Pergamon

Tetrahedron Letters 43 (2002) 8665–8668

TETRAHEDRON LETTERS

A one-flask synthesis of α,α-bisphosphonates via enolate chemistry

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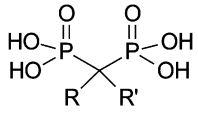
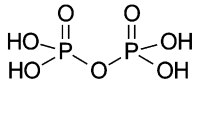
Received 28 August 2002; accepted 27 September 2002

Abstract—Treatment of several carbonyl compounds with excess strong base and diethyl phosphorochloridite results in formation of two carbon–phosphorus bonds at the α carbon. Oxidation of the immediate product with H_2O_2 affords the corresponding α,α-bisphosphonate in moderate to very good yields. © 2002 Published by Elsevier Science Ltd.

Geminal bisphosphonic acids (**1**) have been viewed as relatively stable analogues of inorganic pyrophosphate (**2**), and many representatives of this general structure bind to bone mineral and inhibit the resorption of living bone.[1] A number of these compounds have found clinical use in treatment of bone diseases such as Paget's disease of bone, myeloma, bone metastases, and osteoporosis.[2] Structure–activity research has indicated that bioactivity is highly dependent on the non-phosphorus substituents on the geminal carbon.[3] In particular, some bisphosphonates with nitrogen-containing substituents have shown inhibition of the mevalonate pathway,[4] an important biosynthetic process ultimately leading to isoprenoid synthesis and protein prenylation.



1
(α,α-bisphosphonic acid)



2
(pyrophosphoric acid)

R = OH, R' = CH_3 (etidronate)
R = R' = Cl (clodronate)
R = OH, R' = $CH_2CH_2NH_2$ (palidronate)
R = OH, R' = $(CH_2)_3NH_2$ (alendronate)
R = OH, R' = CH_2(*m*-C_5H_4N) (risedronate)

Widespread interest in the biological activity of geminal bisphosphonates has fostered development of a number of methods for their synthesis. For example, they have been prepared by reaction of a carboxylic acid with phosphorus acid and phosphorus trichloride,[5] by alkylation of tetraalkyl methylenebisphosphonate,[6] by reaction of lactams or amides with trialkylphosphites,[7] by Michael-type addition to ethylidene bisphosphonate esters,[8] and by nucleophilic addition of a dialkyl phosphite to an acyl phosphonate.[9] On occasion, bisphosphonates have been prepared from monophosphonates through C–P bond formation,[10] and preparation of tris phosphono methane from methylene bisphosphonate also has been reported.[11] Furthermore, reaction of P(III) electrophiles with enolates[12] and subsequent oxidation of the phosphorus to afford phosphonate derivatives of ketone, ester, lactone, and amide enolates is well known,[13,14] but procedures for introduction of a bisphosphonate adjacent to a carbonyl group are apparently not available.[15]

During the synthesis of a series of *N*-farnesyl α-phosphono lactams as potential farnesyl:protein transferase inhibitors, we found several α,α-bisphosphonates were formed as by-products in relatively low yields.[14] We reasoned that these α,α-bisphosphonates might be formed by a sequential process including enolate formation, C–P bond formation, a second enolate formation, and final C–P bond formation, and that they might be prepared in higher yield through this strategy if there were sufficient equivalents of base and the phosphorus (III) reagent for two reactions. Given the known impact of some bisphosphonates on isoprenoid synthesis, and our own interest in protein prenylation,[13e,14,16] it became of interest to explore this strategy for bisphosphonate synthesis.

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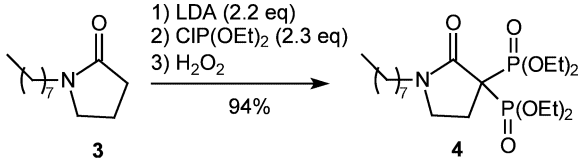
0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02148-2

To test the feasibility of this approach with an accessible *N*-alkyl lactam, commercially available *n*-octyl pyrrolidinone (**3**) initially was selected. After treatment with LDA (2.2 equiv.), subsequent addition of diethyl phosphorochloridite (2.3 equiv.), and oxidation of the reaction mixture with H_2O_2, the bisphosphonate **4** was isolated in a very good yield.[17] Its structure was identified readily through analysis of its ^1H NMR, ^{13}C NMR and DEPT spectra. In particular, the appearance of triplets for the carbonyl carbon ($J=4.6$ Hz) and the α-carbon ($J=135.8$ Hz) in the ^{13}C NMR spectrum supported the proposed structures with two phosphonate groups attached to the same carbon.



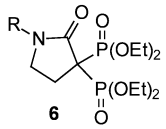
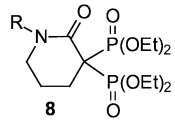
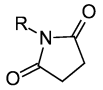
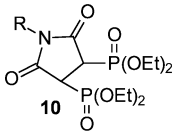
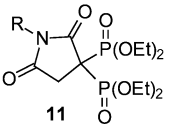
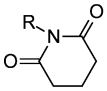
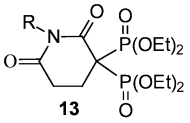
3 **4**

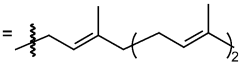
The success of this model reaction, and the availability of some lactams from an earlier study,[14] encouraged efforts to prepare *N*-farnesyl lactam bisphosphonates through this reaction sequence. With the *N*-farnesyl lactam **5**, the bisphosphonate **6** was obtained in a good yield under parallel reaction conditions accompanied by a small amount of the corresponding monophosphonate (5%). With the 6-membered ring lactam **7** the bisphosphonate **8** was still the major product under these conditions although the yield was moderate and more of the monophosphonate was observed (Table 1).

These reaction conditions also were applied to the *N*-farnesyl imides **9** and **12**, in which two equivalent positions for enolate formation are present on the imide rings. Under the standard conditions with the five-membered ring compound **9**, C–P bonds were formed at the two different α-carbons to provide the vicinal bisphosphonate **10**. This assignment was straightforward given observation of one doublet of doublets for the two α-carbons ($J=142.3$, 9.1 Hz), rather than the triplet expected for the α-carbon of a geminal bisphosphonate. With LDA as the base, the yield was just 22% but when LHMDS was employed the yield rose to 46%. Formation of the vicinal bisphosphonate **10** might be explained by formation of a relatively stable aromatic dianion intermediate. In contrast, for the six-membered ring imide **12** where an aromatic dianion is not viable, the monophosphonate was isolated as the major product under these conditions even with LHMDS as the base.

In contrast to these results, when step-by-step phosphorylation conditions (Method B) were applied to the five-membered ring imide **9** the α,α-bisphosphonate **11** was isolated in 30% yield, although the monophosphonate was still the major product and the vicinal bisphosphonate **10** also was obtained in low yield (5%). When the six-membered ring imide **12** was treated under these stepwise conditions, the α,α-bisphosphonate **13** was obtained as the only bisphosphonate product (18%) but the monophosphonate was the major product (48%).

Table 1. Synthesis of bisphosphonate lactams

Lactam	Method	Product(s)	% Yield bis (+ yield mono)
 **5**	A	 **6**	77% (5%)
 **7**	A	 **8**	50% (22%)
 **9**	A	 **10**	46%
9	B	 **11**	30% (43%) (+5% **10**)
 **12**	B	 **13**	18% (48%)

R = 

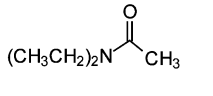
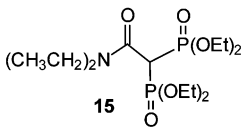
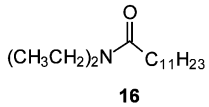
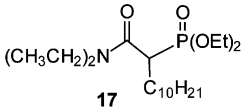
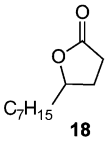
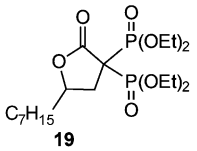
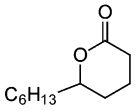
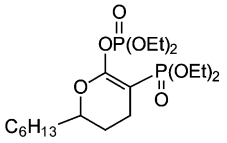
Method A: 1) LDA (2.2 eq); 2) $ClP(OEt)_2$ (2.3 eq); 3) H_2O_2 (10 eq).
Method B:1) LHMDS; 2) $ClP(OEt)_2$; 3) LHMDS; 4) $ClP(OEt)_2$; 5) H_2O_2 (20 eq).

While a phosphonite may not be generally recognized as a good electron-withdrawing group, this finding suggests that it can stabilize an adjacent anion and thus help to discriminate between the two originally equivalent α-carbons of the imide ring.

Preparation of the lactam bisphosphonates as shown above encouraged exploration of this strategy with other carbonyl compounds. As shown in Table 2, with the simple acyclic amide, *N*,*N*-diethylacetamide **14**, treatment with 2 equiv. of LDA and 2 equiv. of the P(III) electrophile, followed by oxidation with H_2O_2, gave the geminal bisphosphonate **15** in good yield. Unfortunately, when the longer chain amide **16** was treated under the same reaction conditions, only the monophosphonate **17** was obtained. The obvious explanation is that formation of the monophosphonate may be a result of the greater degree of steric hindrance imposed by the larger alkyl chain.

Two lactones also were examined and again contrasting results were observed. With the five-membered ring lactone **18**, application of the standard reaction conditions afforded the bisphosphonate **19** in good yield. However, when the same reaction conditions were applied to the six-membered ring lactone **20**, the major product did not give spectral data consistent with a

Table 2. Attempted synthesis of amide and lactone bisphosphonates

Carbonyl Component	Method	Product	% Yield
 **14**	A	 **15**	72%
 **16**	A	 **17**	95%
 **18**	A	 **19**	67%
 **20**	A	 **21**	55%

bisphosphonate. Instead of the single resonance observed for the bisphosphonates, the ^{31}P NMR spectrum of this product showed two peaks at –8.4 and +20.4 ppm, respectively. Furthermore, the ^{13}C NMR spectrum did not show a triplet for the quaternary carbon as would be expected for a bisphosphonate, but rather a doublet of doublets ($J_{CP}=203.2$ and 4.7 Hz). This data clearly reveals the presence of one new C–P bond and one new O–P bond, and the structure was assigned as the phosphonate–phosphate **21**.

In conclusion, these studies have shown that it is possible to obtain geminal bisphosphonates from different carbonyl compounds through reactions with strong base, diethyl phosphorochloridite, and oxidation. The process gives moderate to good yields with *N*-alkyl lactams, but more varied results were obtained with other carbonyl compounds. Further studies on compounds with different ring sizes and substitution patterns will be necessary to better delineate the limits of this approach, as well as to explore the transformations that can be conducted on the carbonyl components in the presence of the bisphosphonate moiety.

Acknowledgements

Financial support from the Roy J. Carver Charitable Trust is gratefully acknowledged.

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17. General procedure for bisphosphonate synthesis. A solution of lactam **3** (211 mg, 1.07 mmol, 1.0 equiv.) in anhydrous diethyl ether (2 mL) was added dropwise via cannula to a stirred solution of LDA [2.2 equiv., prepared in situ from diisopropylamine (0.32 mL, 2.36 mmol) and *n*-butyllithium in hexanes (2.50 M, 0.94 mL, 2.36 mmol)] in anhydrous diethyl ether (5 mL) at −78°C. After 60 min, HMPA (0.42 mL, 2.46 mmol) and diethyl phosphorochloridite (0.36 mL, 2.46 mmol) were added in turn, and the resulting mixture was allowed to warm to 0°C over the course of 2 h. The reaction was quenched by slow addition of hydrogen peroxide (30%, 1.21 mL, 10 equiv.), and the resulting mixture was stirred vigorously at 0°C for 10 min. The organic phase was separated, washed with brine, and dried ($MgSO_4$). After concentration in vacuo, final purification by column chromatography on silica gel (from EtOAc to 8:2 EtOAc:CH_3OH) afforded bisphosphonate **4** (470 mg, 94%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36–4.13 (m, 8H), 3.44 (t, $J=7.0$ Hz, 2H), 3.28 (t, $J=7.3$ Hz, 2H), 2.73–2.58 (m, 2H), 1.56–1.47 (m, 2H), 1.38–1.21 (m, 22H), 0.87 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (t, $J_{CP}=4.6$ Hz), 63.8 (d, $J_{CP}=6.5$ Hz, 2C), 63.3 (d, $J_{CP}=7.0$ Hz, 2C), 52.6 (t, $J_{CP}=135.8$ Hz), 45.2 (t, $J_{CP}=4.0$ Hz), 43.5, 31.8, 29.2, 29.2, 27.0, 26.7, 25.0 (t, $J_{CP}=4.1$ Hz), 22.6, 16.4 (d, $J_{CP}=6.2$ Hz, 2C), 16.4 (d, $J_{CP}=6.2$ Hz, 2C), 14.0; ^{31}P NMR δ 19.9. Anal. calcd for $C_{20}H_{41}NO_7P_2$: C, 51.17; H, 8.80; N, 2.98. Found: C, 51.13; H, 8.90; N, 3.04.