reaction at either the carbonyl carbon or the C-2 ring carbon.

Ichimoto et al.[19] did not study 2,6-dimethyl-4-pyrone but did report the results for oxygen exchange reactions in 4-pyrone and some 4-pyrone derivatives, primarily in alkali solutions of 1.5% [^{18}O]water at 40 °C for 20 h; mass spectrometry was used to analyze the results. At pH 1.0 and at "neutral" pH under the same conditions, 4-pyrone and kojic acid were reported to have incorporated ^{18}O at about one-fifth the value detected in basic solution. They concluded from their studies that "...the ^{18}O incorporation in the ring oxygen is larger than that in the carbonyl oxygen" in acidic, neutral, or basic solution. They also concluded that substitution of a methyl group on the 2- and 6-positions of the heterocyclic ring reduces the rate at which oxygen exchange occurs in the ring. They proposed that an electron-releasing group such as a methyl group suppresses nucleophilic attack at the C-2 and C-6 positions and thus reduces the rate of ring opening for an exchange reaction to occur. From their data it is not possible to assign a number to the magnitude of the rate reduction effected by methyl group substitution. Our results for 2,6-dimethyl-4-pyrone show that at pH 1.09 the only oxygen exchange reaction detected is for the carbonyl oxygen.

The order of magnitude of the rate for the oxygen exchange reaction of the carbonyl oxygen in 2,6-dimethyl-4-pyrone is consistent with data for these reactions in carbonyl groups: cyclopropenones,[23] acetone,[24,25] cyclohexanone,[25] acetophenones,[23,26] and benzophenones.[27] The energy of activation for the carbonyl oxygen exchange reaction of benzophenones in acidic aqueous dioxane is ~19 kcal/mol,[27] which is very similar to the value we obtained for 2,6-dimethyl-4-pyrone. Mechanisms for oxygen exchange reactions in 4-pyrones were proposed by Beak and Carls[17] and by Ichimoto et al.[19] According to these mechanisms, ^{18}O exchange at the carbonyl group occurs upon attack by [^{18}O]water in acidic solution at the C-4 carbon. Our results are in agreement with these proposals.

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Practical Synthesis of an Enantiomerically Pure Synthon for the Preparation of Mevinic Acid Analogues

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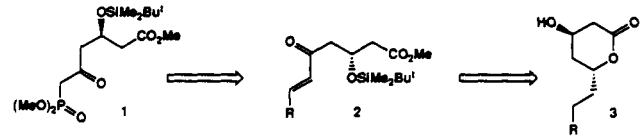
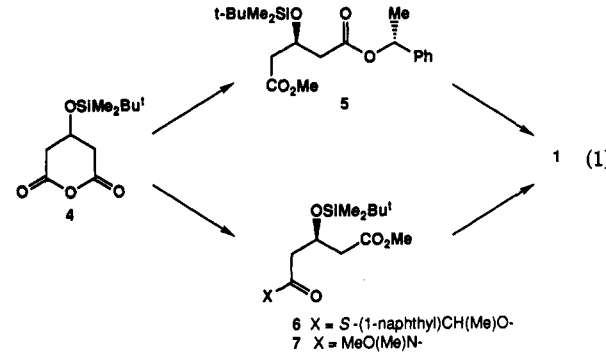
Heathcock and co-workers[1] have elegantly demonstrated the utility of the optically active β-keto phosphonate 1 in their synthesis of compactin and its analogues. This synthon allows for the direct introduction, via a Horner-Emmons condensation, of a highly functionalized side chain suitable for conversion into the 3-hydroxypyranone moiety (e.g., 3) found in the mevinic acid family of HMG-CoA reductase inhibitors and their synthetic analogues.[2]



Heathcock has reported[1,3] two routes to β-keto phosphonate 1 that rely on the highly diastereoselective reaction of prochiral anhydride 4[4] with either (*R*)-1-phenylethanol or (*S*)-1-(1′-naphthyl)ethanol for the introduction of asymmetry (88–95% diastereomeric excess). For the conversion of 5 to 1, it was necessary to desilylate 5 prior to reaction with dimethyl (lithiomethyl)phosphonate to prevent β-elimination of the (*tert*-butyldimethylsilyl)oxy group. Similarly, the condensation of 7 with dimethyl (lithiomethyl)phosphonate is extremely sensitive to reaction conditions due to a competitive retro-aldol reaction and β-elimination of the silyloxy group. Diesters 5 and 6 were converted to β-keto phosphonate 1 in overall yields of 34 and 59%, respectively.



Although this chemistry has been used to prepare 1 in multigram quantities, the cost and availability of the required 1-arylethanols in enantiomerically pure form limit its preparative utility. In this paper, we report an alternative synthesis of 1 that utilizes commerically available (*S*)-1-phenethylamine as the source of chirality and can be used for the large-scale preparation of 1 (Scheme I).

Reaction of anhydride 4 with (*S*)-1-phenethylamine in the presence of triethylamine with toluene as solvent (−78 °C, 4.5 h) gave a 79:21 mixture of diastereomeric acids 8a

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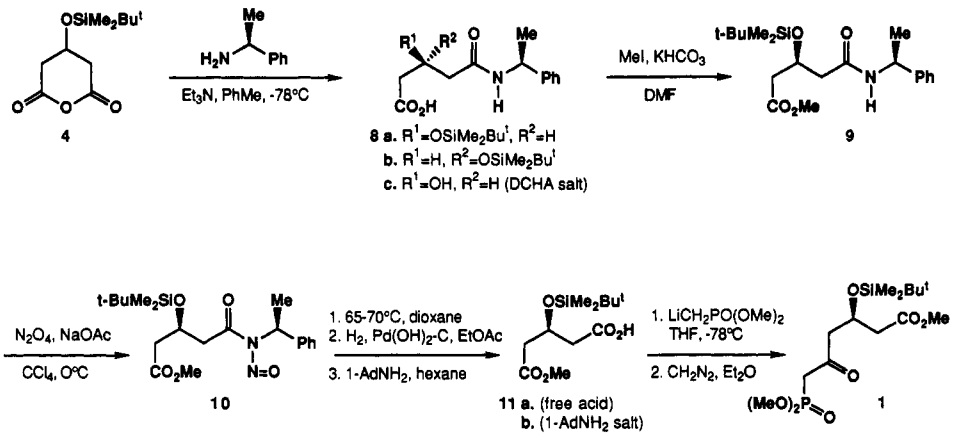
(4) Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657. Anhydride 4 is now commerically available from the Aldrich Chemical Co.

0022-3263/91/1956-3744$02.50/0

Scheme I



and **8b** in essentially quantitative yield. Although the degree of prochiral recognition is rather modest, the crystalline 3*S*,1′*S* diastereomer **8a** is easily separated from the oily 3*R*,1′*S* diastereomer by simple trituration or recrystallization. Thus, acid **8a** was isolated in 72% yield from anhydride **4** as a single enantiomerically pure diastereomer without chromatography. The ratio of the two diastereomers is sensitive to the choice of solvent in this reaction. For example, when this reaction was carried out in either methylene chloride or tetrahydrofuran under the same conditions, the ratios of **8a** to **8b** were 46:54 and 67:33, respectively. The relative and absolute stereochemistry of **8a** was established by a single X-ray crystallographic study of the corresponding methyl ester **9** (vida infra). Relative to the known *S* configuration of the phenethylamine used in the synthesis, the configuration at C-3 is *S*. Since single crystals of **9** exhibited considerable crystallographic disorder (primarily involving the silyl alkyl substituents), a confirmation of the stereochemical assignment was obtained through an independent single crystallographic analysis of the dicyclohexylamine salt of the corresponding acid–alcohol **8c** (see Experimental Section for details). The solid-state conformations of **9** and **8c** are very similar.

It was hypothesized that the β-elimination encountered by Heathcock[1,3] in the reaction of dimethyl (lithiomethyl)phosphonate with diester **5** and ester–amide **7** could be circumvented by carrying out this condensation reaction using half ester **11a** as substrate. In this case, **11a** could be protected from β-elimination by prior or in situ conversion to its carboxylate anion. To this end, ester **9** was prepared by treatment of acid **8a** with methyl iodide and potassium bicarbonate in dimethylformamide (room temperature, 18 h, 97% yield). The conversion of **9** to half-ester **11a** requires the cleavage of an amide in the presence of an ester. This was accomplished quite efficiently via a sequence of reactions involving White rearrangement[5] of the *N*-nitrosoamide **10** obtained by the nitrosation of **9** with dinitrogen tetroxide. Heating **10** in dioxane afforded a mixture of acid **11a** and its corresponding 1-phenethyl ester. The 1-phenethyl ester was converted, without isolation, to acid **11a** by hydrogenolysis of the crude mixture over Pearlman's catalyst. The crude half-ester **11a** was purified by way of its 1-adamantanamine (1-AdNH$_2$) salt, thus providing **11b** in 96% overall yield from ester–amide **9**. Direct treatment of **11b** with dimethyl (lithiomethyl)phosphonate (3.5 equiv, THF, −78 °C) followed by esterification of the crude product with diazomethane afforded the β-keto phosphonate **1** in 78–82% overall yield from **11b**. As expected, no products resulting from β-elimination of the silyloxy group were observed in this reaction.

This entire sequence can be carried out without chromatographic purification of the intermediates and requires only purification of the final product. The foregoing process, which utilizes commerically available (*S*)-1-phenethylamine as a source of chirality, is extremely efficient and has been used to prepare β-keto phosphonate **1** on up to a 100-g scale. Phosphonate **1** reacts with a wide variety of aldehydes in the presence of lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[6] to give high yields of the corresponding enones (e.g., **2**). These enones are excellent precursors of the 3-hydroxypyranone moiety (e.g., **3**) found in many HMG-CoA reductase inhibitors. In addition, we have developed an efficient route to optically pure half-ester **11a** in multigram quantities. Prior to our work, this valuable chiral synthon was difficult to prepare in >80% ee[1b,4] from the product of α-chymotrysin-mediated hydrolysis of dimethyl 3-hydroxypentanedioate.[7]

Experimental Section

^{1}H and ^{13}C NMR spectra were determined at 270 and 67.8 MHz, respectively. ^{13}C NMR chemical shifts (δ) are reported relative to $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0). Desorption chemical ionization (DCI) mass spectra were obtained at a source temperature of 170 °C. Ammonia was used as the CI reagent gas (0.7 Torr). Melting points are uncorrected. Tetrahydrofuran (THF) and diethyl ether were distilled from K/benzophenone. Toluene was stored over 4-Å molecular sieves. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Flash chromatography was performed on Whatman LPS-1 silica gel (13–24 μm).

(3*S*,1′*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-[(1-phenylethyl)amino]-5-oxopentanoic Acid (8a). To a solution of anhydride **4**[4] (7.32 g, 30.0 mmol) in dry toluene (120 mL) at −78 °C (dry ice–EtOH bath) under argon was added dropwise triethylamine (4.20 mL, 30.0 mmol) followed by (*S*)-(−)-1-phenethylamine (4.20 mL, 32.6 mmol). After the solution was stirred at −78 °C for 4.5 h, the cooling bath was removed and the mixture was allowed to warm to rt. After being stirred at rt for 1 h, the mixture was partitioned between EtOAc (100 mL)/THF (50 mL)/5% $KHSO_4$ (175 mL). The organic phase was washed with 5% $KHSO_4$ and saturated NaCl solutions, dried (Na_2SO_4), and evaporated to give crude acids **8ab** as a white semisolid. Esterification of a 25-mg sample of the crude product with CH_2N_2 gave a 79:21 mixture of (3*S*,1′*S*)/(3*R*,1′*S*) methyl esters as determined

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by ^1H NMR (CD_3CN) analysis: TLC (Et_2O/hexane (2:1)) R_f = 0.37 (major, 3*S*,1′*S*) and 0.29 (minor, 3*R*,1′*S*); ^1H NMR (3*S*,1′*S*) δ 0.08 (3 H, s), 0.10 (3 H, s), 0.86 (9 H, s); ^1H NMR (3*R*,1′*S*) δ 0.03 (3 H, s), 0.06 (3 h, s), 0.79 (9 H, s).

The crude mixture of acids **8ab** was triturated with cold Et_2O to give **8a** (8.16 g, 74.5%) as white crystals that showed only a trace of the (3*R*,1′*S*) isomer after esterification with CH_2N_2. Evaporation of the mother liquor gave **8b** (2.76 g) as a thick oil.

The product of the previous experiment was combined with that of an identical run (second run gave 8.28 g of **8a**; total, 16.44 g) and recrystallized from EtOAc/hexane to give pure **8a** (15.79 g, 72%) as white plates: mp 175.5–176.5 °C; TLC (MeOH/CH_2Cl_2 (1:9)) R_f = 0.32; $[\alpha]_D$ −69.2° (*c* 1.12, MeOH); ^1H NMR ($CDCl_3$) δ 0.09 (s, 3 H), 0.11 (s, 3 H), 0.85 (s, 9 H), 1.49 (d, 3 H, *J* = 7.0 Hz), 2.51 (d, 2 H, *J* = 6.5 Hz), 2.57 (d, 2 H, *J* = 4.7 Hz), 4.47 (m, 1 H), 5.15 (quintet, 1 H, *J* = 7.0 Hz), 6.59 (b d, 1 H, *J* = 7.6 Hz), 7.25–7.36 (m, 5 H); ^{13}C NMR (CD_3OD) δ −4.68, −4.53, 18.85, 22.54, 26.37, 43.64, 45.26, 50.12, 68.41, 127.10 128.02, 129.49, 145.32, 172.05, 174.70; IR (KBr) 3323, 2930, 2856, 1695, 1620, 1560, 1303, 1259, 1213, 1155, 1099, 844, 833, 779, 700 cm^{-1}; CIMS *m*/*z* 366 (+ ion), 364 (− ion). Anal. Calcd for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 62.58; H, 8.67; N, 3.72.

(3*S*,1′*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-[(1-phenylethyl)amino]-5-oxopentanoic Acid, Methyl Ester (9). To a solution of acid **8a** (28.560 g, 78.25 mmol) in dry DMF (100 mL) at rt under Ar was added powdered, anhydrous $KHCO_3$ (14.40 g, 144 mmol) and MeI (8.90 mL, 143 mmol). After being stirred at rt for 42 h, the mixture was partitioned between EtOAc (300 mL) and water (300 mL). The organic phase was separated and washed successively with water (3 X 100 mL) and saturated NaCl solution (100 mL), dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by filtration through a short pad of silica gel (~160 g), eluting with Et_2O/hexane (2:3) to give methyl ester **9** (28.524 g, 96%) as a white solid. Trituration of the solid with cold hexane gave pure **9** (28.283 g, 95%) as a white crystalline solid, mp 77–78.5 °C. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 77–78.5 °C; TLC (Et_2O/hexane (2:1)) R_f = 0.37; $[\alpha]_D$ −22.6° (*c* 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.86 (s, 9 H), 1.47 (d, 3 H, *J* = 7.0 Hz), 2.47 (m, 4 H), 3.65 (s, 3 H), 4.50 (quintet, 1 H, *J* = 5.9 Hz), 5.13 (dq, 1 H, *J* = 7.6, 7.0 Hz), 6.49 (b d, 1 H, *J* = 7.6 Hz), 7.22–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −5.16, −4.90, 17.77, 22.00, 25.60, 41.18, 43.85, 48.61, 51.54, 66.69, 126.07, 127.19, 128.57, 143.38, 169.15, 171.40; IR (KBr) 3300, 2955, 2856, 1739, 1639, 1558, 1209, 1149, 1099, 1074, 831, 781, 702 cm^{-1}; CIMS *m*/*z* 246, 214 (+ ion), 380 (− ion). Anal. Calcd for $C_{20}H_{33}NO_4Si$: C, 63.29; H, 8.76; N, 3.69. Found: C, 63.40; H, 9.03; N, 3.62.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Acid, Monomethyl Ester, 1-Adamantanamine Salt (11b). To a solution of **9** (12.00 g, 31.7 mmol) in dry carbon tetrachloride (120 mL) at 0 °C under Ar was added anhydrous NaOAc (7.80 g, 95 mmol). N_2O_4 (*caution*! highly toxic!) was slowly bubbled through the mixture at a rate such that all of the gas was taken up by the solution. The reaction was monitored by TLC (Et_2O/hexane (2:1)) until all of the starting material was consumed. Ar was passed through the solution to chase the excess N_2O_4 and the mixture poured onto a ice–water mixture (200 mL). The mixture was extracted with CH_2Cl_2 (200 mL) and the extract dried (Na_2SO_4) and evaporated at rt (rotovap) to a viscous, yellow oil: TLC (Et_2O/hexane (2:1)) R_f 0.76.

The crude nitrosoamide was immediately taken up in dry dioxane (120 mL) and heated at 75–80 °C (bath temperature) under argon for 1 h. Vigorous gas evolution was observed and the yellow color of the nitrosoamide gradually faded to give a colorless solution. Evaporation of the solution gave a approximate 1:1 mixture of acid **11a** and its corresponding 1-phenylethyl ester: TLC (CH_2Cl_2/hexane (3:1)) R_f (**11a**) 0.05, R_f (ester) 0.37, R_f (nitrosoamide) 0.56.

This mixture was immediately taken up in EtOAc (75 mL), treated with 20% $Pd(OH)_2/C$ (1.50 g), and hydrogenated on a Parr apparatus at 35 psi for 20 h. The mixture was filtered through Celite and the filtrate evaporated to dryness. The crude acid **11a** was taken up in hexane (150 mL) and treated with a solution of 1-adamantanamine (4.80 g, 31.8 mmol) in hexane (150 mL). After standing at rt for 3 h, the precipitated product was collected, washed with hexane, and dried in vacuo to give salt **11b** (12.99 g, 96% overall yield) as a fluffy white, crystalline solid: mp 141–142 °C (softens at 128 °C); TLC (MeOH/CH_2Cl_2 (1:9)) R_f 0.51 (free acid **11a**); $[\alpha]_D$ +14.6° (*c* 0.85, MeOH), $[\alpha]_D$ +12.4° (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.84 (s, 9 H), 1.67 (b s, 6 H), 1.84 (b s, 6 H), 2.12 (b s, 3 H), 2.26–2.55 (m, 3 H), 2.79 (dd, 1 H, *J* = 3.5, 14.7 Hz), 3.64 (s, 3 H), 4.52 (m, 1 H), 7.40 (b s, 3 H); ^{13}C NMR ($CDCl_3$) δ −5.07, −4.41, 17.88, 25.68, 28.97, 35.59, 40.74, 40.97, 42.88, 46.88, 50.79, 51.26, 67.64, 172.17, 176.90; IR (KBr) 3500 (b), 2926, 2852, 1739, 1622, 1550, 1520, 1404, 1087, 835, 773 cm^{-1}; CIMS *m*/*z* 428, 294, 277, 152 (+ ion), 551, 275, 226, 152 (− ion). Anal. Calcd for $C_{22}H_{41}NO_5Si$: C, 61.79; H, 9.66; N, 3.28. Found: C, 61.54; H, 9.78; N, 3.16.

(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoic Acid, Methyl Ester (1). To a solution of dimethyl methylphosphonate (10.70 g, 86.2 mmol) in dry THF (100 mL) at −78 °C under Ar was added dropwise a solution of 1.6 M *n*-BuLi in hexane (50.0 mL, 80 mmol). After the mixture was stirred at −78 °C for an additional 1 h (white precipitate forms), a solution of **11b** (10.0 g, 23.4 mmol) in THF (100 mL) was added dropwise. After being stirred at −78 °C for an additional 1.5 h, the reaction mixture was quenched by the dropwise addition of saturated NH_4Cl solution (50 mL) and the mixture allowed to warm to room temperature. The mixture was acidified with 1 N HCl and extracted with EtOAc (300 mL). The organic phase was washed with 1 N HCl/saturated NaCl (1:3; 2X 100 mL) and saturated NaCl solution, dried over Na_2SO_4 and evaporated to give the crude keto phosphonate acid as a colorless oil: TLC (MeOH/CH_2Cl_2 (1:9)) R_f 0.44.

A solution of the crude acid in Et_2O (50 mL), was cooled in an ice bath and treated with ethereal CH_2N_2 in portions until the yellow color of excess CH_2N_2 persisted. Acetic acid was added to discharge the excess CH_2N_2 and the mixture evaporated to dryness. The crude methyl ester was purified by flash chromatography on silica gel, eluting with acetone/hexane (1:4) to give pure **1** (6.955 g, 78%) as a pale yellow, viscous oil: TLC (acetone/hexane (2:3)) R_f 0.31; $[\alpha]_D$ −1.6°, $[\alpha]_{365}$ −3.5° (*c* 2.58, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.84 (s, 9 H), 2.46 (dd, 1 H, *J* = 6.5, 15 Hz), 2.56 (dd, 1 H, *J* = 5.3, 15 Hz), 2.89 (d, 2 H, *J* = 5.9 Hz), 3.11 (d, 2 H, *J* = 22.3 Hz), 3.67 (s, 3 H), 3.788 (d, 3 H, *J* = 11.1 Hz), 3.792 (d, 3 H, *J* = 11.1 Hz), 4.56 (quintet, 1 H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ −5.07, −4.90, 17.79, 25.60, 42.07, 43.35 (d, *J* = 127 Hz), 51.00, 51.49, 52.96 (d, *J* = 4.0 Hz), 65.37, 171.0, 200.0; IR (film) 2956, 2930, 2857, 1739, 1718, 1258, 1052, 1033, 838, 779 cm^{-1}; CIMS *m*/*z* 400, 383 (+ ion) 381 (− ion). Anal. Calcd for $C_{15}H_{31}O_7PSi$: C, 47.11; H, 8.17. Found: C, 46.88; H, 8.27.

(3*S*,1′*S*)-3-Hydroxy-5-[(1-phenylethyl)amino]-5-oxopentanoic Acid, Dicyclohexylamine Salt (8c). To a suspension of acid **8a** (0.650 g, 1.78 mmol) in dry acetonitrile (20 mL) at rt under Ar was added 48% aqueous HF solution (0.36 mL, ca. 10 mmol). After being stirred at rt for 3.5 h, the resulting clear solution was concentrated, diluted with EtOAc (35 mL), and washed with saturated NaCl solution. The organic phase was dried (Na_2SO_4) and evaporated to dryness to give the crude hydroxy acid (0.455 g) as a colorless oil, TLC (MeOH/CH_2Cl_2 (1:9)) R_f 0.13. The crude hydroxy acid was taken up in EtOAc (8.0 mL)/hexane (5.0 mL) and treated with *N*,*N*-dicyclohexylamine (0.37 mL, 1.86 mmol). The resulting white precipitate was collected and air dried to give **8c** (0.752 g, 96% based on hemihydrate) as a white crystalline solid: mp 136–138 °C; $[\alpha]_D$ −31.1° (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.10–1.41 (m, 10 H), 1.47 (d, 3 H, *J* = 7.0 Hz), 1.66 (b m, 2 H), 1.80 (b m, 4 H), 1.99 (b m, 4 H), 2.20–2.45 (m, 4 H), 2.94 (distorted t, 2 H) 4.23 (m, 1 H), 5.13 (quintet, 1 H, *J* = 7.6 Hz), 7.22–7.32 (m, 7 H), 7.47 (d, 1 H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.74, 25.01, 25.44, 29.50, 43.35, 43.61, 48.80, 53.03, 66.19, 126.35, 127.30, 128.79, 144.06, 171.15, 178.07; IR (KBr) 3405 (b), 2938, 2857, 1640, 1576, 1451, 1395, 1059, 700 cm^{-1}; CIMS *m*/*z* 252, 269 (+ ion), 250 (− ion). Anal. Calcd for $C_{25}H_{40}N_2O_4 \cdot 0.5H_2O$: C, 68.00; H, 9.36; N, 6.34. Found: C, 68.33; H, 9.29; N, 6.37.

X-ray Crystal Structure Determination of 9 and 8c. For both analyses: Unit cell dimensions were obtained from least-squares analysis of the angular diffractometer (Enraf-Nonius CAD-4) settings of 25 reflections (2θ = 40–50°). Intensities were measured at 23° using the θ–2θ variable-scan technique (Cu Kα) and corrected only for Lorentz-polarization factors; backround counts were measured at the extremes of the scans for half the

times of the scans. The structures were solved by direct methods and refined by full-matrix least-squares analysis based on F, using the SDP software package.[8] No crystal decomposition was observed during the data collection.

For 9: Crystals of **9** for X-ray analysis were prepared by recrystallization from EtOAc/hexane. The relative stereochemical configurations were readily assigned since all non-hydrogen atoms were evident in Fourier maps. Least-squares refinements of all coordinates and isotropic temperature factors indicate relatively large rotational motion or packing disorder of the phenyl ring and methyl atoms of the silyl and ester groups. By contrast, the intermolecularly hydrogen-bonded amide (N--O distance = 2.92 Å) and backbone atoms are relatively well defined.

For 8c: This salt crystallizes as a monohydrate (thin plates) from moist EtOAc/hexane solvent mixtures. All non-hydrogen atoms were located and refined assuming individual isotropid motions. Fixed hydrogens were introduced at idealized positions consistent with peaks on difference maps. A final difference map contained only some small peaks attributable to anisotropic motion; however, since the number of "observed" intensities was limited, no attempt was made to refine an anisotropic model (only 9% of the intensities measured beyond $2\theta = 100°$ had $I > 3\sigma$). The observed S configuration at the carbinol center (relative to the known S configuration of the phenethylamine moiety) is consistent with the observed crystal structure of **9**. Intermolecular amide hydrogen bonding is similar to that in **9**; the water molecule is hydrogen bonded to the carbinol and carboxyl oxygen atoms.

Supplementary Material Available: Tables of unit cell data, atomic coordinates, and thermal parameters (13 pages). Ordering information is given on any current masthead page.

(8) Structure Determination Package, A. Frenz and associates, College Station, TX 77804.

New Nitrogenous Sesquiterpenes from Two Philippine Nudibranchs, *Phyllidia pustulosa* and *P. varicosa*, and from a Palauan Sponge, *Halichondria* cf. *lendenfeldi*

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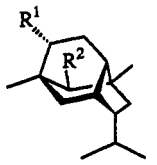
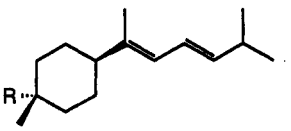
Dorid nudibranchs are shell-less marine molluscs that often contain high concentrations of defensive allomones, which they normally acquire from their sponge diet.[1,2] Nudibranchs of the genus *Phyllidia* are particularly renowned for their toxicity.[3] Hawaiian specimans of *Phyllidia varicosa* contained 9-isocyanopupukeanane (**1**) and 2-isocyanopupukeanane (**2**) (Chart I), both of which were determined to be metabolites of the sponge *Ciocalypta* sp. [ex. *Hymeniacidon* sp.].[4-6] A different isonitrile, 3-isocyanotheonellin (**3**), was isolated from specimens of the same nudibranch from Sri Lanka.[6] Both 9-isocyanopupukeanane (**1**) and its C-9 epimer were obtained from

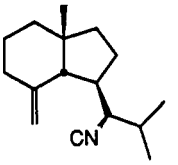
Chart I



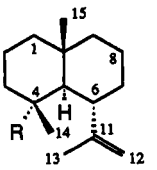
1 R^1 = NC R^2 = H
2 R^1 = H R^2 = NC



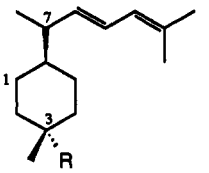
3 R = NC
12 R = NHCHO



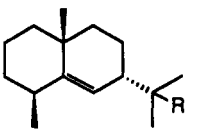
4



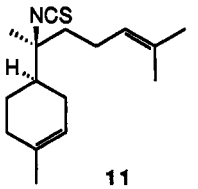
5 R = NC
6 R = NHCHO
7 R = NCS



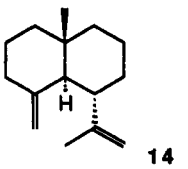
8 R = NC
13 R = NHCHO



9 R = NC
10 R = NCS



11



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the Japanese nudibranch *P. bourguini*.[7] The Mediterranean nudibranch *P. pulitzeri* contained axisonitrile-1 (**4**),[8] which had previously been reported as a metabolite of the sponge *Axinella cannabina*.[9] This paper reports a study of the chemical constituents of Philippine specimens of the nudibranchs *P. varicosa* and *P. pustulosa* and ascribes the origin of some of these metabolites to sponges of the order Halichondrida.

Specimens of both *P. varicosa* and *P. pustulosa* were collected by hand in the channel between Negros Island and Cebu Island and from shallow waters off San Sebastian, Cebu. Despite their abundance in these habitats, they were never encountered on sponges but were always found "swimming" in the water column or crawling over the sand bottom. Each species of nudibranch was stored separately in acetone. The acetone extracts were subjected to a standard separation procedure that involved flash chromatography on silica gel followed by HPLC to obtain pure compounds. Four specimens of *P. varicosa* yielded the novel compounds, 4α-isocyanogorgon-11-ene (**5**, 0.85 mg/animal) and 4α-formamidogorgon-11-ene (**6**, 0.28 mg/animal). Extraction of 19 specimens of *P. pustulosa* gave the novel metabolites, 4α-isocyanogorgon-11-ene (**5**, 2.33 mg/animal), 4α-formamidogorgon-11-ene (**6**, 0.57

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