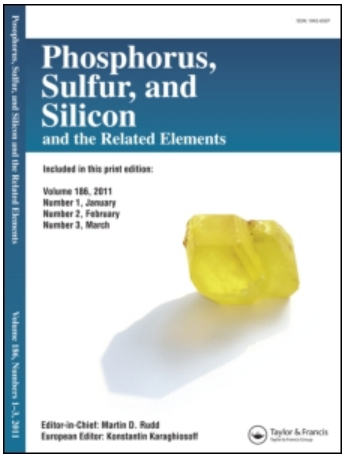

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UNEXPECTED COURSE OF DIMETHYL PHOSPHITE ADDITION TO THE CONDENSATION PRODUCTS OBTAINED FROM *o*-CARBOXYBENZALDEHYDE AND ALIPHATIC AMINES

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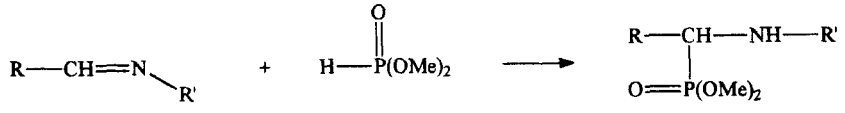
Condensation in equimolar amount of *o*-carboxybenzaldehyde with primary amines, such cyclohexyl and *iso*-propyl, yields oily products which by subsequent addition of dimethylphosphite produce in very good yield amido-amino-phosphonic acid mono-methyl esters, very soluble in water and in protic organic solvents. The by-product of this addition reaction is a cyclic amino-phosphonic acid dimethyl ester. Characterization of these new compounds is made by NMR spectroscopy (^{1}H and ^{31}P), by MS-FAB techniques and IR spectroscopy. A possible reaction mechanism leading to these unexpected products is outlined. Although the phosphorylation reaction is quite complex on the molecular level, this procedure allows to obtained in a very convenient way and by one-pot reaction good yields of amino-phosphonic acid mono-methyl esters containing ancillary moieties (the amido group) suitable for complexing metals. Furthermore, in an extended way, the compounds obtained can be thought of as the non-natural analogs of peptides and therefore they can be of utility in biological tests.

Key words: Amino-phosphonic acid mono- and di-methyl esters, one-pot reaction, non-natural analogs of peptides, ^{1}H and ^{31}P-NMR characterization.

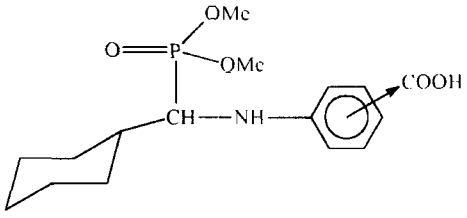
INTRODUCTION

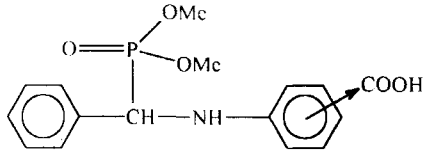
The addition of dimethyl phosphite [H-P(O)(OMe)$_2$] to Schiff bases was found to be a suitable general synthetic route for the preparation in good yields of dimethyl esters of α-amino-phosphonic acids, as indicated by reaction (**I**):



According to our experience such simple reaction can be performed both in neat at room temperatures or in refluxing protic or aprotic solvents and it is catalyzed by a little amount of NaH. Irrespective of the R and R′ moieties present in the Schiff base precursors, i.e., aromatic groups, substituted aromatic rings, alkyl or cycloalkyl fragments, the reaction proceeds in the expected regular way, i.e., formation of the amino-phosphonic acid esters, and even bis-amines react easily to yield di-phosphonate derivatives.[1–7]

According to the general procedure indicated in (**I**) we recently synthesized[7] in good yield, *inter alia*, the following amino-phosphonate esters **1** and **2** containing a free-carboxyl group in the aromatic moiety:





1a = *o*-COOH

1b = *p*-COOH

2a = *o*-COOH

2b = *p*-COOH

^{1}H-NMR spectra and MS-FAB analyses were consistent with the structures given above.[7]

In this paper we wish now to report an unusual course of the phosphorylation reaction depicted in (**I**) when the condensation products between *o*-carboxybenzaldehyde and aliphatic amines were employed as substrates.

RESULTS AND DISCUSSION

In spite of what could be foreseen by the general synthetic procedure listed in (**I**), when the crude oily product obtained by the condensation of 2-carboxybenzaldehyde and cyclohexlamine was caused to react with dimethyl phosphite, in neat at room temperature, two unexpected products (**3**) and (**4**) were isolated.

In fact, after the dimethyl phosphite addition to the oily product, working-up of the reaction mixture with an excess of cold ethylacetate gave a white high-melting solid (major product), whereas from the mother liquors a white compound with lower melting point was then isolated (minor product).

The white solid, which has m.p. 224–226°C (after recrystallization from dioxane) is sparingly soluble in hot ethylacetate, $CHCl_3$, CH_3CN but it dissolves very easily in cold water solutions at $0 \leq pH \leq 14$ and in cold methanol.

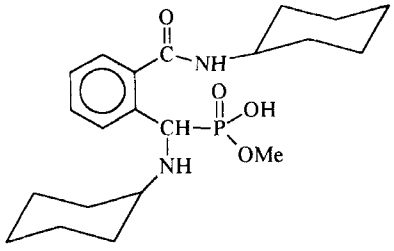
This behaviour strongly contrasts with the known properties of numerous dimethyl and diethyl esters of α-amino-phosphonic acid derivatives so far synthesized[1–7] and thus a systematic NMR analysis as well as MS-FAB investigations were performed.

The main indications which came out from the ^{1}H-NMR spectra were as follows: in the aliphatic region were present 22 protons at 1.22, 1.75 ppm attributable to the cyclohexyl moieties, one sharp doublet was in evidence in the methoxy region at 3.40 ppm (J_{HP} = 10 Hz) accounting for 3 protons, two signals at 2.50 ppm and 3.82 ppm appearing as multiplets accounted for one proton each and were attributed to the NH hydrogens, a doublet was present in the methyne region at 4.61 ppm (J_{HP} = 14.8 Hz)† and accounted for one proton, and finally the multiplets present in the aromatic region at 7.42, 7.72 ppm integrated for 4 protons.

†The coupling constant CH—P is somewhat smaller compared to that one generally found in other amino-phosphonic acid esters so far synthesized (J_{HP} = 20 ÷ 22 Hz).[1–7]

The ^{31}P-NMR spectrum (proton decoupled) showed one sharp singlet at 13.97 ppm, i.e., in the expected region of the phosphonic acid monoesters.[4] The MS-FAB analyses revealed a protonated molecular ion $[M + H]^+$ at m/z = 409 with main fragments ion $[(M + H) - C_6H_{11}—NH_2]^+$ at m/z = 310 and $[(M + H) - H—P(O)(OMe)(OH)]^+$ at m/z = 214.

From all these informations (including elemental analyses as reported in the experimental section) we can conclude that the structure of the white solid should have the molecular formula **3** indicated below, i.e., it is a phosphonic acid mono-ester derivative possessing an amide fragment.



3 (MW = 408)

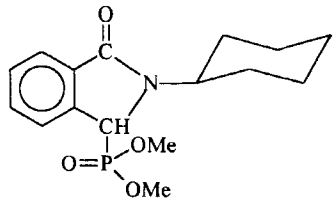
On the other hand, the product isolated from the mother liquors which has m.p. 79 ÷ 80°C, in the ^{1}H-NMR spectrum reveals the presence of a mono-substituted cyclohexyl group (11 H) at 1.32, 1.88 ppm, a multiplet at ca. 2.40 ppm (1 H) due to the NH proton, two sharp doublets (J_{HP} = 10.8 Hz) at 3.58 and 3.73 ppm in the methoxy region (6 H) and one sharp doublet (J_{HP} = 13.0 Hz)‡ for the methyne hydrogen (1 H) at 4.88 ppm plus multiplets in the aromatic region (4 H) at 7.53, 7.80 ppm. The ^{31}P-NMR spectrum (proton decoupled) shows a sharp singlet at 21.399 ppm. From the MS-FAB spectrum a molecular ion $[M + H]^+$ is evident at m/z = 324 and a fragment $[(M + H) - H—P(O)(OMe)_2]^+$ at m/z = 214.

These data (including elemental analyses and IR spectroscopic evidences) coupled with its insolubility in aqueous potassium carbonate solutions led us to assign formula **4** to the lower melting point derivative.

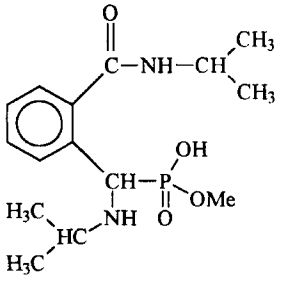
Substituting cyclohexylamine by *iso*-propylamine as the primary base used in the condensation with *o*-carboxybenzaldehyde and then allowing the oily product to react with dimethyl phosphite, does not modify the reaction course. In fact the mono-methyl ester **5**, the corresponding analog of **3**, was isolated from the reaction mixture, and its characteristics are reported in the experimental section.

Evidences concerning the formation of a **6** arise from NMR spectra and MS-

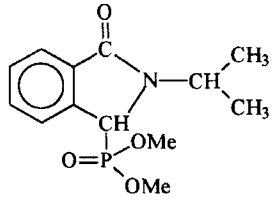
‡Also in this case the coupling constant J_{HP} is smaller compared to that one expected[1-7]; this could be probably due to the cyclic structure of **4**. Closely related cyclic amino-phosphonates are reported in literature to have CH—P coupling constants in the range 17–18 Hz.[8,9] Dimethyl- as well diethyl-phthalidyl-3-phosphonates, prepared according to Reference 10, show in the ^{1}H-NMR spectrum a doublet for the methyne hydrogen at δ 5.72 ppm with J_{HP} = 11.0 Hz.



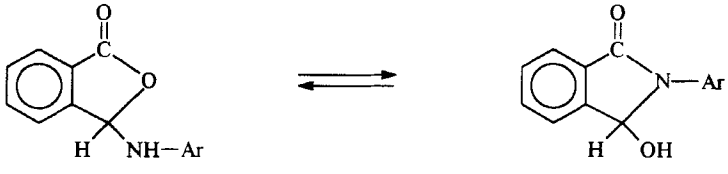
4 (MW = 323)*



5



6



7 8

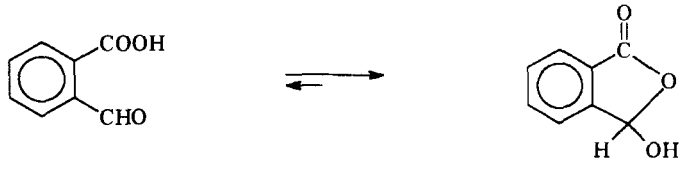
FAB analyses of the crude reaction mixture, but, in this case, pure **6** was not isolated.§

On the contrary, condensation of *o*-carboxybenzaldehyde with aromatic primary amines, yields crystalline compounds possessing structures **7** and **8** which are no more reactive towards dimethyl phosphite, precluding the formation of the expected amino-phosphonates.

The main questions are therefore the followings: why does the addition of dimethyl phosphite to the oily products obtained by condensing *o*-carboxyaldehyde with primary amines occur in such an unexpected and unusual way? How can compounds **3**, **5** and **4**, **6** be formed?

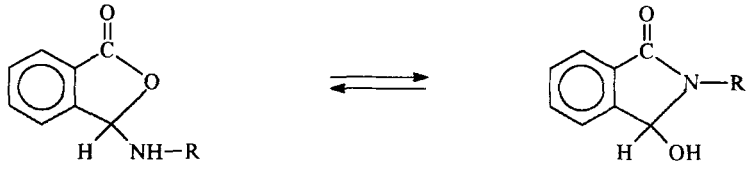
§In the ^{1}H-NMR spectra of the crude reaction mixture are present two methoxy doublet at 3.54 and 3.74 ppm and a CH—P doublet at 4.90 (J_{HP} = 13 Hz), very diagnostic of **6**. The MS-FAB reveals the molecular peak $[M + H]^+$ at m/z = 284, and a strong fragment $[(M + H) - (H—P(O)(OMe)_2]^+$ at m/z = 174.

Such peculiar progress of the phosphorylation reaction can be attributed to the use of *ortho*-carboxybenzaldehyde which exists both in the open (**9**) and in the ring-closed 3-hydroxyphthalide (**10**) structure, depending upon the solvent and temperature.[11-13]



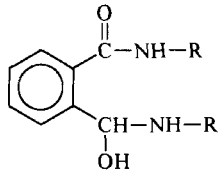
9 **10**

Literature reports[13-16] indicate that primary, as well as secondary amines generally react with 3-hydroxyphthalide (**10**) yielding compounds whose molecular formula can be described by structures **11** or **12**, which in some cases equilibrate between themselves and even with more complex derivatives.



11 **12**

Our preliminary results indicate that, when R = cyclohexyl or *iso*-propyl, structures **11** and **12** slowly change towards a white solid powder possessing structure **13** as indicated by NMR analyses, MS-FAB spectrometry and by comparison with the physical properties of authentic samples with formula **13**, which were obtained by addition of two moles of R—NH_2 to *o*-carboxybenzaldehyde.

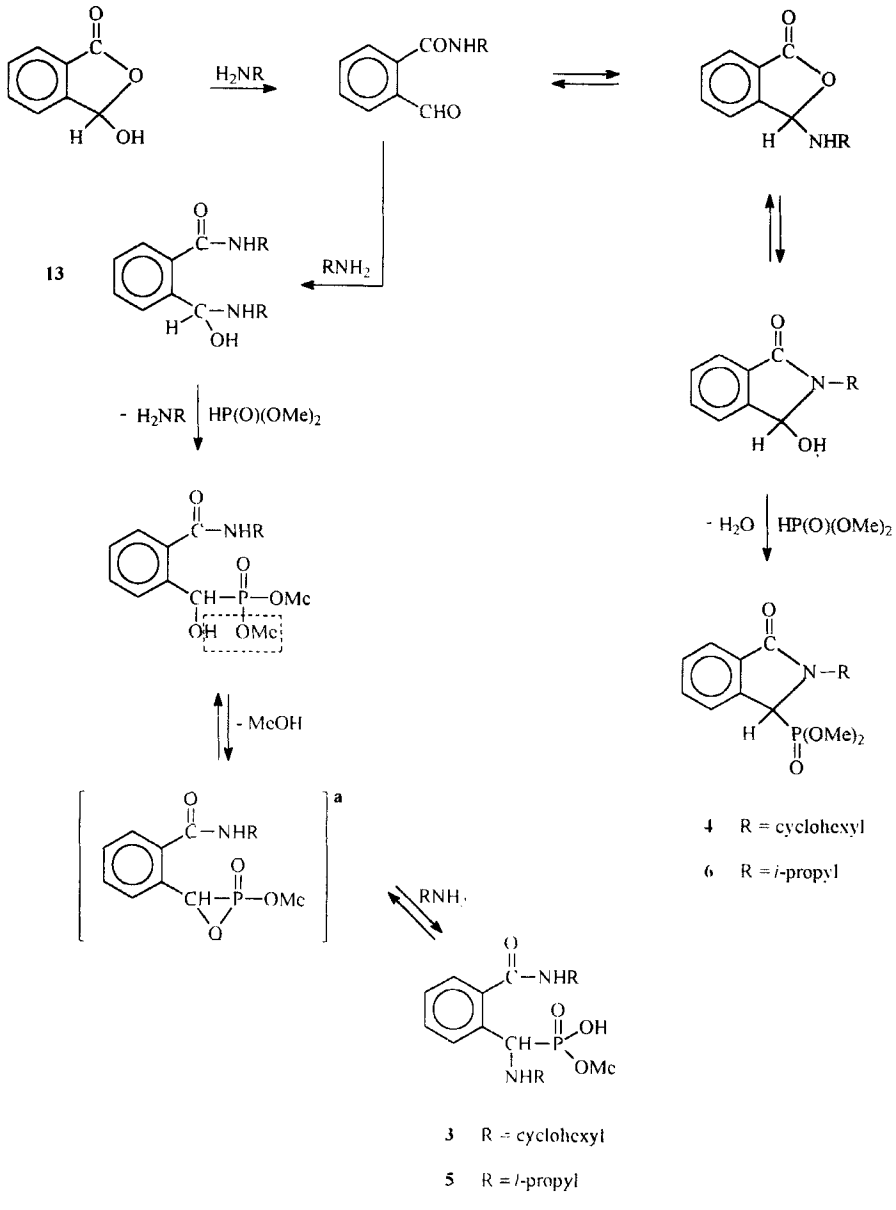


13a R = cyclohexyl

13b R = *i*-propyl

This means that our oily products, which were allowed to react with dimethyl phosphite, are indeed a mixture of different compounds, in which *inter alia* are present structures **11, 12** and **13**.

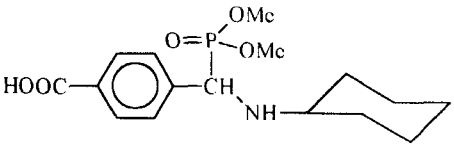
SCHEME I



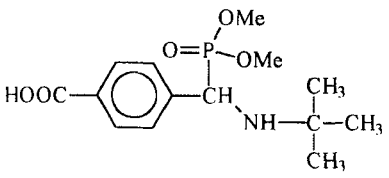
[a]Oxaphosphirans have been postulated as intermediates in the rearrangements of α-diazophosphonates.[17,18]

Thus Scheme I gives a pictorial representation of the intermediates which can produce phosphonate **4, 6** and the mono-esters **3, 5** in the synthetic approach used by us.

Further confirmations of the proposed reaction mechanism reported in Scheme I, come from the following ancillary and indicative experiences:



14



15

i) The Schiff bases N-cyclohexyl-4-carboxybenzylideneamine and N-*t*-butyl-4-benzylideneamine, obtained by condensation of 4-carboxybenzaldehyde with cyclohexylamine and *t*-butylamine, respectively, react in the normal way with dimethyl phosphite yielding the expected amino-methyl phosphonic acid dimethyl esters **14** and **15** (see Experimental section).

This experiment confirms that the unexpected course of the phosphorylation reaction as reported in Scheme I is due to the presence of the *o*-carboxybenzaldehyde.

ii) Phosphonates **1a–b** and **2a–b** as well as **14** and **15**, react normally at the free carboxylic group with cyclohexylamine or *iso*-propylamine yielding the corresponding amides in quantitative yield and such reaction does not affect the chemical constitution of the dimethyl phosphonate group, indicating that base-catalyzed hydrolytic processes, although conceivable,[19] are not responsible for the formation of mono-esters **3** and **5**.

In conclusion this work shows that the condensation of *o*-carboxybenzaldehyde with primary aliphatic amines does not produce Schiff bases but a mixture of cyclic and acyclic condensation products, which, in turn, by the addition of dimethyl phosphite, produce in very good yields and in an easy way amido-amino-phosphonic acid mono-methyl esters.

Although experiments are still in progress in order to elucidate the reaction mechanism, we stress at this point the potentiality of this phosphorylation reaction, which, although very complex on the molecular level, can produce in a very convenient way and by one-pot reaction amino-phosphonic acid mono-methyl esters, extremely soluble in water and possessing ancillary complexing moieties (the amido group) suitable for complexing metals. Furthermore, in an extended way, such compounds can be thought as the non-natural analogs of peptides and therefore can be of utility in biological tests.

EXPERIMENTAL

Amines, aldehydes, dimethyl phosphite as well as solvents and all other chemicals used were commercial products from Aldrich, which were purified before use. All syntheses were performed under a dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard using a Bruker AC-250 instrument operating at 250 MHz. Phosphorus NMR-spectra were recorded at Düsseldorf University with a Bruker AM 200 MHz spectrometer with a resolution >0.003 ppm using 85% H_3PO_4 as external reference.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system. 3-Nitro-benzylalcohol was used as matrix.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1725X FT-IR spectrometer.

Reaction of o-Carboxyaldehyde with Primary Amines

To 7.5 g (0.05 mol) of *o*-carboxybenzaldehyde dissolved in 100 ml of CH_3OH, were added under stirring at room temperature 0.05 mol of cyclohexylamine or *iso*-propylamine, according to the final product desired. The reaction mixture was allowed to reflux for 15 min and then the solvent was removed under reduced pressure. The crude viscous pale yellow oil obtained when cyclohexylamine was used shows ^{1}H-NMR signals at δ ($CDCl_3$, TMS) 1.29, 1.75, 1.98 (m, 11H, cyclohexyl moiety), 3.05 (m, 1H, NH), 6.70 (s, 1H, CH), 7.62 (m, 3H, ArH) and 7.93 (m, 1H, ArH). MS-FAB spectra show major peaks at m/z 232 (base peak), 331, 364 and 463.

On standing the oil obtained modifies its consistency and composition, becoming a white solid. In particular in the NMR spectra the ratio between cyclohexyl/aromatic protons changes from 11/4 to 22/4, and additional peaks are present at 2.75 (m, 1H, NH—R), 3.10 (m, 1H, OH) and 8.50 (br s, 1H, CO—NH—R), indicating that compound **13a** is forming. As a check, compound **13a** was obtained in 90% yield by reacting 2 moles of cyclohexylamine with 1 mol of *o*-carboxybenzaldehyde in refluxing CH_3OH, for 15 min. The white powder obtained has m.p. 130–131°C and its ^{1}H-NMR spectrum shows signals at δ ($CDCl_3$, TMS): 1.16, 1.76 (m, 22H, cyclohexyl H), 2.73 (m, 1H, NH—R), 3.08 (m, 1H, OH), 7.44 (m, 2H, ArH), 7.83 (m, 2H, ArH) and 8.30 (br s, 1H, CO—NH—R), consistent with formula **13a** given in the text. MS-FAB analysis reveals the parent ion $[M + H]^+$ at m/z 331 and a fragment at 232.

Analogous behaviour is observed when reacting *iso*-propylamine with *o*-carboxybenzaldehyde. In fact, compound **13b** a white solid with m.p. 94–96°C, obtained by condensation of two moles of amine with one mole of aldehyde, shows signals, in the ^{1}H-NMR spectrum, at δ ($CDCl_3$, TMS): 1.15 (d, 6H, CH—**CH_3**), 1.21 (d, 6H, CH-**CH_3**), 3.20 (hept, 1H, **CH**-CH_3), 3.44 (hept, 1H, **CH**-CH_3), 7.10 (br s, 1H, OH), 7.42 (m, 2H, ArH), 7.80 (m, 2H, ArH) and 8.58 (br s, 1H, CO—NH—R), consistent with formula **13b** reported in the text; MS-FAB analysis reveals the parent ion $[M + H]^+$ at mz = 251 and a fragment $[(M + H) - H_2N—CH(CH_3)_2]^+$ at m/z = 192.

Compounds **3**, **4**, **5** *and* **6**. The synthetic procedure will be described in detail for **3** and **4**. Sample **5** was obtained according to the same general procedure and for it will be here reported only the ^{1}H-NMR spectrum together with its MS-FAB and elemental analyses.

General procedure. To the crude oil (6 g) obtained from the condensation of *o*-carboxybenzaldehyde and cyclohexylamine was added dimethyl phosphite (3.2 g) with a catalytic amount of NaH and the mixture was stirred for 3 h at room temperature. The thick oil obtained was diluted with 10 ml of a mixture 1:1 of diethyl ether/ethyl acetate, and left to stand overnight. The solid obtained was filtered and purified by crystallization from dioxane to yield 3.3 g (62%) of monoester **3**, m.p. 224–226°C; IR (KBr) (P—O—C) 1045 and 1073, (P=O) 1206 and 1227, (O=C) 1674 cm^{-1}. By elemental analysis **3** was found to occlude 1/2 mol of water; calcd for $C_{21}H_{33}N_2O_4P \cdot 1/2\ H_2O$, C = 60.43; H = 8.15; N = 6.71; found C = 60.21; H = 8.23, N = 6.83.

Compound **4**. To the mother liquors of the reaction mixture which yielded **3**, petroleum ether was added and a white solid was separated, which was purified by crystallization from cold diethyl ether/ethyl acetate to yield 1.5 g (18%) of the diester **4**, m.p. 79–80°C; IR (KBr) (P—O—C) 1029 and 1061, (P=O) 1260, (O=C) 1673 cm^{-1}. Microanalysis for $C_{16}H_{22}NO_4P$, calcd: C = 59.44; H = 6.81; N = 4.81; found: C = 59.26; H = 6.88; N = 4.87.

Compound **5**. Recrystallized from $CHCl_3$/AcOET; m.p. 173–176°C. ^{1}H-NMR δ ($CDCl_3$, TMS): 1.04 (d, 6H, CH_3), 1.44 and 1.61 (two d, 6H, CH_3), 2.95, 3.21 (br m, 1H, **CH**CH_3), 3.46 (d, 6H, J_{HP} = 10.2, OCH_3), 4.28 (hept, 1H, $CHCH_3$), 4.60 (d, 1H, J_{HP} = 14.6, CH), 7.41 (m, 2H, ArH), and 7.73 (m, 2H, ArH). MS-FAB: parent ion $[M + H]^+$ at m/z = 329, base peak $[(M + H) - H_2N—CH(CH_3)_2]^+$ at m/z = 270.

Compounds **14** *and* **15**. They were obtained adding dimethylphosphite to the corresponding Schiff bases, according to the general procedure outlined in (**1**) and already described.[2,3,5,7] The ^{1}H-NMR spectrum of **14** reveals signals at δ ($CDCl_3$, TMS): 1.07, 1.67 (m, 11H, cyclohexyl H), 2.30 (br s, 1H, NH), 3.59 (d, 3H, J_{HP} = 10.6, OCH_3), 3.82 (d, 3H, J_{HP} = 10.4, OCH_3), 4.39 (d, 1H, J_{HP} = 22.8, CH), 7.53 (dd, 2H, ArH) and 8.09 (d, 2H, ArH). MS-FAB: parent ion $[M + H]^+$ at m/z = 342, base peak $[(M + H) - H—PO(OMe)_2]^+$ at m/z = 232.

The ^{1}H-NMR spectrum of **15** reveals signals at δ ($CDCl_3$, TMS): 1.00 (s, 9H, CH_3), 3.56 (d, 3H, J_{HP} = 10.6, OCH_3), 3.82 (d, 3H, J_{HP} = 10.6, OCH_3), 4.30 (d, 1H, J_{HP} = 26.2, CH), 7.55 (dd, 2H, ArH), and 8.05 (d, 2H, ArH). MS-FAB: parent ion [M + H] at m/z = 316, base peak $[(M + H) - H—PO(OMe)_2]^+$ at m/z = 216.

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