; Braz-Filho, R.; Gray, A. I. Eletefine, a stephaoxocane alkaloid from *Cissampelos glaberrima*. *J. Nat. Prod.* **1998**, *61*, 1140–1142.
10. (a) Kaufman, T. S. Sulfonamidoacetal cyclization-based synthesis of a tetrahydrooxazaphenalene lactone related to the ABC-ring system of the stephaoxocanes. *Heterocycles* **2001**, *55*, 323–330; (b) Bianchi, D. A.; Cipulli, M. A.; Kaufman, T. S. Model studies towards stephaoxocanes. Construction of the 8-oxa-1-azaphenalene core of stephaoxocanidine and eletefine. *Eur. J. Org. Chem.* **2003**, 4731–4736; (c) Bianchi, D. A.; Rúa, F.; Kaufman, T. S. Studies on the intramolecular oxa-Pictet–Spengler rearrangement of 5-aryl-1,3-dioxolanes to 4-hydroxy-isochromans. *Tetrahedron Lett.* **2004**, *45*, 411–415; (d) Bianchi, D. A.; Kaufman, T. S. Synthesis of a tricyclic lactone embodying the ABC-ring system of stephaoxocanidine, by tin(IV) chloride–assisted sulfonamidoacetal cyclization and an aromatization promoted by triethylamine. *Arkivoc* **2003**, *x*, 178–188; (e) Bianchi, D. A.; Schmeda-Hirschmann, G.; Theoduloz, C.; Bracca, A. B. J.; Kaufman, T. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2711–2715.
11. (a) Kane, V. V.; Singh, V.; Martin, A. The chemistry of 1,2-carbonyl transposition. *Tetrahedron* **1983**, *39*, 345–394; (b) Morris, D. G. Carbonyl group transpositions. *Chem. Soc. Rev.* **1982**, *11*, 397–434; (c) Silveira, C. C.; Braga, A. L.; Kaufman, T. S.; Lenardão, E. J. Synthetic approaches to 2-tetralones. *Tetrahedron* **2004**, *60*, 8295–8328.
12. (a) Huffman, J. W.; Engle, J. E. Stereochemistry of the cycloheptane ring. II. *Cis*- and *trans*-2-phenylcycloheptanol. *J. Org. Chem.* **1961**, *26*, 3116–3121; (b) Brown, H.; Sharp, R. L. Hydroboration. XXIV. Directive effects in the hydroboration of some substituted styrenes. *J. Am. Chem. Soc.* **1966**, *88*, 5851–5854;

(c) Vishwakarma, L. C.; Fry, A. Relative rates and regioselectivity in the hydroboration of substituted styrenes with 9-borabicyclo[3.3.1]nonane in tetrahydrofuran. *J. Org. Chem.* **1980**, *45*, 5306–5308.

13. (a) Jensen, B. L.; Slobodzian, S. V. A concise synthesis of 1-substituted-2-tetralones by selective diol dehydration leading to ketone transposition. *Tetrahedron Lett.* **2000**, *41*, 6029–6033; (b) Aszodi, J.; Fauveau, P.; Melon-Manguer, D.; Ehlers, E.; Schio, L. Synthesis of new echinocandin derivatives *via* a diol-keto transposition. *Tetrahedron Lett.* **2002**, *43*, 2953–2956.
14. (a) Meinwald, J.; Labana, S. S.; Chadha, M. S. Peracid reactions. III. The oxidation of bicyclo [2.2.1]heptadiene. *J. Am. Chem. Soc.* **1963**, *85*, 582–585; (b) Settine, R. L.; Parks, G. L.; Hunter, G. L. K. The rearrangement of limonene and carvomenthene epoxides. *J. Org. Chem.* **1964**, *29*, 616–618; (c) Ranu, B. C.; Jana, U. Indium(III) chloride–promoted rearrangement of epoxides: A selective synthesis of substituted benzylic aldehydes and ketones. *J. Org. Chem.* **1998**, *63*, 8212–8216; (d) Sankararaman, S.; Nesakumar, J. E. Highly chemo- and regioselective rearrangement of α,β-epoxy ketones to 1,3-dicarbonyl compounds in 5 mol dm^{-3} lithium perchlorate-diethyl ether medium. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3173–3175; (e) Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. Lewis acid-promoted selective rearrangement of trisubstituted epoxides to aldehydes or ketones. *Tetrahedron* **1994**, *50*, 3663–3672; (f) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. Remarkable effect of aluminum reagents on rearrangements of epoxy acylates *via* stable cation intermediates and its application to the synthesis of (*S*)-(+)-sporochnol A. *J. Org. Chem.* **2001**, *66*, 8779–8786; (g) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. Study of the Lewis acid-promoted rearrangement of 2-aryl-2,3-epoxy acylates. *Tetrahedron* **2001**, *57*, 815–825.
15. Dragovich, P. S.; Prins, T. J.; Zhou, R. Palladium-catalyzed, regioselective reduction of 1,2-epoxides by ammonium formate. *J. Org. Chem.* **1995**, *60*, 4922–4924.