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Synthesis of Lanopylin B_1

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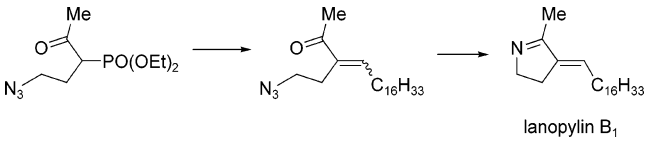
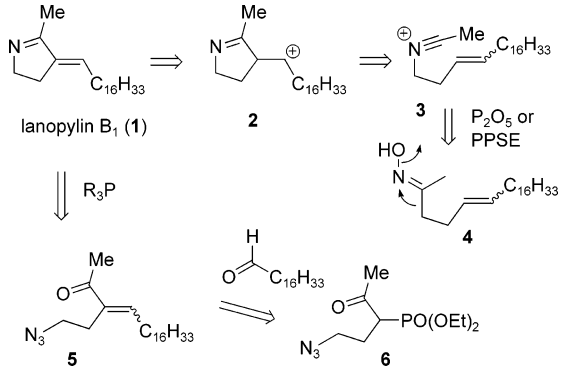


Phase-transfer alkylation of diethyl 2-oxopropylphosphonate (**9**) with 2-iodoalkyl azide afforded 40% of azido phosphonate **6**, which underwent a phase-transfer Horner−Emmons Wittig reaction with heptadecanal to provide 80% of azido enone **5**. An intramolecular aza-Wittig reaction with polymer-bound Ph_3P in toluene at reflux completed the first synthesis of lanopylin B_1 in 76% yield.

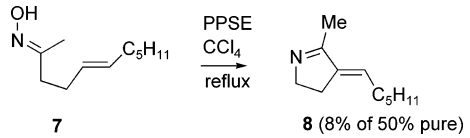
Ebizuka and co-workers isolated lanopylin B_1 (**1**) and a series of congeners with alkyl, isoalkyl, and 11-alkenyl side chains of varying length from an actinomycete strain, *Streptomyces* sp. K99-5041 in 2003.[1] The lanopylins inhibit recombinant human lanosterol synthase with an IC_{50} of 15−41 μM and may therefore be useful for the treatment of hypercholesterolemia. More than 20 years ago, Gawley[2] prepared related 3-alkylidine-2-methyl-1-pyrrolines by treatment of unsaturated oximes in CCl_4 at reflux with P_2O_5 or trimethylsilyl polyphosphate (PPSE),[3] which is prepared in situ from P_2O_5 and hexamethyldisiloxane.[4] Using Gawley's procedure, acid-catalyzed rearrangement of oxime **4** should give nitrilium ion **3**, which could cyclize to give secondary cation **2**. Loss of a proton would give lanopylin B_1 (Scheme 1).

However, Gawley's studies suggested that nitrilium ions will cyclize only to more electron-rich alkenes that form more stable benzylic or tertiary cations.[2] We therefore investigated this sequence with oxime **7** prepared from readily available (*E*)-undec-5-en-2-one.[5] Only traces of the desired pyrroline **8** were obtained with P_2O_5 in CCl_4 at reflux, and only 8% of 50% pure **8** was obtained with PPSE in CCl_4 at reflux (Scheme 2).

SCHEME 1. Retrosynthesis of Lanopylin B_1



SCHEME 2. Unsuccessful Approach to Lanopylin B_1



We therefore considered alternate approaches to **1**. An intramolecular aza-Wittig reaction[6,7] of azido enone **5** should give lanopylin B_1. Enone **5** should be available from the known azido phosphonate **6**[8] and heptadecanal. This approach was particularly attractive since it would permit the introduction of a variety of alkyl side chains from a common intermediate. Vaultier and Carrié reported that alkylation of **9** with 2-iodoethyl azide with NaH in DMF gave 68% of azido phosphonate **6**.[8] In our hands, this procedure gave only 17% of **6**. Alkylation of keto phosphonates is known to be difficult.[9−11] Heathcock reported that NaH in THF was effective for reactive alkylating agents, but not for 1-iodopentane.[9] Using his conditions we obtained 6% of **6**. Ruder described a phase-transfer procedure using tetrabutylammonium bisulfate and aqueous sodium hydroxide in CH_2Cl_2 at reflux.[11] Using this procedure, we were able to obtain azido phosphonate **6** in 40% yield (Scheme 3).

Wittig reaction of **6** with heptadecanal using a phase-transfer procedure with aqueous K_2CO_3 and tetrabutylammonium bisulfate without organic solvent[12] provided 80% of **5** as a 3:1 inseparable mixture of *E* and *Z* isomers. Lower yields were obtained with K_2CO_3 in aqueous THF (45%),[13] with barium hydroxide in wet THF (45%)[14] or NaH in THF (5%).[15] The aza-Wittig reaction was easily

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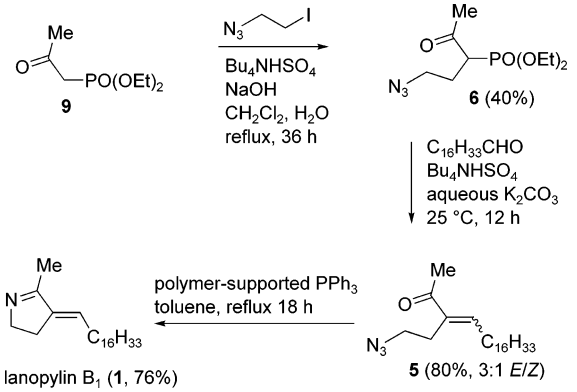
SCHEME 3. Synthesis of Lanopylin B_1 (1)



accomplished by heating **5** (3:1 *E*/*Z* mixture) with polymer-bound Ph_3P[16] in toluene at reflux for 18 h, filtration, and concentration to give 76% of lanopylin B_1 (**1**) with spectral data identical to those reported. Only the desired *E* isomer was obtained, suggesting that both *E*- and *Z*-**5** are converted to **1**. This is not surprising if equilibration of the stereoisomers can occur because **1** should be about 2 kcal/mol more stable than the *Z* isomer because of steric repulsion between the cis methyl and hexadecyl side chains.

Only 50% of **1** was obtained after cyclization of **5** with polymer-bound Ph_3P for 6 h in toluene at reflux, and less than 5% of **1** was obtained in either toluene or ether at 25 °C with the most of the remaining material being unreacted **5** in all cases. Vaultier and Carrié reported that aza-Wittig reactions form pyrrolines from azido ketones and Ph_3P in ether at 25 °C, suggesting that polymer-bound Ph_3P is much less reactive than Ph_3P in solution.[17] This was confirmed by reacting **5** (3:1 *E*/*Z* mixture) with Ph_3P in ether at 25 °C for 20 h to give a 7:1 mixture of **1** and a compound tentatively identified as the *Z* isomer of **1**. However, **1** was chromatographically inseparable from the Ph_3PO byproduct. Flash chromatography gave a 1.5:1 mixture of Ph_3PO and lanopylin B_1 (50% of a 18:1 *E*/*Z* mixture). These results indicate that polymer-bound Ph_3P is much less reactive than free Ph_3P, but difficulties in separating **1** from Ph_3PO make the use of the polymer-bound reagent advantageous in this case. Only the more stable naturally occurring *E*-isomer lanopylin B_1 (**1**) was obtained from the aza-Wittig reaction in toluene at reflux suggesting that equilibration occurred under these conditions. The conversion of the 7:1 mixture of the isomers of **1** to an 18:1 mixture indicates that equilibration also occurred during flash chromatography.

In conclusion, we have completed the first synthesis of lanopylin B_1 in three steps and 24% overall yield using an aza-Wittig reaction with polymer-bound Ph_3P as the key step. This sequence makes a variety of analogues readily available for biological evaluation as lanosterol synthase inhibitors.

Experimental Section

Diphenylphosphino polystyrene (~3 mmol/g, polymer-bound Ph_3P, Aldrich 366455) was washed with toluene to remove any soluble impurities. NMR spectra were run at 400 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants in Hz.

Diethyl 1-(2-Azidoethyl)-2-oxopropylphosphonate (6). To a solution of tetrabutylammonium hydrogen sulfate (1.59 g, 4.68 mmol) in sodium hydroxide (2 M, 4.68 mL) was added a mixture of diethyl (2-oxopropyl)phosphonate (909 mg, 4.68 mL) and 2-iodoethyl azide (2.0 g, 10.3 mmol) in CH_2Cl_2 (4.68 mL). The resulting solution was refluxed for 36 h, cooled, and treated with water (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and concentrated under reduced pressure. The resulting residue was dissolved in Et_2O (100 mL) in order to precipitate tetrabutylammonium iodide. The salt was filtered off, and the filtrate was dried (Na_2SO_4) and concentrated under reduced pressure to give a colorless oil. Flash chromatography on silica gel (3:1 hexanes/EtOAc) afforded 490 mg (40%) of **6** as a colorless oil: ^{1}H NMR 1.29 (t, 3, J = 7), 1.30 (t, 3, J = 7), 1.92−2.32 (m, 2), 2.34 (s, 3), 3.19−3.40 (m, 3), 4.06−4.16 (m, 4); ^{13}C NMR 16.3 (d, J = 6.1), 25.6 (d, J = 3.8), 31.6, 49.6 (d, J = 14.5), 50.2 (d, J = 125.9), 62.7 (d, J = 6.9), 62.9 (d, J = 6.9), 202.6 (d, J = 4.6); IR (neat) 2985, 2937, 2100, 1714.

3-(2-Azidoethyl)-3-eicosen-2-one (5). To phosphonate **6** (80 mg, 0.3 mmol) were added K_2CO_3 (700 mg), H_2O (1.2 mL), tetrabutylammonium hydrogen sulfate (17 mg, 0.05 mmol), and heptadecanal (115 mg, 0.45 mmol). The resulting mixture was stirred at room temperature for 12 h, poured into water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (100:1 hexanes/EtOAc) to give 87 mg (80%) of **5** as an inseparable 3.3:1 *E*/Z mixture: ^{1}H NMR (*E* isomer) 0.85 (t, 3, J = 6.7), 1.15−1.40 (m, 26), 1.40−1.52 (m, 2), 2.24−2.32 (m, 2), 2.29 (s, 3), 2.55 (t, 2, J = 7.0), 3.24 (t, 2, J = 7.0), 6.74 (t, 1, J = 7.3); (*Z* isomer) 0.85 (t, 3, J = 6.7), 1.15−1.40 (m, 26), 1.40−1.52 (m, 2), 2.24−2.32 (m, 2), 2.29 (s, 3), 2.48 (t, 2, J = 7.0), 3.30 (t, 2, J = 7.0), 5.86 (t, 1, J = 7.3); ^{13}C NMR (*E* isomer) 14.1, 22.7, 25.36, 25.40, 28.8, 29.2−29.7 (12 C), 31.9, 50.3, 137.8, 147.4, 199.1; (partial data for *Z* isomer) 30.0, 34.4, 50.7, 137.2, 141.0; IR (neat) 2924, 2853, 2096, 1672; HRMS (DCI/NH_3) calcd for $C_{22}H_{42}N_3O$ (MH^+) 364.3328, found 363.3323.

Lanopylin B_1 (1). To a toluene solution (10 mL) of **5** (33 mg, 0.091 mmol) was added polymer-supported Ph_3P (90 mg, 0.27 mmol, 3 mmol/g). The resulting mixture was refluxed for 18 h under N_2, cooled, filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography on MeOH-deactivated silica gel (100:1 $CHCl_3$/MeOH) to give 22 mg (76%) of pure **1**: ^{1}H NMR 0.88 (t, 3, J = 6.7), 1.24−1.27 (m, 26), 1.38−1.47 (m, 2), 2.06 (t, 3, J = 1.8), 2.10 (dt, 2, J = 7.3, 7.3), 2.45−2.50 (m, 2), 3.84−3.88 (m, 2), 5.72−5.78 (m, 1); ^{13}C NMR 14.1, 15.8, 22.7, 26.7, 28.9, 29.3−29.7 (11 C), 30.5, 31.9, 57.6, 126.6, 143.1, 171.8; IR (neat) 2923, 2853, 1606, 1466, 1383; HRMS (DEI) calcd for $C_{22}H_{41}N$ (M^+) 319.3239, found 319.3244. The spectral data are identical to those reported.[1]

To a dry ether solution (6 mL) of **5** (30 mg, 0.083 mmol) was added Ph_3P (65 mg, 0.25 mmol). The resulting mixture was stirred for 20 h under nitrogen at room temperature and concentrated under reduced pressure to give a 7.2:1 mixture of **1** and a compound tentatively identified as the *Z* isomer of **1**. The residual oily solid was purified by flash chromatography on MeOH-deactivated silica gel (100:1 $CHCl_3$/MeOH) to give a 33 mg of a 1.5:1:0.055 inseparable mixture of Ph_3PO, **1** (51%) and the *Z* isomer (3%): (Partial data for the *Z* isomer were determined from the mixture) 2.26 (t, 3, J = 1.8), 2.28−2.36 (m, 2), 2.55−2.61 (m, 2), 3.72−3.77 (m, 2), 5.62−5.68 (m, 1).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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