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Total Synthesis of the Reported Structure of Neaumycin B

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Abstract

The stereoselective total synthesis of structure **1** assigned to the macrolide natural product neaumycin B is reported in a 2.3% overall yield on 90 mg scale. The synthesis features a gram-scale nickel-catalyzed reductive cross-coupling/spiroketalization tactic to construct the spiroketal core of neaumycin B. The stereostructures of the C3–C6, C8–C14, and C20–C41 segments of synthetic neaumycin B were unambiguously verified by X-ray crystallography.

The first congener of neaumycin was isolated in 2012 by Shen et al. from the soil actinomycete *Streptomyces* sp. NEAU-x21.[1] The structure of neaumycin was then substantially revised in 2015, with the isolation of neaumycin A and the congener neaumycin B, albeit without stereochemistry.[2] In 2018, Jenson and Fenical et al. isolated a substance from a marine microbial *Micromonospora* sp. (strain CNY-010) from the surface of the tropical brown alga *Stypopodium zonale* collected in the Bahamas Islands.[3] A combination of genomic data and 2D NMR studies led to the assignment of neaumycin B to be 1. Preliminary *in vitro* study of neaumycin B against several cancer cell lines displayed significant potency (LD_{50}: 5.6×10^{-5} μg/mL), in particular with selectivity toward U87 human glioblastoma, which is among the most malignant types of gliomas.[4] The bioactivity of neaumycin B holds promise as a lead structure for drug design. The development of a total synthesis of neaumycin B (**1**) would thus be of significance and, as such, has drawn considerable interest.[5a–c] Herein we report the first total synthesis of the reported structure of neaumycin B (**1**).

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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c06573.

Experimental procedures and analytical data for all new compounds (PDF)

Accession Codes

CCDC 2271141-2271144 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

From the retrosynthetic perspective (Scheme 1), we envisioned that neaumycin B (**1**) could be dissected into a linear southern (C1–C17) hemisphere (**2**) and a spirocyclic northern hemisphere (C18–C41) (**3**), which in turn could be united via Stille coupling[6] and macrolactonization, to complete, upon deprotection, neaumycin B (**1**).

The linear southern hemisphere **2** (Scheme 1) was envisioned to arise from an asymmetric 1,2-addition of southwestern (**7**) and southeastern (**8**) fragments, while the spiroketal core of the northern hemisphere (**3**) could be constructed from the linear ketone precursor **4** (Scheme 1), which in turn could be dissected into the northwestern (**5**) and northeastern (**6**) fragments.

Our synthesis began with the northwestern fragment **5** (Scheme 2), the C21–C29 segment of neaumycin B. Union of epoxide (+)-**9** (prepared in two steps from a known compound; see SI for details) and dithiane **10**[7b] proceeded smoothly via a Brook rearrangement/ epoxide ring opening sequence[7a–c] to yield adduct **11**, which underwent benzyl protection, hydrolysis of trimethylsilyl ether, and Cu/TEMPO-catalyzed aerobic oxidation[8] to aldehyde **12** (see X-ray), gratifyingly with no oxidation of sulfur or epimerization at the α position of the carbonyl. A Felkin–Anh selective aldol reaction of the enolate derived from methyl acetate with **12** then delivered the desired *syn* adduct **13** with good diastereoselectivity (15:1). Dithioacetal hydrolysis[9] and Evans–Saksena reduction[10] followed by 1,3-diol protection led to compound **15**, with the desired *anti* configuration. Saponification of the methyl ester and subsequent thioesterification completed synthesis of northwestern fragment **5** on a decagram scale.

We next turned to northeastern (C30–C41) fragment **6** (Scheme 3). Regioselective opening of epoxy alcohol (−)-**16** (91% ee, readily prepared from (*E*)-2-hexene-1-ol via Sharpless epoxidation[11]) with trimethylaluminum[12] led almost exclusively to 1,2-diol **17** (>20:1 1,2-diol/1,3-diol) as indicated by the crude ^{1}H NMR (see Figure S27), which upon biphasic periodate cleavage and dibromo-olefination[13] furnished dibromo-alkene **18** on a 38 g scale. Exposure of **18** to *n*-BuLi and capture of the lithium alkynylide with formaldehyde delivered propargylic alcohol **19**. *Trans*-hydrosilylation directed by the hydroxyl group employing ruthenium catalysis[14a–d] furnished alcohol **20**, with both good regio-, *Z*/*E* selectivity and yield. Oxidation of the resulting allylic hydroxyl with MnO_2 then afforded quantitatively aldehyde **21**, which underwent an Evans aldol[15] reaction with **22** to form **23**; subsequent transamidation yielded Weinreb amide **24**, with the desired *syn* configuration (82%, 2 steps). Monoaddition of allylmagnesium bromide to amide **24** then yielded the β-hydroxyl ketone, which was followed by Narasaka–Prasad reduction[16a–c] (Et_2BOMe, $NaBH_4$) and acetal protection to access 25. Hydroboration/oxidation, followed by an Appel reaction,[17] completed the northeastern fragment **6**.

With northwestern and northeastern fragments **5** and **6** in hand, we set out to examine suitable methods for their union (Scheme 4). Although neither organolithium nor Grignard chemistry successfully delivered the desired coupled ketone in satisfactory yield, fragment coupling was achieved via the recently developed nickel-catalyzed reductive cross-coupling protocol[18] to afford ketone **4** in good yield (76%) on a gramscale. Ketone **4** was then exposed to *p*-toluenesulfonic acid in methanol to achieve deprotection/spiroketalization

and to furnish **26** and the epimer **26′**, as a 1:0.8 mixture, which were separable by chromatography. Pleasingly, exposure of the pure undesired epimer **26′** to the same acidic condition reestablished the equilibrium, thereby permitting harvest of **26** upon each chromatography separation/re-equilibration to achieve **26** in 67% overall yield. A key NOE correlation between H-33 and H-28 (Scheme 4, see Figure S53) verified the stereogenicity of **26**.

To achieve 3,4-dimethoxybenzyl protection at the C27-OH (Scheme 5), **26** was treated first with catalytic tetra-*n*-butylammonium fluoride (TBAF)[19] to affect closure of the five-membered siloxane ring across C35–C37 and leave the C27-OH exposed for selective DMB protection (see Supporting Information for details). Subsequent exposure of the siloxane to methyllithium then unmasked the C35-OH to give **27**, which now serves as the directing group for the future stereoselective epoxidation.

With the thus locked conformation at the C35–C36 bond in **27**, due to $A^{1,3}$ strain invoked by the preinstalled C37 silyl group,[14] epoxidation of the C36–C37 olefin proceeded with exclusive *syn*-selectivity with vanadyl catalysis[20] to furnish 28. Desilylation with TBAF[21] and methylation of C35-OH then gave **30**, followed by hydrogenolysis of the C21 and C23 benzyl ethers to give diol **31**. Chemoselective oxidation of the C21 primary alcohol next delivered *β*-hydroxy aldehyde **32**, which upon treatment with the Wittig phosphoranylidene reagent,[22a,b] yielded olefin **33** with excellent *E* selectivity. Pleasingly, compound **33** was crystalline, thus enabling unambiguous verification of the stereostructure spanning the C20–C41 segment by X-ray crystallography (see Scheme 5).

Next, triethyl silyl protection of the C23-OH in **33**, reduction of ester, and MnO_2 oxidation furnished enal **34**, which was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to affect deprotection of the C27-OH to give **35**. Finally, Takai–Utimoto olefination[23a,b] of aldehyde **35** employing diiodo(tributylstannyl)methane led to **3a** in good yield, but as an unacceptable 4:1 mixture of (*E,E*)/(*Z,E*) isomers.

We therefore revised our synthetic route to a second-generation northern hemisphere (3b, see Scheme 6). *β*-Hydroxy aldehyde **32** was first protected with triethylsilyl, and a Takai–Utimoto reaction[23a,b] was carried out. The steric bulk at the *α*-carbon next to the carbonyl permitted Takai olefination with $CrCl_2/Bu_3SnCHI_2$ to proceed with excellent *E*-selectivity (>20:1), leading to the corresponding vinylstannane.[23a,b] Iodination then afforded *E*-iodide **37** in 78% yield over two steps. DDQ removal of the 3,4-dimethoxybenzyl group then gave **38**. Next Stille cross-coupling[24c] between alkenyl iodide 38 and germylstannane **39**[24a–c] afforded dienyl germane **40**, with no isomerization of the diene. Iodination of germane **40** with *N*-iodosuccinimide then provided access to the second-generation northern hemisphere (**3b**) with excellent stereospecificity.

Turning to the linear southwestern and southeastern fragments (Scheme 7a and b), synthesis of alkyne 7 began from known aldehyde **41** (prepared from D-xylose in five steps[25a,b]). Marshall asymmetric propargylation[26] delivered the *anti*-configured homopropargylic alcohol **42** in good yield, but with modest 4:1 diastereoselectivity (Scheme 7). Adduct **42** was then treated with TBAF to afford diol **43** with excellent purity after chromatography.

To gain proof of the stereostructure of **7**, PMP acetalization of diol **43** furnished crystalline **44**, which upon X-ray crystallography analysis verified the structure of the southwestern segment (C8–C14). Silyl ether protection then completed the southwestern fragment (7).

Synthesis of the southeastern fragment (**8**, Scheme 7b) began with *β*-keto ester **45**. Catalytic asymmetric dynamic kinetic resolution[27] successfully delivered alcohol **46**, in good yield and excellent enantio- and diastereoselectivity. *Tert*-Butyldimethylsilyl (TBS) protection and diisobutylaluminum (DIBAL) reduction of the ester then afforded compound **47**, which upon 4-methoxybenzyl (PMB) protection of the primary alcohol followed by removal of the TMS group under mild basic conditions then revealed terminal alkyne **48**. Semihydrogenation, hydroboration/oxidation, and Cu/(2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)-catalyzed aerobic oxidation8 completed the Southeastern fragment **8**.

Having prepared alkyne **7** and aldehyde **8** (Scheme 8) on a multigram scale, Carreira asymmetric alkynylation[28] cleanly afforded adduct **51** with excellent yield and diastereoselectivity. Subsequent *trans*-reduction of the triple bond with conventional aluminum hydride reagents ($LiAlH_4$, Red-Al), however, failed to give the desired allylic alcohol in appreciable yield. We therefore turned to a Ru-catalyzed hydrostannation/destannation tactic,[29a,b] which gratifyingly led to the desired *trans*-reduction in good yield (72%). Stereochemical assessment of the C7-hydroxyl of 53 was achieved via Mosher ester analysis[30] (see Table S27). Methylation then led to compound **54**, which, after exposure to 50% aqueous trifluoroacetic acid (TFA), cleanly furnished triol **55** as the major product. Selective tosylation and epoxide ring closure, followed by reinstallation of the silyl protecting group, then gave **56** in high overall yield (92%, three steps), which was subjected to BF_3-assisted nucleophilic ring opening with lithium trimethylsilyl (TMS) acetylide to furnish alcohol **57** in near quantitative yield. Methylation employing Meerwein's reagent gave **58**, which was followed by global silyl group removal with TBAF and the hydroxyl groups reprotected with triethylsilyl, which at the end of our synthesis proved much easier to remove. The PMB protecting group in **59** was next removed, and in turn Dess–Martin oxidation[31] of the resulting alcohol followed by Horner–Wadsworth–Emmons (HWE) olefination[32] led to **61**. Finally, bromination of the terminal alkyne and hydrostannation[33] permitted regio- and stereoselective formation of the vinylstannane, completing the synthesis of the linear southern hemisphere **2** on a 1.26 g scale.

With both the northern (**3b**) and southern (**2**) hemispheres successfully prepared (Scheme 9), a Stille union reaction[6] united 2 and 3. To our delight, the desired (*E,E,E*)-1,3,5-triene 62 was formed in excellent yield on an appreciable 200 mg scale with no isomerization of double bonds! The methyl ester was next hydrolyzed to afford seco-acid **63** via transesterification with trimethyltin hydroxide.[34] Macrolactonization, employing Mukaiyama's conditions,[35] afforded the silylprotected macrocycle **64** in good yield.[36] Finally, global removal of triethylsilyl groups gratifyingly proceeded cleanly under mild conditions (TBAF, HOAc, and 0 °C) to complete the synthesis of the reported structure of neaumycin B (**1**) isolated as a white powder. Notably, **1** was prepared on a 90 mg scale in a single batch, with a 2.3% overall yield.

Unfortunately, the ^{1}H NMR spectra of synthetic **1** displayed significant deviations from that of the spectra reported by Fenical et al.[3] In addition, **1** displayed no activity against glioblastoma cells (see Figure S5). Importantly, the stereo-chemical assignments of synthetic **1** were derived from X-ray crystallography analysis of each fragment (Figure 1). That is, crystal structures of compounds **33**, **44**, and **50** (see SI for details) confirmed the stereochemistry that spans C20–C41, C8–C14, and C3–C6 of synthetic neaumycin B (see Figure 1), respectively. The stereogenicity at C7 was also confirmed by Mosher ester analysis (see Table S27 for details). Based on the evidence reported here, we are confident that the synthetic neaumycin B (**1**) prepared here matches the structure reported by Fenical et al.[3]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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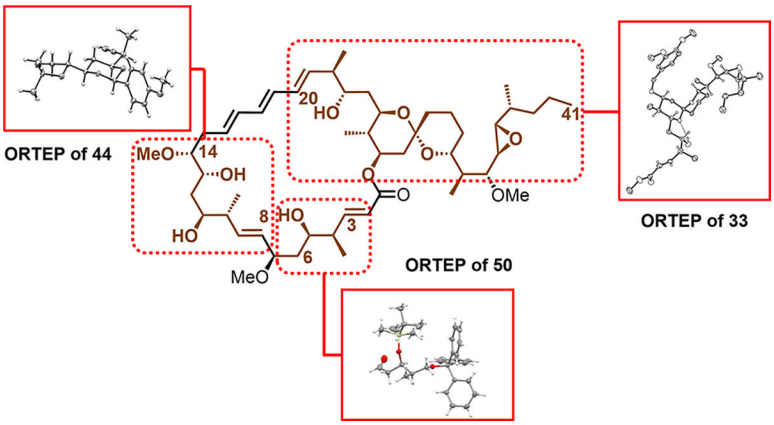
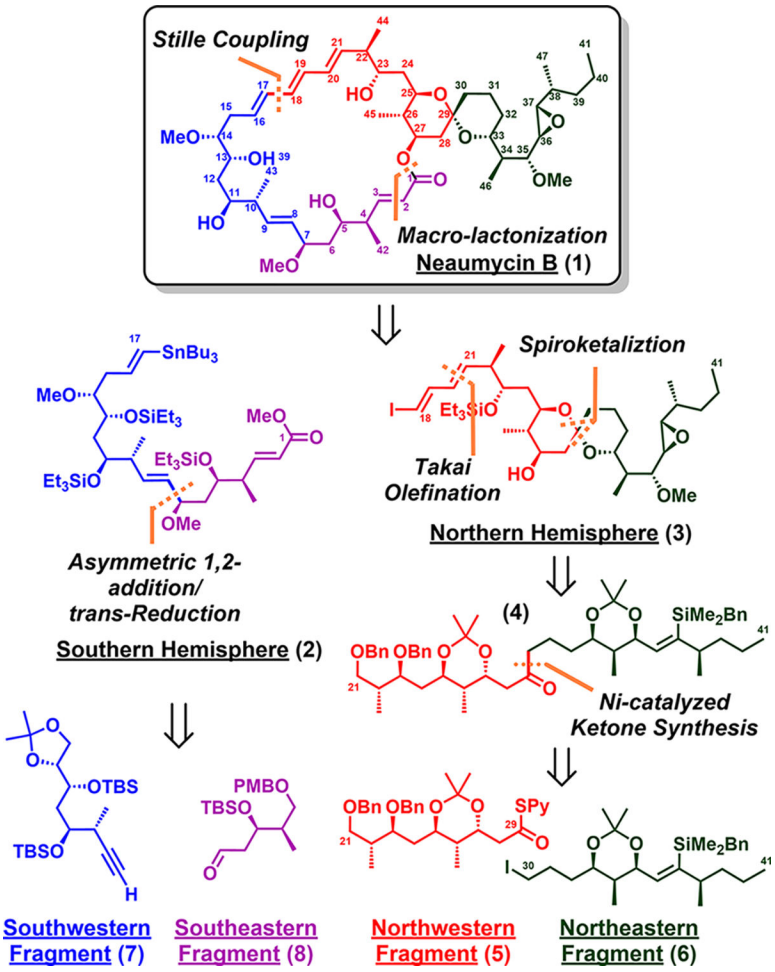
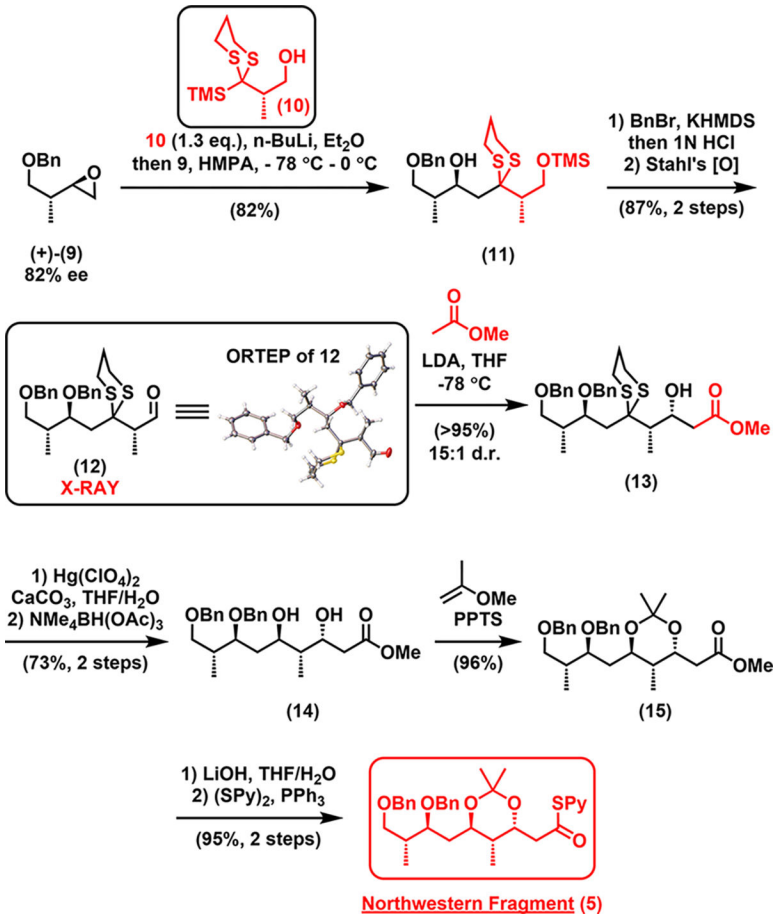


Figure 1.
Crystal Structures of Each Fragment.

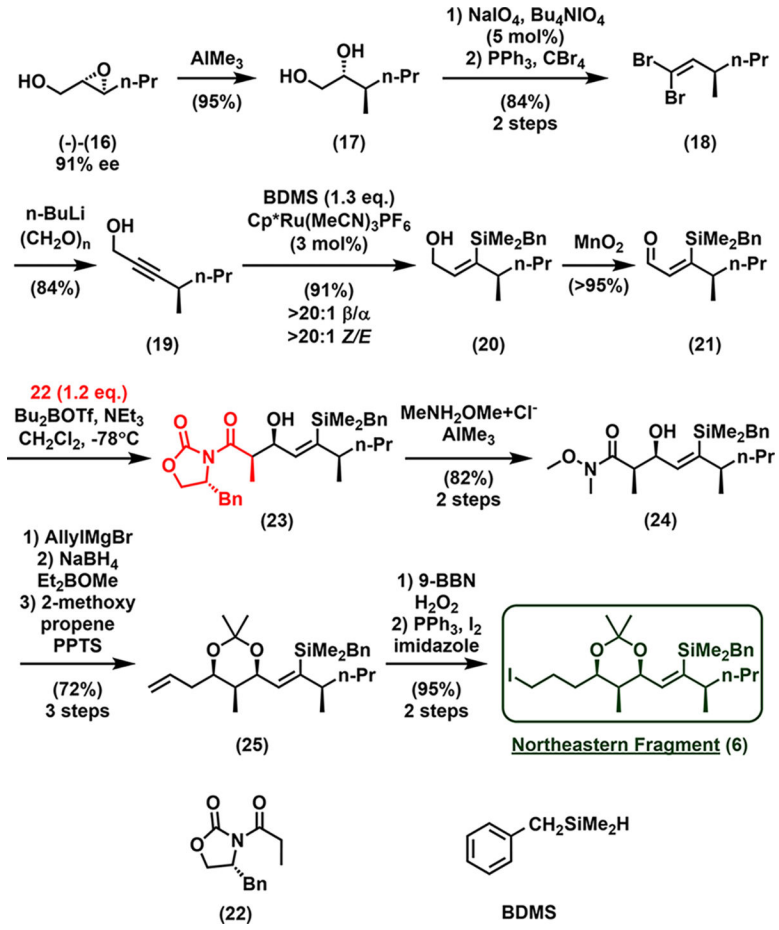


Scheme 1.

Structure and Retrosynthetic Analysis of Neaumycin B (1)

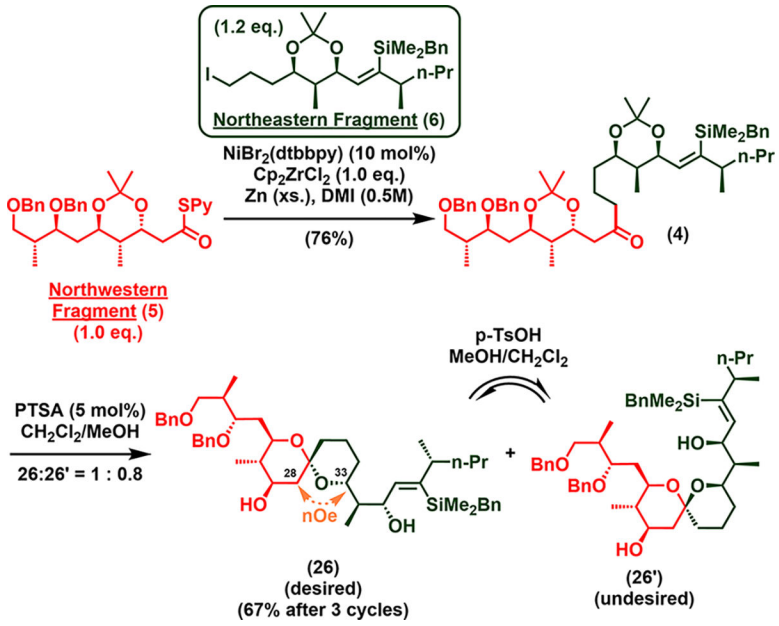


Scheme 2.
Synthesis of the Northwestern Fragment (5)

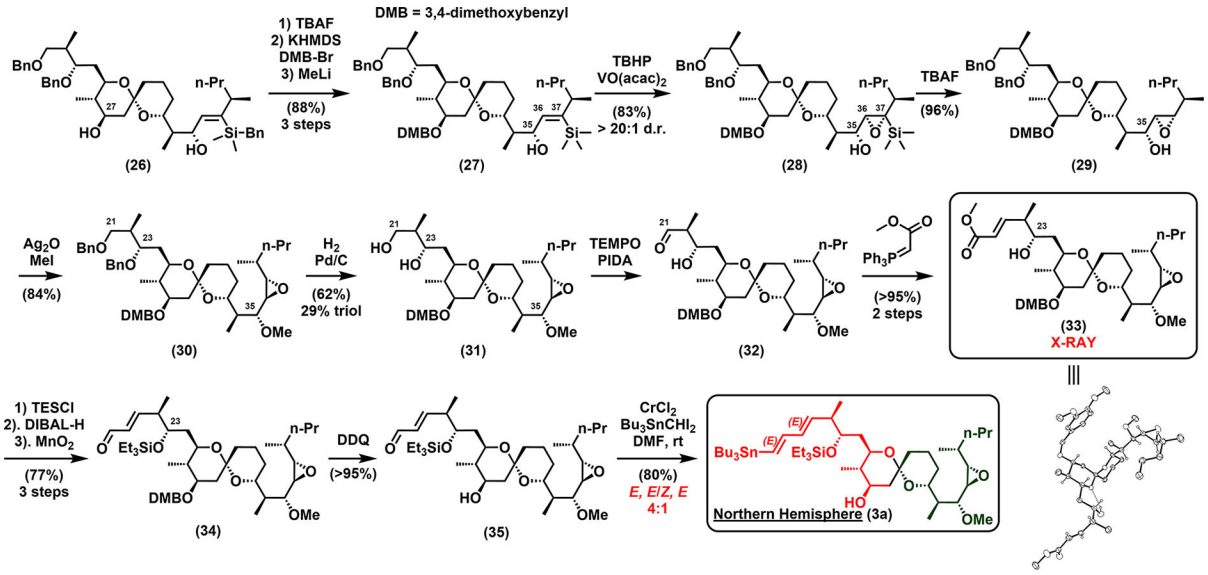


Scheme 3.

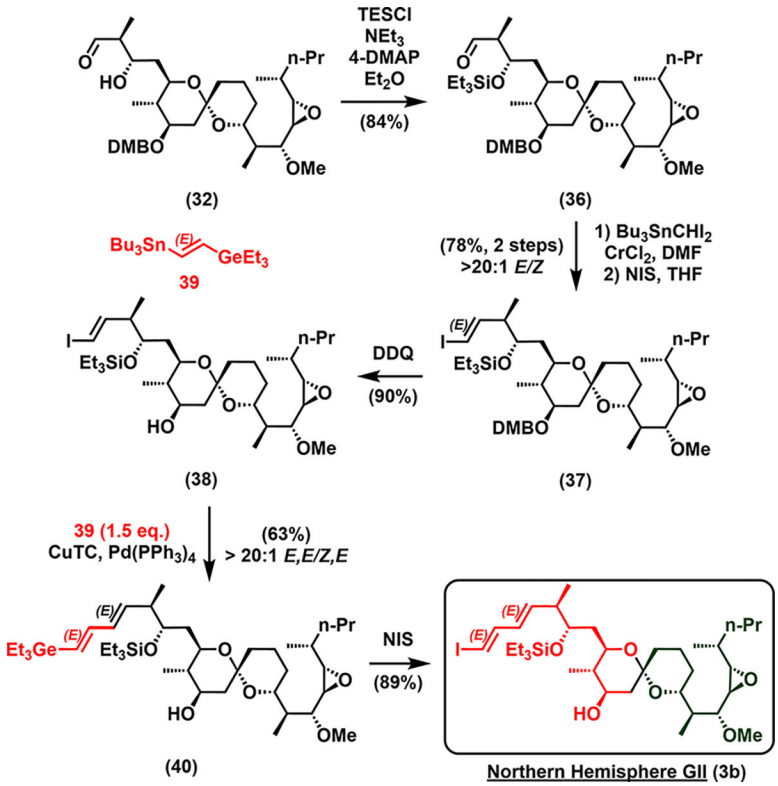
Synthesis of the Northeastern Fragment (6)



Scheme 4.
Fragment Union/Spiroketalization

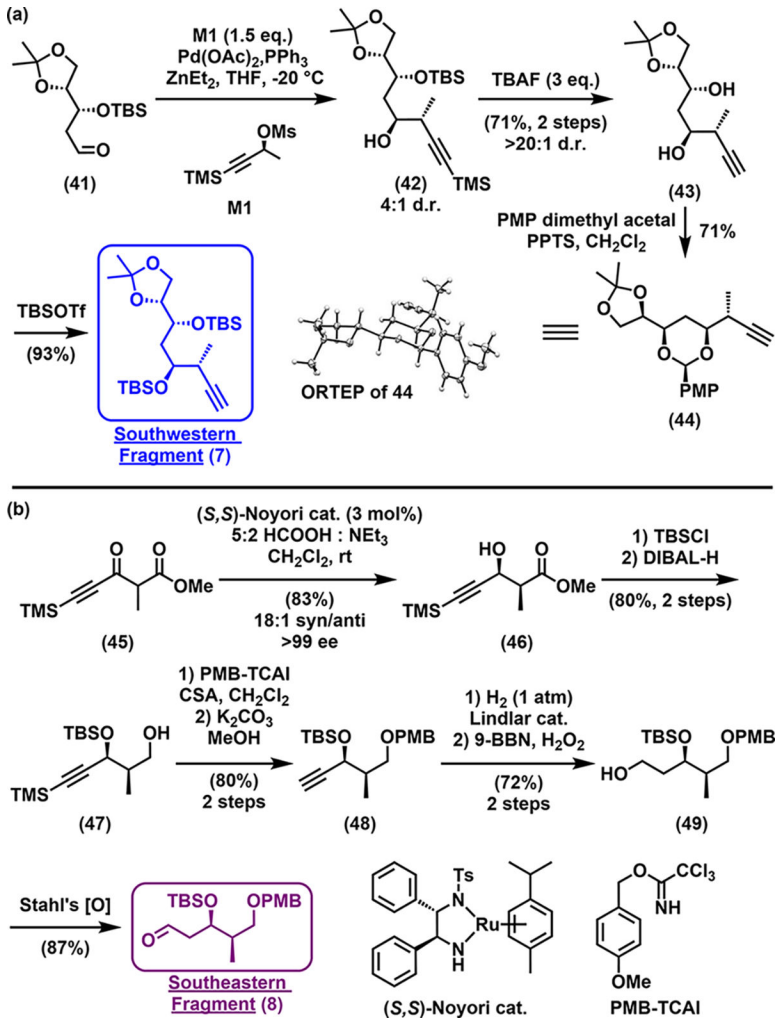


Scheme 5.
Synthesis of the Northern Hemisphere (3a)



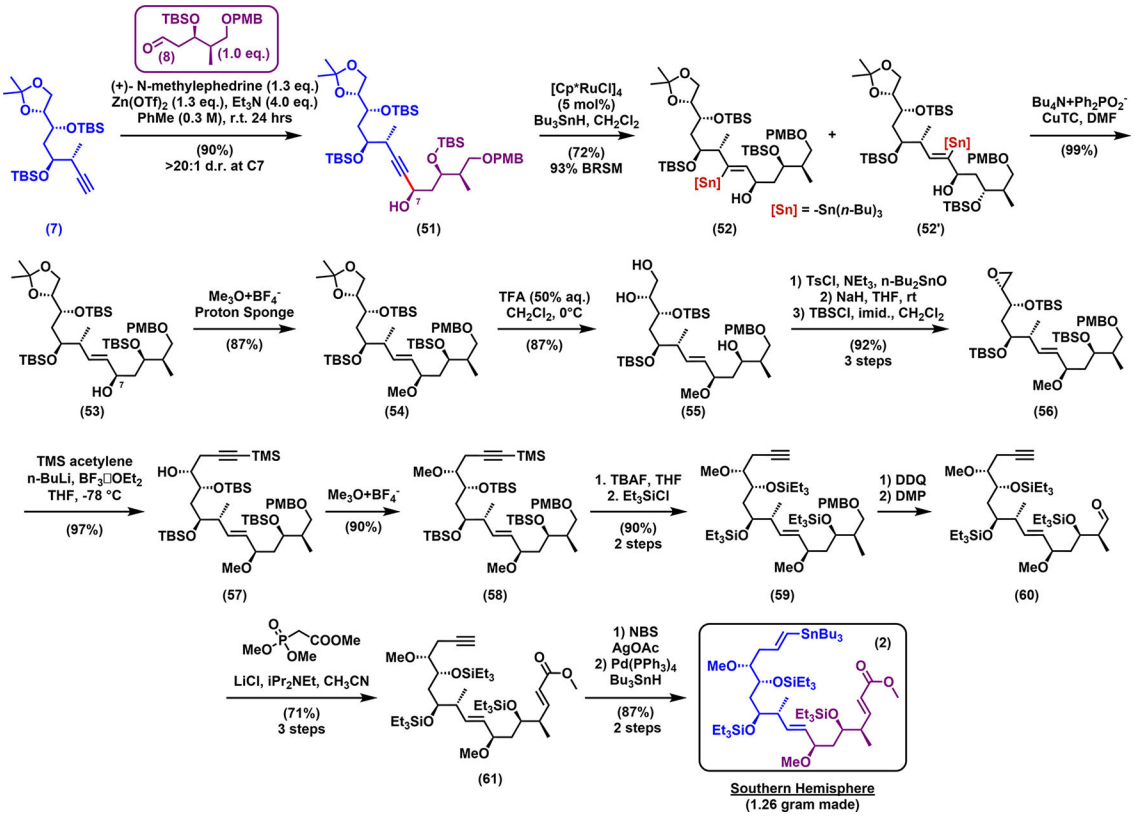
Scheme 6.

Synthesis of the Second-Generation Northern Hemisphere (3b)

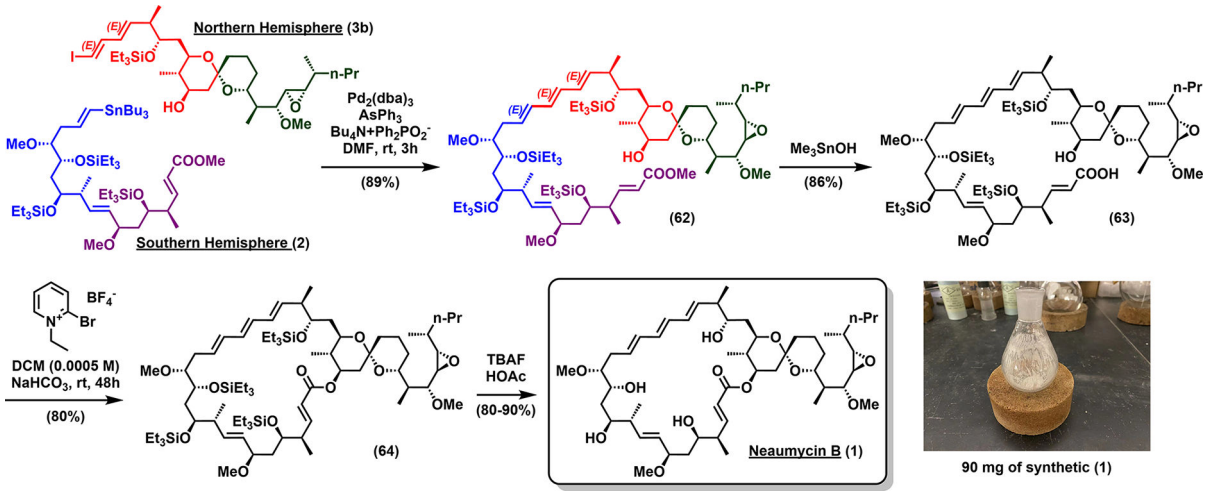


Scheme 7.

Synthesis of Southwestern (7) and Southeastern (8) Fragments



Scheme 8.
Synthesis of the Southern Hemisphere (2)



Scheme 9.
End Game for the Proposed Structure of Neaumycin B (1)