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Stereostructure Clarifying Total Synthesis of the (Polyenoyl)tetramic Acid Militarinone B. A Highly Acid-Labile *N*-Protecting Group for Amides†

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Cite This: https://doi.org/10.1021/acs.orglett.1c01652 Read Online

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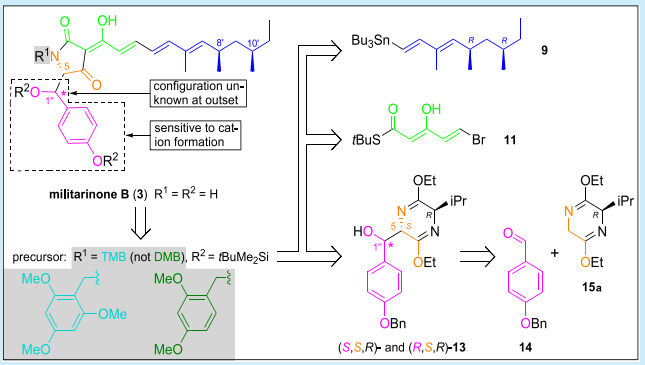
ABSTRACT: The 5*S*, 8′*R*, and 10′*R* configurations of militarinone B (**3**), which is a natural product from *Paecilomyces militaris*, should equal those in its biosynthetic precursor, militarinone C. The configuration at C-1′ emerged from syntheses of the militarinone B candidates 1′′*S*- and 1′′*R*-(5*S*,8′*R*,10′*R*)-**3** from the building blocks **9**, **11**, **14**, and **15a** while introducing TMB as a more acid-labile *N*-protecting group for *β*-ketoamides than DMB. Comparisons of 1′′*S*- and 1′′*R*-(5*S*,8′*R*,10′*R*)-**3** with natural militarinone B (**3**; reisolated from Nature) revealed identity versus distinctness.



Seven natural products are named after the fungus *Paecilomyces militaris*, namely, the (−)-militarinones A[1,2] (**6**), B[2,3] (**3**), C[3] (**1**), D[3] (**5**), E[2] (**4**), and F[2] (**2**) plus (−)-*N*-deoxymilitarinone A[4−7] (**7**; Figure 1). Two of them (B, C) are (polyenoyl)tetramic acids,[8] and five are (polyenoyl)-hydroxypyridones.[9] Earlier total syntheses in this class of compounds led to the militarinones C (**1**[10,11]) and D (**5**[12,6,13]) and to *N*-deoxymilitarinone A (**7**[6]). The present study describes stereoselective total syntheses of the naturally occurring (polyenoyl)tetramic acid militarinone B[3] (**3**) and its unnatural diastereomer *epi*-**3** (formulas are shown in Figure 2).

The configurations of compounds **1**−**7** were mostly unknown when first reported.[1,3,4] An exception are the *syn*-configurations of the methylated stereocenters (C-8′, C-10′)[2] deducible from $\delta_{8'\text{-}CH_3} - \delta_{10'\text{-}CH_3}$ = 2.0−2.2 ppm[14] (Figure 1). Their (*R*)-configurations in **1**, **5**, and **7** emerged from total syntheses[10−12,6,13] and in **1** and **6** from reisolations,[11] Lemieux−Johnson cleavage/$NaBH_4$ reduction tandems, and the identity of the resulting alcohol **8** with authentic (*R*,*R*)-**8** (ref 11 and the present work, respectively). The heterocyclic stereocenter of militarinone C (**1**), C-5, is (*S*)-configured, according to synthesis.[10,11] Since militarinone B (**3**) is believed to be biosynthesized from militarinone C (**1**)[3,2] it should be (5*S*)-configured, too. The (*S*)-configuration of the fourth stereocenter of militarinone B (**3**), C-1′′, became evident after we synthesized the remaining militarinone B candidates, namely **3** and *epi*-**3** (Figure 2), as disclosed below.

Our retrosynthetic analysis of these compounds—**3**, being (1′′*S*,5*S*,8′*R*,10′*R*)-configured and *epi*-**3**, being (1′′*R*,5*S*,8′*R*,10′*R*)-configured—began by the installment of protecting groups (Figure 2). We needed not only *O*-protecting groups, but also an *N*-protecting group. Without (such) an *N*-substituent, the desired tetramic-acid forming step, i.e., Lacey's variant of a Dieckmann cyclization,[15] would fail.[16] The substrates of this step would be made by Stille couplings[17] between a "Western" building block (*S*,*S*)- or (*R*,*S*)-**10** and an "Eastern" building block **9**.[11] The former compounds should be reached from the completely enolized *β*-ketothioester **11** (which we introduced[18] and used[11] previously) and appropriately protected *β*-hydroxytyrosin ester diastereomers (*S*,*S*)- or (*R*,*S*)-**12** through aminolyses.

Considering the last-mentioned esters (*S*,*S*)- or (*R*,*S*)-**12** as aldol adducts, we noticed their similarity to the "azaenolate aldol adducts" (*S*,*S*,*R*)- or (*R*,*S*,*R*)-**13b** (Figure 2). Those had been prepared by Boger et al.[19] and Schobert et al.[20] by applying Schöllkopf's methodology:[21,22] They lithiated the bis(lactim methyl ether) (*R*)-**15b** and added the resulting azaenolate to the (benzyloxy)benzaldehyde **14**. They found great induced diastereoselectivities but almost no simple diastereoselectivity. This was because they obtained an almost equimolar mixture of the (hydroxybenzyl)bis(lactim methyl

Received: May 17, 2021

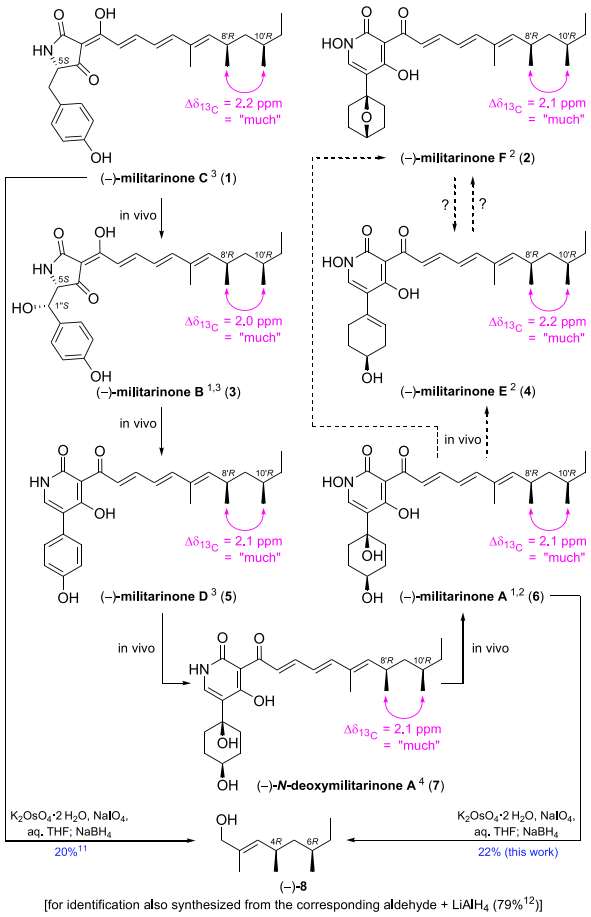


Figure 1. Militarinone family **1**–**7** of natural products. Full configurational assignments by experiment [**1**,[10,11] **3** (this work), **5**,[12,6,13] **6** (this work), **7**[6]] or extrapolation (**2**, **4**).

ether) diastereomers (*S*,*S*,*R*)- and (*R*,*S*,*R*)-**13b**;[19,20] i.e., the newly formed stereocenter in the heterocycle was solely (*S*)-configured, whereas the oxygen-bearing stereocenter was as much (*S*)-configured as (*R*)-configured. The two diastereomers were readily separable by column chromatography.[19,20] We adopted this strategy but followed its originator's recommendations for the less-expensive and faster-forming bis(lactim *ethyl* ether) (*R*)-**15a**.[22b]

Our envisaged route to the militarinone B candidates **3** and *epi*-**3** (Figure 2) required us to choose an *N*-protecting group ("PG" in compounds **12** and **10**). This is because the benzylic C–OH bond in either target appeared to be poised to break in the presence of too strong or too much acid. Such bond breaking could destroy the stereochemical integrity at C-1′′ or lead to a dehydration and/or initiate a ring-enlarging semipinacol rearrangement.[23] We opted for *benzylic* *N*-protecting groups and studied the (polyenoyl)tetramic acid models TBDMS-**16a**–**16c** and **16d** and **16e** of Scheme 1, which we equipped therewith. Two benzyl group variations (in TBDMS-**16a** and TBDMS-**16c**) promised cleavability without an acid. Two other variations (in **16d** and **16e**) were acid-labile. Our *N*-protecting groups of the first type were *para*-nitrobenzyl (in TBDMS-**16a**), which would be reduced to *para*-aminobenzyl (in TBDMS-**16b**) for becoming cleavable by oxidants,[24] and dimethoxy(*ortho*-nitrobenzyl)[25] (in TBDMS-**16c**), which is photolabile at longer wavelengths[26] than *ortho*-nitrobenzyl.[27] Our acid-labile *N*-protecting groups were 2,4-

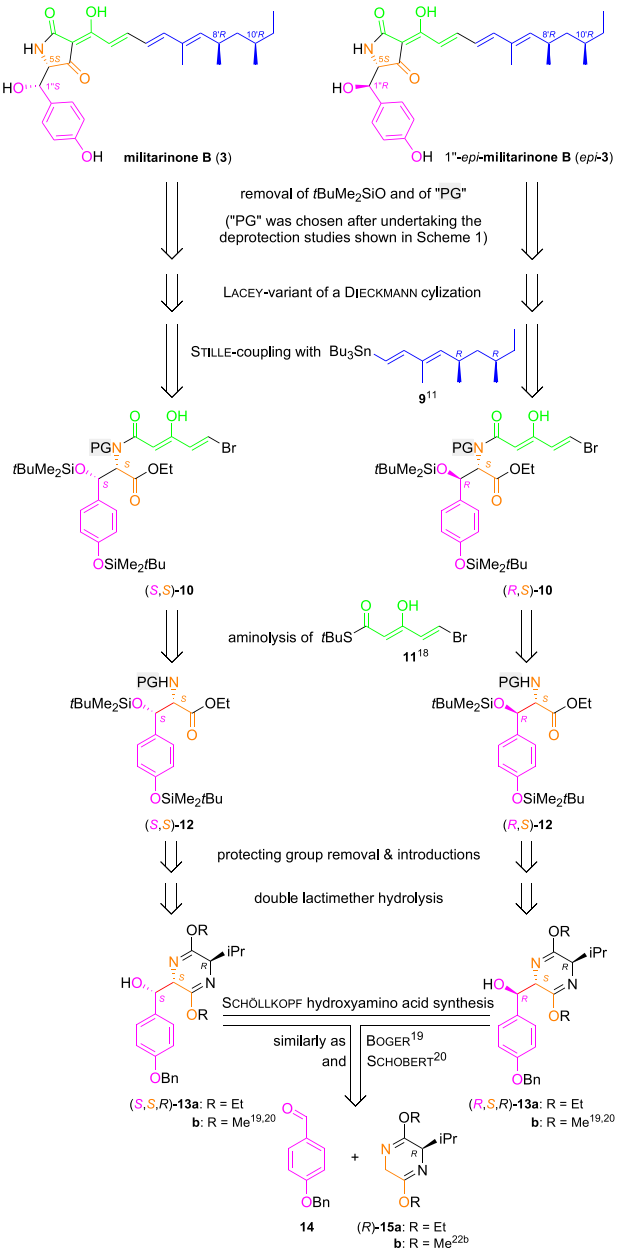


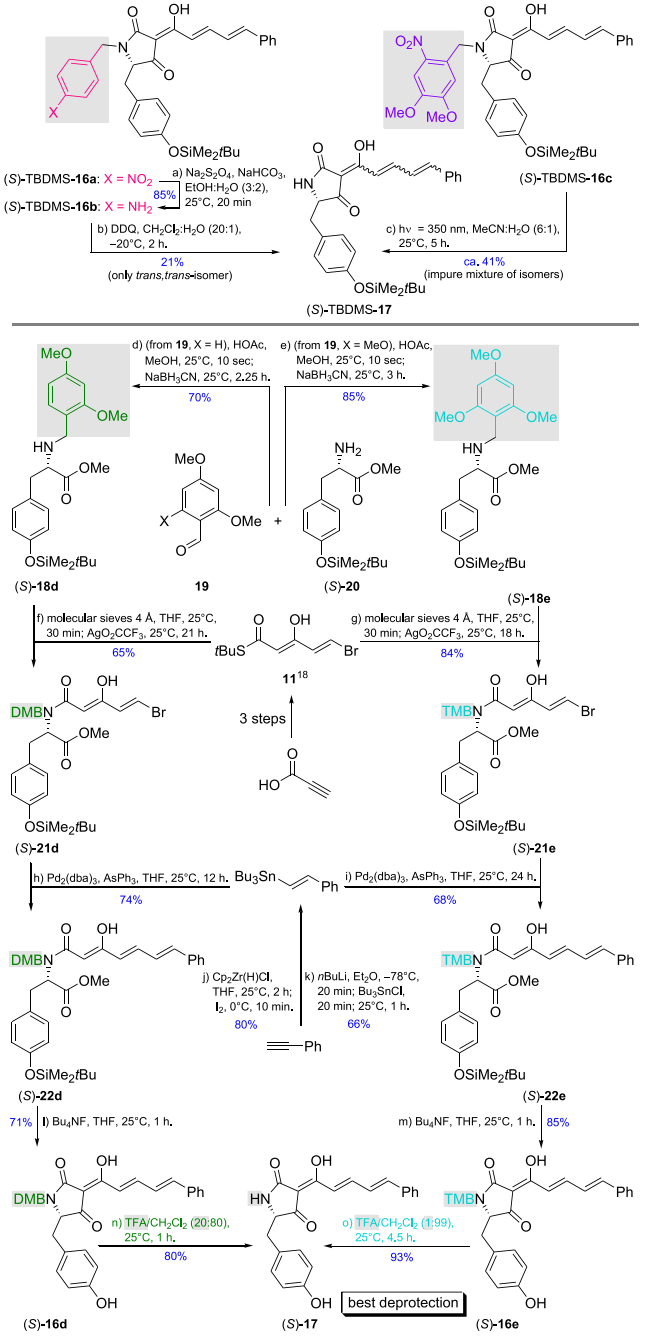
Figure 2. Retrosynthetic analysis of the hitherto conceivable candidates **3** and *epi*-**3** for the structure of natural militarinone B. Emergence of precursors that we had encountered earlier (**9**, **11**) or were the ethyl analogues [(*S*,*S*,*R*)- and (*R*,*S*,*R*)-**13a**] of previously reported methyl esters [(*S*,*S*,*R*)- and (*R*,*S*,*R*)-**13b**] and should be accessible analogously.

dimethoxybenzyl[28] (in **16d**) and 2,4,6-trimethoxybenzyl[29] (in **16e**), but the grading of lability remained to be determined. *N*-2,4,6-trimethoxybenzylated amides of various types are known but they were deprotected—if at all—mainly by hydrogenolysis, secondly by a Birch reduction, and only rarely by acidolysis.

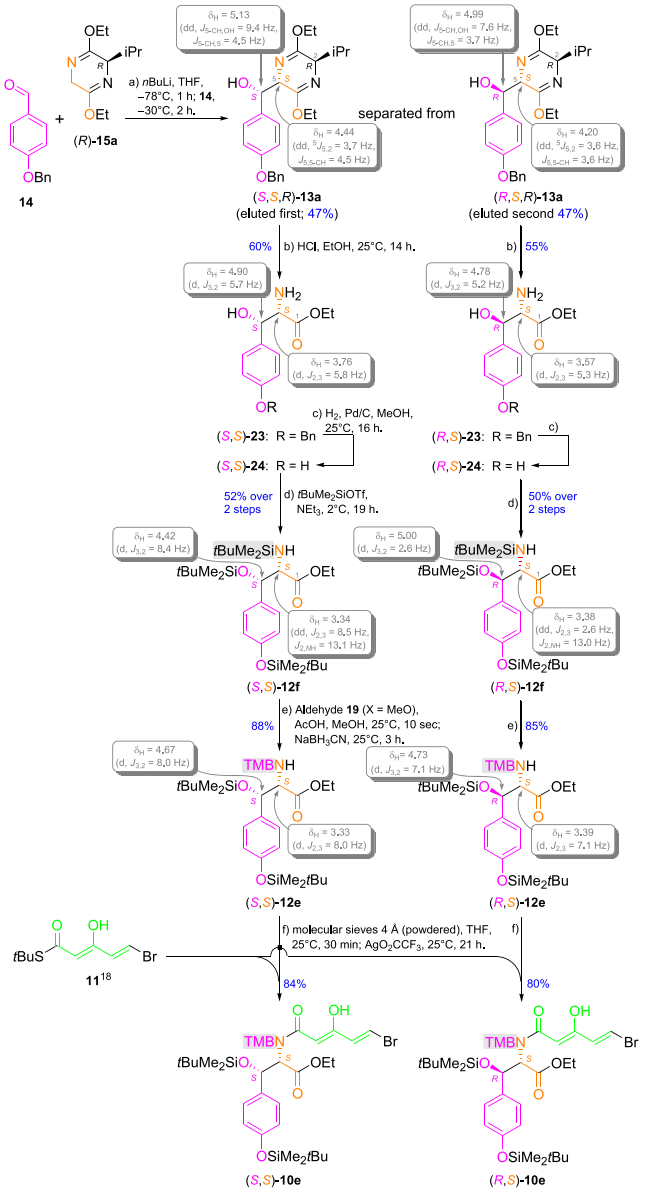
The origins of the less appropriately protected model *N*-benzyl (polyenoyl)tetramic acids TBDMS-**16a** and TBDMS-**16c** are specified in the Supporting Information; those of the more appropriately protected analogues **16d** and **16e** in Scheme 1. We proceeded in accordance with the strategy of Figure 2, the *N*-protections and aminolyses in the lower part of Scheme 2, and the transformations of Scheme 3. A cornerstone of our model syntheses of Scheme 1 was using the *β*-ketoester

https://doi.org/10.1021/acs.orglett.1c01652
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. (Polyenoyl)tetramic Acids Debenzylated Acid-Free (TBDMS-16a,c) or with Dilute Trifluoroacetic Acid (16e > 16d)



Scheme 2. Synthesis of the *N*-TMB-Protected Hydroxytyrosines (*S,S*)- and (*R,S*)-12e and Their Conversion into the "Western" Building Blocks (*S,S*)- and (*R,S*)-10e (500 MHz ^{1}H-NMR Data in $CDCl_3$)



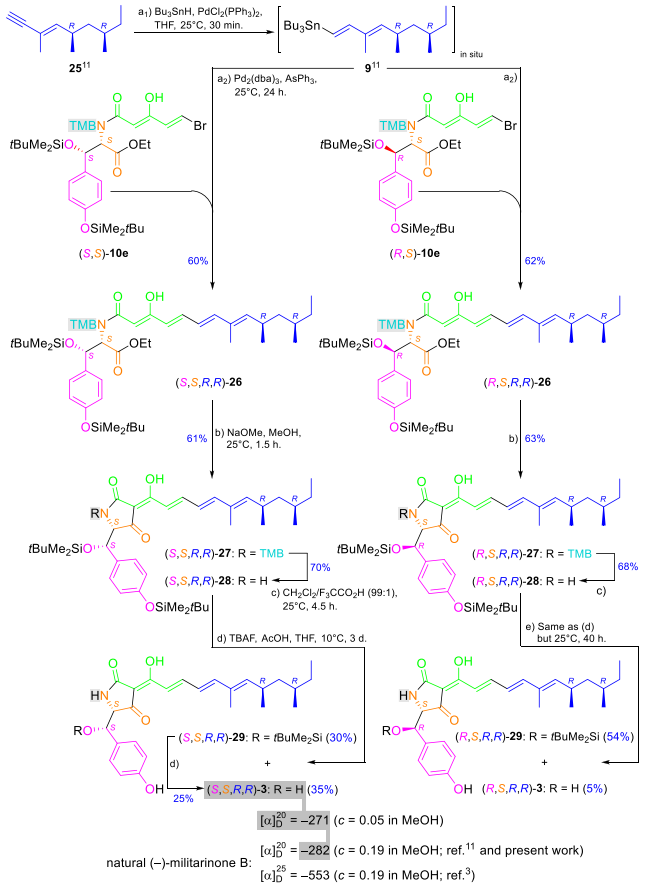
11[18] as a conjunctive reagent for combining the protected amino acids **18d** or **18e** with *trans*-(tributylstannyl)styrene (prepared from phenylacetylene after hydrozirconation and iodinolysis[30]) to the *β*-ketoamides **22d** and **22e**. Their Lacey–Dieckmann cyclizations delivered the respective (polyenoyl)-tetramic acids **16d** and **16e**.

Debenzylating compound TBDMS-**16a** by reduction (→ TBDMS-**16b**) and treatment with DDQ produced <20% of the tetramic acid TBDMS-**17** (Scheme 1). Irradiating compound TBDMS-**16c** gave twice as much TBDMS-**17** yet as an isomeric mixture. F_3CCO_2H/CH_2Cl_2 = 1:4 was needed for the de(dimethoxybenzylation) of compound **16d** at 25 °C (→ **17**; rt, 1 h;[28b] 80%). In contrast F_3CCO_2H/CH_2Cl_2 = 1:99 sufficed for de(trimethoxybenzylating) compound **16e** (→**17**; rt, 4.5 h; 93%). The cleanness and mildness of the last deprotection convinced us of choosing trimethoxybenzyl as the *N*-protecting group in our total syntheses of militarinone B (**3**) and its isomer *epi*-**3** (see Schemes 2 and 3).

We started by an aldol addition of the bis(lactim ethyl ether) (*R*)-**15a** to the (benzyloxy)benzaldehyde **14** (Scheme 2). After separation by flash chromatography,[31] this delivered 47% amounts of the aldols (*S,S,R*)- and (*R,S,R*)-**13a**.[32] Their heterocycles were 2,5-*trans*-disubstituted, not 2,5-*cis*-disubstituted.[33] The diethyl ether (*S,S,R*)-**13a** eluted first and its diastereomer (*R,S,R*)-**13a** second. This was the same order as for the analogous dimethyl ethers (*S,S,R*)- vs (*R,S,R*)-**13b**.[19] In $CDCl_3$ the C-bound protons in the *β*-aminoalcohol moieties of (*S,S,R*)-**13a** vs (*R,S,R*)-**13a** were similarly deshielded ($\Delta\delta$ = 0.22 and 0.14 ppm, respectively) as in their dimethyl counterparts (*S,S,R*)-**13b** vs (*R,S,R*)-**13b** ($\Delta\delta$ = 0.24 and

https://doi.org/10.1021/acs.orglett.1c01652
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. In-Situ Conversion of the Enyne 25 into the "Eastern" Building Block (*R*,*R*)-9. Its Couplings with the "Western" Building Blocks (*S*,*S*)- and (*R*,*S*)-10e and the Final Steps Leading to Militarinone B [(*S*,*S*,*R*,*R*)-3] and Its Epimer (*R*,*S*,*R*,*R*)-3



Compound	*dr*[a]	$t_{retention}$/min in HPLC analysis	^{1}H-NMR signal[b] of heterocyclic H	^{1}H-NMR signal[b] of benzylic H
Natural **3**	98: 2	8.98	4.23 (br. s)	4.99 (d, J_{HH} = 3.8 Hz)
(*S*,*S*,*R*,*R*)-**3**	98: 2	8.99	4.22 (br. s)	4.99 (d, J_{HH} = 3.8 Hz)
(*R*,*S*,*R*,*R*)-**3**	61:39	9.46	4.02 (br. s)	5.04 (d, J_{HH} = 2.7 Hz)

[a]Compound (*S*,*S*,*R*,*R*)-**3** is drawn such that its heteroatom-substituted stereocenters are *syn*-configured, and compound (*R*,*S*,*R*,*R*)-**3** such that they are *anti*-configured. "*dr*" specifies the *syn*:*anti* ratios in reisolated[11] natural militarinone B (**3**) or synthetic (*S*,*S*,*R*,*R*)-**3** but the *anti*:*syn* ratio in synthetic (*R*,*S*,*R*,*R*)-**3**.– [b]NMR data: 500 MHz, $CDCl_3$.

0.08 ppm, respectively[19,20]). The vicinal couplings between these protons was somewhat larger in (*S*,*S*,*R*)-**13** than in (*R*,*S*,*R*)-**13**, regardless of whether they were diethylated or dimethylated: **13a**, ΔJ = 1.0 Hz; **13b**, ΔJ = 0.8 Hz.[19,20] The ethyl esters (*S*,*S*)- and (*R*,*S*)-**23** obtained by hydrolyses of the bislactimethers (*S*,*S*,*R*)- and (*R*,*S*,*R*)-**13a**,[34] respectively, displayed analogous NMR differences (they are shared by the identically configured methyl esters[19]). *O*-Debenzylation [step (c) in Scheme 2], *O*,*O*,*N*-trisilylation [step (d)], and transforming the *N*-silyl into an *N*-trimethoxybenzyl moiety under reductive amination conditions [step (e)] furnished the fully protected hydroxytyrosine diastereomers (*S*,*S*)-**12e** and (*R*,*S*)-**12e**, respectively. Exposure of these compounds to the β-ketothioester **11**[18] and AgO_2CCF_3 let aminolyses occur. They provided the corresponding β-ketoamides—or "Western" building blocks—(*S*,*S*)- and (*R*,*S*)-**10e**.

We continued with a Pd-catalyzed hydrostannylation of the enyne **25** [step (a_1), Scheme 3]; it was derived from (2*R*,4*R*)-2,4-dimethylhexanol (7-step synthesis: see ref 35) in three steps (11% yield over the 10 steps[11]). The resulting dienylstannane **9**—or "Eastern" building block—was so labile that we coupled it without purification with either of the "Western" building blocks (*S*,*S*)- and (*R*,*S*)-**10e** [step (a_2)]. This furnished the chain-extended hydroxytyrosine ethyl esters (*S*,*S*,*R*,*R*)- and (*R*,*S*,*R*,*R*)-**26** in 60% and 62% yield, respectively. Their, Lacey-Dieckmann cyclizations were effected with NaOMe in MeOH [step (b)]. This took longer (1.5 h) than the analogous cyclization of a related methyl ester (15 min[20]). The (tetraenoyl)tetramic acids (*S*,*S*,*R*,*R*)- and (*R*,*S*,*R*,*R*)-**27** resulted in 61% and 63% yield, respectively, after purification by flash chromatography on reversed-phase silica gel.[36] Gratifyingly both compounds released their *N*-bound trimethoxybenzyl protecting groups under as mildly acidic conditions as established for the model de(trimethoxybenzyl-ation) **16e** → **17** (Scheme 1). This delivered the (tetraenoyl)-tetramic acid bis(silyl ethers) (*S*,*S*,*R*,*R*)- and (*R*,*S*,*R*,*R*)-**28** in yields of 70% and 68%, respectively [step (c) in Scheme 3].

Our syntheses were completed by desilylating the tetramic acid bis(silyl ethers) (*S*,*S*,*R*,*R*)- and (*R*,*S*,*R*,*R*)-**28** with HOAc and Bu_4NF (Scheme 3). Exposure of (*S*,*S*,*R*,*R*)-**28** to 16 and 12 equiv of these reagents, as suggested by a literature analogy,[20] gave 74% silicon-free material. It was a 70:30 mixture of the desired tetramic acid (*S*,*S*,*R*,*R*)-**3**, which contains a "*syn*"-configured "Western" moiety, and an "*anti*"-epimer thereof.[37] Doubling the amount of HOAc and working up earlier converted the same substrate into 35% of the tetramic acid (*S*,*S*,*R*,*R*)-**3** (now almost epimer-free: "*syn*":"*anti*" = 98:2) and 30% of the tetramic acid (*S*,*S*,*R*,*R*)-**29** [step (d)]. The latter, HOAc, and Bu_4NF [step (e)] gave a second crop of (*S*,*S*,*R*,*R*)-**3** (25%, "*syn*":"*anti*" = 98:2), its combined yield totaling 43%.

Under the conditions of step (d), the epimeric bis(silyl ether) (*R*,*S*,*R*,*R*)-**28** did not react with HOAc and Bu_4NF. Increasing the temperature by 15 °C let the substrate subside [step (f)] yet preponderantly by a monodesilylation; it rendered the silicon-containing tetramic acid (*R*,*S*,*R*,*R*)-**29** in 54% yield. Didesilylation occurred to a much lesser extent; it delivered the silicon-free tetramic acid (*R*,*S*,*R*,*R*)-**3** with the "*anti*"-configured "Western" moiety in only 3% yield and, worse, jointly with 2% of a "*syn*"-epimer.[37]

The following findings establish that natural militarinone B (**3**) equals (*S*,*S*,*R*,*R*)-**3** (bottom part of Scheme 3): ① their specific rotations are the same; ② **3** was retained as much as (*S*,*S*,*R*,*R*)-**3** in an HPLC comparison but less than (*R*,*S*,*R*,*R*)-**3**; ③ the ^{1}H NMR subspectra of the O–C$^{1''}$(–H)-C$^{5'}$(–H)–N motifs are identical in **3** and (*S*,*S*,*R*,*R*)-**3** but not in (*R*,*S*,*R*,*R*)-**3**.

In conclusion, we accomplished the first total synthesis of the (polyenoyl)tetramic acid natural product (–)-militarinone B (**3**). This revealed that its stereostructure is (*S*,*S*,*R*,*R*)-**3**. The center parts of militarinone B and of the differentially protected model compounds TBDMS-**16a**–**16c** and **17d** and **17e** originated from our group's β-ketothioester **11**.[18] We highlighted 2,4,6-trimethoxybenzyl as an *N*-protecting group for β-ketoamides including β-ketolactames; it was removable at room temperature with as little acid as 1% F_3CCO_2H in CH_2Cl_2. Finally, we proved the absolute configuration of the

https://doi.org/10.1021/acs.orglett.1c01652
Org. Lett. XXXX, XXX, XXX–XXX

(polyenoyl)hydroxypyridone natural product (−)-militarinone A (**6**) following a Lemieux-Johnson cleavage and corrected the sense of rotation of the natural product *N*-deoxymilitarinone A (**7**). Now all members of the militarinone family can be drawn with fact-founded stereoformulas.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01652.

Experimental procedures and characterizations including NMR spectra (PDF)

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Author Contributions

All synthetic work was performed by C.D. under the guidance of R.B. The manuscript was composed by C.D. and R.B.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are indebted to the Deutsche Forschungsgemeinschaft for supporting this work (Project No. BR 881/10). We are grateful to Tamara Ley (Institut für Organische Chemie, Albert-Ludwigs-Universität) for skilled technical assistance. The fungal strain was kindly provided by Prof. Matthias Hamburger (Pharmazeutische Biologie, Universität Basel, Switzerland).

■ DEDICATION

†In memoriam of Ulrich Schöllkopf (Georg-August-Universität Göttingen, Germany).

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https://doi.org/10.1021/acs.orglett.1c01652
Org. Lett. XXXX, XXX, XXX−XXX