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Scott C. Mayer [a] & Madeleine M. Joullié [a]
[a] Department of Chemistry , University of Pennsylvania , Philadelphia, Pennsylvania, 19104-6323
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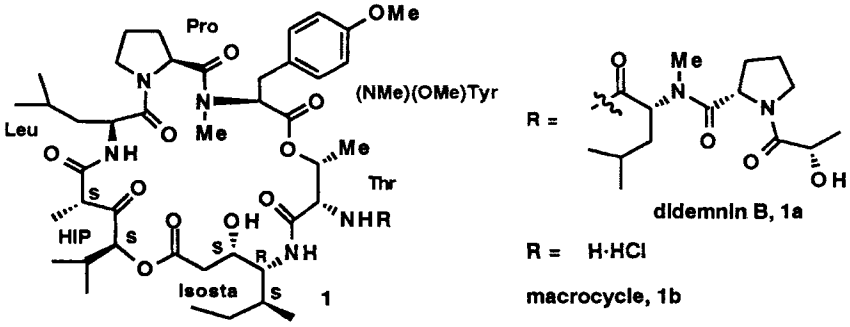
ESTERIFICATION *via* ACID FLUORIDE ACTIVATION

Scott C. Mayer and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania
Philadelphia, Pennsylvania 19104-6323

Abstract: *The esterification of sterically hindered or non-nucleophilic alcohols may often be problematic. The reaction of alcohols with acid fluorides is reported to be superior to standard acid activation protocols frequently used for difficult esterifications. The acid fluoride methodology was used to produce a hindered linkage between a secondary alcohol (4) and a cyclohexyl amino acid 3, a key intermediate in the formation of a constrained ring didemnin analog.*

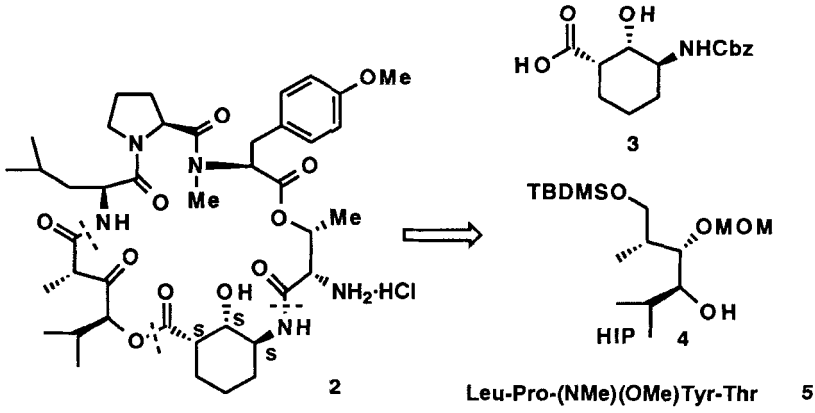


The didemnins (**1**) are a class of biologically active cyclodepsipeptides isolated from a marine tunicate, which have shown considerable antitumor, antiviral, and immunosuppressive activity.[1] Of all the congeners tested so far, didemnin B (**1a**), is the most active.[2-7] We are synthesizing a constrained ring

*To whom correspondence should be addressed

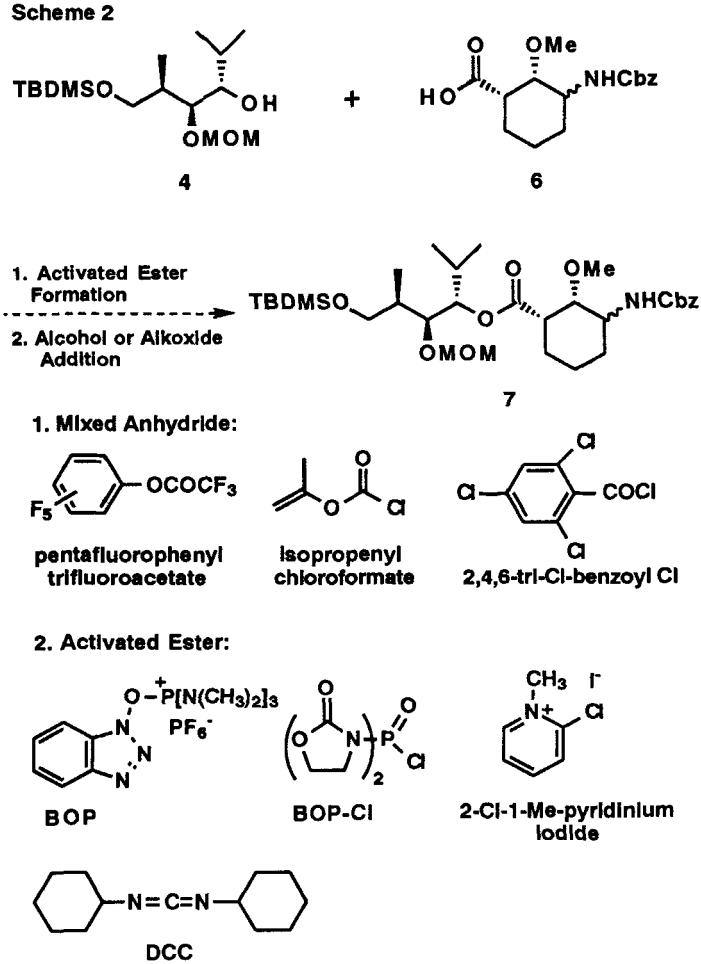
analog (**2**) of this natural product in order to determine the effect of modifying the isostatine hydroxyl group, a structural feature of the macrocycle deemed important for the bioactivity.[8,9] A cyclohexyl amino acid in place of the more flexible isostatine portion should produce a more rigid and structurally stable conformation, a fused ring system (**2**), which could allow for the assessment of the binding site/conformation relationships in the biologically active product. It has been reported that some peptide-like compounds in which (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid (statine) was replaced with (3S,4S)-4-amino-3-hydroxy-5-cyclohexylpentanoic acid exhibited more promising bioactivity as antihypertensive agents.[10-12] A retrosynthetic analysis of the proposed didemnin analog **2** is shown in **Scheme 1**.[13]

Scheme 1



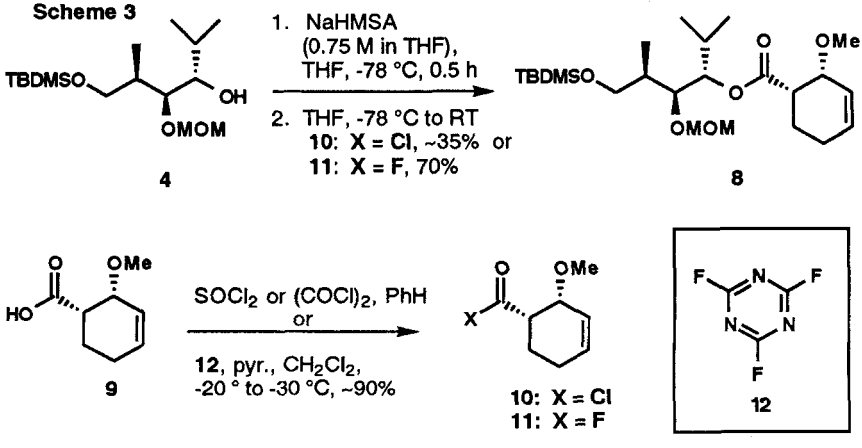
A considerable amount of time was spent investigating conditions suitable for the esterification of the α-(α-hydroxyisovalery)propionyl unit (HIP-alcohol, **4**) with the cyclohexyl amino acid **6** (diastereomeric mixture)[8,9] (**Scheme 2**). Initially, activation of the acid constituent and displacement by the HIP alcohol moiety seemed feasible. The preparation of a mixed anhydride for activation of the

carboxylic acid was attempted with several reagents such as pentafluorophenyl trifluoroacetate,[14] isopropenyl chloroformate (IPCF),[15,16] and 2,4,6-trichlorobenzoyl chloride.[17] Alternatively, the synthesis of activated esters using reagents such as dicyclohexylcarbodiimide (DCC),[18] 2-chloro-1-methyl-pyridinium iodide,[19] N,N-bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl),[20] and 1H-1,2,3-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate



(BOP)[21] were applied to what appeared to be a trivial step, but none of these reagents could accomplish the desired transformation. Only starting materials and in some cases the activated esters (using BOP or DCC) were isolated. Even after varying the amount of the tertiary amine and increasing the catalytic amount of DMAP to stoichiometric amounts,[22] no esterification was observed. The substitution of Bu_3P for the tertiary amine to increase carbonyl activation, as reported by Vedejs,[23] was also unsuccessful. Using isopropyl alcohol instead of the HIP alcohol, esterification could be achieved with the BOP activated ester. Therefore, it appeared that the lack of reactivity was due to the HIP alcohol either because of steric effects or insufficient nucleophilicity. Finally, an ester (**8**), the product of the HIP alkoxide and the acid chloride of the precursor acid **9**, was obtained in modest yield (**Scheme 3**).

Scheme 3



At this point the acid fluoride coupling of amino acids reported by Carpino[24,25] was examined. Acid fluorides (i.e. **11**) are obtained by treating a carboxylic acid (**9**) with cyanuric fluoride (**12**) at low temperatures. Acid fluorides are isolated more easily than acid chlorides, especially at microscale levels and are

often solids. They can be stored for extended periods of time in dry locations, and are more reactive in bond forming reactions. Initially, the alkoxide of the HIP alcohol was added to the acid fluoride (**11**) of 2-methoxy-3-cyclohexenyl-1-carboxylic acid to obtain the ester **8** in 70% yield (**Scheme 3**). To convert the alcohol to its corrresponding alkoxide, several bases were used, and to date sodium hexamethyldisilylazide proved to be the best. Presently, investigations of the coupling of the acid fluoride of **6** with the HIP alkoxide are being carried out. The results will be reported in a full paper after this esterification reaction and coupling to the tetrapeptide are completed.

Conclusions:

Esterification of a hindered alcohol (HIP unit, **4**) has been accomplished using the acid fluoride coupling method of Carpino.[24,25] Standard coupling procedures were unsuccessful because of steric hindrance and weak nucleophilicity of the secondary alcohol. This recently described strategy[24,25] was superior to all reported esterification procedures and will be applied to the coupling of **4** and **3**. The new methodology offers great potential as an alternative to typical activation protocols.

Experimental

General : All manipulations were conducted under an inert atmosphere (argon or nitrogen). All solvents were reagent grade. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). Organic acids and bases were reagent grade. All the other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F-254), plates (0.25 mm), precoated with a fluorescent indicator (0.50 mm plates

were used for preparatory thin-layer chromatography). Visualization was effected with ultraviolet light, phosphomolybic acid reagent (7% w/v) in absolute ethanol, and anisaldehyde reagent (5% v/v) in absolute ethanol containing 5% sulfuric acid and 1% acetic acid. Flash column chromatography was carried out on Merck silica gel 60 particle size (0.040-0.063 mm). Proton and carbon magnetic resonance spectra (^{1}H-, ^{13}C-NMR) were recorded on a Bruker AM-500 (500 MHz) Fourier transform spectrometer using $CDCl_3$ as the solvent. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS-0 ppm) or $CHCl_3$ as an internal reference (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), doublet of quartets (dq),triplet (t), triplet of doublets (td), quartet (q), and multiplet (m). Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281-B or Perkin-Elmer Model 781 spectrometers. Oils were analyzed as neat films between sodium chloride plates. Absorptions are reported in wave numbers (cm^{-1}), and their intensities are designated as strong (s), medium (m), or weak (w). The spectra are calibrated against the 1601 cm^{-1} band of a polystyrene film, and only the most prominent or characteristic absorptions are noted. Optical rotations (in degrees, °) were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line. High resolution mass spectra (HRMS) were obtained on either a VG 70-70HS [a high resolution double focusing mass spectrometer using ammonia Chemical Ionization (CI) or Electron Impact (EI)] or a ZAB-E [using Fast Atom Bombardment (FAB), CI or EI]. The mass spectrometer was interfaced to VG/DEC 11-73 data systems.

(1S,2R)-2-Methoxy-3-cyclohexenyl-1-carboxylic acid (9). To 2-hydroxy-3-cyclohexenyl-1-carboxylic acid[8] (2.44 g, 17.2 mmol), at ambient temperature, was added THF (98 mL). Finely powdered KOH (9.69 g, 173 mmol)

was added in small portions, followed by the addition of tetrabutylammonium hydrogen sulfate (0.244 g, 0.719 mmol, 10% by weight). At this point rapid stirring was initiated and dimethyl sulfate (9.90 mL, 104 mmol, 13.2 g) was added dropwise over a 15 min period. The reaction was stirred for 1 h, cooled to 0 °C, and H_2O (98 mL) added. After 1 h at 0 °C and 18 h at rt, the excess dimethyl sulfate was quenched with 10% NH_4OH (stirred ~15 min). The solution was concentrated to half volume and diluted with Et_2O (20 mL). The aqueous layer was separated, and the resulting organic layer was extracted with saturated $NaHCO_3$ (2 x 15 mL). The aqueous layers were then combined, acidified with 2N $KHSO_4$ to pH 1, and extracted with EtOAc (3 x 80 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography eluting with methanol:chloroform (10:90) to afford **9** (2.49, 93% yield) as a yellow oil; R_f 0.46 (10:90-methanol:chloroform); ^1H NMR (500 MHz, $CDCl_3$) δ 1.88-2.06 (m, 3H), 2.22-2.29 (m, 1H), 2.66 (dt, J=3.9, 15.3 Hz, 1H), 3.43 (s, 3H), 4.06 (d, J=3.6 Hz, 1H), 5.98 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 24.8, 44.4, 57.0, 72.7, 124.4, 132.3, 178.4; IR (neat) 3520 (w), 3040 (s), 3000 (s), 2940 (s), 2830 (m), 2350-3450 (s), 1745 (s), 1710 (s), 1450 (m), 1415 (m), 1300 (m), 1230 (m), 1185 (m), 1150 (w), 1130 (w), 1080 (s), 980 (w), 965 (w), 930 (m), 905 (m), 870 (w), 810 (w) cm^{-1}; HRMS *m/z* calcd for $C_8H_{13}O_3$ (M+H): 157.0864, found 157.0855; $[\alpha]_D^{20}$ -201° (c=2.16, $CHCl_3$).

(1S,2S,3R)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-2-(methoxymethoxy)-3-methylbutyl (1S,2R)-2-methoxy-3-cyclohexene-1-carboxylate (8). To a solution of acid **9** (50.0 mg, 0.320 mmol) in CH_2Cl_2 (2.5 mL) between -20 to -30 °C was added pyridine (25.9 μL, 0.320 mmol), followed by cyanuric fluoride (86.5 μl, 0.960 mmol) dropwise. The reaction was kept at this temperature for 1 h, followed by addition of crushed ice (2 g) and

additional CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with ice cold H_2O (1 mL), dried ($MgSO_4$), filtered, and concentrated to afford the acid fluoride **11**. In another flask a solution of **4** (20.0 mg, 62.4 μmol) in THF (1.0 mL) was prepared and cooled to -78 °C. Sodium hexamethylsilylazide (1.0 mL 0.75 M in THF) was added dropwise, and the mixture stirred at -78 °C for 30 min. The acid fluoride (**11**) in THF (1.0 mL) was added at this temperature and stirred for 15 min and then at rt for 18 h. The solution was concentrated to an oily residue and diluted with EtOAc (20 mL). The organic solution was washed with 5% HCl (2 mL), 5% $NaHCO_3$ (2 mL), and saturated NaCl (2 mL) solutions, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography eluting with ethyl acetate:petroleum ether (4:96) to afford **8** (18.6 mg, 70% yield) as a clear oil; R_f 0.29 (5:95-ethyl acetate:petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 0.90-0.95 (m, 9H), 1.78-1.85 (m, 1H), 1.91-1.97 (m, 3H), 1.98-2.05 (m, 1H), 2.23 (d, J=17.2 Hz, 1H), 2.60 (m, 1H), 3.34 (s, 3H), 3.35 (s, 3H), 3.50-3.53 (m, 2H), 3.81 (q, J=3.6 Hz, 1H), 4.03 (t, J=4.1 Hz, 1H), 4.64 (dd, J=6.5, 23.4 Hz, 2H), 5.05 (td, J=0.9, 4.6 Hz, 1H), 6.00 (ddd, J=4.7, 10.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.4, -5.3, 11.2, 16.3, 18.2, 18.8, 19.6, 25.4, 25.9, 28.9, 37.3, 45.7, 56.0, 56.7, 65.1, 72.5, 78.3, 78.9, 98.6, 124.8, 132.3, 172.7; IR (neat) 3040 (m), 2860-2990 (s), 2825 (m), 1735 (s), 1605 (w), 1465 (m), 1390 (m), 1375 (w), 1365 (w), 1340 (w), 1280 (m), 1255 (s), 1230 (s), 1160 (s), 1140 (s), 1110 (s), 1090 (s), 1040 (s), 985 (w), 920 (m), 880 (w), 840 (s), 815 (w), 775 (m), 735 (w), 715 (w), 665 (w) cm^{-1}; HRMS *m/z* calcd for $C_{23}H_{43}SiO_5$ (M-OMe): 427.2780, found 427.2803; $[\alpha]_D^{20}$ -78.3° (c=0.687, $CHCl_3$). The HIP-alcohol (**4**) was recovered in 20% yield.

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