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# Structure-Elucidating Total Synthesis of the (Polyenoyl)tetramic Acid Militarinone C§

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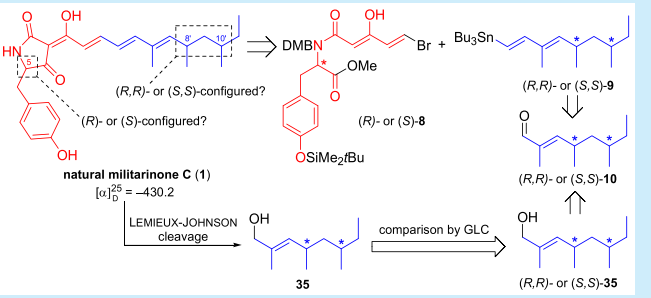
**ABSTRACT:** The (polyenoyl)tetramic acid militarinone C (**1**) heads a family of seven members. Before our work, the configuration of C-5 was unknown whereas the configurations of C-8′ and C-10′ were either (*R*,*R*) or (*S*,*S*). We synthesized the four stereoisomers of constitution **1**, which conform with these insights. This included cross-coupling both enantiomers of the western building block (**8**) with both enantiomers of the eastern building block (**9**). The specific rotations of the resulting **1** isomers suggested that natural **1** is configured like the coupling partners (*S*)-**8** and (*R*,*R*)-**9**. This conclusion was corroborated by degrading natural **1** to alcohol **35** and by proving its configurational identity with synthetic (*R*,*R*)-**35**.




Seven natural products are named after the fungus *Paecilomyces militaris*, (−)-militarinones A[1,2] (**5**), B[3,1] (**2**), C[3] (**1**), D[3] (**3**), E[1] (**6**), and F[1] (**7**) and (+)-*N*-deoxymilitarinone A[4] [**4** (Figure 1)].[5] Two of them (B and C) are (polyenoyl)-

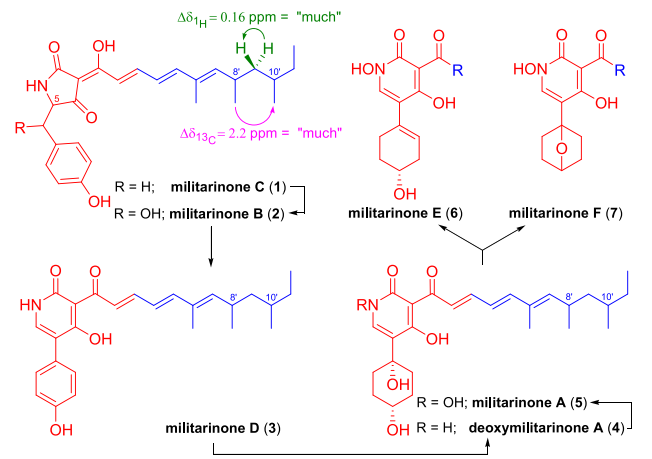



**Figure 1.** Militarinone family of natural products.

tetramic acids,[6] and five are (polyenoyl)pyridones.[7] Our study describes stereoselective total syntheses of the (polyenoyl)-tetramic acid militarinone C[3] (**1**) and three of its diastereomers, and it establishes the (5*S*,8′*R*,10′*R*)-configuration of natural **1**[8] unambiguously. This attribution was not possible originally,[3] although the stereogenic C−$CH_3$ bonds were recognized as *syn*-oriented,[3,9,10] i.e., (*R*,*R*)- or (*S*,*S*)-configured. The (*R*,*R*)-configuration now proven in militarinone C (**1**) should occur in all compounds depicted in Figure 1 because their structures are viewed[3,1] as biogenetically related.

For the same reason, the (*R*,*R*)-configuration of totally synthetic (−)-militarinone D (**1**), proven in 2011,[11] would have indicated the generality of such (*R*,*R*)-configurations in the series, had there not been a conflicting observation in the sequel. (*R*,*R*)-configured *N*-deoxymilitarinone A (**4**) from total synthesis[12] turned out to be levorotatory ($[\alpha]_D^{20}$ = −19.3[12]) as opposed to *N*-deoxymilitarinone A (**4**) from nature, which was dextrorotatory ($[\alpha]_D^{20}$ = +33.3[4]). With the conclusion, accordingly, that natural **4** is (*S*,*S*)-configured, the postulate[3,1] of biogenetic configurational homogeneity of all militarinone side chains is breached.

We took the incertitude about militarinone side-chain configurations beyond the reported cases of (−)-militarinone D (**1**)[11] and *N*-deoxymilitarinone A (**4**)[12] into account when pursuing the first total syntheses of all four militarinone C candidates: (5*S*,8′*R*,10′*R*)-**1**, naturally configured **1**, as it turned out eventually; (5*S*,8′*S*,10′*S*)-**1**, 5-epimer of the unnatural enantiomer of **1**; (5*R*,8′*R*,10′*R*)-**1**, 5-epimer of naturally configured **1**; (5*R*,8′*S*,10′*S*)-**1**, unnatural enantiomer of **1**. In parallel with our effort, the Schobert group took on a total synthesis of the same target militarinone C (**1**). They addressed

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just the (natural) (5*S*,8′*R*,10′*R*)-configuration and disclosed the respective first total synthesis in mid-2018.[13]

In 2014, Hofferberth from our group achieved total syntheses of the (polyenoyl)tetramic acid natural products $\alpha$-lipomycin and its aglycon, $\beta$-lipomycin.[14] His route was very convergent, not in the least because of the use of the newly developed $\delta$-bromo-$\beta$-ketothioester **11**[14] and the previously developed all-*trans*-hexatriene-1,6-bis(tributylstannane)[15] as conjunctive reagents.

Conceiving a related retrosynthetic analysis of the four militarinone C (**1**) candidates, we identified the $\delta$-bromo-$\beta$-ketothioester **11**[14] as a conjunctive building block once more (Figure 2). The western building block (**8**) was traced back to

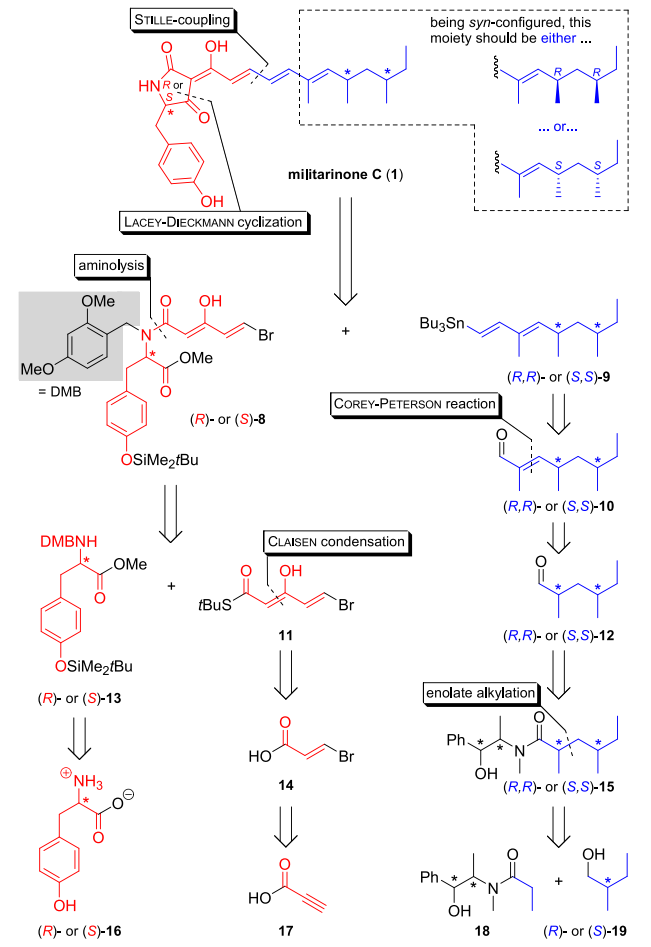
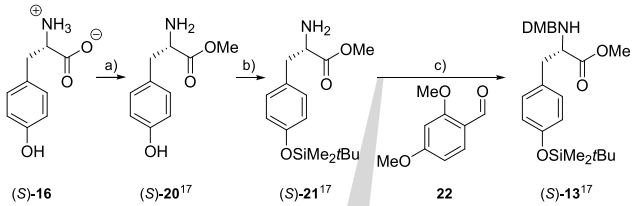



**Figure 2.** Our retrosynthetic analysis of militarinone C (**1**). It engages thioester **11** from our lipomycin work[14] anew.

diprotected tyrosine esters (*R*)- or (*S*)-**13** and the eastern building block [(*R*,*R*)- or (*S*,*S*)-**9**] to $\alpha$-chiral aldehyde (*R*,*R*)- or (*S*,*S*)-**12**. As a late step, we envisaged a Stille coupling of building blocks (*R*)- or (*S*)-**8** and (*R*,*R*)- or (*S*,*S*)-**9**. Thereupon, a Lacey–Dieckmann cyclization[16] should establish the heterocycle. Removal of the protecting groups would render the target(s).

The four syntheses based on the retrosynthesis of Figure 2 are exemplified in Schemes 1–4 by our access to the isomer (5*S*,8′*R*,10′*R*)-**1**, which equals naturally configured **1**. Our routes to the unnatural enantiomer of **1**, (5*R*,8′*S*,10′*S*)-**1**, and to enantiomers (5*S*,8′*S*,10′*S*)- and (5*R*,8′*R*,10′*R*)-**1** of a diastereomer of **1** were strictly analogous; their description is available in the Supporting Information.

**Scheme 1. Synthesis of the N,O-Protected Tyrosine (*S*)-13**[a,20]



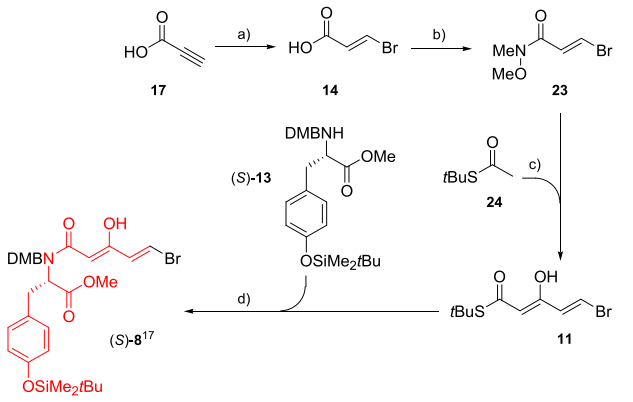

| Entry | Aldehyde **22** (equiv) | $NaBH_3CN$ (equiv) | HOAc (vol-%) | $NaBH_3(OAc)$ (equiv) | NaOAc (equiv) | $t_1$ min | $t_2$ h | % Yield | % *ee* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.5 | 1.5 | 3 | — | — | 120 | 3 | 70 | 0 |
| 2 | 1.2 | 2.0 | 1 | — | — | 60 | 3 | 60 | 71 |
| 3 | 1.1 | — | — | 1.5 | 2.0 | 5 | 20 | 40 | 84 |
| 4 | 1.0 | — | — | 1.5 | 1.5 | 1 | 16 | 42 | 82 |
| 5 | 1.1 | 1.1 | 0.7 | — | — | 90 | 2.5 | 56 | 64 |
| 6 | 1.1 | 1.1 | 0.7 | — | — | 20 | 2.5 | 58 | 85 |
| 7 | 1.1 | 1.5 | 0.7 | — | — | 1 | 2.25 | 55 | 90 |
| 8 | 1.1 | 1.5 | 0.7 | — | — | 0.17 | 2.25 | 62 | 96 |
| 9 | 1.1 | 1.5 | 0.3 | — | — | 0.17 | 2.25 | 70 | 99.5 |

[a]Reagents and conditions: (a) $SOCl_2$, MeOH, 25 °C, 12 h, 95% (ref 17, 99%); (b) *t*Bu$Me_2$SiCl, imidazole, $CH_2Cl_2$, 25 °C, 16 h, 84% (ref 18, 86%); (c) **22**, HOAc or NaOAc, MeOH, 25 °C, $t_1$; $NaBH_3CN$ or $NaBH(OAc)_3$, 25 °C, $t_2$. DMB = 2,4-dimethoxybenzyl.

Methyl *N*-DMB-*O*-TBS tyrosinate [(*S*)-**13**], according to Figure 2 the source of the tyrosine motif of the naturally configured target **1**, was obtained from L-tyrosine [(*S*)-**16**] in three steps (Scheme 1): esterification [→95% (*S*)-**20**[17]], O-silylation [→84% (*S*)-**21**[18]], and reductive amination of 2,4-dimethoxybenzaldehyde (**22**). Although the last transformation [→(*S*)-**13**] had precedent (e.g., ref 19), it eroded the ee significantly (table in Figure 2, entries 2–9) or entirely (entry 1; for conditions, see ref 19). Employing less HOAc (3 to 0.3 vol %) and shortening the delay between the additions of aldehyde **22** and $NaBH_3CN$ (from 120 min to 10 s), we increased the ee of (*S*)-**13** to 99.5% (entries 2 and 5–9).

Our route to western building block (*S*)-**8** began with three known steps (Scheme 2): *trans*-hydrobromination of propiolic

**Scheme 2. Synthesis of Western Building Block (*S*)-8**[a,20]




[a]Reagents and conditions: (a) HBr (concentrated), 100 °C, 1.5 h, 75% (ref 21, 85%); (b) Me(MeO)NH, *N*-methylmorpholine, T3P, $CH_2Cl_2$, 0 °C, 30 min, 85% (ref 14, 86%); (c) LiHMDS, **24**, THF, −78 °C, 1 h; $MgBr_2{\cdot}OEt_2$, 1 h; **23**, 2 h; 75% (ref 14, 83%); (d) thioester **11**, 4 Å molecular sieves (powdered), THF, 25 °C, 30 min; $AgO_2CCF_3$, 25 °C, 24 h;[22] 65%.



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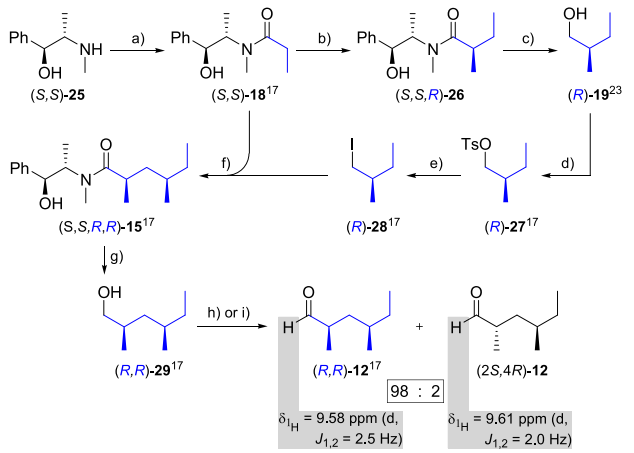
acid (**17**)[21] (→75% **18**), Weinreb amide formation[14] (→85% **23**), and a crossed Claisen condensation with the Mg enolate of *tert*-butyl thioacetate.[14] In step 4, the resulting enol **11** (75% yield) of the desired $\delta$-bromo-$\beta$-ketothioester was aminolyzed in the presence of $AgO_2CCF_3$ and powdered molecular sieves[22] (to prevent any competing hydrolysis) by tyrosinate (*S*)-**13** from Scheme 1 [→65% (*S*)-**8**].

The stereogenic C−$CH_3$ bonds of eastern building block (*R,R*)-**9** were established by asymmetric Myers alkylations[23] of the Li enolate of the amide (*S,S*)-**18**, prepared from pseudoephedrin [(*S,S*)-**26**] and propionic anhydride[23] (Scheme 3). Ethylation of its enolate[24] [→94% (*S,S,R*)-**26**], reduction

**Scheme 3. Establishing the *syn*-Configured C−Methyl Bonds**[a,20,36]

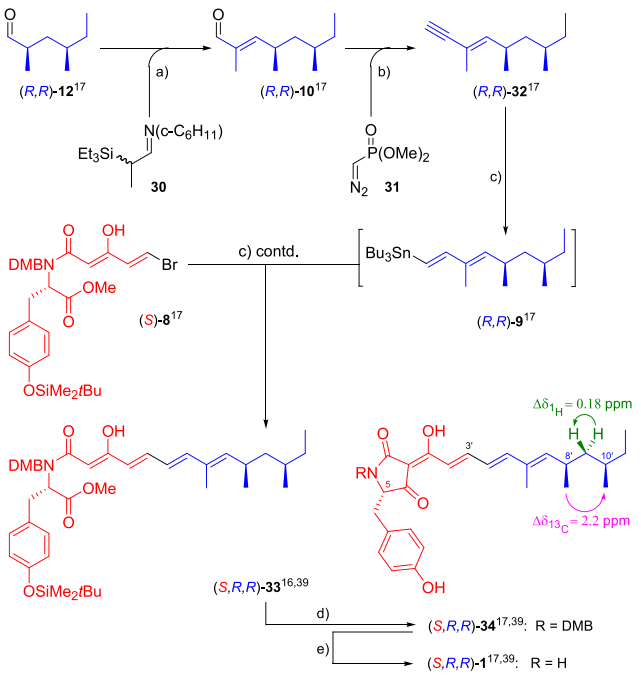



[a]Reagents and conditions: (a) $NEt_3$, propionic anhydride, $CH_2Cl_2$, 25 °C, 30 min, 92% (ref 23, 95%); (b) $iPr_2NH$, LiCl, *n*BuLi, THF, −78 to 0 °C, 5 min; (*S,S*)-**18**, −78 °C, 1 h; 0 °C, 15 min; 25 °C, 5 min; EtI, 25 °C, 15 h; 94% (ref 24, 88%); (c) $iPr_2NH$, *n*BuLi, THF, −78 °C, 10 min; 0 °C, 10 min; $BH_3{\cdot}NH_3$, 0 °C, 15 min; 25 °C, 15 min; (*S,S,R*)-**26**, 25 °C, 2 h; 76% (ref 24, 85%); (d) TsCl, pyridine, 0 °C, 12 h, 83% (ref 25, 99%); (e) NaI, DMF, 60 °C, 1.5 h, 58% (ref 26, 89%); (f) $iPr_2NH$, LiCl, *n*BuLi, THF, −78 to 0 °C, 5 min; (*S,S*)-**18**, −78 °C, 1 h; 0 °C, 15 min; 25 °C, 5 min; (*R*)-**28**, 25 °C, 24 h; 88% (ref 23 for the enantiomer, 94%; ref 24, 95%); (g) $iPr_2NH$, *n*BuLi, THF, −78 °C, 10 min; 0 °C, 10 min; $BH_3{\cdot}NH_3$, 0 °C, 15 min; 25 °C, 15 min; (*S,S,R,R*)-**15**, 25 °C, 2 h; 74% (ref 24, 88%); (h) NMO, 4 Å molecular sieves, $CH_2Cl_2$, 25 °C, 15 min; TPAP (5 mol %), 25 °C, 1 h; 77% (ref 24, 98%); (i) $(COCl)_2$, DMSO, THF, −78 °C, 2 min; 0 °C, 3 min; alcohol (*R,R*)-**29**, −78 °C, 2 min; 0 °C, 15 min; $NEt_3$, 0 to 25 °C; 76%. TPAP = $Pr_4NRuO_4$.

with $LiBH_2{\cdot}NH_3$[23] [→76% alcohol (*R*)-**19**[24]], tosylation [→83% (*R*)-**27**[25]], and a Finkelstein reaction [→58% (*R*)-**28**[26]] provided an iodide of 99% ee. It was combined with another equivalent of the Li enolate of the amide (*S,S*)-**18** to amide (*S,S,R,R*)-**15**[24,27] (88% yield). Reduction with $LiBH_2{\cdot}NH_3$[23] [→74% alcohol (*R,R*)-**29**[24]] and oxidation either with TPAP[24] or by the Ireland modification[28] of Swern's method accomplished the desired aldehyde (*R,R*)-**12** (76−77% yield, 98:2 dr).

Aldehyde (*R,R*)-**12** of Scheme 3 and the azaenolate of $\alpha$-silylimine **30** were subjected to a condensation/hydrolysis sequence,[29] providing 86% of the unsaturated aldehyde (*R,R*)-**10** *E*-selectively (Scheme 4). Alkyne formation by a Seyferth−Gilbert reaction[30] [→81% (*R,R*)-**32**] followed by a $PdCl_2(PPh_3)_2$-catalyzed *cis*-hydrostannylation[30] completed eastern building block (*R,R*)-**9** *in situ*. It Stille-coupled with 0.7 equiv of western building block (*S*)-**8** (Scheme 2) in the

**Scheme 4. Finishing Eastern Building Block (*R,R*)-9 and Reaching Militarinone C [(5*S*,8′*R*,10′*R*)-1] and Three Diastereomers Thereof [(*S,S,S*)-1, (*R,R,R*)-1, and (5*R*,8′*S*,10′*S*)-1]**[a,37]




| specimen of **1** | $[\alpha]_D^{20}$ (*c* = 0.17 in MeOH) |
|---|---|
| natural[3] | −430.2 |
| synthetic[13] = (*S,R,R*) | ? −310 ! |
| synthesized from (*S*)-**8** and (*S,S*)-**9** | ? −350 ? |
| synthesized from (*S*)-**8** and (*R,R*)-**9** | ? −317 ! |
| synthesized from *rac*-**8** and (*S,S*)-**9** | −14 |
| synthesized from *rac*-**8** and (*R,R*)-**9** | +19 |
| synthesized from (*R*)-**8** and (*S,S*)-**9** | +319 |
| synthesized from (*R*)-**8** and (*R,R*)-**9** | +353 |
| natural (this work) | −307 |

[a]Reagents and conditions: (a) **30**, *s*BuLi, THF, −78 °C, 30 min; (*R,R*)-**12**, −20 °C, 2.5 h; isolation of the imine; $CF_3CO_2H$, THF, 0 °C, 1 h; $H_2O$, 0 °C, 14 h; 86%;[29] (b) **31**, KO*t*Bu, THF, −78 °C, 15 min; (*R,R*)-**10**, −78 °C, 5 min; −30 °C, 1.5 h; $NH_4Cl$, −30 °C, 15 min; −30 to 25 °C; 83%;[30] (c) $PdCl_2(PPh_3)_2$ (catalyst), $Bu_3SnH$, THF, 25 °C, 30 min;[30] (*S*)-**8**, $Pd_2(dba)_3$ (catalyst), $AsPh_3$ (catalyst), 25 °C, 24 h; 52%; (d) TBAF, THF, 25 °C, 1 h, 61%;[22] (e) PhSMe, $CH_2Cl_2/F_3CCO_2H$, 25 °C, 1 h, 75%.[33]

presence of $Pd_2(dba)_3$ and $AsPh_3$.[31] The polyenoyl amide (*S,R,R*)-**33** resulted in a 51% yield over the two steps. Treatment with 3.5 equiv of TBAF[22] led to a Lacey−Dieckmann cyclization and desilylation. Purification by flash chromatography on reversed-phase silica gel[32] furnished the DMB-protected tetramic acid (*S,R,R*)-**34** (61%). Exposure to 50 equiv of thioanisole as a cation scavenger in a $F_3CCO_2H/CH_2Cl_2$ mixture (1:4) removed the DMB group.[33] The crude product was dissolved in MeOH to separate it from insoluble impurities.[34] Prepurification by reversed-phase flash chromatography[32] and purification by reversed-phase HPLC[32] delivered target (*S,R,R*)-**1** in 75% yield. Whether it equates to natural militarinone C (**1**) could have emerged from the respective specific rotations had they not differed by as much as $[\alpha]^{20}_{D\ \text{synthetic (S,R,R)-1}} = -317$[35] and $[\alpha]^{20}_{D\ \text{natural 1}} = -430.2$.[3]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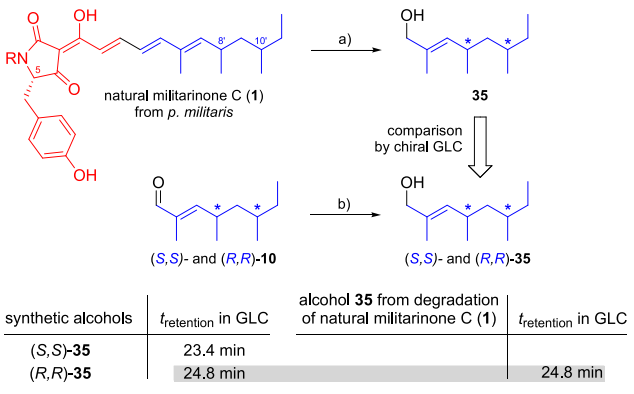
We continued our study by synthesizing another levorotatory diastereomer {(*S,S,S*)-**1**: $[\alpha]_D^{20} = -350$} and two dextrorotatory isomers {(5*R*,8′*S*,10′*S*)-**1**): $[\alpha]_D^{20} = +319$; (*R,R,R*)-**1**: $[\alpha]_D^{20} = +353$}. Altogether, our specific rotations prove that natural **1** is (5*S*)-configured. This is so because the "partial specific rotation" (absolute value) due to the heterocycle of type **1** compounds exceeds the "partial specific rotation" (absolute value) of their side chains by 20-fold. On average, the heterocycle contributes (−317 + −350)/2 and (319 + 353)/2 to $[\alpha]_D^{20}$, i.e., ±335, and the side chain only (−317 − −350)/2 and (319 − 353)/2, i.e., ±17.[38] Or, natural **1** is levorotatory because C-5 is (*S*)-configured and despite C-8′ and C-10′ being (*R*)-configured.

At this stage, we felt obliged to re-isolate militarinone C (**1**) from *P. militaris*[39] to elucidate its side-chain configurations unambiguously: by degrading **1** to a *syn*-dimethylated entity and by comparing it, by chiral GLC, with synthetic reference compounds of known absolute configurations. We cultivated *P. militaris* in 8.4 L of nutrient broth for 32 days. The mycelium was dried and extracted with MeOH (3 × 1 L, 3 × 24 h). After the solvent had been evaporated, a red solid (25.9 g) resulted. It was triturated with $H_2O$ (500 mL). Centrifugation gave a precipitate. After the supernatant was decanted off, this precipitate was triturated with MeOH. The insoluble fraction was precipated by centrifugation. The solution was decanted off and evaporated. This left a red solid (3.52 g). A solution thereof was separated on a Sephadex LH-20 column to afford three militarinone-containing fractions (**A**–**C**). They were purified by reverse-phase HPLC. Altogether, this furnished *N*-deoxymilitarinone A (**4**, 11.5 mg; from fraction **A**), militarinone A (**5**, 177.0 mg; from fraction **A**), militarinone C (**1**, 63.2 mg; from fraction **B**), militarinone B (**2**, 45.0 mg; from fraction **B**), and militarinone D (**3**, 2.4 mg; from fraction **C**).

We trained the degradation of 12 mg of natural militarinone C (**1**) into an alcohol of constitution **35** (Scheme 5) by subjecting solutions (aqueous THF) of 3–8 mg slots of synthetic (*S,S,S*)-**1**, (*R,R,R*)-**1**, (5*S*,8′*R*,10′*R*)-**1**, and (5*R*,8′*S*,10′*S*)-**1** to a one-pot room-temperature Lemieux–Johnson cleavage/$NaBH_4$ reduction. The use of 75 mol % $K_2OsO_4{\cdot}2H_2O$, >30 equiv of $NaIO_4$, and 120 equiv of $NaBH_4$ gave the respective alcohol **35** reproducibly. The "larger"-scale reactions of synthetic **1** isomers allowed us to record meaningful $^1$H NMR spectra of **35** even if it typically contained some residual solvent. The "large"-scale route to **35**, from natural **1**, even allowed us to determine the yield [20% (reaction a of Scheme 5)]. Regardless of the scale, the configuration of **35** could be identified unambiguously by chiral GLC. This became clear after we obtained both the (*R,R*)-enantiomer and the (*S,S*)-enantiomer of the same alcohol **35** selectively from $LiAlH_4$ reductions of the aldehydes (*R,R*)-**10** (Scheme 4) and (*S,S*)-**10** (SI), respectively [79–80% yield (reactions b of Scheme 5)]. The retention time of the synthetic alcohol (*S,S*)-**35** was 23.4 min, and that of synthetic (*R,R*)-**35** was 24.8 min. The latter value equaled the retention time of the alcohol **35** prepared from natural **1**. This equality proves that the methylated stereocenters of militarinone C (**1**) are *R,R*-configured.

**Scheme 5. Degrading Natural Militarinone C and Converting Our Synthetic Intermediates (*S,S*)- and (*R,R*)-10 to *syn*-Dimethylated Allyl Alcohols of Constitution 35**[a]




[a]Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$ (35 mol %), $NaIO_4$ (14 equiv), 1:1 $H_2O$/THF, 25 °C, 1.5 h; $K_2OsO_4{\cdot}2H_2O$ (20 mol %), $NaIO_4$ (10 equiv), 25 °C, 1 h; $K_2OsO_4{\cdot}2H_2O$ (20 mol %), $NaIO_4$ (10 equiv), 25 °C, 1 h; $NaBH_4$ (120 equiv), 25 °C, 1.5 h; 20%; (b) $LiAlH_4$, $Et_2O$, 25 °C, 1.5 h; 80% for (*S,S*)-**35**, 79% for (*R,R*)-**35**.

In conclusion, militarinone C (**1**) was synthesized first by Schobert et al.[13] and now by us. Our synthesis was slightly shorter (21 steps vs ∼22[13] steps altogether). Our longest linear sequence comprised 13 steps (vs 18 steps[13]) and totaled 2.8% yield (vs 2.5%[13]). Besides naturally configured militarinone C (5*S*,8′*R*,10′*R*)-**1**, we synthesized its enantiomer (5*R*,8′*S*,10′*S*)-**1** and the diastereomers (*S,S,S*)-**1** and (*R,R,R*)-**1** analogously (for details, see the Supporting Information). Moreover, we re-isolated natural militarinone C (**1**) and degraded it to an alcohol that was identical with synthetic (*R,R*)-**35**. These supplements to our total synthesis proved that natural militarinone C (**1**) is (5*S*,8′*R*,10′*R*)-configured. If all members of the militarinone family interrelate biosynthetically (Figure 1),[1,3] our configurational assignment of **1** corroborates Gademann's conclusion[11] about the ubiquity of an *R,R*-configuration in all side chains.

Independent of such inferences, we suggest that pure (*R,R*)-*N*-deoxymilitarinone A (**4**) is dextrorotatory like the natural product[4] and not levorotatory as reported for a synthetic specimen[12] (see the second paragraph). This is because a 50:50 mixture of militarinone C diastereomers synthesized from *rac*-**8** and (*R,R*)-(*sic*!)-**9** was dextrorotatory {$[\alpha]_D^{20} = +19$ (Scheme 4)}.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00431.

Experimental procedures, characterizations, and NMR spectra of the synthetic natural product [(5*S*,8′*R*,10′*R*)-**1**] and its synthetic diastereomers (*S,S,S*)-**1**, (5*R*,8′*S*,10′*S*)-**1**, and (*R,R,R*)-**1** (PDF)

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### Author Contributions

All synthetic work was performed by C.D. under the guidance of R.B., and all isolation work by C.D. under the guidance of M.K., M.H., and O.P. The manuscript was composed by C.D. and R.B.

### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

§Dedicated to Professor Siegfried Hünig (Julius-Maximilians-Universität Würzburg) on the occasion of his 99th birthday.

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(36) The enantiomorphous compound (*S*)-**19** is commercially available.
(37) The pair of enantiomers of a diastereomer of this compound were synthesized, too, as described in the Supporting Information.
(38) In accordance with the last number, the (*S*,*S*)-configured side chain in a 1:1 mixture of (5*S*,8′*S*,10′*S*)- and (5*R*,8′*S*,10′*S*)-**1** led to $[\alpha]^{20}_D = -14$; similarly, the (*R*,*R*)-configured side chain in a 1:1 mixture of (5*S*,8′*R*,10′*R*)- and (5*R*,8′*R*,10′*R*)-**1** caused $[\alpha]^{20}_D = +17$ (details in Scheme 4).
(39) Eventually, this allowed us to redetermine $[\alpha]^{20}_{D\ \text{reisolated natural 1}} = -310$ (Scheme 4). This value matches $[\alpha]^{20}_{D\ \text{synthetic (S,R,R)-1}} = -317$ better than $[\alpha]^{20}_{D\ \text{synthetic (S,S,S)-1}} = -350$ (Scheme 4), which, if true, supports the finding that natural **1** is 8′*R*- and 10′*R*-configured.


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