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Neaumycin: A New Macrolide from *Streptomyces* sp. NEAU-x211

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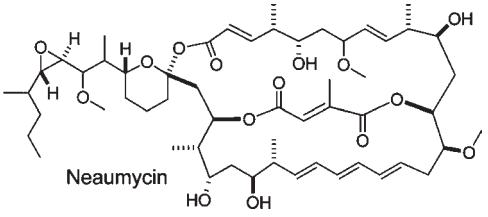
ABSTRACT



Neaumycin, a new 30-membered macrolide featuring an internal diester bridge, a molecular architecture that is unprecedented among known macrolide natural products, was isolated from a soil actinomycete strain *Streptomyces* sp. NEAU-x211. The structure of neaumycin was elucidated on the basis of comprehensive mass and NMR spectroscopic interpretation, including the relative stereochemistry of four independent coupling systems.

Natural products remain the best sources of drugs and drug leads and serve as outstanding small molecule probes for dissecting fundamental biological processes.[1] Despite their high value, however, they are poorly represented in all current small molecule libraries, and large libraries of pure natural products are not available.[1,2] We recently initiated a Natural Products Library Initiative to isolate microbial natural products and assemble them into a pure natural product library.[3] We strategically selected bacteria, particularly actinomycetes for their proven track record as prolific natural product producers, as the preferred sources of natural products so that quantities of them can be produced by large scale microbial fermentation.[4]

Here, we report the isolation and structural elucidation of a new macrolide, named neaumycin, from *Streptomyces* sp. NEAU-x211. *S.* sp. NEAU-x211 is a soil actinomycete isolated from HunLunbeier, Inner Mongolia, China, whose 16S rRNA shows 98.89% sequence identity with *Streptomyces caviscabies* ATCC 51928 [Supporting Information (SI)]. Neaumycin is a 30-membered macrolide featuring an internal diester bridge, a molecular architecture that is unprecedented among known macrolide natural products.[5]

Neaumycin was isolated as a white solid from *S.* sp. NEAU-x211 culture (SI). The structure of neaumycin was elucidated on the basis of comprehensive mass and NMR spectroscopic data interpretation (Figure 1; SI). ESI-MS in

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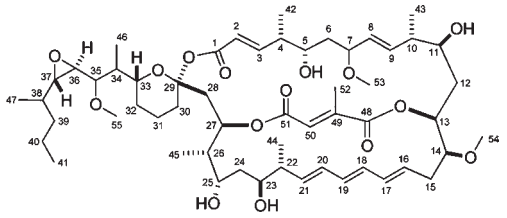

Figure 1. Structure of neaumycin. The relative stereochemistry shown in the four coupling systems of C-4/C-5, C-10 to C-14, C-22 to C-33, and C36/C-37 are independent.

negative mode yielded an $[M - H]^-$ ion at m/z 985.7 and high resolution ESI-MS in positive mode afforded an $[M + Na]^+$ ion at m/z 1009.58287, establishing the molecular formula of neaumycin as $C_{55}H_{86}O_{15}$ and indicating 13 degrees of unsaturation. ^{13}C NMR (Table 1) revealed resonances for three carbonyl groups (δ_C 168.7, 166.62, and 166.61) and six double bonds (δ_C 152.5, 144.2, 138.8, 138.3, 134.9, 132.5, 131.6, 130.3, 128.7, 128.0, 126.2, and 121.5), accounting for 9 of the 13 degrees of unsaturation and suggesting neaumycin features four rings.

Three structural fragments, A, B, C, can be readily deduced on the basis of 2D NMR (COSY, HMBC, ROSEY) correlations (Figure 2, Table 1, and Table S1). Fragment A consists of C-1 (δ_C 166.6) to C-13 (δ_C 74.2). The connectivity from C-2 to C-10, including C-42, C-43, and C-53, and from C-11 and C-13 were established based on COSY correlations and supported by HMBC correlations of H_3-42 (δ_H 1.11) with C-3 (δ_C 152.5), C-4 (δ_C 44.4), and C-5 (δ_C 75.4); H-5 (δ_H 3.56) and H_3-53 (δ_H 3.24) with C-7 (δ_C 85.3); and H_3-43 (δ_H 1.02) with C-9 (δ_C 138.8) and C-10 (δ_C 39.9). The conjugated C-2 (δ_C 121.5)/C-3 double bond was assigned to be *trans* based on the large coupling constant ($J_{2,3}$ = 15.5 Hz), which was further supported by the ROESY correlation between H-2 (δ_H 5.81) and H-4 (δ_H 2.32). The *trans* configuration for the C-8 (δ_C 128.0)/C-9 double bond was deduced based on the ROESY correlations between H-7 (δ_H 3.75) and H-9 (δ_H 5.78) and between H-8 (δ_H 5.25) and H-10 (δ_H 2.18). Finally the assignment of C-1 to conjugate with the C-2/C-3 double bond was further supported by its HMBC correlations with H-2 and H-3 (δ_H 6.78). Although COSY correlation between H-10 and H-11 (δ_H 3.34) was not observed, the connectivity between C-10 and C-11 (δ_C 67.6) was established based on the HMBC correlations of H_3-43 with C-11, H-11 with C-9, and H-12 (δ_H 1.71) with C-10.

Fragment B extends from C-14 (δ_C 81.0) to C-28 (δ_C 34.1). The connectivity from C-14 to C-28, including C-44 and C-45, was similarly established based on COSY correlations and further supported by HMBC correlations. The geometry of three conjugated double bonds from C-16 to C-21 was established by the H−H coupling constants and ROESY correlations. Thus, both the C-16 (δ_C 126.2)/C-17 (δ_C 134.9) and C-20 (δ_C 131.6)/C-21 (δ_C 138.3) double bonds were assigned to be *trans* based on ROESY correlations between H-15 (δ_H 2.12) and H-17 (δ_H 5.74)/H-16 (δ_H 5.32) and H-18 (δ_H 6.02) and between H-19 (δ_H 5.89) and H-21 (δ_H 5.30)/H-20 (δ_H 6.06) and H-22 (δ_H 2.15), respectively. Although, the overlapping or close ^1H NMR resonances between H-17 and H-19 and between H-18 and H-20 precluded from determining their ROESY correlations definitively, the large coupling constant ($J_{18,19}$ = 14.3 Hz) permitted the *trans* configuration assignment for the C-18/C-19 double bond. Finally, the chemical shifts and coupling constants for the three *trans* double bonds also compare favorably with those of similar structural moieties in the literature.[6]

Fragment C covers C-29 (δ_C 98.8) to C-41 (δ_C 14.5), including C-46 (δ_C 10.1), C-55 (δ_C 58.3), and C-47 (δ_C 17.1). COSY and HMBC correlations easily defined the sequence from the terminal CH_3 (C-41), via an epoxide ring C-37 (δ_H 2.56, δ_C 60.1) and C-36 (δ_H 3.17, δ_C 63.6), to the OCH_3 (C-55, δ_H 3.57, δ_C 58.3) substituted C-35 (δ_C 80.2); the *trans* configuration of the epoxide was deduced based on ROESY correlations between H-37 (δ_H 2.56) and H-35 (δ_H 3.32) and between H-36 (δ_H 3.17) and H-38 (δ_H 1.50). No COSY correlation between H-35 and H-34 (δ_H 1.58) was observed, but HMBC correlations of H_3-46 (δ_H 0.93) with C-35, C-34 (δ_C 44.1), and C-33 (δ_C 72.7) allowed the connectivity between C-35 and C-34/C-33. The structural moiety from C-34 to C-30 (δ_C 36.4) was readily assigned based on COSY correlations. The quaternary carbon C-29 was assigned to be a ketal on the basis of its characteristic ^{13}C chemical shift (δ_C 98.8). HMBC correlation of H-30 (δ_H 1.40) with C-29 finally completed the assembly of fragment C.

The remaining ^1H and ^{13}C NMR resonances were suggestive of a mesaconate residue. The latter was confirmed by HMBC correlations of H_3-52 (δ_H 2.36) with C-48 (δ_C 168.7), C-49 (δ_C 144.2), and C-50 (δ_C 128.7) and by comparison of the NMR data with mesaconic acid or other known derivatives.[7]

The assembly of fragments A, B, C, as well as the mesaconate moiety, into the planar neaumycin structure was achieved by careful analysis of key COSY, HMBC, and ROESY correlations as depicted in Figure 2. First, although COSY correlation between H-13 and H-14 was not observed, the HMBC correlation of H-12 with C-14 and the ROESY correlation between H-13 and H-14 gave rise to the connectivity of fragments A and B through C-13 and C-14. Second, the ROESY correlation between H-28 and H-33 not only defined the relative stereochemistry of C-29 and C-33 but also supported the ring closure to a trans-disubstituted tetrahydropyran and connection between fragments B and C through C-28 and C-29. The latter was further supported by the HMBC correlation of

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Table 1. ^{1}H and ^{13}C NMR Data of Neaumycin ($CDCl_3$, δ in ppm, J in Hz)[a]

no.	^{1}H NMR	^{13}C	no.	^{1}H NMR	^{13}C
1		166.6	29		98.8
2	5.81 (d 15.5)	121.5	30	1.40 (o)	36.4
3	6.78 (dd 15.5, 10.0)	152.5	30	1.68 (o)	
4	2.32 (o)[b]	44.4	31	1.53 (o)	20.3
5	3.56 (o)	75.4	31	1.75 (o)	
6	1.50 (o)	40.6	32	0.998 (o)	29.2
6	1.59 (o)		32	1.72 (o)	
7	3.75 (t like 8.6)	85.3	33	3.49 (t like 11.5)	72.7
8	5.25 (o)	128.0	34	1.58 (o)	44.1
9	5.78 (o)	138.8	35	3.32 (o)	80.2
10	2.18 (o)	39.9	36	3.17 (brd 7.0)	63.6
11	3.34 (o)	67.6	37	2.56 (o)	60.1
12	1.71 (o)	37.7	38	1.50 (o)	35.1
12	1.91 (t 13.0)		39	1.30 (o)	35.6
13	4.95 (brd 10.5)	74.2	39	1.43 (o)	
14	3.39 (o)	81.0	40	1.38 (o)	20.4
15	2.12 (o)	34.6	41	0.95 (o)	14.5
15	2.80 (m)		42	1.11 (o)	17.2
16	5.32 (o)	126.2	43	1.02 (d 6.5)	10.4
17	5.74 (o)	134.9	44	1.13 (o)	17.4
18	6.02 (dd 11.3, 14.3)	130.3	45	0.81 (d 6.5)	13.6
19	5.89 (dd 11.3, 14.3)	132.5	46	0.93 (o)	10.1
20	6.06 (dd 11.3, 15.0)	131.6	47	1.07 (d 6.5)	17.1
21	5.30 (o)	138.3	48		168.7
22	2.15 (o)	45.0	49		144.2
23	3.31 (o)	77.6	50	6.70 (brs)	128.7
24	1.24 (o)	37.4	51		166.6
24	2.165 (o)		52	2.36 (brs)	14.1
25	3.90 (t 10.5)	77.2	53	3.24 (s)	55.8
26	1.48 (o)	21.8	54	3.43 (s)	57.9
27	4.88 (dt 10.5, 3.6)	71.4	55	3.57 (s)	58.3
28	1.31 (o)	34.1			
28	2.54 (o)				

[a] ^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz, and assignments were based on HSQC, COSY, HMBC, and ROESY experiments (Table S1). [b] 'o' denotes overlapping signals.

H-28 with C-29. Third, the upfield ^{13}C chemical shifts of the two carbonyl groups (C-51 at δ_C 166.6 and C-48 at δ_C 168.7) in the mesaconate moiety suggested that both carbonyls would be esterified.[7] The HMBC correlation of H-13 with C-48 and the downfield chemical shift of H-13 (δ_H 4.95) positioned an ester bond between C-48 and C-13. Siminarly, H-27, another downfield proton (δ_H 4.88), showed HMBC correlation with either carbonyl group C-1 (δ_C 166.62) or C-51 (δ_C 166.61) (due to overlapping signals). The assignment of esterification of C-27 by C-51 was subsequently based on the ROSEY correlation between H_3-45 and H-50. Finally, there was still one degree of unsaturation unaccounted for, requiring another ring in the final structure. The upfield chemical shift of C-1 indicated it to be an ester carbonyl, which could possibly connect to one of the oxygens left (i.e., O-5, O-11, O-23, O-25, and O-29) to form a macrocyclic ring. The upfield chemical shifts of H-5 (δ_H 3.56), H-11 (δ_H 3.34), H-23 (δ_H 3.31), and H-25 (δ_H 3.90), however, suggested that all of these positions would unlikely be esterified. Therefore, C-1 had to be connected with C-29 through an ester bond, and this assignment was further supported by the ROESY correlation between H-5 and H-27. This completed the strucral elucidation of neaumycin as a new

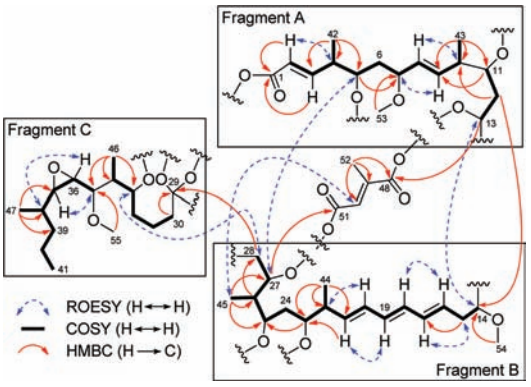

Figure 2. Key COSY, HMBC, and ROESY correlations supporting the structures of fragments A, B, C, as well as the mesaconate moiety, and their final assembly into neaumycin.

30-membered macrolide featuring an internal diester bridge (Figures 1 and 2).

The neaumycin structure contained 19 chiral centers. While complete stereochemistry assignment is beyond the scope of the current study, we adopted the J-based method,[8] combining with ROESY correlations, to narrow down possible diastereomers. Signal overlap and cross peak broadening hampered the $^{2,3}J_{H,C}$ measurements for H_2-6 with C-5 or C-7, H-34 with C-35 and C-36, and H-35 with C-34 and C-46. Nevertheless, the relative stereochemistry of four individual coupling systems of C-4/C-5, C-10 to C-14, C-22 to C-33, and C-36/C-37 were established based on the informative $^{2,3}J_{H,C}$ and $^{3}J_{H,H}$ values obtained and key ROESY correlations (Figure 3).

Figure 3A depicted the relative stereochemistry of the C-4/C-5 coupling system. The *anti* orientation of H-4/H-5 was suggested by a large $^{3}J_{H,H}$ (10.5 Hz), while the *gauche* orientations of H-4/HO-C-5 and H-5/C-42 were indicated by a large $^{2}J_{H,C}$ (6.5 Hz) and a small $^{3}J_{H,C}$ (1.9 Hz), respectively. This assignment was supported by ROESY correlations between H-5 and H_3-42, H-5 and H-3, and H^{l}-6 and H-3. The coupling constants between H_2-6 with C-5 and C-7 were not determined due to the close chemical shifts of ^{l}H-6 (δ_H 1.50) and ^{h}H-6 (δ_H 1.59). The relative stereochemistry between C-5 and C-7 therefore remains unknown.

Figure 3B depicted the relative stereochemistry of the C-10 to C-14 coupling system. First, the *gauche* orientation of H-10/H-11 was suggested by the small $^{3}J_{H,H}$ (not observed). The *anti* orientation of H-10/HO-C-11 was determined based on the small $^{2}J_{H,C}$ (3.1 Hz). The ROESY correlations between H-9 and H-11 and between H-10 and H-11 supported the *guache* orientation of H-11 to both C-9

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and H-10. Second, the *anti* orientation of H-11/^{l}H-12 was suggested by the large $^{3}J_{H,H}$ (7.2 Hz). The *anti* orientation of ^{h}H-12/HO-C-11 was consistent with a small $^{3}J_{H,H}$ of H-11 with ^{h}H-12 (2.3 Hz), a small $^{3}J_{H,C}$ of H-11 with C-13 (2.0 Hz), a small $^{2}J_{H,C}$ of ^{h}H-12 with C-11 (1.6 Hz), and a large $^{2}J_{H,C}$ of ^{l}H-12 with C-11 (6.6 Hz). Similarly, the *anti* orientation of H-13/^{h}H-12 was suggested by the large $^{3}J_{H,H}$ (10.5 Hz), while the *anti* orientation of ^{l}H-12/RO-C-13 was concluded based on a small $^{3}J_{H,H}$ of ^{l}H-12 with H-13 (on observed), a small $^{3}J_{H,C}$ of H-13 with C-11 (1.3 Hz), a small $^{2}J_{H,C}$ of ^{l}H-12 with C-13 (0.5 Hz), and a large $^{2}J_{H,C}$ of ^{h}H-12 with C-13 (7.8 Hz). The ROSEY correlation between ^{l}H-12 and H-13 also supported this assignment. Finally, the *gauche* orientation of H-13/H-14 was suggested by the large $^{2}J_{H,C}$ of H-13 with CH_3O−C-14 (7.5 Hz) and H-14 with RO−C-13 (6.3 Hz), respectively. This assignment was consistent with the small $^{3}J_{H,H}$ between H-13 and H-14 (not observed) and supported by the ROSEY correlation between H-13 and H-14. Taken together, these observations established the relative configuration from C-10 to C-14.

Figure 3C summarized the assignment of the relative stereochemistry of the C-22 to C-33 coupling system. First, the relative configuration of C-22/C-23 was established by the large $^{3}J_{H,H}$ and $^{2}J_{H,C}$ of H-22 with H-23 (8.5 Hz) and C-23 (6.8 Hz), respectively. Second, extension from C-22/C-23 to C-25 was based on (i) a large $^{3}J_{H,H}$ of H-23 with ^{h}H-24 (9.7 Hz), a small $^{3}J_{H,C}$ of H-23 with C-25 (2.5 Hz), a small $^{2}J_{H,C}$ of ^{l}H-24 with C-23 (0.9 Hz), and a large $^{2}J_{H,C}$ of ^{h}H-24 with C-23 (5.9 Hz) and (ii) a large $^{3}J_{H,H}$ of ^{l}H-24 with H-25 (10.1 Hz), a large $^{2}J_{H,C}$ of ^{l}H-24 with C-25 (7.4 Hz), and a small $^{2}J_{H,C}$ of ^{h}H-24 with C-25 (2.1 Hz), respectively. This assignment was supported by the ROSEY correlations between ^{l}H-24 and H-22 and between H-23 and H-25. Third, the correlation from C-25 to C-27 was based on the large $^{3}J_{H,H}$ of H-25 with H-26 (9.2 Hz) and H-26 with H-27 (10.5 Hz) and the large $^{2}J_{H,C}$ of H-26 with C-27 (7.5 Hz), which was fully supported by the NOSEY correlations between H-24 and H-45, H-25 and H-45, H-25 and H-27, H-27 and H-45, and H-28 and H-45. Fourth, the relative conformation of C-27/C-28 was based on a large $^{3}J_{H,H}$ of H-27 with ^{l}H-28 (12.0 Hz), a small $^{3}J_{H,H}$ of H-27 with ^{h}H-28 (3.6 Hz), and a large $^{2}J_{H,C}$ of ^{l}H-28 with C-27 (6.7 Hz) and supported by the ROESY correlation between ^{h}H-28 and H-27. Finally, the ROESY correlation between ^{h}H-28 and H-33 indicated that both C-28 and H-33 are at the axial orientation. As the tetrahydropyran ring is relatively rigid and the C-27 side chain apparently adopted one dominant configuration, the ROESY correlations between ^{h}H-28 and H-27, ^{h}H-28 and H_3-46, and especially H-27 and H-5 led the assignment of a *gauche* orientation between H-27 and C-29 and an *anti* orientation between C-27 and O-29/33. Taken together, these observations established the relative stereochemistry from C-22 to C-33.

The relative stereochemistry from C-33 to C-35 was not assigned because the key $^{2,3}J_{H,C}$ constants were not observed. The C-36/C-37 epoxide was established to be *trans* based on the ROESY correlations between H-36 and H-38 and between H-37 and H-35 (Figure 2).

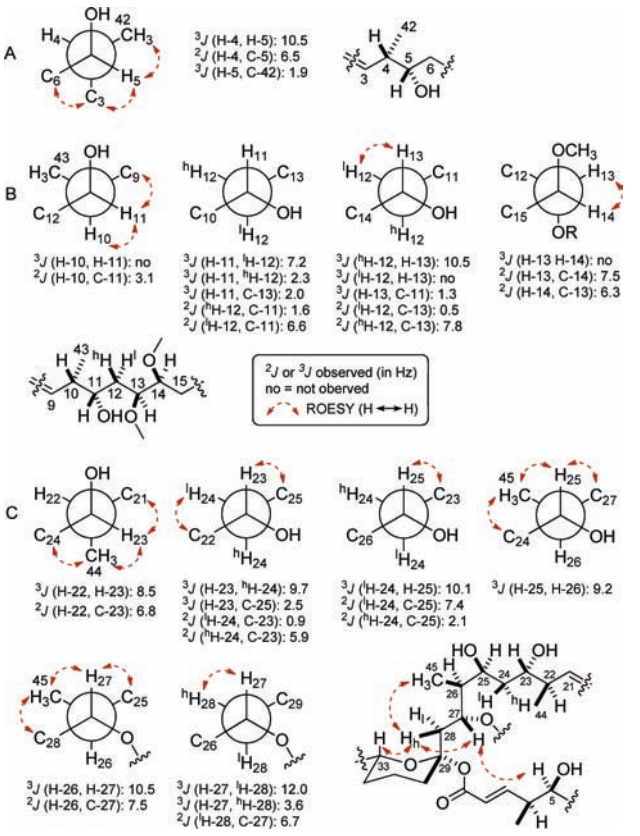

Figure 3. Determination of relative stereochemistry of three individual coupling systems of (A) C-4/C-5, (B) C-10 to C-14, and (C) C-22 to C-33 on the basis of $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ constants and key ROSEY correlations.

Neaumycin was tested for cytotoxicity against selected cancer cell lines. No significant inhibitory activity was observed at 1.0 μM under the conditions tested.

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Supporting Information Available. Detailed experimental procedures, HR-ESI-MS spectrum, and assorted 1D and 2D NMR spectra for neaumycin (Table S1 and Figures S1 to S11). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.