Actinofuranones A and B, Polyketides from a Marine-Derived Bacterium Related to the Genus *Streptomyces* (Actinomycetales)[⊥]

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Two new polyketides, actinofuranones A (**1**) and B (**2**), were isolated from the culture extract of a marine-derived *Streptomyces* strain designated CNQ766. The structures of **1** and **2** were elucidated by interpretation of NMR and other spectroscopic data and by chemical derivatization. The relative stereochemistries of these new molecules were assigned on the basis of analysis of NOE data and vicinal $^1H-^1H$ coupling constants, while the absolute configurations of the asymmetric centers were determined using the modified Mosher's method.

Actinomycetes are common soil bacteria that possess an unparalleled ability to produce structurally diverse secondary metabolites. These compounds often serve as leads for the development of new pharmaceuticals and remarkably account for approximately 120 of the drugs with clinical applications.[1] The recent discovery of numerous phylogenetically unique groups of actinomycetes from marine sediments,[2] coupled with the isolation of structurally novel secondary metabolites from these new sources, clearly adds an important new dimension to microbial natural products research.[3,4] In particular, we recently reported the cultivation from marine sediments of what appears to be a new actinomycete taxon (family Streptomycetaceae) that we have tentatively called MAR4.[2a] Chemical studies of MAR4 strains are now providing several new secondary metabolites including antibiotic terpenoid chloro-dihydroquinones.[5] Interestingly, MAR4 strains share a common biosynthetic theme in that they consistently produce rare, hybrid secondary metabolites of mixed polyketide/terpenoid origin. This observation is further supported by the analysis of strains producing compounds in the marinone series[6] and the recognition that they too belong to the MAR4 group.

In this paper, we report the isolation of two new secondary metabolites from a MAR4 strain, CNQ766, cultured from a sediment sample collected from Guam. In saline culture, this strain produces several compounds of mixed polyketide/terpenoid origin structurally related to the antibiotic A80915C[5] and two new polyketides, actinofuranones A (**1**) and B (**2**), the structures of which were elucidated by chemical and spectroscopic methods.

Strain CNQ766 was cultured at 27 °C by rotary shaking in replicate 2.8 L Fernbach flasks each containing 1 L of culture medium. Cultures were extracted using Amberlite XAD-7 resin, and the resin was eluted with acetone. The crude extract obtained after solvent removal (3.2 g from 30 L) was subjected to C_{18} flash column chromatography, followed by reversed-phase HPLC on a C_8 Betasil column, to yield actinofuranones A (**1**) and B (**2**) in 15 and 1.5 mg, respectively. Actinofuranones A and B each showed weak in vitro cytotoxicity against mouse splenocyte T-cells and macrophages with IC_{50} values of 20 μg/mL.[7]

Actinofuranone A (**1**) was isolated as an optically active yellow oil ($[\alpha]_D$ −20, CH_3OH). A molecular formula of $C_{22}H_{34}O_5$ was confirmed by high-resolution mass spectrometric data that showed a pseudomolecular ion at *m/z* 401.2300 $[M + Na]^+$. The molecular formula indicated actinofuranone contained six double-bond equivalents, which by interpretation of NMR data (Table 1) could be attributed to four carbon−carbon double bonds (C-4/C-5, C-10/C-11, C-12/C-13, and C-16/C17), one carbonyl carbon at δ_C 202.7 (C-3), and one ring system. Other preliminary structural data that could be obtained from the IR spectrum were the presence of hydroxyl and carbonyl functional groups (absorptions at 3368 and 1694 cm^{-1}, respectively). The ^1H NMR spectrum revealed the presence of six methyl groups [H_3-1 (δ_H 1.38), H_3-18 (δ_H 1.59), H_3-19 (δ_H 1.61), H_3-20 (δ_H 1.73), H_3-21 (δ_H 0.84), and H_3-22 (δ_H 1.55)], three methylenes [H_2-6a/6b (δ_H 2.59/2.66), H_2-8 (δ_H 1.58), and H_2-9 (δ_H 2.14)], and seven methine proton signals [H-7 (δ_H 3.87), H-11 (δ_H 5.84), H-12 (δ_H 6.30), H-13 (δ_H 5.53), H-14 (δ_H 2.32), H-15 (δ_H 3.60), and H-17 (δ_H 5.40)]. The ^{13}C NMR spectrum showed the presence of one carbonyl carbon (C-3), one quaternary hemiketal carbon (C-2), and four sp^2 quaternary carbons (C-4, C-5, C-10, and C-16).

The full planar structure of **1** was assigned through interpretation of 1D and 2D NMR spectroscopic data recorded in CD_3CN (Table 1). From the $^1H-^1H$ COSY spectrum, three fragments were established. The first fragment, constructed on the basis of a cross-peak between H-17 and H_3-18, was a two-carbon unit consisting of a terminal methyl group attached to a sp^2-hybridized methine. A second fragment, consisting of five methine protons (H-11 to H-15), showed a series of correlations that established a hydroxyl group at C-15 ($^1H-^1H$ COSY correlation between H-15 and the hydroxyl proton at δ_H 2.50). These data established a five-carbon fragment possessing a secondary hydroxyl group. For the third fragment, cross-peaks were observed between the methylene protons H_2-6 and H-7, which showed $^1H-^1H$ COSY correlations to a hydroxyl proton signal at δ_H 2.95 and to H_2-8. Finally, a cross-peak between H_2-8 and H_2-9 was also observed, which established a second four-carbon fragment also possessing a secondary hydroxyl group.

Interpretation of HMBC NMR data allowed the $^1H-^1H$ COSY-defined fragments of **1** to be connected as shown in Figure 1. The first two fragments were connected to the quaternary carbon C-16 on the basis of HMBC correlations from the methyl proton at δ_H 1.55 (H_3-22) to the carbons C-16, C-17, and C-15. This unit was then expanded to include another three-carbon unit based on HMBC NMR correlations from the methyl proton signal at δ_H 1.73 (H_3-20). Specifically, H_3-20 showed correlations to the quaternary carbon C-10 and the methine carbon C-11, which, along with the above data, connected C-11 of the second fragment to C-9 of the third unit through the olefinic quaternary carbon (C-10). Furthermore, the methyl proton signal at δ_H 1.61 (H_3-19) showed HMBC correlations to the olefinic carbons (C-4, C-5) and to the carbonyl carbon (C-3). Finally, the methyl proton at δ_H 1.38 (H_3-1) showed HMBC correlations to the quaternary hemiketal carbon (C-2) and

[⊥] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

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Table 1. NMR Spectroscopic Data for Actinofuranone A (**1**) in CD_3CN

C/H #	δ_H (*J* Hz)	δ_C		COSY	HMBC	1D-NOE[a]
1	1.38 s	22.3	CH_3		C-2, C-3	
2		102.9	C			
3		202.7	C			
4		109.6	C			
5		184.7	C			
6a	2.59 dd (14.5, 5.0)	37.9	CH_2	6b, 7	C-4, C-5, C-7, C-8	
6b	2.66 dd (14.5, 7.5)			6a, 7	C-4, C-5, C-7, C-8	
7	3.87 m	69.2	CH	6, OH-7, 8		
8	1.58 m	36.1	CH_2	9		
9	2.14 m	36.3	CH_2	8	C-8, C-10, C-11, C-20	
10		137.2	C			
11	5.84 d (11.0)	126.1	CH	12	C-9, C-12, C-13, C-20	
12	6.30 dd (15.0, 11.0)	127.8	CH	11, 13	C-11, C-13, C-14	20
13	5.53 dd (15.0, 8.5)	136.3	CH	12, 14	C-11, C-14, C-21	15
14	2.32 m	41.7	CH	13, 15, 21	C-12, C-13, C-15, C-21	22
15	3.60 dd (8.5, 3.5)	82.4	CH	14, OH-15	C-17	13, 17, 21
16		138.0	C			
17	5.40 q (7.0)	122.0	CH	18	C-15, C-22	15, 21
18	1.59 d (7.0)	13.1	CH_3	17	C-16, C-17	22
19	1.61 s	5.9	CH_3		C-3, C-4, C-5	
20	1.73 s	16.6	CH_3		C-9, C-10, C-11	12
21	0.84 d (6.5)	17.8	CH_3	14	C-13, C-14, C-15	15, 17
22	1.55 s	11.1	CH_3		C-15, C-16, C-17	14, 18
OH-2	5.03 br s					
OH-7	2.95 br s			7		
OH-15	2.50 d (3.5)			15		

[a] These are 1D-NOE correlations of selected protons used to assign relative stereochemistry.

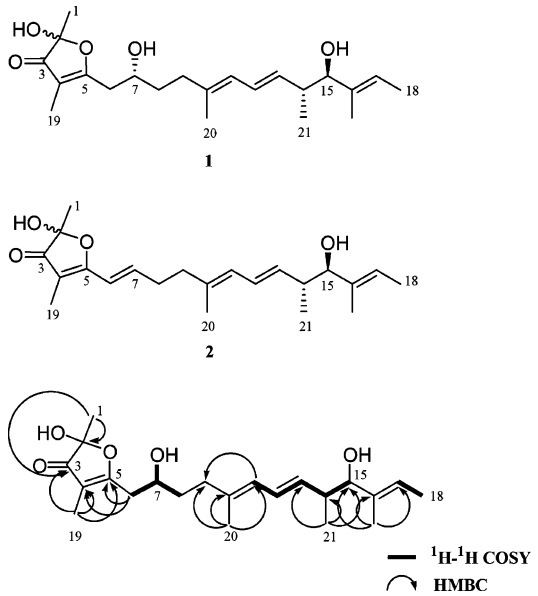

Figure 1. Key $^1H-^1H$ COSY and HMBC data of **1**.

to the carbonyl carbon (C-3). These data, and an HMBC correlation between H_2-6 and C-5, established the five-membered ring as 2,4-dimethylfuran-4-en-3-one, with the linear chain connected at C-5.

The relative stereochemistry of actinofuranone A was assigned by analysis of vicinal proton−proton coupling constants and by NOE difference NMR measurements. From the magnitude of the $^3J_{HH}$ vicinal coupling constants (8.5 Hz) between H-14 and H-15, these two protons were assigned an *anti* configuration.[8] This is consistent with the data for 4-methylhex-1,4-dien-3-ol, in which the $^3J_{H,H}$ coupling constants for the *syn* and *anti* configurations are between 5.5 and 6.5 and 7.5−9.0 Hz, respectively.[9] 1D-NOE correlations were also observed from H-14 to H_3-22 and from H_3-21 to both H-17 and H-15. These data indicated that H-15 was *gauche* to both C-16 and the methyl group H_3-21, thus establishing the relative configuration of the C-14/C-15 stereocenters. The double-bond configuration was also assigned by NOE NMR experiments. Irradiation at the resonance frequency of H_3-20 caused an NOE enhancement of the H-12 signal, and irradiation of H_3-22 resulted in an enhancement of H_3-18, indicating actinofuranone A possesses 10*E* and 16*E* double-bond geometries. The geometry of the remaining C-12−C-13 double bond was assigned as 12*E* on the basis of the classical *trans* vicinal coupling constant (15.0 Hz) between H-12 and H-13.

Actinofuranone B (**2**) was isolated by the same purification procedure as described for **1**. The structure of compound **2** was also determined by analysis of 1D and 2D NMR spectroscopic data recorded in CD_3CN (Table 2). The molecular formula of actinofuranone B, $C_{22}H_{32}O_4$, which indicated 7 degrees of unsaturation, was determined by HR-ESI-TOFMS on the basis of a pseudomolecular ion peak $[M + Na]^+$ at *m*/*z* 383.2212. The NMR data for **2**, including chemical shifts and coupling constants, were almost identical to **1** (Table 2). From the ^1H NMR spectrum, six methyl groups [H_3-1 (δ_H 1.39), H_3-18 (δ_H 1.59), H_3-19 (δ_H 1.67), H_3-20 (δ_H 1.76), H_3-21 (δ_H 0.84), and H_3-22 (δ_H 1.55)], two methylene groups [H_2-8 (δ_H 2.44) and H_2-9 (δ_H 2.23)], and eight methine groups [H-6 (δ_H 6.49), H-7 (δ_H 6.72), H-11 (δ_H 5.86), H-12 (δ_H 6.30), H-13 (δ_H 5.56), H-14 (δ_H 2.32), H-15 (δ_H 3.60), and H-17 (δ_H 5.40)] were observed. From the ^{13}C NMR spectrum, one quaternary hemiketal carbon (C-2) and two olefinic quaternary carbon (C-10, C-16) signals were observed, while one carbonyl carbon (C-3) and two more olefinic quaternary carbons (C-4, C-5) could be assigned from the HMBC NMR spectrum. Comparison of the NMR data for **2** with those of **1** indicated the presence of a double bond at C-6 and C-7; thus the gross structure was assigned as the 6,7-dehydration product of actinofuranone A.

As in **1**, the relative stereochemistry of actinofuranone B was deduced by analysis of vicinal proton−proton coupling constants and by interpretation of NOE difference spectroscopic data. The relative configuration of C-14/C-15 was assigned on the basis of a large $^3J_{HH}$ vicinal coupling constant (8.5 Hz) between H-14 and H-15 and on the basis of NOE correlations between H-14/H_3-22, H_3-21/H-17, and H_3-21/H-15. These data indicated the methyl group (H_3-21) was on the same side as the C-16/C-17 double bond. The geometry of the olefinic bonds was assigned as 10*E*, 16*E* on the basis of NOE correlations between H_3-20 and H-12 and between H_3-22 and H_3-18, respectively, while H-6/H-7 and H-12/H-13 were assigned an *E* configuration due to their large vicinal coupling constants.

Table 2. NMR Spectral Data for Actinofuranone B (**2**) in CD_3CN

C/H #	δ_H (*J* Hz)	δ_C		COSY	HMBC	1D-NOE[b]
1	1.39 s	22.3	CH_3		C-2, C-3	
2		102.7	C			
3		202.5[a]	C			
4		109.6[a]	C			
5		178.2[a]	C			
6	6.49 d (16.0)	118.9	CH_2	7	C-5, C-8	
7	6.72 dd (16.0, 6.5)	143.4	CH	6, 8	C-5, C-8	
8	2.44 td (7.0, 6.5)	32.1	CH_2	7, 9	C-6, C-8, C-9	
9	2.23 t (7.0)	38.9	CH_2	8	C-7, C-8, C-10, C-11, C-20	
10		136.8	C			
11	5.86 d (11.0)	126.5	CH	12	C-9, C-12, C-13, C-20	
12	6.30 dd (15.0, 11.0)	127.6	CH	11, 13	C-11, C-13, C-14	20
13	5.56 dd (15.0, 8.5)	136.8[a]	CH	12, 14	C-11, C-14, C-21	
14	2.32 sept (8.5)	41.6	CH	13, 15, 21	C-12, C-13, C-21, C-15	22
15	3.60 dd (8.5, 3.5)	82.4	CH	14, OH-15	C-17	21
16		138.1[a]	C			
17	5.40 q (6.5)	122.0	CH	18	C-15, C-22	21
18	1.59 d (6.5)	13.1	CH_3	17	C-16, C-17	22
19	1.67 s	5.6	CH_3		C-3, C-4, C-5	
20	1.76 s	16.5	CH_3		C-9, C-10, C-11	12
21	0.84 d (6.5)	17.8	CH_3	14	C-13, C-14, C-15	15, 17
22	1.55 s	11.0	CH_3		C-15, C-16, C-17	14, 18
OH-2	4.95 br s					
OH-15	2.44 d (3.5)			15		

[a] The chemical shifts of these resonances were assigned from the HMBC spectrum. [b] These are 1D-NOE correlations of selected protons used to assign relative stereochemistry.

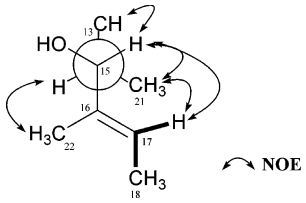

Figure 2. NOE correlations used to establish the relative configuration of **1**.

One other comment is necessary regarding the NMR assignments of the structures of **1** and **2**. In the ^{13}C NMR spectrum of **1** the carbon signals for C-4 and C-5 were doubled at δ_C 109.61/109.63 and 184.65/184.69. These data were consistent with actinofuranone A existing as a 1:1 mixture of epimers at the C-2 hemiketal center. This has been previously reported for other compounds that contain a similar functional group.[10,11] For compound **2**, due to small sample size and a comparably poor signal-to-noise ratio in the ^{13}C NMR spectrum, the chemical shifts of C-4 and C-5 were derived from the HMBC spectrum; thus doubling was not observed.

The absolute stereochemistries of the hydroxyl-bearing carbons in **1** (C-7 and C-15) were determined by the advanced Mosher method.[12] The Mosher method is based on using the diamagnetic effect of an introduced phenyl ring to assign the absolute stereochemistry of an enantiopure organic compound by comparing the NMR data of the diastereomeric MTPA ester derivatives.[12] Treatment of **1** with (*R*)- and (*S*)-MTPA-Cl [α-methoxy-α-(trifluoromethyl)phenylacetyl chloride] gave the (*S*)- and (*R*)-MTPA ester derivatives in good yields. The mono-(*S*)- and (*R*)-MTPA esters (**3** and **4**) and di-(*S*)- and (*R*)-MTPA esters (**5** and **6**) were purified by RP-HPLC, and their ^1H NMR spectra were obtained. In the ^1H NMR spectra of the mono-Mosher ester derivatives positive $\Delta\delta_{S-R}$ ($\delta_S - \delta_R$) values were observed for H-11 (+0.12), H-12 (+0.14), H-13 (+0.13), and H_3-20 (+0.06), while negative $\Delta\delta_{S-R}$ values were observed for H-7 (−0.01), H-17 (−0.06), and H_3-22 (−0.23). From the di-Mosher ester derivative,[13] positive $\Delta\delta_{S-R}$ values were observed for H-11, H-12, H-13, H_3-20, and H_3-21, while negative $\Delta\delta_{S-R}$ values were observed for H-1, H-6, H-17, H_3-18, H_3-19, and H_3-22 (Figure 3). These data allowed assignment of the absolute configurations of C-7 and C-15 as 7*R* and 15*R*.

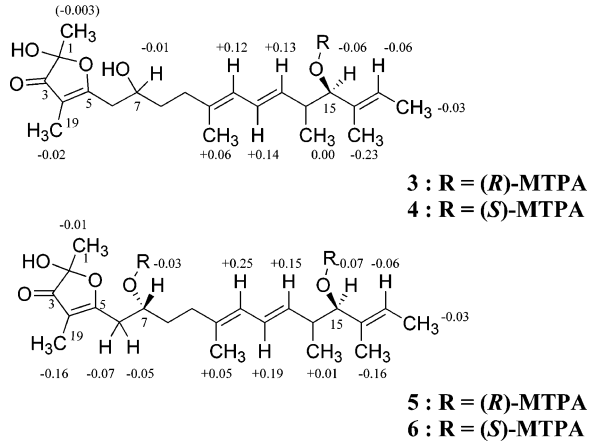

Figure 3. $\Delta\delta_{S-R}$ values for mono-MTPA derivatives (**3** and **4**) and di-MTPA derivatives (**5** and **6**) derived from actinofuranone A.

The absolute stereochemistry of C-15 in **2** was determined to be 15*R* also by application of the advanced Mosher method. Positive $\Delta\delta_{S-R}$ values were observed for H-11 (+0.11), H-12 (+0.13), and H-13 (+0.13), while negative $\Delta\delta_{S-R}$ values were observed for H-15 (−0.06), H-17 (−0.07), H_3-18 (−0.04), and H_3-22 (−0.001).

Actinofuranones A and B are relatively rare polyketides possessing a 3-furanone ring system with a C-2-hemiketal and a C-5 unsaturated alkyl chain. The closest related structures, siphonarienfuranone[14] and aglajne,[15] are not of microbial origin, but were isolated from marine invertebrates. These compounds are furanones that have a hemiketal at C-2 and are decorated with alkyl chains at C-5. Not unexpectedly, these related structures also exist as a mixture of epimers at the hemiketal stereocenter. Also a series of closely related 3-furanones, the aurafurons, have recently been reported from a strain of terrestrial myxobacteria.[10] The finding of structurally related compounds from a variety of sources, especially in the case of marine invertebrates, is often used as circumstantial evidence to suggest that these compounds are acquired by the invertebrate from a microbial symbiont[16] or through diet.[17] In this case though, given their relatively simple polyketides structures, the occurrence of this class of compounds in three different

organisms may simply be due to the coincident coevolution of these biosynthetic pathways in response to a similar environmental pressure.

Experimental Section

General Experimental Procedures. The optical rotations were measured on an Autopol automatic polarimeter (Rudolph Research, Flanders, NJ). UV spectra were measured on a Varian Cary UV−visible spectrophotometer. IR spectra were obtained with a Perkin-Elmer 1600 Series FTIR spectrophotometer as a film on a NaCl disk. ^{1}H and ^{13}C NMR spectra were obtained in CD_3CN on a Varian Inova spectrometer at 500 and 125 MHz, respectively. HR-ESI-TOFMS data were obtained at The Scripps Research Institute, La Jolla, CA. Reversed-phase HPLC separations were performed using a semipreparative C_8 Betasil column (250 × 10 mm) at a flow rate of 2 mL/min using a Waters pump and a Knauer variable UV detector.

Collection and Cultivation of Strain CNQ766. The bacterium, strain CNQ766, was cultured from a marine sediment sample collected from a depth of 500 m off the island of Guam in 2002. On the basis of an NCBI BLAST analysis of the 16S RNA gene sequence of this strain (GenBank accession number AY464546), it shares no more than 97.8% sequence identity with previously reported *Streptomyces* sp. and thus may represent a new species within the genus. Strain CNQ766 was cultured in 30 replicate 2.8 L Fernbach flasks each containing 1 L of fermentation medium CKA (5 g of starch, 4 mL of 50% hydrolyzed fish solubles, 2 g of menhaden meal, 2 g of kelp powder, 2 g of chitosan in 1 L of seawater) for 7 days at 28 °C, after which XAD-7 resin (ca. 20 g/L) was added to the culture and shaking was continued for 3 h. After 3 h, the resin from 1 L was filtered through cheesecloth and washed with 1 L of deionized water to remove salts. Next, the filtered resin was eluted with acetone to yield the crude extract. Removal of solvent under vacuum gave 3.2 g of crude extract (from 30 L overall).

Isolation of Actinofuranones A and B (1 and 2). The crude extract (3.2 g) was adsorbed onto diatomaceous earth (Celite) and subjected to C_{18} reversed-phased flash chromatography eluting with a step gradient from 20 to 100% methanol in water. Compounds **1** and **2** were observed in the 60% methanol/water fraction and were subsequently purified by reversed-phase HPLC chromatography using a C_8 Betasil column (250 × 10 mm) eluting with 55% acetonitrile at a flow rate of 2 mL/min with UV detection at 254 nm. Actinofuranone A (**1**) eluted at 18 min (**1**, 15 mg, 0.47% yield) and actinofuranone B (**2**) eluted at 68 min (**2**, 1.5 mg, 0.047% yield).

Actinofuranone A (1): yellow oil; $[\alpha]_D$ −20 (*c* 0.1, CH_3OH); IR (thin film) ν_{max} 3368, 2926, 1694, 1378, 1266, 1017, 960 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 241 (4.0), 282 (3.8) nm; ^{1}H NMR (500 MHz, CD_3CN) and ^{13}C NMR (125 MHz, CD_3CN), see Table 1; HR-ESI-TOFMS *m*/*z* $[M + Na]^+$ 401.2300 ($C_{22}H_{34}O_5Na$, calcd 401.2303).

Actinofuranone B (2): yellow oil; $[\alpha]_D$ −37 (*c* 0.075, CH_3OH); IR (thin film) ν_{max} 3395, 2930, 1697, 1633, 1446, 1418, 1377, 1225, 1016, 958 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 241 (4.0), 317 (3.7) nm; ^{1}H NMR (500 MHz, CD_3CN) and ^{13}C NMR (125 MHz, CD_3CN), see Table 2; HR-ESI-TOFMS *m*/*z* $[M + Na]^+$ 383.2212 ($C_{22}H_{32}O_4Na$, calcd 383.2198).

Preparation of Mosher Ester Derivatives. Actinofuranone A (**1**, 0.5 mg) was dissolved in dry CH_2Cl_2 (1 mL) in a HPLC vial (8 mL capacity) that was capped with a septum. To this was added 1 mg of DMAP ((dimethylamino)pyridine), 20 μL of (*S*)-MTPA chloride, and 0.1 mL of dry pyridine. The mixture was then stirred at RT under a N_2 atmosphere. The reaction was monitored by LC-MS analysis (50 μL aliquot of the reaction mixture diluted with 500 μL of CH_3CN) on a Luna C_8 column (XBD-C8, 3.5 μm, 4.6 × 50 mm) using aqueous CH_3CN as the mobile phase with a linear gradient (10−100% over 20 min) at a flow rate of 0.7 mL/min. The reaction, which was complete after 2 h, yielded the mono- and di-(*R*)-MTPA derivative mixture from **1**. The (*S*)-MTPA derivatives were prepared in the same manner using (*R*)-MTPA-Cl. This procedure was also used to prepare the corresponding MTPA derivatives of **2**.

Purification of (*R*)- and (*S*)-MTPA Ester Derivatives. The reaction mixtures ((*R*)- and (*S*)-MPTA ester derivatives) were purified separately by reversed-phase HPLC chromatography using an Altima C_{18} column (250 × 10 mm) using a linear gradient of MeCN in H_2O (20 to 100% over 40 min then hold at 100% for 20 min; flow rate of 2 mL/min; detection by UV at 210 and 254 nm). The mono-(*S*)- and (*R*)-MTPA ester derivatives of **1** (**3** and **4**, respectively) eluted at 48 and 51 min, while the di-(*S*)- and (*R*)-MTPA ester derivatives of **1** (**5** and **6**, respectively) eluted at 54 and 58 min. The (*S*)- and (*R*)-MTPA ester derivatives of **2** (**7** and **8**) eluted at 48 and 50 min, respectively.

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Supporting Information Available: The 1D ^{1}H, ^{13}C, and 2D NMR spectra of **1** and ^{1}H and ^{13}C NMR spectra of **2**, and the ^{1}H NMR data for MTPA derivatives are available free of charge via the Internet at http://pubs.acs.org.

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