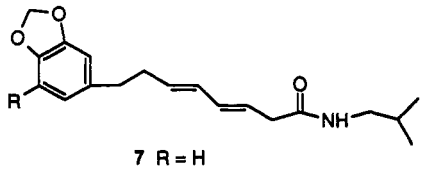
should experience a shielding effect from the phenyl ring. In the ^1H NMR spectrum of the *S,S* diastereomer one methylene resonance is shifted upfield (δ 0.97) relative to the resonance of the same group (δ 1.41) in the ^1H NMR spectrum of the natural product, providing additional support for the *S* configurational assignment. On the basis of this evidence, the complete structure of villiramulin A is proposed as structure 1.

A molecular formula of $C_{18}H_{26}O$, requiring six degrees of unsaturation, was obtained from high resolution mass spectrometry (M^+ 258.1977) of the second unknown, villiramulin B. Comparison of the ^1H and ^{13}C NMR spectra of this unknown with those of villiramulin A indicated that both compounds had similar skeletons.

One of the most notable differences in the spectral data of these two compounds was the absence of the ^1H and ^{13}C NMR resonances corresponding to the methylenedioxy ring of villiramulin A. Instead, the coupling pattern and integration of the aromatic ^1H NMR resonances indicated that the aromatic ring of this structure was para substituted. A broad, singlet ^1H resonance at δ 5.23 indicated that one substituent was a hydroxyl group. Vinylic and aliphatic resonances in the ^1H NMR spectrum indicated that the second substituent was a 12-carbon chain, resembling the one assigned to the structure of villiramulin A but without the secondary alcohol. This assignment was supported by the absence of carbinol resonances in both the ^1H and ^{13}C NMR spectra. On the basis of these observations, the structure of villiramulin B was proposed as shown in structure 2.

Villiramulins A and B represent relatively unusual structures. An extensive literature search revealed only two compounds (7 and 8), isolated recently from *Asarum chingchengense*,[6] that bear an aromatic ring substituted with the diene substructure common to the villiramulins. However, the villiramulins clearly differ in the remainder of their skeletons. Furthermore, when villiramulin B was tested for leafcutter ant repellency at the estimated natural concentration, significant activity was observed.[7] In contrast, while villiramulin A was isolated from an active fraction, the pure compound did not show significant activity at the estimated natural concentration. These results suggest that villiramulin B may be a major part of *P. villiramulum*'s defenses against leafcutters but that further studies might lead to both other biologically active compounds and other interesting structures.



7 R = H
8 R = OMe

Experimental Section

The NMR spectra were recorded on Bruker AC-300 and AMX-600 instruments on $CDCl_3$ solutions with TMS as an internal standard. Both low and high resolution EIMS were obtained at 70 eV; only selected ions are reported here.

Plant Collection. Leaves of *P. villiramulum* were collected in the vicinity of Gamboa, Panama. The samples were air dried at ambient temperature and stored in plastic bags until extracted.

Isolation. Dried *P. villiramulum* leaves (263.0 g) were ground in a Waring blender and then steeped in $CHCl_3$ for approximately 24 h. Concentration of the $CHCl_3$ extract in vacuo afforded 21.0 g of residue. A portion of this residue (17.0 g) was subjected to dry column chromatography, with an EtOAc/hexane gradient (30–100%). Fractions were collected with every 5% increment in the EtOAc concentration.

Two fractions were collected that exhibited ant repellency, and further purification of these fractions ultimately yielded two pure compounds. Each fraction was subjected to flash column chromatography with an EtOAc/hexane gradient (5–35%). The more polar fraction was then purified by reverse phase Seppak and radial dispersion chromatography (5–25% EtOAc/hexane), and gave one compound in nearly pure form. Final purification of this sample using reverse phase HPLC ($MeOH/H_2O$ gradient) afforded compound 1 (10 mg). Additional purification of the less polar subfraction through radial dispersion chromatography (5–6% EtOAc in hexane) yielded pure compound 2 (60 mg).

Villiramulin A (1): oil; $[\alpha]^{25}_D = -22°$ (c = 0.40, $CHCl_3$); ^1H and ^{13}C NMR data, cf. Table I; EIMS *m/z* (relative intensity) 302 (M^+, 4), 135 (100), 105 (3), 77 (10), 45 (11); HREIMS calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1901.

Villiramulin B (2): oil; ^1H NMR δ 7.03 (2H, d, J = 8.5 Hz, H-3′, H-5′), 6.74 (2H, d, J = 8.5 Hz, H-2′, H-6′), 6.01 (2H, m, H-8, H-9), 5.57 (2H, m, H-7, H-10), 5.23 (1H, br s, 4′-OH), 2.62 (2H, t, J = 7.2 Hz, H-12), 2.32 (2H, dt, J = 7.0, 8.2 Hz, H-11), 1.36–1.23 (10H, m), 0.88, (3H, d, J = 6.9 Hz, H-1); ^{13}C NMR 153.53 (s), 134.12 (s), 132.98 (d), 131.07 (d), 130.89 (d), 130.11 (d), 129.43 (d, 2), 115.26 (d), 115.12 (d), 34.94 (t), 34.66 (t), 32.57 (t), 31.70 (t), 29.32 (t), 28.85 (t), 22.58 (t), 14.06 (q); EIMS *m/z* (relative intensity) 258 (M^+, 6), 150 (2), 107 (100), 79 (14), 67 (24), 41 (11); HREIMS calcd for $C_{18}H_{26}O$ 258.1983, found 258.1984.

(*R*)-(−)-2-Heptanol. Optically pure (*R*)-(−)-2-heptanol was purchased from Aldrich: $[\alpha]^{25}_D = -10.6°$ (c = 2.83, $CHCl_3$); lit.[8] $[\alpha]^{17}_D = -10.48°$ (neat).

Esterification of (*R*)-(−)-2-Heptanol with (*S*)-(+)-*O*-Methylmandelic Acid. A catalytic amount of DMAP was added to a solution of (*R*)-(−)-2-heptanol, (*S*)-(+)-*O*-methylmandelic acid, and DCC (ca 0.08 mmol each) in methylene chloride (2 mL). After 24 h, precipitated dicyclohexylurea was removed by filtration and the solvent was removed in vacuo. The resulting residue was dissolved in hexane and combined with hexane (5 mL) used to wash the urea cake. The combined hexane solution was washed with cold 1 N HCl (1 × 2 mL), saturated $NaHCO_3$ (1 × 2 mL), and saturated NaCl (1 × 1 mL). The organic phase was then filtered through Celite. The solvent was removed under reduced pressure to afford a nearly pure product that contained a small amount of urea. This mixture was dissolved in hexane and filtered through Celite to afford 21.1 mg (88%) of the pure *R,S* ester 3: ^1H NMR δ 7.46–7.43 (2H, m), 7.39–7.27 (3H, m), 4.97 (1H, m), 4.74 (1H, s), 3.42 (3H, s), 1.63–1.23 (8H, m), 1.09 (3H, d, J = 6.3 Hz), 0.86 (3H, t, J = 6.9 Hz).

Esterification of (*R*)-(−)-2-Heptanol with (*R*)-(+)-*O*-Methylmandelic Acid. The esterification procedure outlined above for compound 3 was followed with (*R*)-(−)-2-heptanol (0.04 mmol scale) and (*R*)-(−)-*O*-methylmandelic acid to afford 3.0 mg (25%) of the pure *R,R* ester 4: ^1H NMR δ 7.45–7.41 (2H, m), 7.39–7.28 (3H, m), 4.94 (1H, m), 4.72 (1H, s), 3.41 (3H, s), 1.59–1.25 (4H, m), 1.21 (3H, d, J = 6.3 Hz), 1.19–0.86 (4H, m), 0.78 (3H, t, J = 6.7 Hz).

Esterification of Villiramulin A (1) with (*R*)-(+)-*O*-Methylmandelic Acid. A catalytic amount of DMAP was added to a solution of compound 1 (≈0.01 mmol), (*R*)-(+)-*O*-methylmandelic acid (≈0.01 mmol), and DCC (≈0.01 mmol) in methylene chloride (2 mL). After 24 h, workup of the reaction afforded 3.2 mg (≈70%) of the pure *R* acid ester 5: $[\alpha]^{25}_D = -32°$ (c = 0.38, $CHCl_3$); ^1H NMR δ 7.45–7.40 (2H, m), 7.38–7.32 (3H, m), 6.72 (1H, d, J = 7.8 Hz), 6.67 (1H, s), 6.62 (1H, d, J = 7.8 Hz), 5.99 (2H, m), 5.91 (2H, s), 5.55 (2H, m), 4.94 (1H, m), 4.73 (1H, s), 3.41 (3H, s), 2.62 (2H, t, J = 8.3 Hz), 2.33 (2H, dt, J = 7.1, 8.0 Hz), 2.01 (2H, dt, J = 7.1, 8.0 Hz), 1.76–1.31 (6H, m), 1.08 (3H, d, J

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= 6.2 Hz); ^{13}C NMR 170.39, 147.49, 145.60, 136.42, 135.76, 132.42, 131.13, 130.87, 130.41, 128.67, 128.54, 128.50, 127.38, 127.06, 121.09, 108.85, 108.07, 100.71, 82.82, 71.99, 57.29, 35.60, 34.71, 32.38, 29.04, 24.83, 24.64, 19.62 ppm; EIMS *m/z* (relative intensity) 450 (M^+, 0.76), 284 (3), 135 (100), 121 (78), 105 (6), 71 (28), 57 (44); HREIMS calcd for $C_{28}H_{34}O_5$ 450.2406, found 450.2402.

Esterification of Villiramulin A with (*S*)-(+)-*O*-Methylmandelic Acid. Compound 1 (≈0.01 mmol) was esterified with (*S*)-(−)-*O*-methylmandelic acid (≈0.01 mmol) following the procedure outlined above. This reaction gave 2.7 mg (≈60%) of the pure *S* acid ester 6: $[\alpha]^{26}_D = +35°$ ($c = 0.20$, $CHCl_3$); ^{1}H NMR δ 7.45–7.40 (2H, m), 7.38–7.32 (2H, m), 6.72 (1H, d, J = 7.8 Hz), 6.67 (1H, s), 6.62 (1H, d, J = 7.8 Hz), 5.96 (2H, m), 5.92 (2H, s), 5.55 (2H, m), 4.91 (1H, m), 4.72 (1H, s), 3.41 (3H, s), 2.62 (2H, t, J = 8.3 Hz), 2.33 (2H, dt, J = 7.1, 8.0 Hz), 1.87 (2H, m), 1.76–1.47 (4H, m), 1.20 (3H, d, J = 6.2 Hz), 0.97 (2H, m); EIMS *m/z* (relative intensity) 450 (M^+, 0.76), 284 (3), 135 (100), 121 (78), 105 (6), 71 (28), 57 (44); HREIMS calcd for $C_{28}H_{34}O_5$ 450.2406, found 450.2408.

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Synthesis of Nucleoside 3'-Alkylphosphonates: Intermediates for Assembly of Carbon-Bridged Dinucleotide Analogues

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Several 3'-modified nucleosides have been prepared, through an initial Wittig or Horner–Wadsworth–Emmons condensation with an adenosine 3'-ketone, followed by catalytic hydrogenation of the resulting olefin. Subsequent reaction of the 3'α-methylene carboxylate with the lithium salt of diethyl ethylphosphonate gave a β-keto phosphonate, while reaction of the methylene carboxylate with LDA, diethyl chlorophosphite, and O_2 gives the corresponding α-phosphono ester. These new nucleoside phosphonates can be viewed as analogues of natural phosphates and also can serve as synthetic intermediates for preparation of carbon-bridged dinucleotide analogues. To give the first such example, the β-keto phosphonate **13** was allowed to react with a nucleoside 5'-aldehyde, affording the dinucleoside enone **23**.

The synthesis and biological evaluation of antisense nucleotides, synthetic oligomers of defined sequence intended to bind with complementary, natural polynucleotides, is an area of substantial current interest.[1] While many details of the biological properties and therapeutic potential of antisense oligomers are yet to be determined, it is clear that significant problems of in vivo stability must be overcome. In particular, stability to endogenous nucleases must be improved if synthetic oligomers are to have a lifetime sufficient to demonstrate significant biological activity.

Many different approaches have been initiated to attain synthetic oligonucleotide analogues with enhanced resistance to nuclease activity. These strategies often involve substitution of various functional groups for the natural phosphodiester linkage, including both phosphorus-containing (e.g. phosphorothioates[2] and methylphosphonates)[3] and non-phosphorus-containing groups (e.g. carbonates,[4] carbamates,[5] and sulfur-based groups[6]). Oligonucleotides constructed entirely of repeating units other than the natural phosphates might achieve stability at the price of unattractive hybridization and/or solubility properties. However, oligonucleotides "capped" with but two terminal methylphosphonate groups,[7a] or a hydroxylamine linkage,[7b] have greatly enhanced stability with respect to important nucleases, while maintaining a structure based primarily on the natural phosphate diesters. Still another possibility, one not yet extensively explored, is to incorporate selected linkages capable of inhibiting nuclease activity through reaction with active site amino acids.

Our continuing interest in the chemistry of β-keto phosphonates,[8] and α-phosphono esters and lactones,[8e,9] has led us to attempt assembly of new dinucleotide analogues based on reactions of nucleoside phosphonates. In particular, the potential for incorporation of 3'-alkylphosphonate groups on a nucleoside template appeared to allow for the possibility of constructing new all-carbon chains bridging two nucleosides. In this report, synthesis of a number of new 3'-modified nucleosides is described, along with the preparation of the first dinucleotide analogue bridged by an enone system.

Results and Discussion

The keto phosphonate central to this strategy, compound **13**, requires extension of a carbon chain from the nucleoside 3'-carbon. The nucleoside ketone **1** represents an attractive starting material for that operation for several reasons. Ketone **1** is available in just two steps from commercially available adenosine,[10] and its use should lead to the appropriate enantiomer without need for either glycosidic bond formation or resolution. At the same time, it must be recognized that 3'-keto nucleosides are prone to elimination of the purine or pyrimidine base, leading to enone formation.

Introduction of a carbon chain at C-3' of nucleoside **1** has been accomplished through a Wittig reaction and also might be possible through a more convenient Horner–Wadsworth–Emmons (HWE) condensation (Scheme I). In fact, upon treatment with the sodium enolate of phosphono ester **2**, ketone **1** underwent the desired

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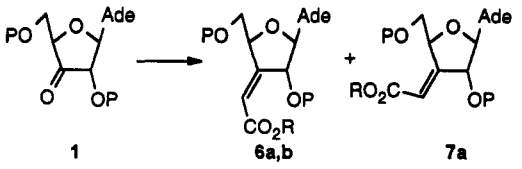
Scheme I



1 6a,b 7a

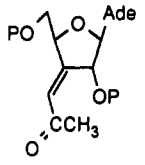
P = tBDMS
a R = CH_3
b R = CH_2CH_3

2 $(CH_3O)_2P(O)CH_2C(O)CH_3$ 62% (5:1 **6a**:**7a**)

3a, b $(C_6H_5)_3P{=}CHC(O)R$ 88% (**6** only)

4 $(C_6H_5)_3P{=}CHC(O)CH_3$ 10%

5 $(EtO)_2P(O)CH_2P(O)(OEt)_2$ —



8

condensation without substantial purine elimination. Even though this condensation gives about a 5:1 mixture of olefin stereoisomers **6a** and **7a**, since the olefin stereochemistry is lost upon reduction in the next step, this issue is not critical. On the other hand, methoxycarbonyl phosphorane **3a** reacted as expected[11,12] with ketone **1** and gave only stereoisomer **6a** in good yield. Phosphorane **3b** gave the corresponding ethyl ester **6b**.

The success of these reactions prompted attempted condensations of ketone **1** with both the keto phosphorane **4** and methylenebis(phosphonate) **5**. However, attempted reaction of **4** with ketone **1** gave only a low yield (ca. 10%) of an olefin product (**8**), and treatment of the anion of bis(phosphonate) **5** with ketone **1** resulted only in loss of the purine, verifying literature cautions.[13] Even though the methodology exists to convert the methyl ketone **8** to the desired β-keto phosphonate **13**, through formation of the kinetic enolate, carbon–phosphorus bond formation,[8e] and catalytic hydrogenation, this route was not pursued due to the low yield of the condensation.

The stereochemistry of olefins **6** and **7** was tentatively assigned as *Z* and *E*, respectively, on the basis of their NMR spectra. In the ^1H NMR spectrum of **6a**, the 4′-hydrogen appeared at δ 5.43 (m), and the methoxy group appeared at δ 3.76. In contrast, the 4′-hydrogen of isomer **7a** was observed at δ 5.80 and the methoxy group at δ 3.69. Similar phenomena have been reported for modified carbohydrates such as the (*E*)- and (*Z*)-(alkoxycarbonyl)-methylene derivatives of a hexofuranose,[14] presumably resulting from a deshielding effect of a carbonyl group *cis* to C-4′.

Hydrogenation of these olefins, either compound **6a**, **6b**, or a mixture of compounds **6** and **7**, over 10% Pd/C gave a single reduced product, and this compound was initially assigned as the desired α-isomer **9** on the basis of its spectral data (Scheme II). Surprisingly, when the olefin **6b** was treated with H_2 and a wet Pd/C catalyst (Aldrich, Degussa type), the only observed product was the 5′-deprotected olefin **10**.[15] This fortuitous discovery turned out to be very helpful for confirmation of the 3′-stereochemistry of compound **9**. Reduction of the partially deprotected olefin **10** with excess $NaBH_4$ and subsequent reaction with tBDMSCl gave a major product identical to compound **9b** prepared by hydrogenation. This stereoselectivity is consistent with initial reaction of the free 5′-hydroxy group with borohydride and intramolecular delivery of hydride from the more hindered β-face of this complex.[16] In contrast, direct reduction of olefin **6a** with excess $NaBH_4$ in methanol afforded a different methyl ester, assigned as the 3′-β-isomer **12**, along with some by-products assumed to be primary alcohols.[12] Presumably, in this series hydride attack from the less hindered α-face leads to the 3′-β-isomer.

Once the stereochemistry of the 3′-modified nucleoside **9** was established unequivocally, phosphonate **13** was prepared from this ester according to the procedure of Mathey and Savignac.[17] Thus reaction of ester **9a** with the anion of diethyl methylphosphonate gave the expected β-keto phosphonate **13** in good yield (85%). This keto phosphonate undergoes HWE condensation with benzaldehyde under standard reaction conditions (K_2CO_3/18-crown-6/THF), producing enone **14** in 94% yield and with exclusively *E* stereochemistry (J = 16.3 Hz). As a final confirmation of structure, catalytic hydrogenation of enone **14** afforded the corresponding ketone **15**.

The 3′-modified nucleoside **9** also offered entry to a second series of nucleoside phosphonates, for conversion of ester **9** to the 3′-α-phosphono ester **16** could be envisioned by application of our newest method for C–P bond formation (Scheme III).[8e,9b] Direct treatment of ester **9a** with lithium hexamethyldisilizide and diethyl phosphorochloridite, followed by air oxidation, afforded a small amount of the desired phosphono ester **16** (<5%) while an N^6-phosphorylated product was isolated as the major product. To minimize formation of this byproduct, ester **9** was protected as its *N*,*N*-dibenzoyl derivative **17**. Phosphorylation of **17** using the same chlorophosphite/oxidation sequence provided the desired phosphonate **18** in better yield. Subsequent deprotection of compound **18** by treatment with methanolic ammonia gave phosphonate **16**, identical with material prepared by direct phosphonylation of compound **9**. The α-phosphono esters **18** and **16** can be viewed both as 3′-modified nucleosides and as potential synthetic intermediates for HWE condensations and other phosphono ester reactions.

Finally, to demonstrate that highly functionalized β-keto phosphonates can be used in assembly of dinucleotide analogues, the known nucleoside 5′-aldehyde **22** was prepared as a counterpart of phosphonate **13** in an HWE condensation. Although in most cases the 5′-aldehyde **22**

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