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Stereoselective Synthesis of Phosphorothioate and Alkylphosphinate Analogs Using a L-Tryptophan Derived Chiral Auxiliary

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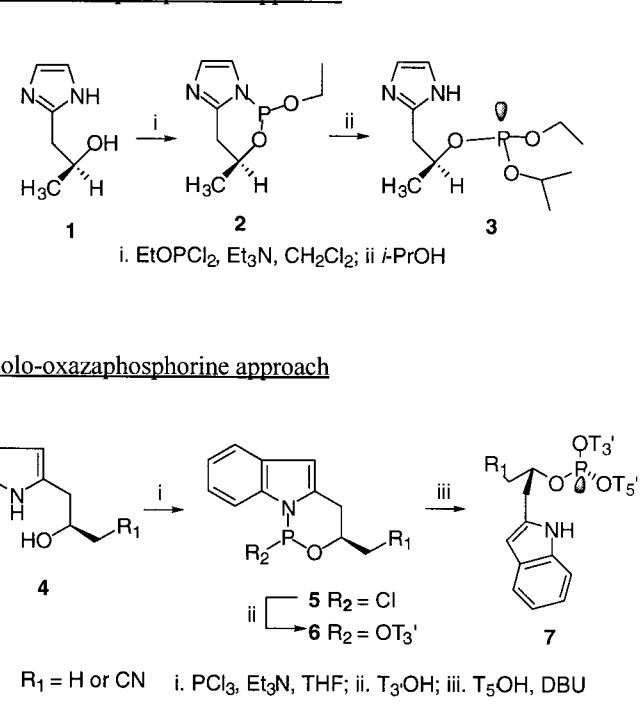
Abstract—A novel phosphorus containing ring system incorporating both imidazole and indole moieties has been synthesized and investigated. A new L-tryptophan derived chiral auxiliary which incorporates those elements has been prepared and used for the stereoselective synthesis of novel indolophosphorothioate and alkylphosphinate analogs.

Introduction

The therapeutic potential of oligonucleotide phosphorothioates (PS-oligos) is well recognized.[1] One of the major drawbacks of PS-oligos is their polydiastereomerism due to the generation of a new chiral center at each phosphorothioate linkage. The PS-oligos currently employed in clinical trials and biological studies are obtained as mixtures



Scheme 1.

Keywords: diastereoselection; imidazoles; indoles; nucleotides.

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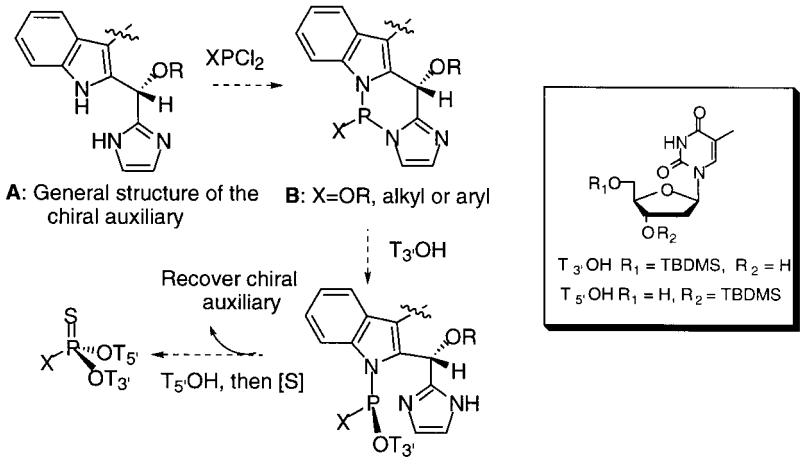


Scheme 2.

of diastereomers. Several approaches[2] have been designed to address the stereoselective synthesis of PS-oligos. The most advanced one to date is the oxathiaphospholane method developed by Stec and coworkers.[3] However, it suffers from the fact that the required chiral precursors have to be separated by chromatography.

We have been involved for some time in synthesizing diastereomerically pure phosphorothioates.[4] Our investigations on the stereoselective synthesis of phosphorothioates and their potential application to solid phase synthesis have led to the following results.

In the imidazo-oxazaphosphorine approach[4c] as shown in Scheme 1, the reaction of the chiral hydroxypropylimidazole **1** with ethyl dichlorophosphite and triethylamine gave a mixture of diastereomeric imidazophosphorines **2**. Heating the reaction mixture effected a presumably triethylammonium chloride catalyzed epimerization to a single diastereoisomer of **2**. Reaction of the latter with a variety of alcohols converted **2** to the phosphite triester **3**, and hence to the corresponding phosphorothioate in a stereospecific manner. Extreme hydrolytic instability of **2**, and our inability to synthesize an analog of **2** in which the ethyl group is replaced by a nucleoside convinced us to investigate a more stable azole, such as indole, as a leaving group.

As illustrated in the indolo-oxazaphosphorine approach,[4f] the reaction of hydroxyalkylindoles **4** with phosphorus trichloride provided **5**, which was converted to a mixture of diastereomeric indolophosphorines **6** by reaction with 5′-O-protected thymidine. The latter could not be equilibrated to a single diastereomer under basic or acidic conditions without decomposition. The indole residue could act as a leaving group, provided the 5′-hydroxy group of thymidine was activated by a strong base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The displacement reaction proceeded in a stereospecific manner.

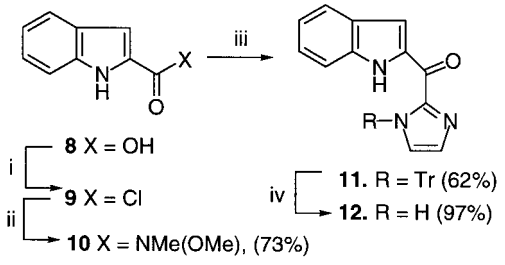
It seemed logical to link the two leaving groups by a chiral substituted methylene group. This would provide a recoverable chiral auxiliary suitable for the synthesis of both chiral phosphonates and phosphate analogs, as illustrated in Scheme 2. In addition, ring system **B** has never been synthesized before, and it therefore would be a worthwhile target for synthesis and evaluation of reactivity.

Results and Discussion

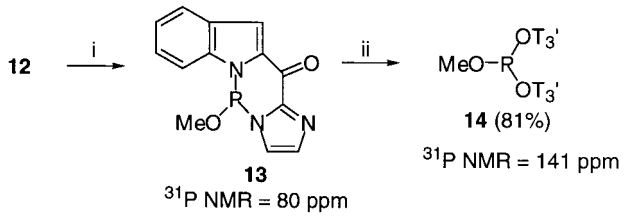
Model studies

Two key issues needed to be addressed, which are whether the six-membered ring will be formed when such an auxiliary reacts with dichlorophosphorus compounds, and whether the imidazole and indole moieties will leave sequentially when reacted with nucleosides. We therefore synthesized achiral and racemic model compounds to test the feasibility of the methodology.

Treatment of 1-(phenylsulfonyl) indole with *n*-butyllithium, followed by quenching with DMF, gave 1-(phenylsulfonyl)-2-indolecarboxaldehyde.[5] *N*-trityl imidazole was then reacted with *n*-butyllithium, and added to the aldehyde. However, no desired coupling product was obtained, presumably due to the steric hindrance introduced by two large protecting groups on indole and imidazole. In order to circumvent this problem, we carried out an analogous reaction with an unprotected indole. As shown in Scheme 3, indole-2-carboxylic acid **8** was transformed via its acid chloride **9** to Weinreb amide **10**, and the latter was treated with two equivalents of the *N*-tritylimidazole anion to give **11**. Deprotection gave achiral ketone **12**. Although not appropriate for the synthesis of a chiral phosphonate or phosphorothioate, we investigated the reaction of **12** with



Scheme 3. (i) $SOCl_2$, Et_3N, DME, 0°C to RT; (ii) $CH_3NH(OCH_3)\cdot HCl$, CH_2Cl_2, 0°C to RT; (iii) *n*-BuLi, *N*-trityl imidazole, THF, −78°C to RT; (iv) AcOH/MeOH, reflux.

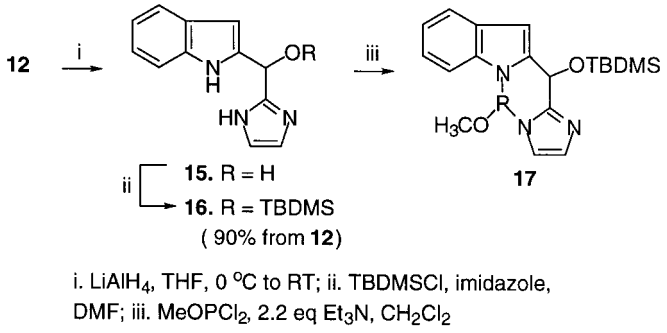


Scheme 4. (i) $MeOPCl_2$, 2.2 equiv. Et_3N, CH_2Cl_2, 0°C to RT; (ii) T_3OH, CH_2Cl_2, RT.

methyl dichlorophosphite to establish the stability and reactivity of cyclic phosphite derivative **13**.

A model reaction with **12** is shown in Scheme 4. Ketone **12** in freshly distilled dichloromethane containing triethylamine in a dry NMR tube was treated with methyl dichlorophosphite at 0°C. ^{31}P NMR showed that the original resonance at around 180 ppm corresponding to methyl dichlorophosphite disappeared and the new resonance at 80 ppm corresponding to **13** was formed immediately. 5′-O-*tert*-butyldimethylsilyl thymidine ($T_{3'}OH$)[6] dissolved in dichloromethane was then added to the reaction mixture. In contrast to imidazo-oxazaphosphorine,[4c] the reaction went slowly. After allowing the reaction to proceed at ambient temperature for about 15 h, the original resonance at 80 ppm disappeared and a new resonance at 141 ppm was observed. The product turned out to have structure **14**. That meant thymidine not only displaced imidazole, but also displaced the indole moiety. Since indole is not a good leaving group under such mild conditions, we reasoned that the conjugation of indole with the adjacent electron withdrawing carbonyl group made it a better leaving group. Having established that ring systems of type **13** are readily formed, we then proceeded to reduce the ketone **12** to alcohol **15**, which was protected as its TBDMS ether **16**. When **16** was treated with methyl dichlorophosphite, ^{31}P NMR revealed two resonances at 88.6 ppm (major) and 80.3 ppm (minor) corresponding to **17**. After heating at 55°C to equilibrate those two products, the resonance at 88.6 ppm shifted to 80.3 ppm. Without purification, $T_{3'}OH$ in dry dichloromethane was added into the solution of **17** in the NMR tube. No reaction happened initially. The solution was allowed to stand overnight at room temperature. A reaction started to occur, but was very slow and after several days, less than 10% of **17** had reacted. In contrast to the normally very reactive and therefore unstable imidazo-oxazaphosphorine intermediate, the cyclic compound **17** could be separated by silica gel column chromatography and fully characterized (Scheme 5).

We suspected that the lack of reactivity of **17** was due to steric hindrance, and thus carried out molecular modeling to establish the most stable conformation of **17**. Cyclic compound **17** equilibrated to give the thermodynamically more stable conformation. For related systems,[4g,7] this had



Scheme 5. (i) $LiAlH_4$, THF, 0°C to RT; (ii) TBDMSCl, imidazole, DMF; (iii) $MeOPCl_2$, 2.2 equiv. Et_3N, CH_2Cl_2.

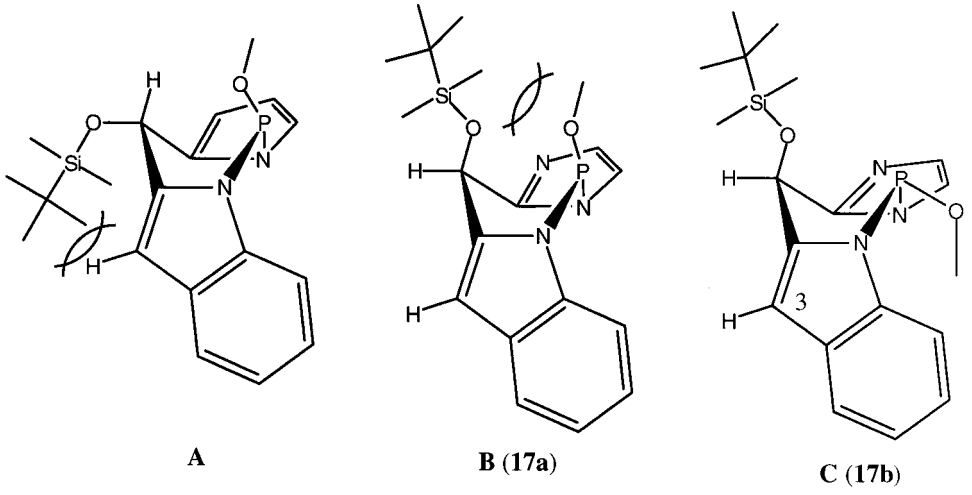
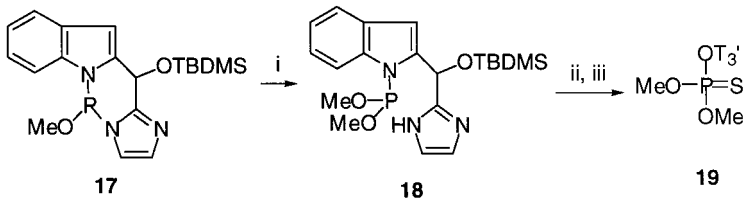


Figure 1.



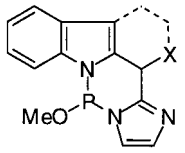
Scheme 6. (i) MeOH, RT; (ii) $T_{3'}OH$, DBU, CH_2Cl_2, RT; (iii) Beaucage's reagent.

meant that an exocyclic methoxy group is axially or pseudo-axially disposed, whereas the bulky silyloxy group prefers an equatorial arrangement (i.e. **A**, boat conformation). Depending on whether the phosphorus containing six-membered ring adopts a boat or chair-like conformation, the two substituents have a *trans* or *cis* relationship. Much to our surprise, calculation (Macromodel, version 5.5)[8] indicated that the most stable conformation was a boat, in which the TBDMS group was axially disposed and the methoxy group took up the pseudo-equatorial conformation (**17b**) (Fig. 1). This is presumably due to the fact that the hydrogen attached to the 3-position of indole exerts enough steric hindrance to make the relatively unhindered axial conformation an energy minimum, in which the only interaction of any consequence is a flag–pole interaction with the phosphorus lone pair. 2D-NOESY spectrum of **17** showed a cross-peak between the carbinol proton and H-3 of indole. No cross-peaks were observed between the silyloxy protons and the methoxyl protons or H-3 of indole. These results are in agreement with conformation **C**. This conformation also explains why the displacement of the imidazole is so slow, since the approach of a nucleophile is blocked by the bulky OTBDMS group.

In order to confirm that steric hindrance was the cause for the slow reaction of **17** with $T_{3'}OH$, we repeated the reaction with a smaller alcohol (Scheme 6). Upon the addition of methanol to a solution of **17** in dichloromethane, ^{31}P NMR revealed the new peak within 20 min at around 146 ppm which was assigned to dimethyl phosphite **18**. When **18** was treated with $T_{3'}OH$ in the presence of DBU, a further displacement occurred. The ^{31}P NMR shifted to 140 ppm, indicating the formation of phosphite triester. Sulfurization by Beaucage's reagent (3H-1,2-benzodithiole-3-one 1,1-dioxide)[9] yielded phosphorothioate **19**. After purification, **16** was recovered in 80% yield.

Synthesis of the chiral auxiliary

So far, we demonstrated that six-membered ring system **A** incorporating the heteroatoms of an indole and imidazole connected to a trivalent phosphorus can be readily formed. Due to steric hindrance, the normally extremely rapid displacement of the imidazole moiety went efficiently only when a small alcohol such as methanol was used. In order to investigate whether the displacements of imidazole and (base catalyzed) indole could be carried out sequentially and in a stereoselective and expeditious manner, we decided to substitute the X group in **A** (**17**, X=OTBDMS) by a ring (see dotted lines). Molecular modeling indicated this structure was much less hindered to the displacement at phosphorus.

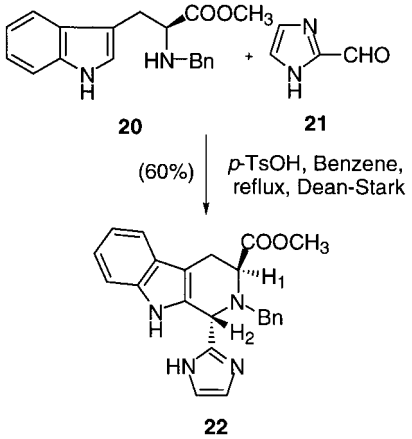


A

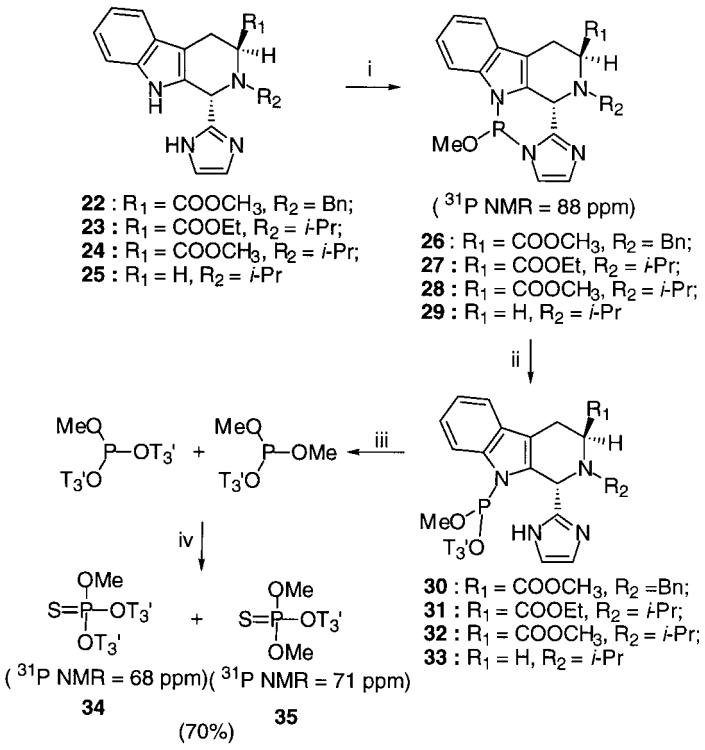
An easy way to construct such a ring system containing a chiral center is based on the Pictet–Spengler reaction of a tryptophan derivative with an appropriate aldehyde, as outlined in Scheme 7. Reaction of imidazole 2-carboxaldehyde[10] and N_b-benzyltryptophan methyl ester[11] in the presence of *p*-toluenesulfonic acid gave the desired product as one diastereomer. The reported[12,13] uncatalyzed reaction proceeded in an unsatisfactory manner. Cook and coworkers[11] have shown that analogous reactions led to the formation of the *trans* diastereomer, and this was confirmed by a 2D-NOESY spectrum of **22** which did not show any cross-peaks between H_1 and H_2. The stereochemistry of the chiral auxiliary **22** was assigned accordingly.

Stereoselective synthesis of phosphorothioate

Reaction of **22** with methyl dichlorophosphite and triethylamine in dichloromethane was carried out in a dry NMR tube (Scheme 8). ^{31}P NMR revealed the appearance of a single new peak at 88 ppm, corresponding to the formation of **26** as a single diastereomer. Addition of one equivalent of 5′-O-TBDMS-thymidine ($T_{3'}OH$) resulted in the rapid formation of **30** (^{31}P NMR=143 ppm), accompanied by the formation of a small amount of material with ^{31}P NMR at 141 ppm. We suspected that the latter material

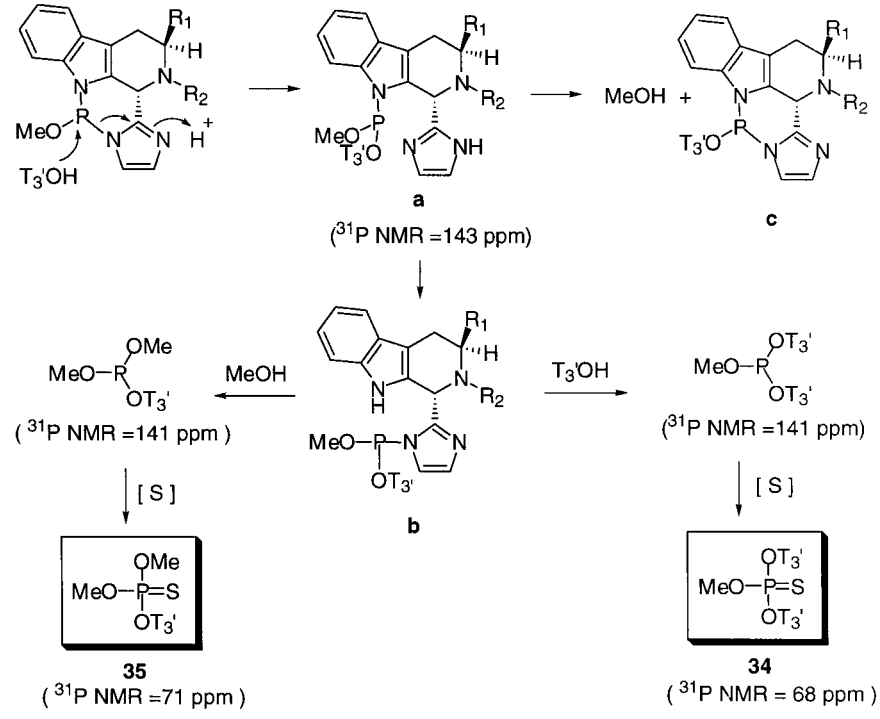


Scheme 7.

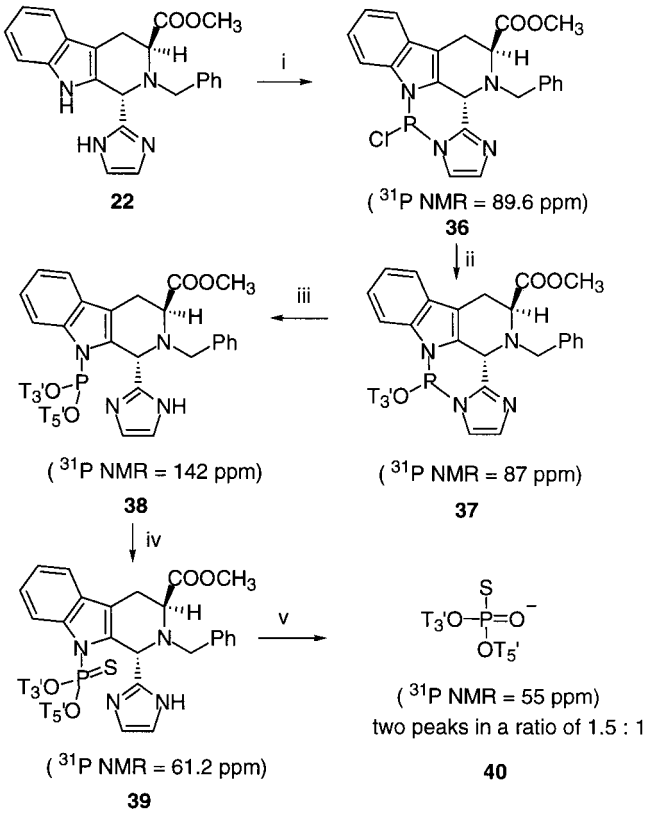


Scheme 8. (i) $MeOPCl_2$, 2.2 equiv. Et_3N, CH_2Cl_2 or $CDCl_3$; (ii) 3.0 equiv. 5′-O-TBDMS-thymidine in CH_2Cl_2; (iii) Heated at 55°C, 15 h; (iv) Beaucage's reagent.

was the product of a double displacement, and therefore repeated the reaction with an excess of $T_3'OH$. The major product **30** (^{31}P NMR=143 ppm) formed immediately. Heating the mixture at 55°C for 15 h gave exclusively material with ^{31}P NMR at 141 ppm. Sulfurization with Beaucage's reagent proceeded as expected to give materials having the characteristic thiophosphate triester ^{31}P NMR resonances at around 70 ppm. Surprisingly, it consisted of a mixture of the expected dithymidyl thiophosphate **34**, accompanied by up to 33% of the dimethoxy thiophosphate **35**, which were separated by flash chromatography.



Scheme 9.



Scheme 10. (i) PCl_3, 2.2 equiv. Et_3N, CH_2Cl_2; (ii) 1.0 equiv. 5′-O-TBDMS-thymidine in CH_2Cl_2; (iii) 3′-O-TBDMS-thymidine; (iv) Beaucage's reagent. (v) Triton B in methanol.

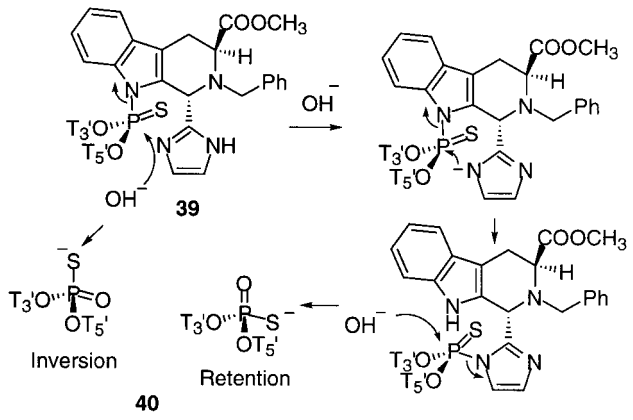
Rigorous exclusion of possible contamination by changing the solvent used, and running the reactions on the ethyl ester **23**, N_b-isopropyl auxiliary **24** and descarbomethoxy auxiliary **25** established that the source of methanol necessary to form the dimethoxy derivative **35** was the phosphorus attached methoxy group. The sequence of reactions proposed in Scheme 9 explains the formation of **35**. $T_{3'}OH$ first displaces imidazole to yield a species of type **a**. Since imidazole is a good nucleophile, it can displace the methoxy group to form methanol and **c**. Alternatively, the displacement of indole by imidazole gives **b**. Reactions of **b** with either $T_{3'}OH$ or methanol, followed by sulfurization would give **34** or **35**.

An indolophosphorothioate **39** could be obtained in a stereoselective manner as described in Scheme 10. Reaction of chiral auxiliary **22** with phosphorus trichloride in dichloromethane containing triethylamine gave a 10:1 mixture of diastereomeric chlorophosphites **36** with ^{31}P NMR at about 89.6 ppm. Addition of $T_{3'}OH$ gave **37** which had a ^{31}P MMR resonance around 87 ppm, typical for this type of compound. Addition of 3′-O-TBDMS-thymidine ($T_{5'}OH$) in dichloromethane provided **38**, with ^{31}P NMR signal at 142 ppm, within 10 min. Virtually no double displacement happened at this stage. Sulfurization with Beaucage's reagent and isolation gave the novel indolophosphorothioate **39**, with ^{31}P NMR at 61.2 and 59.5 ppm, as a mixture of diastereomers in a ratio of 10:1. After chromatographic purification, the ratio increased to 20:1.

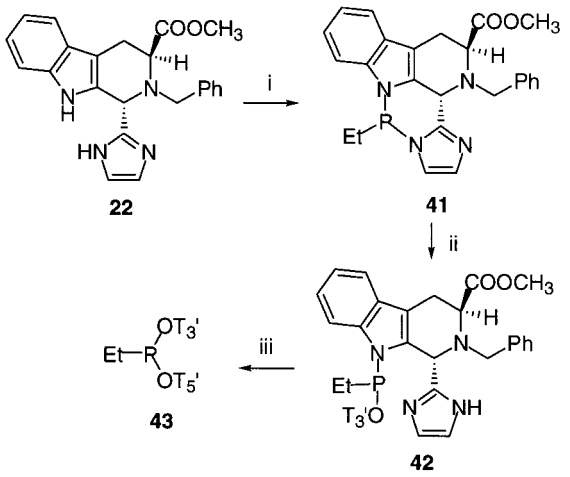
Unfortunately, the displacement of the chiral auxiliary with *N*-benzyltrimethylammonium hydroxide did not proceed in a stereoselective manner, and phosphorothioate **40** was obtained as a 3:2 mixture of diastereomers. This is again most likely due to competing single and double displacements, as outlined in Scheme 11.

Stereoselective synthesis of alkylphosphinate

The stereoselective synthesis of alkylphosphinate is illustrated in Scheme 12. Chiral auxiliary **22** in dry dichloromethane containing triethylamine was added to dichloroethyl phosphine in dry dichloromethane at −78°C, and the mixture was warmed up slowly to room temperature. Intermediate **41** was formed immediately, with ^{31}P NMR resonances at



Scheme 11.



Scheme 12. $EtPCl_2$, 2.2 equiv. Et_3N, CH_2Cl_2; (ii) 1.0 equiv. 5′-O-TBDMS-thymidine in CH_2Cl_2; (iii) DBU, 3′-O-TBDMS-thymidine.

76.4 and 74.9 ppm, in a ratio of 1:20. Then $T_{3'}OH$ was added slowly at −78°C. The mixture was allowed to warm up to room temperature. ^{31}P NMR showed two new resonances at 142.5 and 142.0 ppm in a ratio of 20:1. Purification by flash chromatography gave alkylphosphinamidite **42** as a single diastereomer. Stereospecific displacement of the indole moiety with $T_{5'}OH$ and DBU in dichloromethane was not successful, and a mixture of epimeric alkylphosphinates **43** were obtained. The epimerization process is most likely due to partial double displacement, as depicted in Scheme 11.

In order to avoid double displacement, attempts were made to block the nitrogen of imidazole by acyl, trityl, 2-(trimethylsilyl)ethoxylmethyl (SEM) or methyl groups. Unfortunately, all attempts to do so were unsuccessful.

Since imidazole is a good nucleophile, its participation can be understood. An alternative approach to solve the problem would be to use other more acidic and hence less nucleophilic heterocyclic compounds such as tetrazole. We are currently developing this methodology.

In conclusion, we demonstrated the new type of chiral auxiliary incorporating indole and imidazole can be easily prepared from tryptophan, from which a novel chiral indolophosphorothioate could be obtained. Our investigation on the stereoselective synthesis of phosphorothioate and alkylphosphinate led us to develop a new type of chiral auxiliary incorporating tetrazole and indole.

Experimental

General methods

Mass spectra were recorded on MS25RFA and ZAB 2F HS mass spectrometers. ^1H NMR and ^{13}C NMR were recorded on a Varian XL 200 and Unity 500 spectrometers and are referenced with respect to the residual signals of the solvent. The assignments of proton spectra are based on COSY experiments. ^{31}P NMR spectra were recorded on a Varian Unity 500 spectrometer and are referenced to the external 85% H_3PO_4 signal as 0 ppm. THF was distilled from sodium benzophenone ketyl, triethylamine from calcium hydride, dichloromethane from phosphorus pentoxide and methanol from magnesium. Phosphorus trichloride was first degassed by refluxing for 2 h under argon followed by fractional distillation and was stored under argon. Beaucage's reagent was a gift from Isis Pharmaceuticals, Carlsbad, CA. All other reagents were purchased from Aldrich.

Indole-2-carboxylic acid Weinreb amide 10

To a solution of indole-2-carboxylic acid **8** (645 mg, 4.0 mmol) in anhydrous 1,2-dimethoxyethane (DME) (15 ml) was added triethylamine (0.80 ml, 5.7 mmol). Thionyl chloride (0.58 ml, 8.0 mmol) was then added very slowly at 0°C over a period of 10 min, and the reaction mixture stirred at 0°C for half an hour. The precipitate was filtered off, and the filtrate was concentrated in vacuo to give crude **9** as a dark brown solid. Crude **9** and *N*,*O*-dimethylhydroxylamine hydrochloride (390 mg, 4.0 mmol) were dissolved in dry dichloromethane (10 ml), the solution was cooled down to 0°C and pyridine (0.71 ml, 8.8 mmol) was added. The mixture was stirred at ambient temperature for 1 h and evaporated in vacuo. The residue was partitioned between brine and a 1:1 mixture of dichloromethane and ether, and the organic layer dried over magnesium sulfate. Purification by column chromatography gave the desired Weinreb amide **10** (0.60 g, 73% from acid) as a bright yellow solid.

^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (br, 1H, NH), 7.71 (d, 1H, H-4, $J_{4\text{-}5}$=8.0 Hz), 7.46 (d, 1H, H-7, $J_{7\text{-}6}$=7.5 Hz), 7.31 (m, 1H, H-6), 7.26 (s, 1H, H-3), 7.15 (m, 1H, H-5), 3.82 (s, 3H, OCH_3), 3.42 (s, 3H, NCH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 161.52, 135.74, 128.08, 127.81, 124.66, 122.36, 120.23, 111.67, 107.81, 61.18, 33.11; MS (CI, NH_3) *m/z* 205 ($(M+1)^+$, 60.4%), 174 (35.3%), 144 (100%).

2-Indolyl-*N*-trityl-2-imidazolyl ketone 11

n-Butyllithium solution in hexane (1.6 M) (1.37 ml, 2.2 mmol) was added to a stirred solution of *N*-trityl imidazole (620 mg, 2.0 mmol) in dry THF (20 ml) at −78°C under argon. The resulting solution was stirred at −78°C for half an hour and warmed gradually to room temperature for an hour. The original colorless solution turned to red gradually. The mixture was re-cooled to −78°C and indole-2-Weinreb amide **10** (204 mg, 1.0 mmol) in dry THF (10 ml) was added. The mixture was allowed to warm up to room temperature and stirred for an additional hour. The reaction mixture was then poured into a mixture of 5% hydrochloric acid and ether at 0°C, the mixture was partitioned between brine and a mixture of ether and dichloromethane (1:1). Purification by flash chromatography afforded the desired product **11** (280 mg, 62%) as a yellow solid and recovered Weinreb amide **10** (70 mg, 35%).

^1H NMR (500 MHz, $CDCl_3$) δ 10.50 (br, 1H, NH), 7.62 (d, 1H, H-4, $J_{4\text{-}5}$=8.0 Hz), 7.35 (m, 2H, H-7 and H of imidazole), 7.24–7.29 (m, 11H, 9H of trityl, H-6, H of imidazole), 7.12–7.18 (m, 7H, 6H of trityl, H-3), 7.06 (m, 1H, H-5); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.80, 144.91, 142.67, 137.10, 135.68, 129.81, 127.61, 127.58, 127.32, 127.27,

127.21, 125.52, 122.97, 120.36, 112.10, 111.34, 78.08; MS (FAB, NBA) *m/z* 454 $(M+1)^+$.

2-Indolyl-2-imidazolyl ketone 12

2-Indolyl-*N*-trityl-2-imidazolyl ketone **11** (440 mg, 1.0 mmol) was dissolved in 5% acetic acid/methanol (10 ml), the mixture was brought to reflux for half an hour. The solvent was removed in vacuo and the residue was taken up in ethyl acetate, washed with saturated sodium bicarbonate solution, distilled water and brine, respectively, and dried over magnesium sulfate. Purification by flash chromatography yielded the product as a yellow solid (0.20 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.46 (br, 1H, NH of imidazole), 11.47 (br, 1H, NH of indole), 8.01 (s, 1H, H of imidazole), 7.76 (m, 1H, H-4), 7.65 (m, 1H, H-7), 7.52 (s, 1H, H of imidazole), 7.36 (s, 1H, H-3), 7.33 (m, 1H, H-6), 7.12 (m, 1H, H-5); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.74, 146.26, 138.99, 135.22, 131.79, 128.45, 126.61, 123.75, 121.72, 121.36, 113.64, 112.57; HRMS (EI) $C_{12}H_9N_3O$ calcd: 211.0746, found: 211.0748.

Phosphite triester 14

To a solution of methyl dichlorophosphite (7.4 μl, 0.078 mmol) in dry dichloromethane (0.2 ml) in a scrupulously dried NMR tube at 0°C was added slowly a solution of **12** (15 mg, 0.07 mmol) in dry dichloromethane (0.6 ml) containing triethylamine (21.7 μl, 0.156 mmol). The NMR tube was then sealed. When ^{31}P NMR showed the disappearance of starting material and the formation of a new resonance at 80 ppm assigned to **13**, 5′-O-TBDMS thymidine[6] (30 mg, 0.084 mmol) in dry dichloromethane was added. The NMR tube was allowed to stand at room temperature for 15 h. The crude mixture was purified by flash chromatography to afford the product as a white solid (26 mg, 81%).

^{31}P NMR (202.3 MHz, $CDCl_3$) δ 140.84; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (br, 1H, NH), 9.19 (br, 1H, NH), 7.45 (2s's, 2H, 2×H-6), 6.36 (m, 2H, 2×H-1′), 4.79–4.89 (m, 2H, 2×H-3′), 4.10 (m, 2H, 2×H-4′), 3.79–3.90 (m, 4H, 2×H-5′), 3.56 (d, 3H, OCH_3), 2.42–2.52 (m, 2H, H-2′), 2.11 (m, 2H, H-2′), 1.89 (2 s's, 6H, 2×C═CMe), 0.93 (2 s's, 18H, 2×$SiC(CH_3)_3$), 0.12 (2 s's, 12H, 2×$Si(CH_3)_2$); MS (FAB, NBA/NaCl) *m/z* 795 (M+Na−1).

2-Indolyl-2-imidazolyl carbinol 15

2-Indolyl-2-imidazolyl ketone **13** (210 mg, 1.0 mmol) in dry THF was added slowly into a suspension of lithium aluminum hydride (38 mg, 1.0 mmol) at 0°C, and the mixture was allowed to stir at room temperature for 10 min. A few drops of ethyl acetate were added to the reaction mixture to destroy the excess lithium aluminum hydride. Fieser work-up[14] gave alcohol **15**, which was used in the next step without further purification.

Silyloxy ether 16

tert-Butyldimethylsilyl chloride (180 mg, 1.2 mmol) was added to a solution of **15** (213 mg, 1.0 mmol) in DMF (10 ml) containing imidazole (136 mg, 2.0 mmol) at room temperature. The solution was stirred for 2 h. The solvent was removed under high vacuum, the residue was dissolved in ethyl acetate, washed with water and brine, respectively. Purification by flash chromatography provided the desired product as a light yellow solid (310 mg, 95% from **12**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (br, 1H, NH of imidazole), 8.90 (br, 1H, NH of indole), 7.57 (d, 1H, H-4, $J_{4\text{-}5}$=7.5 Hz), 7.29 (d, 1H, H-7, $J_{6\text{-}7}$=8.0 Hz), 7.13 (m, 1H, H-6), 7.07 (m, 1H, H-5), 7.03 (s, 1H, H of imidazole), 6.96 (s, 1H, H of imidazole), 6.46 (s, 1H, H-3), 6.18 (s, 1H, HCOTBDMS), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, $Si(CH_3)$), 0.07 (s, 3H, $Si(CH_3)$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 148.48, 138.34, 136.07, 128.21, 127.95, 121.70, 120.38, 119.59, 115.40, 110.92, 99.22, 66.63, 25.65, −5.23, −5.46; HRMS (EI) $C_{18}H_{25}N_3OSi$ calcd: 327.1767, found: 327.1770.

Cyclic phosphite monoester 17

To a solution of methyl dichlorophosphite (6.4 μl, 0.067 mmol) in dry dichloromethane (0.2 ml) in a scrupulously dried NMR tube at 0°C was added slowly a solution of **16** (20 mg, 0.06 mmol) in dry dichloromethane (0.6 ml) containing triethylamine (18.4 μl, 0.132 mmol). The NMR tube was then sealed and the reaction was followed by ^{31}P NMR. After 24 h at 50°C, the crude mixture was purified by flash chromatography to afford **17** as a white solid (16 mg, 70%).

^{31}P NMR (202.3 MHz, $CDCl_3$) δ 80.47; ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, 1H, H-4, $J_{4\text{-}5}$=8.0 Hz), 7.64 (d, 1H, H-7, $J_{6\text{-}7}$=7.5 Hz), 7.33 (m, 1H, H-5), 7.24–7.27 (m, 2H, H-6 and H of imidazole), 7.21 (m, 1H, H of imidazole), 6.73 (s, 1H, H-3), 6.06 (s, 1H, HCOTBDMS), 3.52 (d, 3H, OCH_3, $^3J_{H\text{-}P}$=9.0 Hz), 0.80 (s, 9H, $SiC(CH_3)_3$), 0.26 (s, 3H, $Si(CH_3)$), 0.19 (s, 3H, $Si(CH_3)$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 147.27 (d, C-2 of imidazole, $^3J_{P\text{-}C}$=5.5 Hz), 140.17 (d, C-2, $^2J_{P\text{-}C}$=24.7 Hz), 139.43 (d, C adjacent to *N*−1 of indole, $^2J_{C\text{-}P}$=7.3 Hz), 130.35 (d, C-5 of imidazole, $^2J_{C\text{-}P}$=8.24 Hz), 129.49 (d, C between C-3 and C-4 of indole, $^3J_{C\text{-}P}$=3.66 Hz), 123.60 (C-5), 122.00 (C-6), 121.46 (d, C-4 of imidazole, $^3J_{P\text{-}C}$=19.23 Hz), 121.17 (d, C-7, $^3J_{C\text{-}P}$=12.8 Hz), 110.89 (d) C-4, $^4J_{C\text{-}P}$=17.4 Hz), 107.74 (C-3), 61.45 (CHOTBDMS), 52.92 (d, OCH_3, $^2J_{P\text{-}C}$=8.13 Hz), 25.55 ($SiC(\mathbf{C}H_3)_3$), 18.05 ($Si\mathbf{C}(CH_3)_3$), −4.91 ($SiCH_3$), −5.33 ($SiCH_3$); HRMS (FAB) $(M+H)^+$, calcd: 388.1610, found: 388.1613.

Dimethyl indolyl phosphite 18

Methanol (0.10 ml) was added to the mixture containing **17** obtained from the previous experiment in an NMR tube. Within 30 min, ^{31}P NMR indicated the completion of the reaction. The crude mixture was purified by flash chromatography to afford **18** as a white solid (16 mg, 65% from **16**).

^{31}P NMR (202.3 MHz, $CDCl_3$) δ 147.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (br, 1H, NH of imidazole), 8.67 (br, 1H, NH of indole), 7.89 (d, 1H, H-4, $J_{4\text{-}5}$=8.0 Hz), 7.53 (d, 1H, H-7, $J_{7\text{-}6}$=7.5 Hz), 7.09–7.15 (m, 2H, H-5, H-6),

6.96 (m, 2H, 2H of imidazole), 6.68 (s, 1H, H-3), 6.35 (s, 1H, CH(OTBDMS)), 3.45 (d, 3H, OCH_3, $J_{H\text{-}P}$=12.5 Hz), 3.28 (d, 3H, OCH_3, $J_{H\text{-}P}$=13.0 Hz), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.062 (s, 3H, $Si(CH_3)$), 0.036 (s, 3H, $Si(CH_3)$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 148.64, 142.59, 142.45, 138.54, 138.51, 129.76, 128.92, 123.74, 121.29, 120.71, 115.56 (d, $^4J_{C\text{-}P}$=2.77 Hz), 115.02, 106.03 (d, $^3J_{C\text{-}P}$=3.77 Hz), 99.39, 52.28 (d, $^2J_{C\text{-}P}$=17.5 Hz), 51.65 (d, $^2J_{C\text{-}P}$=18.4 Hz), 25.80, −4.91, −5.33.

Phosphorothioate 19

To a solution of **18** (20 mg, 0.06 mmol) in dry dichloromethane (0.25 ml) in a NMR tube was added a solution of 5′-O-TBDMS-thymidine (42 mg, 0.12 mmol) in dry dichloromethane (0.45 ml) containing DBU (45 μl, 0.30 mmol) at room temperature. The NMR tube was then sealed. ^{31}P NMR indicated the reaction went to completion within 20 min. The mixture was then loaded to the top of column to run a fast column to filter off DBU (acetonitrile: dichloromethane=1:1). The solvent was removed in vacuo and the residue was re-dissolved in dichloromethane and Beaucage's reagent (24 mg, 0.12 mmol) was added. After 10 min, the mixture was diluted with dichloromethane, washed with brine and dried over magnesium sulfate. Purification by flash chromatography provided the desired product **19** as a white solid (24 mg, 82%) and recovered **16** (16 mg, 80%).

^{31}P NMR (202.3 MHz, $CDCl_3$) δ 70.98; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (br, 1H, NH), 7.51 (s, 1H, H-6), 6.38 (dd, 1H, H-1′, $J_{1'\text{-}2'}$=9.0, 5.5 Hz), 5.11 (m, 1H, H-3′), 4.26 (m, 1H, H-4′), 3.90 (m, 2H, H-5′), 3.76 (2 d's, 6H, 2×OCH_3, $J_{H\text{-}P}$=13.5 Hz), 2.50 (m, 1H, H-2′), 2.11 (m, 1H, H-2′), 1.92 (s, 3H, C=CMe), 0.94 (9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 163.21, 149.99, 135.02, 111.21, 85.81 (d, $J_{C\text{-}P}$=4.5 Hz), 84.65, 79.29, 63.39, 54.74, 39.22 (d, $J_{C\text{-}P}$=5.53 Hz), 29.70, 25.76, 18.18, 12.33, −5.56, −5.59; MS (ES) *m/z*= 479 (M−H), 959 (M+M−H).

2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-2-imidazole 22

N_b-Benzyl-L-tryptophan methyl ester **20** (310 mg, 1.0 mmol), imidazole-2-carboxylic aldehyde **21** (960 mg, 1.0 mmol) and *p*-toluene sulfonic acid (380 g, 0.2 mmol) were dissolved in benzene (50 ml). The mixture was then brought to reflux using Dean–Stark water trap to remove water. After 18 h, the solvent was removed in vacuo. The residue was purified by flash chromatography to furnish the desired product **22** as a yellow solid (251 mg, 65%).

^1H NMR (500 MHz, CD_2Cl_2) δ 9.91 (br, 1H, NH of indole), 7.50 (d, 1H, H-4, $J_{4\text{-}5}$=7.5 Hz), 7.28–7.36 (m, 5H, H of phenyl), 7.22 (d, 1H, H-7, $J_{7\text{-}6}$=7.0 Hz), 7.01–7.10 (m, 2H, H-5, H-6), 6.93 (s, 2H, H of imidazole), 5.60 (s, 1H, (NH)N=CC**H**N(Bn)), 3.98–4.02 (m, 2H, C**H**$COOCH_3$, 1H of C$\mathbf{H}_2$Ph), 3.86 (d, 1H, 1H of C$\mathbf{H}_2$Ph, J=14.0 Hz), 3.70 (s, 3H, $COOCH_3$), 3.21 (m, 2H, C$\mathbf{H}_2$CHCOOCH_3); ^{13}C NMR (125.7 MHz, CD_2Cl_2) δ 173.24, 148.67, 139.00, 137.25, 131.98, 128.89, 127.74, 126.98, 121.95, 119.39, 118.35, 111.60, 106.04, 60.61, 57.76, 55.94, 52.02, 51.20, 23.54, 21.18, 14.35; HRMS (EI) $C_{23}H_{22}N_4O_2$ calcd: 386.1743, found: 386.1745.

2-Isopropyl-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-2-imidazole 23

Ethyl ester **23** was prepared using the same procedure as described for the preparation of **22**.

^1H NMR (500 MHz, CD_2Cl_2) δ 11.67 (br, 1H, NH of imidazole), 10.02 (br, 1H, NH of indole), 7.45 (d, 1H, H-4, $J_{4\text{-}5}$=7.5 Hz), 7.29 (d, 1H, H-7, $J_{7\text{-}6}$=8.0 Hz), 6.95–7.07 (m, 4H, H-5, H-6, 2H of imidazole), 5.36 (s, 1H, (NH)N=CC**H**N(*i*-Pr)), 4.22 (m, 1H, CH_2C**H**COOEt), 4.00–4.10 (m, 2H, $COOC\mathbf{H}_2CH_3$), 3.50 (d, 1H, C$\mathbf{H}_2$CHCOOEt, J=15.0 Hz), 3.22 (m, 1H, C**H**$(CH_3)_2$), 2.98 (ddd, 1H, C$\mathbf{H}_2$CHCOOEt, J=15.0, 8.0 and 1.5 Hz), 1.15 (m, 6H, $CH(C\mathbf{H_3})_2$, $COOCH_2C\mathbf{H_3}$), 1.07 (d, 3H, $CH(C\mathbf{H_3})_2$, J=7.0 Hz); MS (EI) *m/z* 352 (M^+).

2-Isopropyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-2-imidazole 24

N_b-isopropyl auxiliary **24** was prepared using the same procedure as described for the preparation of **22**.

^1H NMR (500 MHz, CD_2Cl_2) δ 11.62 (br, 1H, NH of imidazole), 9.90 (br, 1H, NH of indole), 7.47 (d, 1H, H-4, $J_{4\text{-}5}$=7.5 Hz), 7.30 (d, 1H, H-7, $J_{7\text{-}6}$=8.0 Hz), 6.98–7.09 (m, 4H, H-5, H-6, 2H of imidazole), 5.37 (s, 1H, (NH)N=CC**H**N(*i*-Pr)), 4.26 (dd, 1H, CH_2C**H**$COOCH_3$, J=6.0 and 1.5 Hz), 3.63 (s, 3H, $COOCH_3$), 3.51 (d, 1H, C$\mathbf{H}_2$CHCOOCH_3, J=15.0 Hz), 3.24 (m, 1H, C**H**$(CH_3)_2$), 3.00 (ddd, 1H, C$\mathbf{H}_2$CHCOOCH_3, J=15.0, 6.6 and 2.0 Hz), 1.18 (d, 3H, $CH(C\mathbf{H_3})_2$, J=6.5 Hz), 1.07 (d, 3H, $CH(C\mathbf{H_3})_2$, J=6.5 Hz); ^{13}C NMR (125.7 MHz, CD_2Cl_2) δ 177.88, 150.76, 136.00, 131,59, 128.50, 126.60, 121.64, 119.13, 118.02, 115.53, 111.14, 104.82, 54.70, 54.57, 52.64, 52.25, 24.82, 20.93, 19.65; MS (EI) *m/z* 338 (M^+).

2-Benzyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-2-imidazole 25

Decarbomethoxy **25** was prepared using the same procedure as described for the preparation of **22**.

^1H NMR (500 MHz, CD_2Cl_2) δ 9.37 (br, 1H, NH of imidazole), 8.82 (br, 1H, NH of indole), 7.48 (d, 1H, H-4, $J_{4\text{-}5}$=7.5 Hz), 7.25 (d, 1H, H-7, $J_{7\text{-}6}$=7.5 Hz), 7.05–7.12 (m, 2H, H-5, H-6), 6.94 (2 s's, 2H of imidazole), 5.22 (s, 1H, (NH)N=CC**H**N(*i*-Pr)), 3.19 (m, 1H, C$\mathbf{H}_2CH_2$N(*i*-Pr), 2.94 (m, 1H, NC**H**$(CH_3)_2$), 2.73–2.83 (m, 3H, C$\mathbf{H}_2$C$\mathbf{H}_2$N(*i*-Pr)), 1.19 (d, 3H, NC**H**$(CH_3)_2$, J=6.5 Hz), 1.04 (d, 3H, NC**H**$(CH_3)_2$, J=6.5 Hz); ^{13}C NMR (125.7 MHz, CD_2Cl_2) δ 149.04, 136.32, 132.48, 128.17, 126.57, 121.38, 118.70, 117.99, 115.44, 110.93, 108.15, 55.64, 50.57, 41.59, 21.63, 14.39; MS (EI) *m/z* 280 (100%, M^+).

Cyclic phosphite monoesters 26, 27, 28, 29

To a solution of methyl dichlorophosphite (4.1 μl, 0.044 mmol) in dry dichloromethane (0.45 ml) in a NMR tube at 0°C was added slowly a solution of **22** (17 mg, 0.044 mmol)

dissolved in dichloromethane (0.25 ml) containing triethylamine (12.8 μl, 0.092 mmol) under argon. The NMR tube was then sealed and allowed to stand at room temperature until ^{31}P NMR showed the disappearance of the resonance at 180 ppm and the formation of the new resonances at around 88 and 91 ppm (10:1). The crude **26** was used in the next reaction without further purification.

Similarly, compounds **27**, **28** and **29** were prepared from **23**, **24** and **25**, respectively.

Phosphorothioates 34 and 35

To the previous NMR tube containing **26** was added 5′-O-TBDMS-thymidine (47 mg, 0.132 mmol) in dry dichloromethane (0.5 ml) at room temperature. The NMR tube was then sealed. ^{31}P NMR indicated the formation of new resonance at 142.1 ppm immediately. Upon heating at 55°C overnight, peaks at 142.1 ppm shifted to 140 ppm. Beaucage's reagent (11 mg, 0.053 mmol) was added to the reaction mixture. After 10 min, the reaction mixture was diluted with dichloromethane and washed with water and brine. Purification by flash chromatography afforded **34** (16 mg, 46.6%) and **35** (5 mg, 23.6%), both as white solids.

When **27**, **28** or **29** were used instead of **26**, similar results were obtained.

Dithymidine phosphorothioate **34**: ^{31}P NMR (202.3 MHz, $CDCl_3$) δ 68.03; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (br, 2H, NH of thymidines), 7.46 (2H, H-6 of thymidines), 6.36 (m, 2H, H-1′), 5.09 (m, 2H, H-3′), 4.24 (m, 2H, H-4′), 3.88 (m, 4H, H-5′), 3.76 (d, 3H, OCH_3, $J_{P\text{-}H}$=13.5 Hz), 3.52 (m, 2H, H-2′), 2.11 (m, 2H, H-2′), 1.88 (s, 6H, 2×CH_3), 0.92 (2S's, 18H, 2×$Si(C(CH_3)_3)$, 0.12 (12H, 2×$Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, CD_2Cl_2) δ 163.62, 150.33, 134.92, 111.25, 85.68, 84.62 (d, $J_{C\text{-}P}$=4.5 Hz), 79.67, 63.34, 54.80, 39.15 (d, $J_{C\text{-}P}$=4.7 Hz), 25.91, 25.62, 18.33, 12.52, −3.61, −5.39, −5.46; MS (CI) *m*/*z* 804 $(M+1)^+$.

Dimethoxy phosphorothioate **35**: ^{31}P NMR (202.3 MHz, $CDCl_3$) δ 70.98; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (br, 1H, NH), 7.51 (s, 1H, H-6), 6.38 (dd, 1H, H-1′, $J_{1'\text{-}2'}$=9.0 Hz, 5.5 Hz), 5.11 (m, 1H, H-3′), 4.26 (m, 1H, H-4′), 3.90 (m, 2H, H-5′), 3.76 (2 d's, 6H, 2×OCH_3, $J_{H\text{-}P}$=13.5 Hz), 2.50 (m, 1H, H-2′), 2.11 (m, 1H, H-2′), 1.92 (s, 3H, C═CMe), 0.94 (9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 163.21, 149.99, 135.02, 111.21, 85.81 (d, $J_{C\text{-}P}$=4.5 Hz), 84.65, 79.29, 63.39, 54.74, 39.22 (d, $J_{C\text{-}P}$=5.5 Hz), 29.70, 25.76, 18.18, 12.33, −5.56, −5.59; MS (ES) *m*/*z*=479 (M−H), 959 (M+M−H).

Indolophosphorothioate 39

To a cooled solution of phosphorus trichloride (4.43 μl, 0.051 mmol) in dry dichloromethane in a NMR tube at 0°C was added slowly a solution of **22** (19.6 mg, 0.051 mmol) in dichloromethane containing triethylamine (15.6 μl, 0.11 mmol). The NMR tube was sealed. ^{31}P NMR indicated the formation of peaks at 90.9 and 89.6 ppm in a ratio of 1 to 11. A solution of 5′-O-TBDMS-thymidine (19 mg, 0.054 mmol) in dry dichloromethane (0.4 ml) containing triethylamine (7.9 μl, 0.056 mmol) was added slowly at 0°C, the NMR tube was sealed and allowed to stand at room temperature. After ^{31}P NMR showing the formation of a major resonance at 87.0 ppm, a solution of 3′-O-TBDMS-thymidine[6] (19.9 mg, 0.056 mmol) in dry dichloromethane (0.4 ml) was added to the reaction mixture at 0°C. The NMR tube was sealed and warmed up slowly. ^{31}P NMR indicated the formation of resonance at 142 ppm within 10 min. Beaucage's reagent (12 mg, 0.061 mmol) was then added to the mixture, a major phosphorus resonance at 61 ppm was formed within 5 min. The reaction mixture was diluted with dichloromethane and washed with water and brine, dried over magnesium sulfate. Purification by flash chromatography furnished the desired product **39** (25 mg, 42.3%) as a white solid.

^{31}P NMR (202.3 MHz, $CDCl_3$) δ 61.2 ppm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (br, 1H, NH of imidazole), 8.69 (2 br's, 2H, NH of thymidines), 8.05 (d, 1H, H-4 of indole, $J_{4\text{-}5}$=8.0 Hz), 7.55 (d, 1H, H-7 of indole, $J_{7\text{-}6}$=7.5 Hz); 7.46 (2 s's, C═CH of thymidines); 7.21–7.36 (m, 7H, H-5, H-6 of indole and benzyl aromatic protons), 6.98 (s, 1H, H of imidazole), 6.77 (s, 1H, H of imidazole), 6.21 (t, 1H, H-1′), 5.51 (s, 1H, NCHimidazole), 5.42 (m, 1H, H-1′), 5.08 (m, 1H, H-3′), 4.17–4.22 (2H, H-3′ and C**H**$_2$Ph), 4.02 (m, 1H, CH_2C**H**$COOCH_3$), 3.51–4.04 (m, 10H, H-4′ and H-5′ of thymidines, C**H**$_2$Ph, COOC**H**$_3$), 3.08–3.16 (m, AB of ABX system, C**H**$_2$$CHCOOCH_3$), 1.98–2.17 (m, 3H, H–2′), 1.89 (2s's, 6H, 2×CH_3C═C), 1.74 (m, 1H, H-2′), 0.81 (2s's, 18H, 2×$Si(CH_3)_2C(CH_3)_3$), −0.03 (4s's, 12H, 2×$Si(CH_3)_2C(CH_3)_3$; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.49, 163.47, 150.13, 150.01, 147.55, 138.72, 137.85, 137.78, 135.56, 134.66, 132.69, 132.65, 129.03, 128.77, 127.52, 127.45, 123.94, 122.82, 118.94, 116.86, 116.18, 116.12, 114.73, 111.35, 111.22, 85.20 (d, C-4′, $^{3}J_{C\text{-}P}$=5.4 Hz), 85.13, 84.82 (d, C-4′; $^{3}J_{C\text{-}P}$=10.1 Hz), 84.67, 79.61 (d, C-3′, $^{2}J_{C\text{-}P}$=2.77 Hz), 71.85, 67.56 (d, $J_{C\text{-}P}$=7.29 Hz), 63.14, 55.87, 55.03, 52.26, 52.10, 40.48, 38.98 (P**C**H_2CH_3, $J_{C\text{-}P}$=1.1 Hz), 25.88, 25.80, 25.63, 20.33, 18.15, 17.79, 12.50, 12.48, −4.67, −4.88, −5.54, −5.56; HRMS (EI) $C_{55}H_{75}N_8O_{12}PSSi_2$ calcd: 1158.4501, found: 1158.4505.

Alkyl phosphinate 42

To a solution of dichloroethyl phosphine (12.5 μl, 0.11 mmol) in dry dichloromethane (0.20 ml) in a scrupulously dried NMR tube at −78°C was added slowly a solution of **22** (44 mg, 0.11 mmol) in dry dichloromethane containing triethylamine (35 μl, 0.24 mmol). The NMR was then sealed. When ^{31}P NMR showed resonance at around 75 ppm, 5′-O-TBDMS thymidine (49 mg, 0.13 mmol) in dichloromethane (0.5 ml) was added to the NMR tube at 0°C. The reaction mixture was allowed to warm up to room temperature and stand for half an hour. The reaction mixture was diluted with dichloromethane, washed with water and brine. Purification by flash column chromatography afforded the desired product **42** (50 mg, 57%) as a white solid.

^{31}P NMR (202.3 MHz, $CDCl_3$) δ 142.70; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 9.35 (br, 1H, NH of imidazole), 8.27 (br, 1H, NH of thymidine), 7.83 (d, 1H, H-4 of indole, $J_{4\text{-}5}$=8.0 Hz), 7.52 (d, 1H, H-7 of indole, $J_{7\text{-}6}$=7.5 Hz), 7.15–7.34 (m, 7H, H-5, H-6 of indole and benzyl aromatic protons), 6.95 (s, 1H, H of imidazole), 6.89 (s, 1H, H of imidazole), 6.09 (t, 1H, H-1′), 5.40 (s, 1H, NCHimidazole), 4.45 (m, 1H, H-3′), 4.08 (m, 1H, H-4′), 3.84–3.95 (m, 3H, H-5′, $CH_2C\mathbf{H}COOCH_3$, CH_2Ph), 3.68–3.73 (m, 5H, H- 5′, CH_2Ph, $COOC\mathbf{H}_3$), 3.01–3.10 (m, AB of ABX system, $C\mathbf{H}_2CHCOOCH_3$), 2.44–2.49 (m, 1H, H–2′), 2.00 (m, 1H, H-2′), 1.79–1.87 (m, 5H, $CH_3C{=}C$, $PC\mathbf{H}_2CH_3$), 0.95–1.01 (m, 3H, $PCH_2C\mathbf{H}_3$), 0.91 (s, 9H, $Si(CH_3)_2C(C\mathbf{H}_3)_3$), 0.07 (s, 3H, $Si(C\mathbf{H}_3)_2C(CH_3)_3$), 0.06 (s, 3H, $Si(C\mathbf{H}_3)_2C(CH_3)_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.64, 163.38, 149.84, 147.96, 138.94, 135.47, 129.95, 128.63, 128.51, 128.28, 127.50, 122.65, 120.97, 118.83, 115.90, 114.65, 110.70, 86.23 (d, C-4′, $^3J_{C\text{-}P}$=8.29 Hz), 84.98, 79.47 (d, C-3′, $^2J_{C\text{-}P}$=18.35 Hz), 63.27, 57.20, 55.17, 55.06, 53.14, 52.01, 38.81 ($P\mathbf{C}H_2CH_3$, $J_{C\text{-}P}$=4.53 Hz), 25.96, 24.22 (d, C-2′, $^3J_{C\text{-}P}$=10.9 Hz), 21.39, 18.36, 7.50 (d, $PCH_2\mathbf{C}H_3$, $J_{C\text{-}P}$= 19.2 Hz), −5.34, −5.37, HRMS (EI) $C_{41}H_{53}N_6O_7PSi$ calcd: 800.3483, found: 800.3486.

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8. (a) Each structure was built up first and pre-minimized. The Monte-Carlo search was followed to find the global minimum of each structure. The force field used for the calculation was AMBER and the minimization method was TNCG. (b) Conformer **17b** is about 4 kcal/mol more stable than conformer **17a**.
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