CH_3), 1.30 and 1.29 (s, 3 H, CH_3), 1.2–1.7 (m, 2 H, CH_2), 0.85 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.38; H, 10.64.

Electrochemical Allylation of Benzaldehyde. A mixture of benzaldehyde (424 mg, 4 mmol), allyl chloride (2 mL, 24 mmol), $SnCl_2$ (152 mg, 0.8 mmol), and Et_4NOTs (500 mg) in MeOH (5 mL)–AcOH (1.4 mL)–5% HCl (0.5 mL) was electrolyzed in a H-type divided cell separated by a sintered glass, using platinum foils as electrode at 40–50 °C. A constant current (15 mA, 3.4 F/mol) was applied by a regulated DC power supply (Metronix Model 543B). The usual workup gave **2a** (302 mg, 51%) and benzaldehyde pinacol (270 mg, 30%) as crystals.

Registry No. **1a**, 100-52-7; **1b**, 98-01-1; **1c**, 120-57-0; **1d**, 122-78-1; **1e**, 111-71-7; **1f**, 367-47-5; **1g**, 2704-78-1; **2a**, 936-58-3; **2b**, 6398-51-2; **2c**, 6052-61-5; **2d**, 61077-65-4; **2e**, 36971-14-9; **2f** (isomer 1), 99146-85-7; **2f** (isomer 2), 99146-86-8; **2g**, 97039-57-1; $SnCl_2$, 7772-99-8; $SnSO_4$, 7488-55-3; $Sn(OAc)_2$, 638-39-1; SnO, 21651-19-4; $SnCl_4$, 7646-78-8; allyl chloride, 107-05-1; aluminum, 7429-90-5; tin, 7440-31-5; acetophenone, 98-86-2; 2-phenylbut-3-en-2-ol, 6051-52-1.

Synthesis of New Dipeptide Analogues Containing Novel Ketovinyl and Hydroxyethylidene Isosteres via Grignard Addition to Chiral α-Amino Aldehydes

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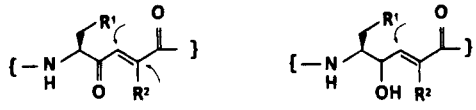
There is a tremendous amount of current interest in the study of dipeptide analogues.[1] These isosteres of natural dipeptides are proving valuable for producing mechanism-based enzyme inhibitors[2] and proteolytically stable peptides,[3] both of which hold great promise as therapeutic agents. We report the preparation of two new dipeptide analogues, ketovinyl **1** and hydroxyethylidene **2** (R^1 = phenyl, R^2 = H), which are designed to be Phe-Gly replacements; their synthesis is achieved through the novel reaction of vinylmagnesium bromide and Boc-L-phenylalaninal.



1 **2**

These particular analogues are important because they incorporate the key structural features of the known[1] trans double bond and ketomethylene/hydroxyethylene isosteres and are designed to (1) enable the preparation of potential site-directed alkylating agents[4,5] (arrows in **1** and **2** indicate possible points of attack of enzyme nucleophiles such as cysteine thiol), (2) provide a tool for drug design,[6] utilizing the conformational restriction about C-2 and C-3, (3) be used to prepare angiotensin converting enzyme inhibitors[7] based on benzoyl-Phe-Gly-Pro, and (4) function as statine mimics, for use in structure–activity studies on pepstatin-based renin inhibitors.[8]

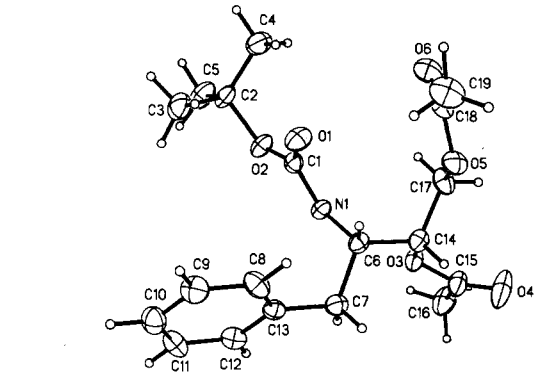
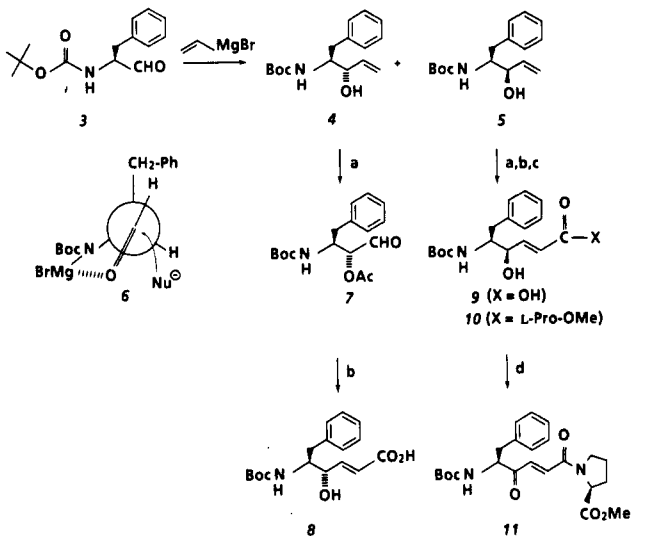


Figure 1. X-ray crystal structure of diacetate **13**.

Scheme I[a]



[a] Key: (a) Ac_2O, pyridine, room temperature; then, O_3, MeOH, followed by dimethyl sulfide workup. (b) $Ph_3P{=}CHCO_2Et$, THF, room temperature; followed by NaOH-H_2O-MeOH. (c) *i*-BuOCOCl, NMP, followed by L-Pro-OMe·HCl and NMP. (d) periodinane, CH_2Cl_2, room temperature.

Preparation of Dipeptide Analogues. Optically pure α-(acylamino)aldehydes are readily available[9] from natural α-amino acids; their reaction with Grignard reagents presents, in principle, an outstanding opportunity for the synthesis of enantiomerically pure compounds. We therefore chose Grignard addition products **4** and **5** as key synthetic intermediates.

Boc-L-phenylalanine methyl ester was reduced[10] with DIBAL in toluene to Boc-L-phenylalaninal **3**, which was treated with vinylmagnesium bromide (THF, −78 °C to room temperature) to produce a mixture (56:44) of threo and erythro allylic alcohols **4** and **5** in 66% combined yield (Scheme I). To our knowledge this is the first example of such a reaction, although the addition of saturated or-

(1) (a) For an extensive review and mechanistic discussion see: Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263. (b) Rich, D. H.; Holladay, M. W. *Tetrahedron Lett.* **1983**, *24*, 4401 and references cited therein.

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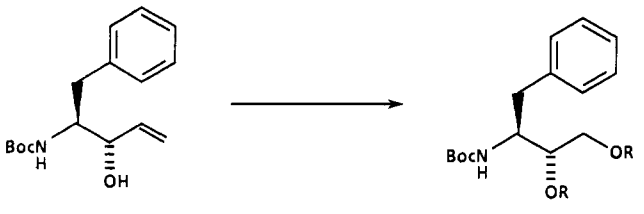
0022-3263/85/1950-5399$01.50/0

ganomagnesium compounds to protected α-amino-aldehydes can be cited as precedent.[1] The stereoselectivity was further improved in favor of the chelation-controlled Cram product **4** by carrying out the addition at 25 °C, which gave a 70:30 ratio of **4** to **5**; at higher temperatures a greater proportion of N–H protons should be removed to form **6** prior to aldehyde carbonyl addition, resulting in the preferential formation[11] of threo alcohol **4**.

Unambiguous stereochemical assignment for **4** (and thus for **5**) was made by converting compound **4** into diacetate **13**, the structure of which was determined by X-ray analysis (Figure 1). This conversion was accomplished by the following sequence: alcohol **4** was acetylated with acetic anhydride–pyridine and ozonized with a $NaBH_4$–NaOH workup to give the protected 3-amino 1,2-diol **12**; this diol was then acetylated to produce diacetate **13**, which formed crystals suitable for X-ray analysis.



4 *12* R = H *13* R = Ac

Both pure epimers **4** and **5** are desired for purposes of biological evaluation, because when incorporated into final products **2** either the *R* or *S* configuration at the hydroxymethine carbon may be critical for enzyme inhibition;[12] therefore, alcohols **4** and **5** were routinely separated by HPLC and individually elaborated as depicted in Scheme I. Compound **4** was acetylated with acetic anhydride–pyridine and ozonized with a dimethyl sulfide workup to produce a mixture of acetoxyaldehyde[13] **7** and its methyl hemiacetal. These compounds were smoothly homologated with (carbethoxymethylene)triphenylphosphorane[14] in THF, and the resulting Wittig product was saponified and recrystallized to give hydroxyethylidene Phe-Gly analogue **8** (45% overall yield from **4**). The desired trans configuration was confirmed by ^1H NMR ($J_{2,3}$ = 17 Hz). The above reaction sequence was also carried out on **5** to give the epimeric Phe-Gly analogue **9** (49% overall yield from **5**).

To incorporate these new isosteres into a peptide, an analogue of the known ACE inhibitor[7] benzoyl-Phe-Gly-Pro was prepared. Compound **9** was coupled to L-proline methyl ester by using the mixed carbonic anhydride procedure of Benoiton[15] to give hydroxyethylidene peptide **10** (62% yield). This was oxidized with Dess–Martin periodinane[16] to give the desired ketovinyl analogue **11** in 61% yield after silica gel chromatography.

The above synthetic route is sufficiently flexible to allow for the preparation of a wide variety of dipeptide analogues containing the ketovinyl and hydroxyethylidene isosteres. The new dipeptide analogues are available in both desired stereoisomeric forms and are easy to prepare and incorporate into peptides of interest. In addition, novel Grignard adducts **4** and **5** constitute potential intermediates for chiral amino sugar synthesis via Rapoport's[17] methodology, for alkaloid synthesis,[18] and for pharmacologically active 3-amino 1,2-diol preparation.[19] In this latter connection, we recently discovered that *N*-acyl derivatives of amino diol **12** are novel inhibitors of human renin.[20]

Experimental Section

Melting points are uncorrected. NMR spectra were determined on 80- and 200-MHz instruments and were taken in deuteriochloroform unless otherwise noted; chemical shifts are reported in δ values relative to tetramethylsilane as an internal standard. IR spectra were taken in chloroform unless otherwise noted. Optical rotations were measured on a polarimeter with a 10-cm cell. TLC was performed on Merck silica gel F-254 plates. Organic extracts were dried over sodium sulfate.

(3*S*,4*S*)-*N*-[(*tert*-Butyloxy)carbonyl]-4-amino-3-hydroxy-5-phenylpentene (4). To a cooled (−78 °C) solution of freshly prepared Boc-L-phenylalaninal[10] (50 g, 0.2 mmol) in THF (500 mL) was added dropwise 1 M vinylmagnesium bromide in THF (400 mL, 2 equiv). After the addition was complete, the reaction mixture was allowed to warm to room temperature and was poured into saturated aqueous ammonium chloride. The resulting slurry was extracted with several portions of ether, and the combined ether extracts were dried and evaporated to give a mixture of allylic alcohols **4** and **5** in a 56:44 ratio as determined by HPLC (eluting with 60% MeOH in H_2O, 2 mL/min). The crude product was purified by chromatography on silica gel, eluting with 20% EtOAc in toluene, to give **4** (19 g, 34% yield) which was recrystallized from EtOAc–hexanes to give **4** as white needles: mp 102–103 °C; $[\alpha]^{25}_D$ −53° (*c* 1, $CHCl_3$); TLC R_f 0.26 (20% EtOAc–hexanes); ^1H NMR δ 1.4 (s, 9 H), 2.6–3.0 (m, 1 H), 7.3 (br s, 5 H). Melting points and optical rotation were unchanged by two subsequent recrystallizations. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.35; N, 5.04. Found: C, 69.29; H, 8.15; N, 5.01.

(3*R*,4*S*)-*N*-[(*tert*-Butyloxy)carbonyl]-4-amino-3-hydroxy-5-phenylpentene (5). Also isolated from the above experiment was **5** (18 g, 32% yield), which was recrystallized from EtOAc–hexanes to give **5** as white needles: mp 125–126.5 °C; $[\alpha]^{25}_D$ −23° (*c* 1, $CHCl_3$); TLC R_f 0.21 (20% EtOAc–hexanes); ^1H NMR δ 1.35 (s, 9 H), 2.6–2.9 (m, 2 H), 3.3 (br s, 1 H), 3.96 (br s, 1 H), 4.2–4.3 (m, 1 H), 4.7 (d, 1 H), 5.2–5.45 (m, 2 H), 5.85–6.1 (m, 1 H), 7.2–7.4 (m, 5 H). Melting points and optical rotation were unchanged by two subsequent recrystallizations. Anal. Found: C, 69.39; H, 8.06; N, 5.05.

(4*S*,5*S*)-*trans*-*N*-[(*tert*-Butyloxy)carbonyl]-5-amino-4-hydroxy-6-phenylhex-2-enoic Acid (8). The allylic alcohol **4** (1 g, 3.6 mmol) was dissolved in acetic anhydride (10 mL), and pyridine (5 drops) was added. This solution was allowed to stand overnight and was poured into a slurry of sodium bicarbonate (20 g) and water (75 mL). After gas evolution ceased, the mixture was extracted with several portions of ether. The organic layers were combined and dried, and the solvent was evaporated to give crystalline acetate of **4**: 1.1 g (96% yield); mp 58–61 °C. The acetate of **4** was dissolved in methanol (15 mL) and cooled to −78 °C, and ozone was bubbled into the solution until a blue color persisted. The excess ozone was purged with oxygen, and dimethyl sulfide (0.5 g) was added. The solution was warmed to 0 °C and stirred at 0 °C for 2 h. The solvent evaporated and the residue taken up in ether and washed with water and brine. The organic solution was dried and evaporated. The residue was dissolved in methylene chloride and filtered through a short pad of silica. The filtrate was evaporated to give an oily mixture of aldehyde **7** and its methyl hemiacetal. The aldehyde, without further

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purification, was dissolved in THF and treated with (carbethoxymethylene)triphenylphosphorane[14] (2 g, 5.7 mmol). The reaction was stirred at room temperature for 10 h and was evaporated. The residue was chromatographed on silica gel, eluting with ether–hexanes (1:1) to give an oily ester that was dissolved in methanol–water (4:1) and treated with sodium hydroxide (500 mg) in water (1 mL). This mixture was stirred at room temperature for 30 min, the solvent was evaporated, and the residue was dissolved in water. This solution was washed with ether and acidified to pH 2 with 1 N HCl, and the product was extracted into ethyl acetate. The organic layer was dried and evaporated to obtain, after recrystallization from MeOH–H_2O, **8**: 520 mg (45% yield); mp 149–151 °C; $[\alpha]^{25}_D$ −100° (*c* 0.64, MeOH); IR (KBr) 3400, 1710, 1695, 1675, 1660 cm^{-1}; ^1H NMR (CD_3OD) δ 1.35 (s, 9 H), 2.6–3.0 (m, 2 H), 3.85–3.95 (m, 1 H), 4.3 (br s, 1 H), 6.0–6.15 (m, 1 H, J = 17 Hz), 6.92–7.05 (m, 1 H, J = 17 Hz), 7.15–7.35 (m, 5 H). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.43; H, 7.21; N, 4.36. Found: C, 63.52; H, 7.16; N, 4.32.

(4*R*,5*S*)-*trans*-*N*-[(*tert*-Butyloxy)carbonyl]-5-amino-4-hydroxy-6-phenylhex-2-enoic Acid (9). Allylic alcohol **5** (1 g, 3.6 mmol) was subjected to the same reaction conditions as described for **4** in the above procedure to give **9** (560 mg, 49% yield) after recrystallization from MeOH–H_2O: mp 167–168 °C; $[\alpha]^{25}_D$ +5.3° (*c* 1, MeOH); IR (KBr) 3380, 1690, 1640 cm^{-1}; ^1H NMR (CD_3COCD_3/$CDCl_3$) 1.35 (s, 9 H), 2.5–3.2 (m, 2 H), 3.7–4.2 (m, 1 H), 4.30–4.55 (m, 1 H), 5.65 (d, 1 H), 5.95–6.30 (m, 1 H, J = 17 Hz), 6.9–7.4 (m, 6 H). Anal. Found: C, 63.75; H, 7.32; N, 4.43.

Boc-L-Phe-ψ-[(R)CHOHCH=]Gly-L-Pro-OMe (10). Compound **9** (159 mg, 0.5 mmol) was dissolved in a solution of methylene chloride (3 mL) and *N*-methylpiperidine[15] (NMP) (52 mg, 0.52 mmol) and cooled to −10 °C. Isobutyl chloroformate (63 mg, 0.46 mmol) was added in methylene chloride; the solution was stirred for 3.5 min, and a mixture of L-proline methyl ester hydrochloride (250 mg, 1.5 mmol) and *N*-methylpiperidine (150 mg, 1.5 mmol) in methylene chloride was added. The reaction was stirred at −10 °C for 0.5 h and at 0 °C for 5 h. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic phase was washed with citric acid (0.5 M), 5% $NaHCO_3$, water, and brine and then dried and evaporated to give **10** (131 mg, 61% yield), which was recrystallized from EtOAc–hexanes: mp 182.5–184 °C; $[\alpha]^{25}_D$ −62° (*c* 0.96, $CHCl_3$); ^1H NMR δ 1.35 (s, 9 H), 1.9–2.3 (m, 5 H), 2.8 (d, 2 H), 3.75 (s, 3 H), 3.5–4.2 (m, 3 H), 4.3–4.8 (m, 3 H), 6.35–6.65 (m, 1 H, J = 17 Hz), 6.85–7.40 (m, 6 H). Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.87; H, 7.45; N, 6.47. Found: C, 63.90; H, 7.43; N, 6.48.

Boc-L-Phe-ψ-[COCH=]Gly-L-Pro-OMe (11). To Dess-Martin periodinane[16] (152 mg, 0.36 mmol) in methylene chloride (2 mL) at room temperature was added a solution of **10** (78 mg, 0.18 mmol) in methylene chloride (1 mL). The resulting cloudy suspension, which became clear over a 20-min period, was stirred at room temperature for 1.5 h and was added to a stirred aqueous mixture of sodium thiosulfate (1 g) and $NaHCO_3$ (2 g). After the mixture was stirred for 20 min, the organic layer was separated from the aqueous layer, washed with 5% $NaHCO_3$, dried, and evaporated to give crude **11** as a yellow foam, 66 mg. A more polar impurity was removed by silica gel chromatography, eluting with ether, to give pure **11** (45 mg, 58% yield) as an off-white foam: mp 60 °C (with previous softening); $[\alpha]^{25}_D$ −43° (*c* 0.43, $CHCl_3$); HPLC one peak, retention time 2.20 min (70% MeOH in H_2O, 2 mL/min); IR 1742, 1700, 1645 cm^{-1}; UV λ_{max} (MeOH) 229 nm (12 300); ^1H NMR δ 1.42 (s, 9 H), 1.9–2.2 (m, 4 H), 2.9–3.3 (m, 2 H), 3.66 (s, 3 H), 3.6–3.9 (m, 2 H), 4.5–4.7 (m, 1 H), 4.70–4.83 (m, 1 H), 5.15 (d, 1 H), 6.95–7.40 (m, 7 H). Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.50. Found: C, 64.11; H, 7.19; N, 6.40.

(2*R*,3*S*)-*N*-[(*tert*-Butyloxy)carbonyl]-3-amino-2-hydroxy-4-phenylbutanol (12). The allylic alcohol **4** (1 g, 3.6 mmol) was acetylated as described above in the preparation of **8**, and crystalline acetate of **4** was dissolved in methanol (20 mL) and cooled to −78 °C. Ozone was bubbled into the solution until a blue color persisted, and the excess ozone was purged with oxygen. A solution of sodium borohydride (240 mg) in methanol (1 mL) was added, and the mixture was allowed to warm to room temperature and stir for 0.5 h. A solution of sodium hydroxide (300 mg) in water (5 mL) was added, and the mixture was stirred for an additional 1 h at room temperature. Citric acid (0.5 M) was added until pH 7 was obtained, and the solution was evaporated; the product was extracted with ethyl acetate, and this solution was washed with citric acid (0.5 M), sodium bicarbonate (5%), and brine and evaporated to obtain **12** as an oil. Compound **12** was purified by crystallization from ethyl acetate–hexanes to give pure **12** as colorless crystals: 820 mg (80% yield); mp 88.5–90.5 °C; $[\alpha]^{25}_D$ −36.8° (*c* 1, $CHCl_3$); ^1H NMR δ 1.40 (s, 9 H), 2.90 (d, 2 H), 3.40–3.70 (m, 5 H), 3.80–4.00 (m, 1 H), 5.10 (d, 1 H), 7.20–7.41 (m, 5 H). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.23; N, 4.97. Found: C, 64.02; H, 8.31; N, 4.86.

(2*R*,3*S*)-*N*-[(*tert*-Butyloxy)carbonyl]-3-amino-2-acetoxy-4-phenylbutyl Acetate (13). Diol **12** was acetylated with acetic anhydride–pyridine at room temperature to give, after recrystallization from CH_2Cl_2–hexanes, pure **13**: 90% yield; mp 94–96 °C; ^1H NMR δ 1.38 (s, 9 H), 2.01 (s, 3 H), 2.10 (s, 3 H), 2.71 (d, 2 H), 3.91–4.30 (m, 3 H), 4.52–4.81 (m, 1 H), 4.95–5.20 (m, 1 H), 6.90–7.41 (m, 5 H). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.44; N, 3.83. Found: C, 62.22; H, 7.29; N, 3.74.

Crystals of **13** were orthorhombic, space group $P2_12_12_1$. The cell parameters were a = 9.828 (3) Å, b = 11.732 (3) Å, c = 17.457 (8) Å, V = 2013 Å^3, and d_{calcd} = 1.21 g cm^{-3} for Z = 4. The intensity data were measured on a Nicolet R3m-E diffractometer with Mo Kα radiation (λ = 0.710 73 Å) in the θ–2θ mode. The crystal size was 0.41 × 0.42 × 0.50 mm. The structure was solved by using the direct-methods routine SOLV of G. M. Sheldrick available from Nicolet. Of the 2027 total reflections, 1873 were considered to be observed [$I \geq 1.25\ \sigma(I)$]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and given thermal parameters equal to 1.2× the thermal parameters for carbon atoms to which they were bonded. The largest residual e density peak corresponded to an H atom bonded to an N atom. Refinement (for 238 adjustable parameters) converged at R = 0.043, R_w = 0.046, and GOF = 1.23.

Acknowledgment. We thank O. P. Anderson and Cynthia K. Schauer for the X-ray crystal structure. The Nicolet R3m-E diffractometer and computing system at Colorado State University were purchased with funds provided by NSF (Grant CHE-81-03011).

Registry No. **3**, 72155-45-4; **4**, 99113-28-7; **4** acetate, 99113-29-8; **5**, 99113-30-1; **7**, 99113-31-2; **8**, 99113-32-3; **8** ethyl ester, 99113-33-4; **9**, 99113-34-5; **10**, 99128-00-4; **11**, 99128-01-5; **12**, 99113-35-6; **13**, 99113-36-7; $Ph_3P{=}CHCO_2Et$, 1099-45-2; L-Pro-OMe·HCl, 2133-40-6; vinyl bromide, 593-60-2.

Supplementary Material Available: Lists of atomic coordinates, thermal parameters, bond lengths, bond angles, anisotropic temperature factors, and hydrogen coordinates (5 pages). (Observed and calculated structure factors available from the authors.) Ordering information is given on any current masthead page.

Rearrangements of Oxahomoadamantane Derivatives in Acidic Media. 2[1]

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Rearrangement reactions of 4-oxahomoadamantan-5-one[2] and its 2-*anti*-hydroxy derivative[1] have been reported previously. In continuation of our work we were interested in a systematic study of the rearrangements of all possible isomers of 2-substituted oxahomoadamantanones in acidic

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