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Enamine Catalysis in the Synthesis of Chiral Structural Analogues of *gem*-Bisphosphonates Known To Be Biologically Active

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The synthesis of chiral γ-keto bisphosphonates is described. Michael addition of cyclic ketones to vinyl *gem*-bisphosphonate catalyzed by 0.1 mol equiv. (*S*)-(+)-1-(2-pyrrolidinyl)-pyrrolidine and benzoic acid gave the products in yields of up to 86 %, *dr* (*cis*/*trans*) > 1:99 and *ee* of up to 99 %.

Introduction

Many *gem*-bisphosphonates, compounds with a P–C–P linkage, are well known for their biological activity. The most common ones are currently in clinical use for the prevention and treatment of several bone disorders, such as osteoporosis, Paget's disease of the bone, bone metastasis resulting from multiple myeloma or certain forms of cancer, rheumatoid arthritis, periodontal disease and inflammation.[1] Examples (**A**–**C**) are shown in Figure 1. In recent years *gem*-bisphosphonates have become the subject of renewed attention, since it was discovered that some are potent growth inhibitors of protozoa responsible for diseases considered by the World Health Organization as major tropical diseases.[2] These include *Trypanosoma cruzi*, the pathogen that causes Chagas' disease, *T. brucei*, which causes sleeping sickness, and *Plasmodium falciparum*, responsible for malaria. A few attempts have been made to discover molecular targets for drug design. Potential candidates were found to be farnesyl diphosphate synthase[3] and hexokinase.[4] The first is an enzyme that catalyzes the formation of the precursor of farnesyl diphosphate, a molecule involved in protein prenylation, and a precursor of sterols, dolichols, ubiquinones and heme a. The second catalyzes the first step in glycolysis. Both are strongly inhibited by certain *gem*-bisphosphonates.

In addition, it has been shown that some *gem*-bisphosphonates inhibit the growth of several cancer cell lines.[5] The development of novel synthetic methods for existing or new bisphosphonates is thus highly desirable. Asymmetric methods could provide interesting candidates to interact with chiral allosteric sites of proteins.

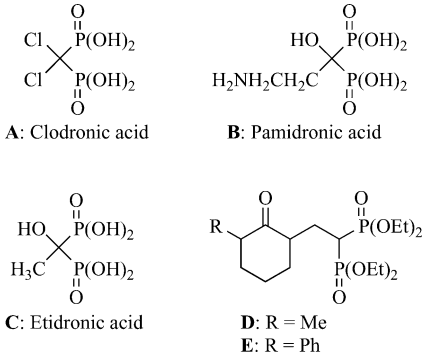

Figure 1. Examples of biologically active bisphosphonates.

For some time we have been interested in novel methods of synthesis mediated by organocatalysts.[6] This chemistry has the advantage of being environmentally friendly, economically attractive and mild conditions are generally required.[7] Recently we reported that simple piperazine and some 2,5-disubstituted chiral derivatives catalyze the Michael addition of unmodified aldehydes to nitroalkenes in good yields of up to 88 %.[6b] In asymmetric reactions excellent *dr* values of up to 97:3 and high *ee* values of up to 85% were obtained. Since the first reports on the enantioselective Michael addition for C–C bond formation by enamine catalysis in 2000,[8] many chiral organocatalysts have been used. This subject was reviewed recently,[9] and many acceptors may now be used (nitroalkenes, enones, vinyl sulfones, alkylidene malonates, maleimides, α,β-unsaturated aldehydes, imides, α-substituted vinyl cyanoacetates, acetylenic esters), and there have even been very elegant multicomponent domino (tandem, cascade) reactions involving 1,4-conjugate additions.[10] The first reports on

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asymmetric organocatalytic Michael addition reactions to vinyl bisphosphonate appeared very recently with aldehydes[11]and β-keto esters[12] as donors. Non-asymmetric versions of additions to vinyl bisphosphonates were known, with Grignard reagents,[13] organolithium compounds[3] and carbanions generated with sodium ethoxide,[14] tertiary amine,[15] lithium amide base[16] or inorganic base.[14] In this paper we present a method for the synthesis of enantioenriched γ-keto bisphosphonates, which are chiral analogues of compounds known to have potent anti-arthritic and anti-inflammatory activity[15,16] (**D** and **E**, Figure 1) by using enamine chemistry mediated by chiral diamines.

Results and Discussion

The vinyl bisphosphonate needed as starting material was prepared from paraformaldehyde and commercially available tetraethyl methylenediphosphonate according to a literature procedure.[17] A simple cyclic ketone, cyclohexanone, was chosen initially for the development of the method, and conditions often successful in other organocatalytic addition reactions were selected: 10-fold excess of ketone to vinyl bisphosphonate and 10 mol-% catalyst.[9]

A few amines were evaluated as potential catalysts (Figure 2). Piperazine, which we found useful in the Michael addition of aldehydes to β-nitroalkenes,[6b] gave no reaction, and when used neat or in the presence of acids (*p*TsOH, tartaric acid), neither did its *N*-methyl derivative **II**. The same occurred with pyrrolidine derivative **V**. A commercially available proline derivative, (*S*)-(+)-1-(2-pyrrolidininylmethyl)pyrrolidine, which has been very successful as an organocatalyst in several reactions, was tried next and led to a smooth addition reaction.[7,18] The reaction conditions were then optimized, and the results are presented in Tables 1 and 2. Generally asymmetric induction did not vary much with a change in solvent. Even brine, an environmentally benign reaction medium, well suited to large-scale applications, could be used. However, the reaction was particularly slow, requiring 89 h for complete substrate conversion. LiCl as additive gave one of the best results at $t_{1/2}$, but some racemization took place with time (Table 2, Entries 3, 4). By lowering the temperature to 0 °C, the reaction was considerably retarded (Entry 9). After 168 h, a conversion of only 63% was obtained and there was no improvement in the *ee* result. Increasing of the catalyst load to 20 mol-% did not provide any advantage either. The best results were obtained in [bmin]PF_6 (*ee* 46%, Table 1).

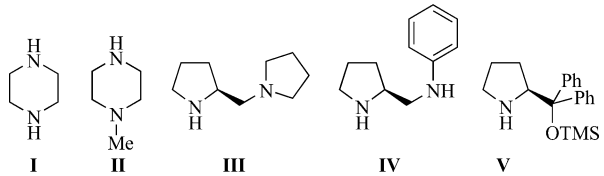
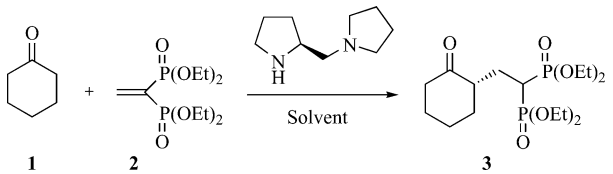


Figure 2. Catalysts screened during the optimization.

Table 1. Effect of solvents on the asymmetric Michael addition of cyclohexanone to tetraethyl vinylidene bisphosphonate.[a]



1 2 3

Entry	Solvent	Time [h]	Conversion [%]	*ee* [b] [%]
1	CH_2Cl_2	17	100	32
2	CH_2ClCH_2Cl	17	100	34
3	$CHCl_3$	17	100	30
4	EtOH	17	100	32
5	DMF	17	100	32
6	[bmin]PF_6	17	100	46
7	Brine	89	100	36

[a] Conditions: room temperature, bisphosphonate (1 mM)/ketone/catalyst 1:10:0.1. [b] Determined by ^{13}C NMR spectroscopy with (*S*,*S*)-2,3-butanediol.[19] The absolute configuration of the major product is *S*.[19]

Table 2. Effect of additives, temperature and catalyst load on the Michael addition reaction.[a]

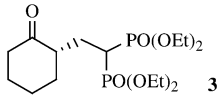
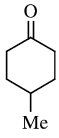
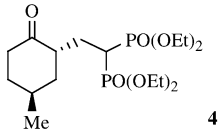
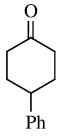
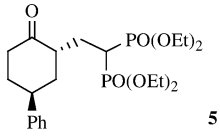
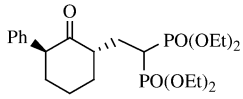
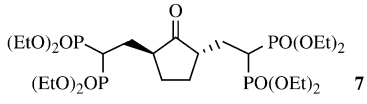
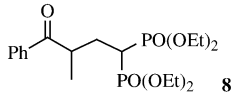
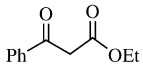
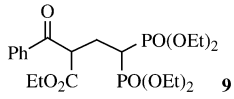
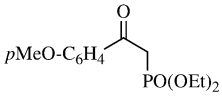
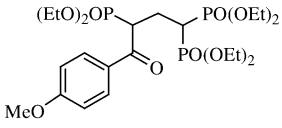
Entry	Solvent	Additive	Time [h]	Conversion [%]	*ee*[b] [%]
1	CH_2Cl_2	none	17	100	32
2	CH_2Cl_2	PhCOOH	17	100	40
3	CH_2Cl_2	LiCl	17	50	48
4	CH_2Cl_2	LiCl	24	100	24
5	CH_2Cl_2	CH_3COOH	17	100	20
6	CH_2Cl_2	CF_3COOH	17	100	36
7	CH_2Cl_2	*p*TsOH·H_2O	40	50	6
8[c]	CH_2Cl_2	PhCOOH	17	100	30
9[d]	CH_2Cl_2	PhCOOH	168	63	26
10	CH_3CN	LiCl	17	100	30
11	THF	PhCOOH	17	100	26
12	Toluene	PhCOOH	17	100	30
13[e]	CH_2Cl_2	PhCOOH	17	100	32

[a] Conditions: room temperature, bisphosphonate (1 mM)/ketone/catalyst/additive 1:10:0.1:0.1. [b] Determined by ^{13}C NMR spectroscopy with (*S*,*S*)-2,3-butanediol.[19] The absolute configuration was found to be *S*.[19] [c] Reaction with 20 mol-% catalyst and additive. [d] Reaction at 0 °C. [e] Catalyst **IV** used instead.

However, in a few experiments, the reactions in DCM with PhCOOH as additive gave better yields and only slightly lower *ee* values; hence these conditions were used afterwards. Diamine **IV** was also tried (Table 2, Entry 13), but it provided no advantage over **III**.

With a catalyst and optimized reaction conditions, we proceeded to explore the synthetic potential of the reaction, trying other ketones as substrates (Table 3). The reactions were very clean, and no ketone condensation products were formed. Large differences in reactivity were observed as the nature of the substrate was varied. 4-Substituted cycloalkanones reacted smoothly to give 2,4-disubstituted adducts in high yields, very high *dr* (*cis*/*trans* > 1:99) values and high *ee* (up to 99%) values. 2-Phenylcyclohexanone did not react in CH_2Cl_2 with PhCOOH. The reaction was possible

Table 3. Asymmetric synthesis of carbonyl-containing *gem*-bisphosphonates by Michael addition catalyzed by **III**.[a]

Entry	Donor	Product	Time	Yield[b] [%]	*dr*[c] [*cis*/*trans*]	*ee*[d] [%] [min/maj]
1		 **3**	17 h	61	–	40
2		 **4**	17 h	86	18:82	83:71
3		 **5**	7 h	78	8:92	62:76
4[e]		 **6**	7 d	80	14:86	0
5		 **7**	1.5 h	58	1:99[f]	99
6		 **8**	6 d	no reaction	–	–
7		 **9**	1 h	53	–	0
8		 **9**	17 h	35	–	0

[a] Conditions: room temperature, bisphosphonate (1 M)/ketone/catalyst/PhCOOH 1:10:0.1:0.1. [b] After isolation by column chromatography. [c] Determined by ^{31}P NMR spectroscopy. [d] Determined by ^{13}C NMR spectroscopy (Entry 1),[19,20] or by chiral HPLC neat or after conversion into 2,4-dinitrophenylhydrazones (Entries 2, 5).[21] [e] Reaction in [bmin]PF_6, conversion shown. [f] Determined by NMR spectroscopy. The HPLC traces of the 2,4-dinitrophenylhydrazones show the presence of a 9% *meso cis*-disubstituted product, which is not observed by NMR spectroscopy; hence this is probably the result of isomerization during derivatization.

in [bmin]PF_6, but with a conversion of only 80% after 7 d (Entry 4) and 20% of an unknown additional product. Product **6** was racemic.

Cyclopentanone was very reactive. A 10-fold excess of ketone gave full substrate conversion within 1.5 h. However, a 6:94 mixture of 2-mono- and 2,5-disubstituted cyclopentanone was formed. With a 1:1 ratio of ketone to bisphosphonate, a conversion of 60% was obtained after 1 h, and the mono- and disubstituted ketones were formed in a similar ratio. Thus, either the 2-monosubstituted cyclopentanone is more reactive towards the catalyst than the unsubstituted ketone or an enamine intermediate reacts with the vinyl phosphonate to produce an iminium salt that is so reactive that after protonation it is deprotonated again to form a new enamine, before hydrolysis takes place. Hence there is a second addition, and the product is mostly disubstituted. The cyclopentanone obtained is chiral and shows a high optical rotation in $CHCl_3$. It is therefore *trans*-disubstituted, with C_2-symmetry. A *cis*-disubstituted compound would be *meso* and optically inactive. Some problems were encountered during the chromatographic purification of this compound. It seemed to be sensitive to silica gel, but could be isolated if chromatographed fast on a small column. Perhaps a retro Michael reaction causes decomposition. We are continuing our work in this area. The result obtained suggests, however, that this methodology could provide a useful approach to chiral 2,5-disubstituted cyclopentanones, for which only a few methods are available at present.[22]

A linear ketone was also tried as a Michael donor but there was no reaction even after 6 d. With a β-keto ester, addition product **9**, which is known to be biologically

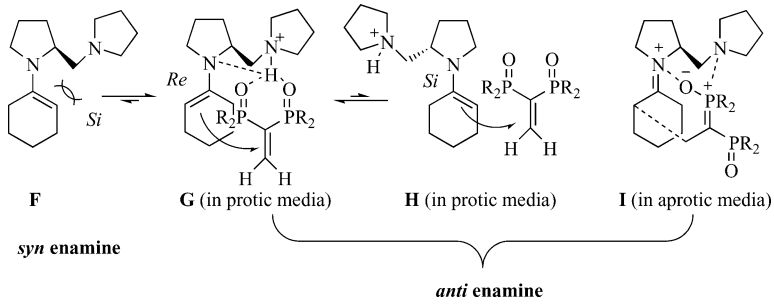


Figure 3. Proposed facial selectivity for the transition state.

active,[15] was formed smoothly in good yield, but unfortunately it was racemic. The addition reaction also proceeded with a β-ketophosphonate,[23] but the triphosphonate produced was also racemic.

The stereochemistry of the products was analyzed. The absolute configuration at position 2 of cyclic ketone **3** was determined from the ^{13}C NMR spectrum of the diastereomeric acetals formed with (2*S*,3*S*)-2,3-butanediol.[19] Hence, the set of more intense signals in the spectrum, i.e. those of the major diastereomeric acetal, corresponds to the model for the 2*R* diastereoisomer of a cyclohexanone derivative substituted at position 2 after derivatization with (2*R*,3*R*)-2,3-butanediol. The model in our case, according to CIP mIes, is that used for 2-benzylcyclohexanone. Therefore, the configuration of the major enantiomer of product **3** is 2*S*, since a (2*S*,3*S*)-2,3-butanediol derivative was used for our study. This absolute configuration is consistent with the preferential formation of an *anti* enamine (Figure 3) in which the double bond is oriented away from the bulky substituent at position 2 of the pyrrolidine ring. Enamine approach from the *Re* face gives a tight acyclic synclinal transition state **G**, which is stabilized by electrostatic interactions between the partially positive nitrogen atom of the enamine, the negatively charged oxygen atom of the phosphonate group, and the protonated nitrogen atom on the second ring. This is in agreement with that generally observed in Michael addition reactions of ketones catalyzed by pyrrolidines: the configuration of the transition state depends on the functionality at position 2 of the pyrrolidine ring.[7f,9c,24] With catalyst protonation, hydrogen bonding in the transition state favours the *anti* enamine. In aprotic media, our products also have a 2*S* configuration. Presumably, under these conditions, the nitrogen atom on the second ring stabilizes the positively charged phosphorus atom in transition state **I**.

The relative configuration of **4** was determined to be *trans* on the basis of a NOESY experiment.[25] This implies an axial approach of the electrophile to cyclohexenyl ring **K**, where both the pyrrolidine ring of the preformed enamine and the 4-methyl substituent have the thermodynamically more stable equatorial orientation to minimize 1,3-allylic strain and 1,3-diaxial interactions (Figure 4). This agrees with existing knowledge on reactions of pyrrolidine enamines of 1,4-disubstituted cyclohexanones.[26] These results provide further evidence supporting the current wave of thought that in organocatalytic reactions mediated by chiral amines, enamines are involved as intermediates.

Racemic mixtures were prepared for HPLC or NMR spectroscopy by the known DBU-mediated Michael addition.[14] In these reactions, which proceed via intermediate enolates, thermodynamically more stable *cis*-2,4-cyclohexanones were formed. Probably, as a result of strong coordination between the charged groups, equatorial attack takes place to give a product with the opposite configuration, or there is some proton transfer (enolate equilibration) during the reaction. Chiral and racemic 2,5-cyclohexanones have the same *trans* configuration, as determined by a NOESY experiment,[27] which agrees with the existing knowledge on enamine and enolate reactions.

Conclusions

We have developed a highly diastereo- and enantioselective method to synthesize cyclic γ-keto *gem*-bisphosphonates, which are chiral structural analogues of biologically active compounds. The values obtained for *ee* and *dr* are up to 99% and (*cis*/*trans*) > 1:99, respectively. With cyclohexanone and its derivatives, monoalkylated products were obtained, whereas with cyclopentanone, an unexpected reaction occurred and a C_2-symmetric disubstituted product formed preferentially. Hence this method could be useful for the synthesis of other chiral C_2-symmetric 2,5-disubstituted cyclopentanones for which there are not many methods of synthesis available at present. With propiophenone no adduct was obtained. Our studies in this area are continuing.

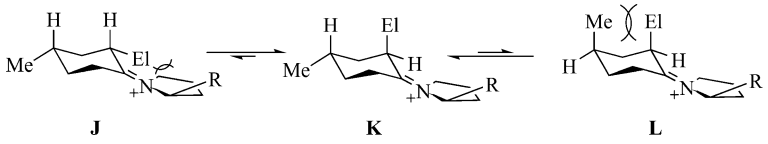


Figure 4. Conformational preference for product formation.

Experimental Section

General Procedure for the Asymmetric Catalytic Michael Addition Reaction: To vinyl *gem*-bisphosphonate (1.0 mmol) in dry dichloromethane (0.1 mL) was added the ketone (10.0 mmol), (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.1 mmol) and benzoic acid (0.1 mmol). The solution was stirred at room temperature, under argon, for the times specified. The reaction was then quenched with a concentrated solution of ammonium chloride, and the products extracted with dichloromethane. The extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated by a rotary evaporator to give the product, which was purified by column chromatography on silica gel.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data for the new compounds, selected NMR spectra and HPLC traces, are provided.

Acknowledgments

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