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Phosphates of bridgehead alcohols as putative inositol monophosphatase inhibitors: molecular design and synthetic approach

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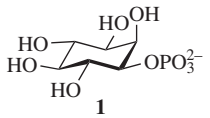
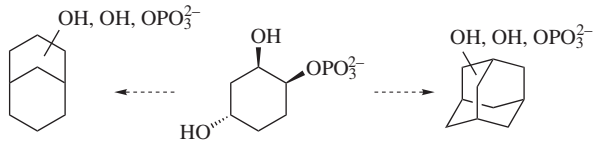
To enhance the lipophilicity of D-3,5,6-trideoxyinositol monophosphate, the IMPase inhibitor, its bridgehead analogues were suggested on the basis of molecular modeling. Adamantane-1,2- and 1,4-diols were converted into their 1-phosphates *via* the step of benzylic protection of the secondary hydroxy groups; the Baeyer–Villiger oxidation of 1-hydroxyadamantan-2-one occurred to initially cleave C(1)–C(2) bond.

Inositol monophosphatase (IMPase) plays an important role in the regulation of cell communication process in mammalian brain. The enzyme catalyzes the hydrolysis of *myo*-inositol-1-phosphate **1** and can be inhibited by lithium ions. This is believed to be essential in the lithium treatment of manic-depressive psychosis. Alternative inhibitors of IMPase are attractive therapeutic targets, but their application is limited by low bioavailability *in vivo* caused by their high polarity and inability to cross lipophilic blood-brain barrier. Thus, much effort was undertaken to overcome the requirement for polarity for IMPase inhibitors.[1,2] One of the strategies suggests a design of the compounds interacting with hydrophobic regions of the enzyme active site.



1

To enhance lipophilicity of the known inositol monophosphatase inhibitor, namely, D-3,5,6-trideoxyinositol monophosphate **2**,[3] we proposed to use our method[4] of the 'insertion' of the parent structure into lipophilic bicyclo[3.3.1]nonane or adamantane core. Herein, we carried out a molecular modeling study for the suggested templates and tried to elaborate the synthetic routes to the most promising structure.



2

Molecular docking† into the spatial model of the IMPase active site was performed for a number of phosphoric acid esters of bicyclo[3.3.1]nonane and adamantane alcohols **A**–**E** and **H**-**I** (Figure 1) with an alternation of two hydroxyl and one phosphate substituents similar to that in structure **2**.

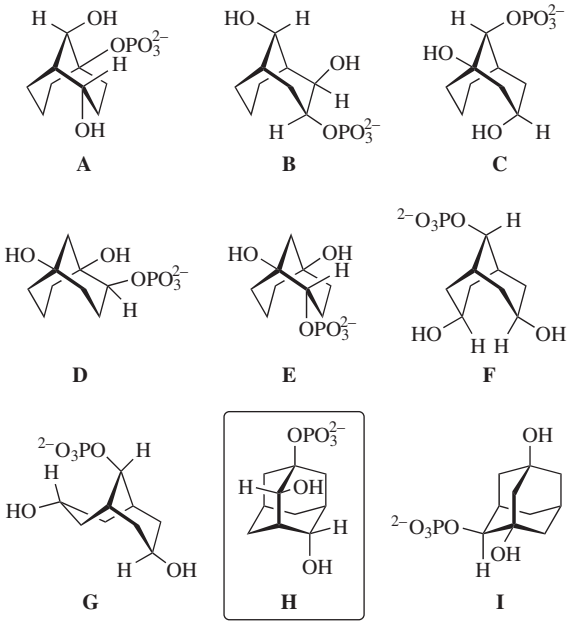
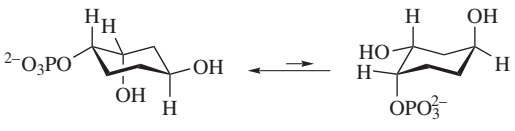


Figure 1 Structures docked to the IMPase active site.

According to the modeling data, only one of the two possible ring flip conformers of **2** is present in the equilibrium mixture, the one with phosphate group in equatorial position (**2a**) being favorable for the enzyme binding. Thus, the functional carcasses of structures **A**, **B** and **H** entirely match with the structure of the parent inhibitor. Moreover, their additional (in comparison with **2**) rings are stretched to a vacant liphophilic pocket in the enzyme active site, the positioning of **H** and **A** being sterically more advantageous than that of **B** [Figure 2(*a*)].



2a **2b**

Docking studies indicate that the structures **C** and **I** do not fit the enzyme binding site, and the binding mode of the structures **D** and **E** is also poor due to the improper location of hydroxyl at

† The molecular docking into three-dimensional structure of the human IMPase determined by X-ray crystallography (from Protein Data Bank) was performed with the Silicon Graphics Group computing complex using Sybyl software package for molecular modeling and QSAR studies.

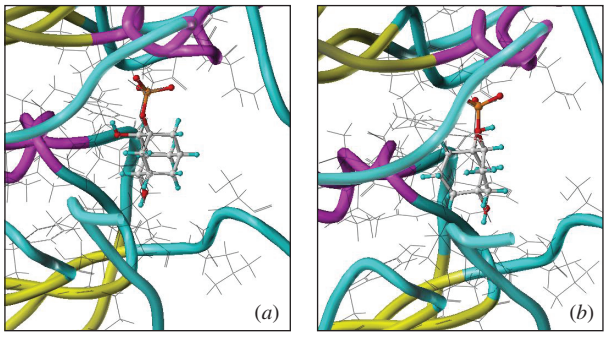
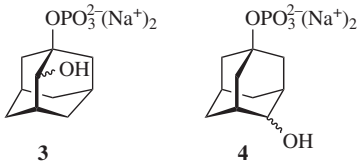


Figure 2 Models of (*a*) **H** and (*b*) **E** bound at the active site of IMPase. The steric hindrance for the binding of **E** is clearly seen; the bridgehead core of **H** is pointed directly to the empty pocket.

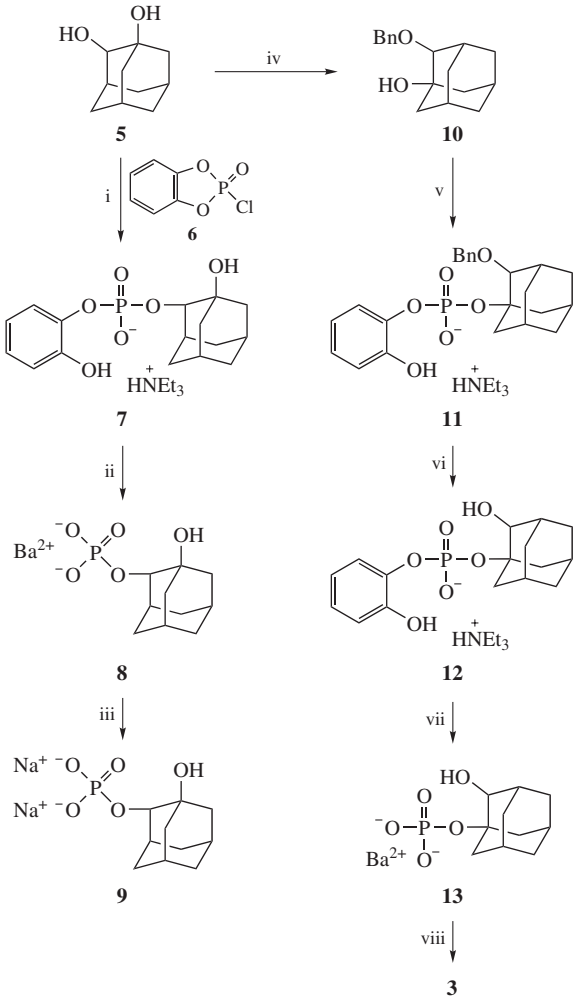
C^5 (for **D**) or at C^1 (for **E**) in bicyclo[3.3.1]nonane. Besides, an additional six-membered ring of **E** is pointed to the area occupied by C^6-hydroxyl of D-3,5,6-trideoxyinositol monophosphate **2** [Figure 2(*b*)]. Interestingly, the modeling predicts a good binding affinity for bicyclo[3.3.1]nonane derivatives **F** and **G** (Figure 1) with functional carcasses different from **2a** but with close orientation of the three pharmacophoric groups.

In general, the docked compounds can be arranged in the following sequence in diminishing the predicted activity: **H** → **A** → → **F/G** → **B**, while the inhibitory properties of **C**, **D**, **E**, **I** being scarcely probable. Synthetic realization of this structural type requires both methods for the preparation of the corresponding bridgehead triols and their selective phosphorylation. As though the synthesis of compounds **B**, **F** and **G** is complicated due to the absence of the substituents in the bridged positions, we tried to elaborate a synthetic route to structure **H** with the best predicted activity.

First, we studied the applicability of the known phosphorylating agent, *o*-phenylene phosphorochloridate,[5,6] in the reaction with known adamantane diols aiming to obtain phosphates **3** and **4**, structurally close to compound **H**.



Adamantane-1,2-diol **5** was prepared in four steps from adamantan-1-ol through the rearrangement of protoadamantanone.[7–9] Phosphatation of diol **5** with equivalent amount of *o*-phenylene phosphorochloridate **6**[5] (Scheme 1) led to the formation of the only secondary phosphate **7**,‡ while benzylation of the secondary hydroxyl in diol **5** (structure **10**)§ allowed us to obtain the desired compound **11** with a phosphate group at the bridged atom (the resonance at –5.49 ppm is observed in ^{31}P NMR spectrum, and a signal of adamantane C^1 atom at 80.8 ppm in ^{13}C NMR spectrum has J_{CP} 7.8 Hz). Hydrogenolysis of benzylic ether **11** over palladium-charcoal afforded secondary alcohol **12**, while 2-hydroxyphenyl moiety of the latter was removed by the action of bromine water with the formation of barium salt **13**. Ion exchange reaction of **13** with sodium sulfate in water gave



Scheme 1 *Reagents and conditions*: i, **6**, NEt_3, THF, room temperature, then NEt_3, H_2O, room temperature, 51%; ii, Br_2/H_2O, $Ba(OAc)_2$, room temperature, 52%; iii, Na_2SO_4, room temperature, 48 h, 100%; iv, NaH, BnCl, DMF, room temperature, 15 h, 74%; v, **6**, NEt_3, THF, room temperature, then NEt_3, H_2O, room temperature, 49%; vi, H_2, Pd/C, MeOH, room temperature, 5 h, 84%; vii, Br_2/H_2O, $Ba(OAc)_2$, room temperature, 42%; viii, Na_2SO_4, room temperature, 48 h, 100%.

the target sodium salt **3** (as stable trihydrate) in a quantitative yield.¶ In ^{13}C NMR spectrum of **3** C^2 and C^1 signals are observed at 76.77 ($^3J_{CP}$ 3.8 Hz) and 80.62 ppm ($^2J_{CP}$ 7.11 Hz), respectively, as distinct from the spectrum of isomeric phosphate **9** [70.6 ppm (C^2, $^2J_{CP}$ 6.9 Hz), 79.95 ppm (C^1, $^3J_{CP}$ 3.7 Hz)]. The only resonance at –0.34 ppm is present in ^{31}P NMR spectrum of compound **3**. The absence of barium ions in all sodium salts reported herein was confirmed by atomic emission spectroscopy.

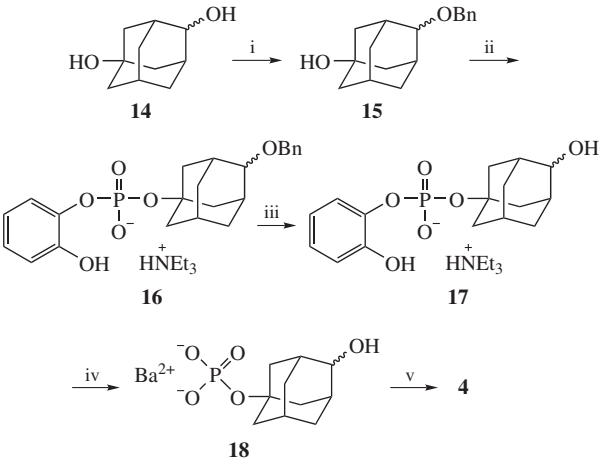
Compound **4** was synthesized analogously (Scheme 2) from adamantane-1,4-diol **14** (prepared by reduction of 1-hydroxyadamantan-4-one[11] with lithium aluminum hydride). Compounds **14**–**18** and **4** were formed as mixtures of diastereomers at C^4 in a ratio of 1:1 (as follows from the integral intensities of H–C^4 resonances at ~3.6 or ~3.8 ppm in ^{1}H NMR spectra). Phosphate group in the sodium salt **4** is manifested at –0.1 ppm in ^{31}P NMR spectrum.

These experiments confirmed the applicability of *o*-phenylene chloridophosphate for the phosphorylation of adamantane diols, so we tried to elaborate a synthetic route to adamanatane-1,2,4-triol (corresponding to structure **H**). One of the easiest way seemed to be a rearrangement of 1-hydroxy-3-oxahomoadamantan-2-one

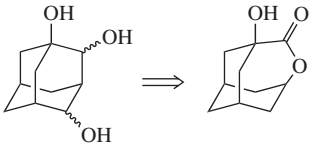
‡ In ^{1}H NMR spectrum of compound **7** a characteristic resonance of C^2 proton at 4.35 ppm is shifted to a lower field in comparison with the one in the initial diol **5**. $^3J_{HP}$ of the C^2 proton with phosphorus atom is ~7 Hz, which conforms to the literature data for the secondary phosphates.[10]

§ Attempts to use trimethylsilyl or tetrahydropyranyl protection groups failed (in the latter case the protective group was cleaved by *o*-phenylene phosphorochloridate with formation of compound **7**).

¶ Barium and sodium salts **8** and **9** were also obtained (for the synthetic details and characteristics of new compounds, see Online Supplementary Materials).



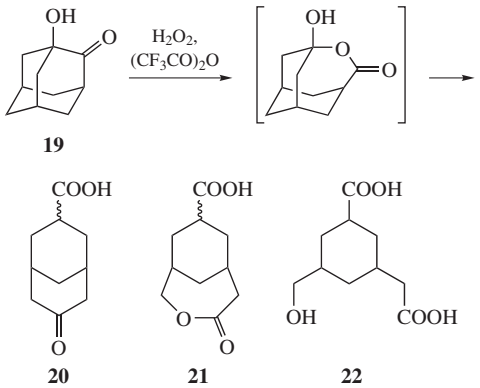
Scheme 2 *Reagents and conditions*: i, NaH, BnCl, DMF, room temperature, 15 h, 72%; ii, **6**, NEt_3, THF, room temperature, then NEt_3, H_2O, room temperature, 74%; iii, H_2, Pd/C, MeOH, room temperature, 5 h, 93%; iv, Br_2/H_2O, $Ba(OAc)_2$, room temperature, 46%; vi, Na_2SO_4, room temperature, 48 h, 100%.



Scheme 3

(Scheme 3) as analogous to the method of synthesis of different adamantane-2,4-diol isomers.[12]

To obtain the necessary lactone, the corresponding ketol, namely 1-hydroxyadamantan-2-one **19** (prepared from adamantane-1,2-diol by Jones oxidation[7]) was subjected to Baeyer–Villiger oxidation with hydrogen peroxide in trifluoroacetic anhydride. However, this reaction led to a complex mixture of products, the predominant one (>70%) proved to be cyclohexane hydroxydicarboxylic acid **22**. The identification of **22** was based on the mass spectrometry data (*m*/*z* 214 $[M-2H]^+$), ^{13}C NMR data (two signals of carboxylic groups at 173.77 and 182.35 ppm and a resonance of carbon atom neighbour to hydroxyl at 68.32 ppm) and NMR data of the dimethyl ester of **22** obtained by treatment of the acid with ether solution of diazomethane (see Online Supplementary Materials).



Scheme 4

Baeyer–Villiger reaction mixture contained also bicyclic keto acid **20** (*m*/*z* 181 $[M-H]^+$), the formation of which can be rationalized by the ring opening of the unstable isomeric lactone – 1-hydroxy-2-oxahomoadamantan-3-one (Scheme 4).†† Further oxidation of **20** leads to lactone **21**, a small amount of which has also been detected in the reaction mixture (*m*/*z* 197 $[M-H]^+$). Obviously, acid **22** is a product of lactone **21** ring opening.‡‡

It should be mentioned, that oxidation only at the OH-substituted carbon of 1-hydroxyadamantan-2-one **19** was not expected and represents an example of highly regioselective proceeding of Baeyer–Villiger reaction. Among structurally similar α-substituted ketones regioselectivity of this type was observed in the oxidation of *cis*-4-*tert*-butyl-2-fluorocyclohexanone, the major product resulting from migration of the CHF substituent (though still both isomeric lactones were isolated in a ratio of 7.2:1 in CH_2Cl_2).[15]

Attempts to carry out Baeyer–Villiger reaction for **19** with *m*-chloroperoxybenzoic acid or hydrogen peroxide in *tert*-butanol in the presence of SeO_2 as well as introduction of the bulky substituent to the substrate and subsequent oxidation of 1-benzyloxyadamantan-2-one also led to the formation of complex mixtures, in which the desired lactone was not detected.

In summary, we have suggested a new class of putative IMPase inhibitors on the basis of molecular modeling and proved the applicability of *o*-phenylene phosphorochloridate for the bridgehead polyols phosphorylation. Baeyer–Villiger oxidation of 1-hydroxyadamantan-2-one was found to proceed regioselectively towards unstable 1-hydroxy-2-oxahomoadamantan-3-one and thus cannot be used in the synthetic route to adamanatane-1,2,4-triol. Studies of the alternative preparative strategies are ongoing and will be reported in due course.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.09.003.

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†† Another synthetic way to ketoacid **20** has been reported by Renzoni and Borden.[13]

‡‡ Interestingly, similar deformation of adamantane core to cyclohexane derivative in one synthetic operation was observed only under severe oxidative conditions (O_3/SiO_2 for 2,4-didehydroadamantane).[14]

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