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Synthesis of Optically Active *N*-(4-Hydroxynon-2-enyl)pyrrolidines: Key Building Blocks in the Total Synthesis of *Streptomyces coelicolor* Butanolide 5 (SCB-5) and Virginiae Butanolide A (VB-A)

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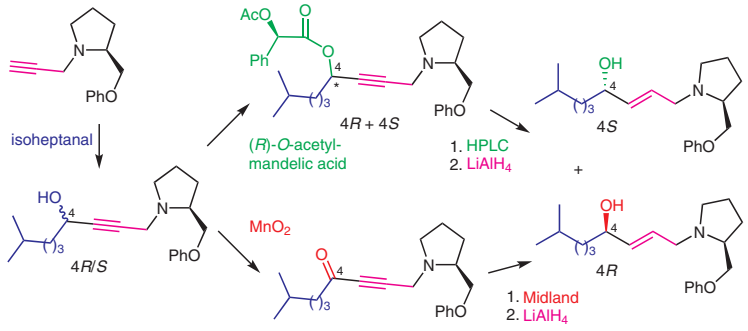

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Abstract Starting from 5-methylhexanal and (*S*)-configured *N*-propargylprolinol ethers, coupling delivered *N*-(4-hydroxynon-2-ynyl)prolinol derivatives as mixtures of C4 diastereomers. Resolution of the epimers succeeded after introduction of an (*R*)-mandelic ester derivative and subsequent HPLC separation. Alternatively, suitable oxidation gave the corresponding alkynyl ketone. Midland reagent controlled diastereoselective reduction afforded a defined configured propargyl alcohol with high selectivity. $LiAlH_4$ reduction and Mosher analyses of the allyl alcohols enabled structure elucidation. The suitably protected products are used as key intermediates in enantioselective *Streptomyces* γ-butyrolactone signaling molecule total syntheses.

Key words propargyl alcohols, allyl alcohols, *N*-allylprolinol derivatives, *O*-acetylmandelic acid, enantioselective reduction, Mosher analysis

Antibiotic production in *Streptomyces* sp. such as *S. virginiae* and *S. coelicolor* is triggered by small molecule hormones.[1] A widely distributed and well-characterized series of signaling molecules are the *trans*-(2-substituted 3-hydroxymethyl)-γ-butyrolactones.[2] After the first discovery of the so-called A-factor (the only 2-acyl-γ-butyrolactone of this series known so far) by Khokhlov and co-workers,[3] 16 further species displaying a 2-(1′-hydroxyalkyl) side chain have been isolated. The Virginiae butanolide (VB)/Gräfe VB-Factor family displays (1′*S*) configuration,[4] the *Streptomyces coelicolor* butanolide (SCB)/IM-2/Gräfe SCB-Factor 1 family (1′*R*) configuration.[5]

Focusing on the bioactivity of the γ-butyrolactones (GBL, Figure 1), the substitution pattern of the C2-bound (1′-hydroxyalkyl) side chain and the relative and the absolute configuration of the stereogenic centers (stereotriad 2,3,1′) play a crucial role.[6] Because of the limited pool of accessible defined GBL's, most investigations have been run using compounds isolated from natural sources and biosynthesis using genetically modified *Streptomyces* strains. Until now, total syntheses of defined optically active VB- and SCB/IM-2-type natural products and diastereomers/enantiomers are sparsely reported.[7]

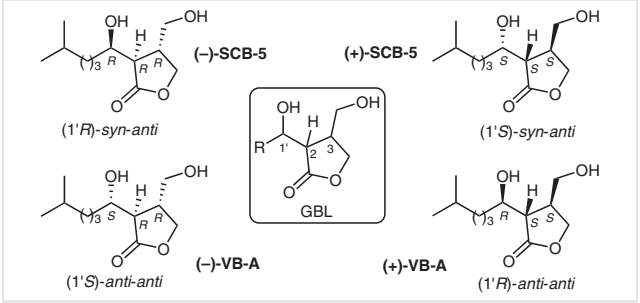

Figure 1 Absolute and relative configurations of Virginiae butanolide A type γ-butyrolactone stereotriads [R = *i*Pr(CH$_2$)$_3$]: (–)-SCB-5 (2*R*,3*R*,1′*R* = 1′*R*-*syn*-*anti*), (+)-SCB-5 (1′*S*-*syn*-*anti*), (–)-VB-A/Gräfe VB-Factor I (2*R*,3*R*,1′*S* = 1′*S*-*anti*-*anti*), (+)-VB-A/Gräfe VB-Factor I (1′*R*-*anti*-*anti*)

The convergent total syntheses of GBL's **A** published so far involved aldol reactions and Claisen condensation/β-keto ester reduction sequences coupling the side-chain

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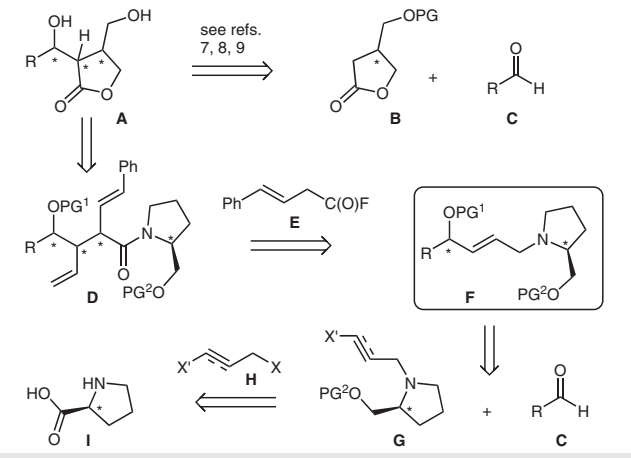
fragments **C** and paraconyl alcohol derivatives **B** completing the stereotriad within the last step with varying selectivities (Scheme 1).[7–9] In this connection, Bibb, Takano and coworkers succeeded in synthesizing both enantiomers of SCB-1/Gräfe Factor 1 and Gräfe VB-Factor II.[7f] The generation of six representative VB and SCB substitution pattern compounds by Mori and Chiba in 1990 should be mentioned as pioneering work.[8] However, assignment of the configurations of the stereogenic centers had to be corrected by Sakuda and Yamada in 1991.[9]

An alternative attempt should build up the stereotriad with high diastereoselectivity prior to the completion of the substitution pattern of the GBL's. For a first total synthesis of the VB-A (Gräfe VB-Factor I)/SCB-5 substitution pattern, a more linear strategy was chosen (Figure 1, Scheme 1).

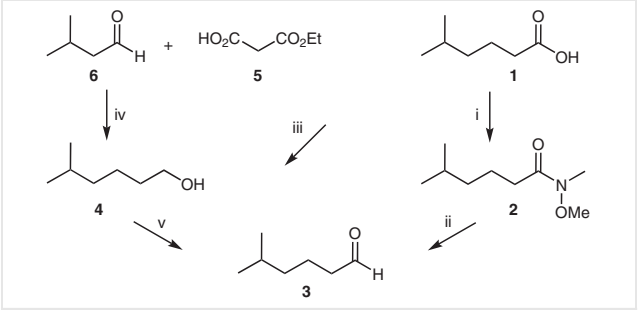
An alternative retrosynthesis involves a separation of generation of the stereogenic centers and the complete assembly of the β-hydroxy lactone moiety (Scheme 1). In this connection, the target lactone **A** was traced back via few steps to a γ,δ-unsaturated amide **D**. The *N*-acylpyrrolidine **D** is the product of a diastereoselective zwitterionic aza-Claisen rearrangement of 4-phenylbutenoic acid fluoride **E** and *N*-allylpyrrolidine **F**.[10] Intending to run the key rearrangement likewise as an auxiliary-controlled and a substrate-controlled process, both defined allyl alcohol configuration and defined (protected) 2-(hydroxyalkyl)pyrrolidine moieties had to be installed. Thus, a coupling of a metalated alkene **G** (X′ = metal) and a metalated alkyne (+ reduction) to isoheptanal **C** (R = 4-MeC_5H_{10}) was envisaged. *N*-Allylprolinol derivatives **G** (X′ = H, halide, $SnBu_3$) and the corresponding *N*-propargyl building blocks should serve as reactants, which had to be synthesized from L-(–)-proline (**I**), propargyl bromide and suitable allyl halides **H** following literature procedures.



Scheme 1 Retrosynthesis of γ-butyrolactone natural products **A**. R = 4-MeC_5H_{10}: SCB-5/VB-A (Gräfe VB-Factor I) [for comparison: R = 5-MeC_6H_{12}: SCB-1 (Gräfe SCB-Factor 1)/Gräfe VB-Factor II]

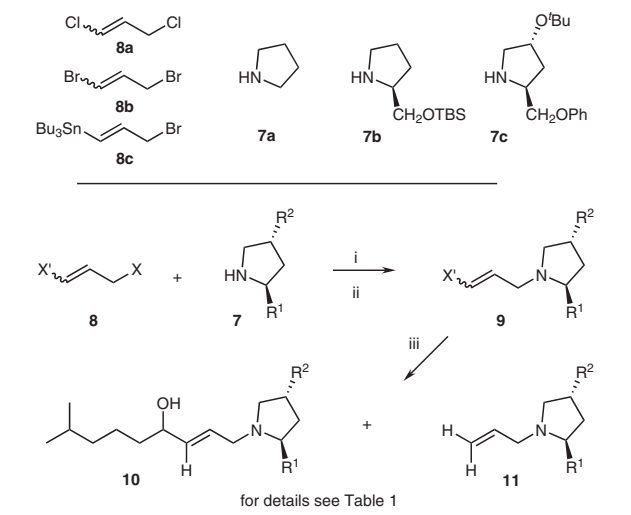
The syntheses of allylamines **F** (compounds **21**, **22**) commenced by assembling the building blocks **C** (compounds **2**, **3**) and **G** (compounds **9**, **14**).

Commercially available 5-methylhexanoic acid (**1**) was converted into the Weinreb amide **2** following a procedure reported by Gosh and Gong (Scheme 2).[11] DIBAL-H reduction gave 5-methylhexanal (**3**) in >83% yield over two steps. Alternatively, $LiAlH_4$ reduction of acid **1** to carbinol **4** and subsequent TEMPO oxidation delivered aldehyde **3** in optimized 96% yield (two steps).[12] Alternatively, a four-step sequence according to literature procedures was started from monoethyl malonate (**5**) and 3-methylbutanal (**6**). Knoevenagel–Doebner condensation, subsequent DIBAL-H reduction and double bond hydrogenation delivered alcohol **4** (61%, 3 steps).[13] In contrast to the TEMPO version as mentioned above (97%), a final Swern oxidation afforded aldehyde **3** in 75% yield only.[12c,13d]



Scheme 2 Synthesis of 5-methylhexanal (**3**). *Reagents and conditions*: (i) DCC, DMAP, $[MeO(Me)NH_2]^+Cl^-$, Et_3N, CH_2Cl_2, 23 °C, 24 h, 99%; (ii) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 84%; (iii) $LiAlH_4$, THF, 23 °C, 24 h, >99%; (iv) (a) pyridine, piperidine, 23 °C to 80 °C, 77 h, 85%; (b) DIBAL-H, CH_2Cl_2, –78 °C to 23 °C, 24 h, 76%; (c) H_2, Pd/C, EtOH, K_2CO_3, 23 °C, 16 h, 94%; (v) version 1 (Swern oxidation): DMSO, $C_2Cl_2O_2$, Et_3N, CH_2Cl_2, –78 °C to 23 °C, 8 h, 75%; version 2: TEMPO, KBr, $NaHCO_3$, NaOCl, CH_2Cl_2, H_2O, 0 °C, 1 h, 97%. For details, see refs. 11–13 and the Supporting Information.

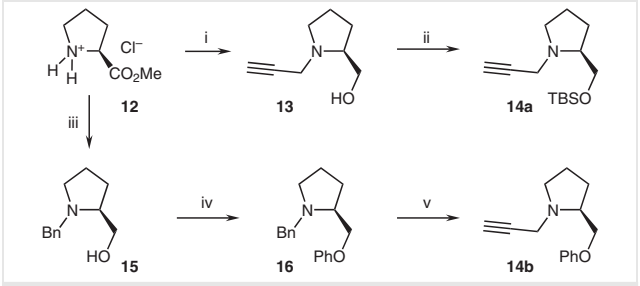
The optically active pyrrolidines **7b** and **7c** were synthesized according to literature procedures, starting from the corresponding amino acids L-(–)-proline and *trans*-4-hydroxy-L-(–)-proline, respectively (Scheme 3).[10g,14] N-Allylation employing allyl halides **8** gave the corresponding 3-functionalized *N*-allylpyrrolidines **9** in 66–89% yield (Table 1).[15] Furthermore, tin–iodine exchange succeeded via standard procedures. Treatment of pyrrolidines **9b** and **9e** with I_2 afforded the vinyl iodides **9c** and **9f** in 66% and >99% yield, respectively.[16] All attempts to couple 5-methylhexanal (**3**) and the *N*-allylpyrrolidines **9** via Grignard-type procedures gave disappointing results despite wide variation of the reaction conditions. Vinyllithium derivatives from (chloroallyl)pyrrolidine **9a** (Li*D*tBB) and the corresponding stannane **9b** (*n*BuLi) gave some racemic allyl alcohol **10** ($R^1 = R^2 = H$) in 14% and 58% yield, but the processes proved to be not robust (Table 1; entries 1, 2).[15b,17] If anything, most runs (**9e**–**9g**;



Scheme 3 Synthesis of *N*-allylpyrrolidines **9** and allyl alcohol **10**. *Reagents and conditions*: (i) variation A: THF, 23 °C, 12–20 h, 86% (**9a**), 89% (**9b**); variation B: Et_3N, PhMe, 65 °C, 67% (**9d**); variation C: *i*Pr_2NEt, THF, 23 °C, 16–60 h, 76% (**9e**), 80% (**9g**, *Z*/*E* = 1:6); (ii) I_2, CH_2Cl_2, 23 °C, 2.5–3 h, 66% (**9c** from **9b**), >99% (**9f** from **9e**); (iii) variation A: Li, DtBB (di-*tert*-butylbiphenyl), THF, 0 °C, 3 h, then **3**, THF, –78 °C to 23 °C, 12 h, 14% (**10** from **9a**); variation B: *n*BuLi, THF, –78 °C, then **3**, THF, –78 °C to 23 °C, 12 h, 58% (**10** from **9b**); variation C: *n*BuLi, PhMe, –78 °C, then **3**, PhMe, –78 °C to 23 °C, 12 h, 40% (**11** from **9f**), 66% (**11** from **9g**). For further details, see Table 1 and the Supporting Information.

Table 1, entries 5–7) delivered some *N*-allylpyrrolidine **11** (R^1 = CH_2OPh, R^2 = O*t*Bu) which indicated a rapid competing proton transfer from aldehyde **3** to lithiated **9**, thus enforcing us to abandon this sequence. Obviously, the Brønsted basicity of the metalated vinyl system dominates and steric reasons might have suppressed any addition.

Switching to *N*-propargylpyrrolidine derivatives **14** promised the use of less sterically congested, more nucleophilic building blocks for coupling with aldehyde **3** (Scheme 4). The assembly of the *N*-propargylprolinol derivatives started from L-(–)-proline methyl ester hydrochloride (**12**).[18] After N-substitution with propargyl bromide and subsequent DIBAL-H reduction, the *N*-propargylprolinol **13** was protected as TBS ether **14a** in 52% yield (3 steps). The generation of phenyl ether **14b** required intermediate protection of the nitrogen for avoiding side reactions. N-Benzylation and $LiAlH_4$ reduction gave *N*-benzylprolinol (**15**; 88% yield, 2 steps).[18c,19] For phenyl ether introduction, the Mitsunobu reaction or O-mesylation with mesyl chloride/Williamson ether formation gave disappointing results.[20] In contrast, treatment of prolinol **15** with phenyl iodide and CuI/Cs_2CO_3[21] afforded the corresponding phenyl ether **16** in 97% yield. Finally, hydrogenolysis of the benzylamine and subsequent treatment with propargyl bromide gave the desired *N*-propargylprolinol derivative **14b** in 87% yield (2 steps).[22]



Scheme 4 Synthesis of *N*-propargylamines **14**. *Reagents and conditions*: (i) (a) propargyl bromide, Et_3N, $MgSO_4$, PhMe, 65 °C, 4 h, 75%; (b) DIBAL-H, THF, –78 °C, 12 h, then –15 °C, 4 h, 83%; (ii) TBSCl, imidazole, THF, 0 °C to 23 °C, 16 h, 84%; (iii) (a) BnBr, Et_3N, CH_2Cl_2, 23 °C, 3 d, 91%; (b) $LiAlH_4$, THF, 0 °C to 23 °C, 21 h, 97%; (iv) PhI, CuI, Cs_2CO_3, phenanthroline, PhMe, reflux, 9 d, 97%; (v) (a) H_2, Pd/C, MeOH, 23 °C, 7 d, >99%; (b) propargyl bromide, Et_3N, THF, 23 °C, 3 d, 88%. For further details, see the Supporting Information.

Table 1 Synthesis of *N*-Allylpyrrolidines

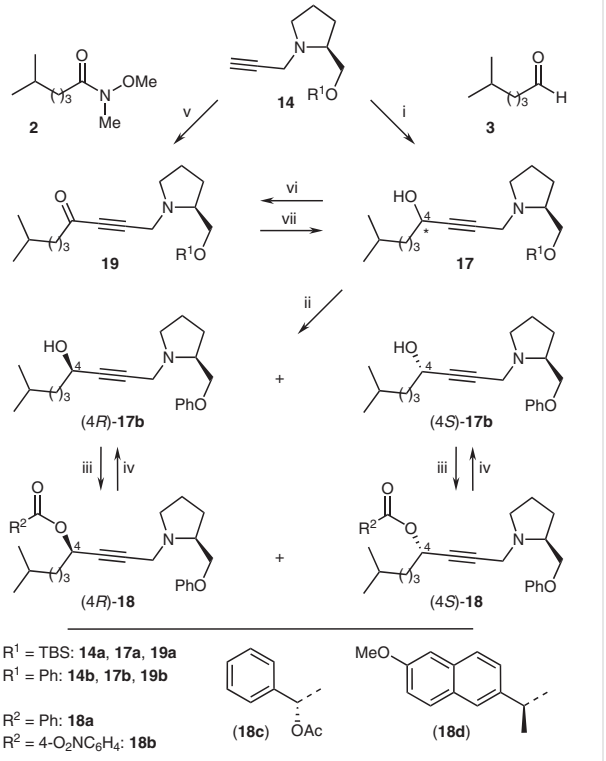
Entry	Amine **7**	Olefin **8**	Allylamine **9**	X′	R^1	R^2	Yield (%)			Remarks
							9	**10**	**11**	
1	**7a**	**8a**	**9a**	Cl	H	H	86	(a) 14	n.d.[a]	varying yields
2	**7a**	**8c**	**9b**	Bu_3Sn	H	H	89	(a) 58	n.d.[a]	varying yields
3	–	–	**9c**	I	H	H	66[b]	–	n.d.[a]	
4	**7b**	**8b**	**9d**	Br	CH_2OTBS	H	67	–	impure	
5	**7c**	**8c**	**9e**	Bu_3Sn	CH_2OPh	O*t*Bu	76	–	(c) <40	competing aldol-type processes
6	–	–	**9f**	I	CH_2OPh	O*t*Bu	>99[c]	–	(c) 40	competing aldol-type processes
7	**7c**	**8a**	**9g**	Cl	CH_2OPh	O*t*Bu	80 (1:6)[d]	–	(c) 66	competing aldol-type processes

[a] Not detected because of low boiling point, removed via Rotavapor.
[b] From **9b**.
[c] From **9e**.
[d] (*Z*/*E*).

Starting from alkynes **14** and aldehyde **3**, additions were performed under standard conditions (Scheme 5).[23] Overall, the less Brønsted basic alkynyl anion effected no competing proton transfers and the reduced steric congestion enabled smooth additions. 5-Methylhexanal (**3**) was treated with lithiated alkynes **14a** and **14b** (*n*BuLi/THF) affording propargyl alcohols **17a** in 62% and **17b** in 91% yield, respectively, as mixtures of C4 diastereomers (about 1:1 and 4:5 *R*/*S*). In contrast to silyl ether **17a** (inseparable diastereomers under widely varied conditions), the phenyl ether **17b** diastereomers were separated via laborious preparative HPLC. Intending to facilitate the resolution of the diastereomers (4*R*/*S*)-**17b**, several ester derivatives **18** were generated. Formation of benzoate (4*R*/*S*)-**18a** and 4-nitrobenzoate (4*R*/*S*)-**18b** succeeded under standard conditions,[24] in nearly quantitative yields. Analysis of the ^{1}H NMR data revealed a perfect overlapping for all signals in connection with benzoates (4*R*/*S*)-**18a** and (4*R*/*S*)-**18b**. The ^{13}C NMR data of esters (4*R*/*S*)-**18a** and (4*R*/*S*)-**18b** displayed some separated peaks for (4*R*)- and (4*S*)-**18a** and (4*R*)- and (4*S*)-**18b**. Unfortunately, HPLC separation of the diastereomers of **18a** and **18b** failed.

Obviously, the long distance between the stereogenic centers of the diastereomers (rigid alkyne moiety) had to be considered. Therefore, introduction of an ester function incorporating a defined remote stereogenic center was recommended. Upon treatment of carbinol (4*R*/*S*)-**17b** with (*R*)-*O*-acetylmandelic acid chloride,[25] the esterification succeeded in 87% yield delivering a mixture of four diastereomers **18c** (Scheme 5). Apparently, the original (*R*)-configured stereocenter of the mandelic acid moiety suffered from some (*S*/*R*) epimerization under the applied reaction conditions.[25b,c] Separation and structure elucidation required laborious HPLC techniques. In contrast, reaction of (4*R*/*S*)-**17b** with (*R*)-*O*-acetylmandelic acid under Steglich conditions (DCC/DMAP)[26] avoided accompanying epimerization, and the mandelic ester (4*R*/*S*)-**18c** was isolated in 92% yield. Preparative HPLC separation gave (4*R*)-**18c** (42% yield) and (4*S*)-**18c** (50% yield). Finally, ester formation using (*S*)-2-(6-methoxynaphthalenyl)propanoic acid/DCC/DMAP gave the corresponding esters **18d** in 78% yield and a d.r. of 36.5:63.5, which were separated via preparative HPLC.[27] In comparison to the mandelic acid derivatives **18c**, an incipient kinetic resolution of the diastereomers **18d** in combination with a somewhat lower yield recommended prioritizing the **18c** series. Regeneration of diastereomerically pure carbinols **17b** succeeded applying Zemplén conditions (K_2CO_3, MeOH).[28] Carbinol (4*S*)-**17b** was obtained from ester (4*S*)-**18c** (97% yield) and from (4*S*)-**18d** (90% yield). Carbinol (4*R*)-**17b** was generated from (4*R*)-**18c** (99% yield) and from (4*R*)-**18d** (88% yield).

A stereoselective access to likewise (4*R*)- and (4*S*)-carbinols **17b** should avoid any laborious separation problems (Scheme 5). In this connection, a reagent-controlled reduction of an alkyl alkynyl ketone **19** was chosen. Starting from Weinreb amide **2**, treatment with lithiated propargylamine **14a** gave ketone **19a** in 34% yield only. The analogous reaction using alkyne **14b** delivered ketone **19b** in 51% yield. Side reactions such as aza-Michael addition of the hydroxylamine to the alkynyl ketone could not be completely suppressed.[29] Alternatively, Dess–Martin oxidation[30] of propargyl alcohol **17a** was tested, and the corresponding ketone **19a** was isolated in 83% yield. Furthermore, MnO_2 oxidation[31] of carbinol **17b** gave ketone **19b** in 80% yield. Comparison of the sequences acid **1** to ketone **19b**, the four-step



Scheme 5 Synthesis and separation of propargyl alcohols (4*R*)-**17** and (4*S*)-**17**. *Reagents and conditions*: (i) *n*BuLi, Et_2O or THF, –78 °C to 23 °C, 3 h, then **3**, Et_2O or THF, –78 °C to 23 °C, 16 h–2 d, 62% (**17a**, d.r. 1:1, inseparable via HPLC), 91% (**17b**, d.r. 4:5, separable via HPLC); (ii) HPLC separation [Nucleosil OH (Diol), hexane/EtOAc 85:15 + 1% Et_3N]; (iii) (a) BzCl, Et_3N, CH_2Cl_2, 23 °C, 24 h, >99% (**18a**, d.r. ~57:43, inseparable via HPLC) or (b) 4-$O_2NC_6H_4C(O)Cl$, Et_3N, CH_2Cl_2, 23 °C, 24 h, >99% (**18b**, d.r. ~55:45, inseparable via HPLC) or (c) (*R*)-*O*-acetylmandelic acid chloride, Et_3N, CH_2Cl_2, 23 °C, 22 h, 87% (**18c**, mixture of 4 diastereomers, partly separable via HPLC) or (d) (*R*)-*O*-acetylmandelic acid, DCC, DMAP, CH_2Cl_2, 23 °C, 2 d, 92% [**18c**, d.r. (4*R*/4*S*) 46:54, separable via HPLC] or (e) (*S*)-2-(6-methoxynaphthalenyl)propanoic acid, DCC, DMAP, CH_2Cl_2, 23 °C, 2 d, 78% [**18d**, d.r. (4*R*/4*S*) 36.5:63.5, separable via HPLC]; (iv) K_2CO_3, MeOH, 23 °C, 24 h, 99% [(4*R*)-**17b** from (4*R*)-**18c**], 97% [(4*S*)-**17b** from (4*S*)-**18c**], 88% [(4*R*)-**17b** from (4*R*)-**18d**], 90% [(4*S*)-**17b** from (4*S*)-**18d**]; (v) *n*BuLi, THF, –78 °C to 23 °C, 3 h, then **2**, THF, –78 °C to 23 °C, 16 h, 34% (**19a**), 51% (**19b**); (vi) (a) Dess–Martin reagent, CH_2Cl_2, 23 °C, 5 h, 83% (**19a** from **17a**) or (b) MnO_2, CH_2Cl_2, 23 °C, 6 d, 80% (**19b** from **17b**); (vii) *R*-Alpine-Borane (*B*-isopinocampheyl-9-borabicyclo-[3.3.1]nonane), THF, 23 °C, 3 d, 69% [**17b** from **19b**, d.r. (4*R*)-**17b**/(4*S*)-**17b** 95:5]. For details, see the Supporting Information.

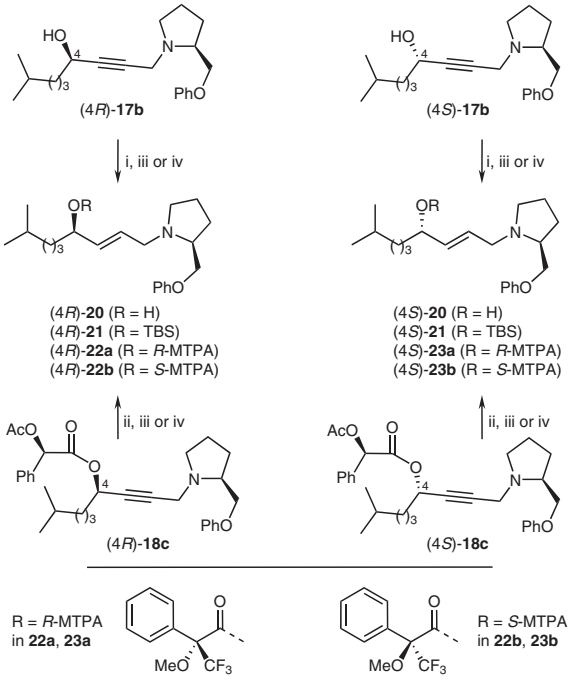
sequence via alcohol **4** and aldehyde **3** gave about 70% yield overall, the two-step sequence including the costly Weinreb amide **2** afforded significantly lower 50% yield (Scheme 2, Scheme 5).

For a reagent-controlled diastereoselective propargyl ketone **19** reduction (Scheme 5), Midland's reagent (*R*-Alpine-Borane) gave a convincing result.[32] Reduction of ketone **19b** afforded carbinol (4*R*)-**17b** in 69% yield and a d.r. of about 95:5 [(4*R*)-**17b**/(4*S*)-**17b**] according to direct HPLC analysis and HPLC separation after mandelic ester **18c** formation.

After assembly of propargyl alcohol (4*R*/*S*)-**17b** (mixture of diastereomers) and the diastereomerically pure propargyl alcohols (4*R*)- and (4*S*)-**17b**, as well as the corresponding esters (4*R*)- and (4*S*)-**18c**, $LiAlH_4$ reduction[33] enabled selective *trans*-olefin **20** formation (Scheme 6). The reaction of carbinol **17b** (mixture of diastereomers) gave allyl alcohol **20** (mixture of diastereomers, d.r. ~46:54) in 85% yield. Again, resolution of the diastereomers (4*R*)- and (4*S*)-**20** required laborious preparative HPLC. Treatment of mandelic esters (4*R*)- and (4*S*)-**18c** with $LiAlH_4$ allowed ester removal and alkyne reduction in a single step.[34] Allyl alcohol (4*S*)-**20** was obtained from ester (4*S*)-**18c** in >99% yield, the analogous conversion using (4*R*)-**18c** gave (4*R*)-**20** in 99% yield. Focusing on workup and purification of the carbinols (4*R*)- and (4*S*)-**20**, reduction of the neat propargyl alcohols (4*R*)- and (4*S*)-**17b** proved to be the best method. Finally, protection of the OH function as a silyl ether was carried out under standard conditions.[35] Reaction of (4*R*)-**20** with TBSOTf/2,6-lutidine delivered the corresponding silyl ether (4*R*)-**21** in 90% yield, (4*S*)-**21** was generated from carbinol (4*S*)-**20** in 83% yield.

Since none of the amino alcohol intermediates **17**–**21** crystallized, structure elucidation was carried out via modified Mosher analysis (Scheme 6).[36] Most convincing results were found starting from allyl alcohols **20**. Reaction of carbinol (4*R*)-**20** with (*R*)- and (*S*)-Mosher acid (MTPA-OH, DCC/DMAP), respectively, gave the corresponding esters (4*R*)-**22a**/**b** in 63%/80% yield. Reaction of carbinol (4*S*)-**20** with (*R*)- and (*S*)-Mosher acid (MTPA-OH, DCC/DMAP) afforded esters (4*S*)-**23a**/**b** in 87%/70% yield. Comparison of the ^{1}H NMR data unequivocally enabled assignment of the absolute configuration at the C4 allyl alcohol centers.

The stereoselective synthesis of enantiopure Virginiae butanolide and *Streptomyces coelicolor* butanolide hormones required efficient access to the optically active (2,3,1′) stereotriads characterizing the key fragments of this series of natural products. Since zwitterionic aza-Claisen rearrangements developed earlier proved to serve as reliable tools to generate such stereotriads with high selectivities, the syntheses of suitably substituted allylamines **20** and **21** were required. The reaction of 5-methylhexanal (**3**) with *N*-propargylprolinol derivatives **14** delivered *N*-(4-hydroxyalk-2-ynyl)pyrrolidines **17** in up to 91% yield as mixtures of diastereomers. Separation succeeded after O-protection as mandelic esters **18c** via preparative HPLC [(4*R*)-**18c**: 42% yield, (4*S*)-**18c**: 50% yield]. Alternatively, Braunstein oxidation delivered the alkynyl ketones **19**; ketone **19b** was then treated with Midland's reagent delivering the product propargyl alcohol moiety (4*R*)-**17b** with defined configuration (52% yield, 2 steps). Finally, $LiAlH_4$ reduction and subsequent allyl alcohol protection delivered the desired key building blocks (4*R*)-**21** in 89% yield and (4*S*)-**21** in 82% yield. Always, structure elucidation of the allyl alcohols **20** was performed via careful Mosher analyses.



Scheme 6 Synthesis of defined configured, protected allyl alcohols (4*R*)-**21** and (4*S*)-**21**. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C to 23 °C, 2 d, 39% (4*R*)-**20** + 46% (4*S*)-**20** [from (4*R*/*S*)-**17b**]; (ii) $LiAlH_4$, THF, 23 °C, 19 h, 99% [(4*R*)-**20** from (4*R*)-**18c**], >99% [(4*S*)-**20** from (4*S*)-**18c**]; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to 23 °C, 20 h, 90% [(4*R*)-**21** from (4*R*)-**20**], 83% [(4*S*)-**21** from (4*S*)-**20**]; (iv) *R*- or *S*-MTPA-OH, DCC, DMAP, CH_2Cl_2, 23 °C, 4 d, 63% [(4*R*)-**22a** from *R*-MTPA-OH and (4*R*)-**20**], 80% [(4*R*)-**22b** from *S*-MTPA-OH and (4*R*)-**20**], 87% [(4*S*)-**23a** from *R*-MTPA-OH and (4*S*)-**20**], 70% [(4*S*)-**23b** from *S*-MTPA-OH and (4*S*)-**20**]; MTPA-OH = 2-methoxy-2-(trifluoromethyl)phenylacetic acid. For further information, including an alternative seven-step synthesis of racemic *N*-(4-benzyloxy-8-methylnon-2-en-1-yl)pyrrolidine, see the Supporting Information.

Overall, starting from known reactants (*S*)-prolinol phenyl ether, propargyl bromide and 5-methylhexanal (**3**), propargyl alcohol **17b** was synthesized via two steps in 80% yield. The generation of single diastereomer protected allyl alcohols (4*R*)-**21** and (4*S*)-**21** was achieved via three further steps via an *O*-acetylmandelic acid ester sequence (HPLC separation of the diastereomers) delivering (4*R*)-**21** in >37% yield and (4*S*)-**21** in 41% yield. Alternatively, a diastereo-

selective four-step sequence (Midland reduction) gave (4*R*)-**21** in >46% yield overall. The optically active allylamines are used as key fragments in an SCB-5 and a VB-A/Gräfe VB-Factor I total synthesis.

Thin-film IR spectra were recorded with a Jasco FT/IR-4100 spectrophotometer with single reflection horizontal ATR (ZnSe window). Optical rotations were recorded with an MC 241 polarimeter (Perkin-Elmer). ^{1}H NMR, ^{13}C NMR and 2D NMR (COSY, HSQC, HMBC, NOESY) spectra were recorded at room temperature with a Bruker Avance III HD 300, Avance II 400 or Avance III HD 400 spectrometer, in $CDCl_3$ using the signal of residual $CHCl_3$ (^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm) as internal standard. FD mass spectra were obtained using a Finnigan MAT 95 system and ESI mass spectra were measured using a Waters Micromass QTOF Ultima 3 spectrometer. HRMS ESI spectra were recorded using an Agilent G6545A Q-ToF spectrometer. Column chromatography was performed on MN silica gel 60M (Macherey-Nagel GmbH & Co. KG) with a grain size of 0.040–0.063 nm. An analytical HPLC system was used to analyze the products: Knauer HPLC Pump 64 connected to a HPLC column (see the Supporting Information), Knauer Variable Wavelength Monitor (λ = 254 or 220 nm) and Knauer Differential Refractometer. Preparative HPLC system: Knauer WellChrom Preparative Pump K-1800 connected to a HPLC column, Knauer Variable Wavelength Monitor (λ = 254 or 220 nm) and Bischoff RI detector 8100. A selection of experimental procedures is given in the following. For all procedures and the numbering used in the ^{1}H and ^{13}C NMR spectra, see the Supporting Information.

(*R*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-yn-4-ol [(4*R*)-17b] and (*S*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-yn-4-ol [(4*S*)-17b]

*n*BuLi (1.12 mL, 3.03 mmol, 1.5 equiv, 2.7 M in PhMe) was added dropwise to a solution of pyrrolidine **14b** (434.9 mg, 2.02 mmol, 1.0 equiv) in Et_2O (15 mL) at –78 °C and the mixture was stirred for 2.5 h at this temperature. 5-Methylhexanal (**3**; 739.7 mg, 6.478 mmol, 3.2 equiv) in Et_2O (10 mL) was added and stirring was continued for 23 h with warming to room temperature. The organic layer was washed with brine (15 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine (3 × 100 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether, 1:5 to 1:1) to afford a diastereomeric mixture of alcohols (4*R*)-**17b** and (4*S*)-**17b** (602.5 mg, 1.829 mmol, 91%) as a yellow oil. The diastereomers (d.r. 4:5) were separated in an analytical amount by HPLC [Nucleosil OH (Diol), EtOAc/hexane 15:85 + 1% Et_3N, 30 mL/min, 34 bar] for characterization.

(4*R*)-17b

$[\alpha]_D^{22}$ –91.1 (*c* 1.00, CH_2Cl_2); R_f = 0.20 (EtOAc/petroleum ether, 1:3; vanillin, UV).

HPLC: t_0 = 1.44 min, *k* = 7.00 [Nucleosil OH (Diol), EtOAc/hexane 15:85 + 1% Et_3N, 2 mL/min, 52 bar].

IR (thin film): 3389 (m, br), 2952 (m), 2867 (m), 1600 (s), 1587 (m), 1496 (s), 1467 (m), 1366 (w), 1301 (w), 1241 (s), 1172 (m), 1079 (m), 1039 (s), 913 (w), 882 (w), 752 (s), 691 (s), 610 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 2 H, H-9), 6.96–6.87 (m, 3 H, H-8, H-10), 4.36 (tt, ^3J = 6.6 Hz, ^5J = 1.8 Hz, 1 H, H-14), 3.97 (dd, ^2J = 9.4 Hz, ^3J = 5.7 Hz, 1 H, H-6a), 3.89 (dd, ^2J = 9.4 Hz, ^3J = 5.7 Hz, 1 H, H-6b), 3.66 (d, ^5J = 1.8 Hz, 2 H, H-11), 3.16–3.03 (m, 2 H, H-2, H-5a), 2.71–2.63 (m, 1 H, H-5b), 2.31 (s, 1 H, H-20), 2.06–1.95 (m, 1 H, H-3a), 1.90–1.69 (m, 3 H, H-3b, H-4), 1.68–1.58 (m, 2 H, H-15), 1.57–1.49 (m, 1 H, H-18), 1.48–1.38 (m, 2 H, H-16), 1.23–1.13 (m, 2 H, H-17), 0.87 (d, ^3J = 6.6 Hz, 6 H, H-19, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0 (C-7), 129.5 (C-9), 120.8 (C-10), 114.6 (C-8), 86.3 (C-12), 80.2 (C-13), 70.9 (C-6), 62.7 (C-14), 60.1 (C-2), 53.7 (C-5), 42.4 (C-11), 38.7 (C-17), 38.4 (C-15), 28.7 (C-3), 28.0 (C-18), 23.2 (C-4, C-16), 22.7 (C-19), 22.7 (C-19′).

MS (ESI): *m*/*z* (%) = 330.25 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{32}NO_2^+$: 330.2433; found: 330.2432.

(4*S*)-17b

$[\alpha]_D^{22}$ –96.6 (*c* 1.00, CH_2Cl_2); R_f = 0.20 (EtOAc/petroleum ether, 1:3; vanillin, UV).

HPLC: t_0 = 1.44 min, *k* = 7.67 [Nucleosil OH (Diol), EtOAc/hexane 15:85 + 1% Et_3N, 2 mL/min, 52 bar].

IR (thin film): 3383 (m, br), 2951 (m), 2868 (m), 1600 (s), 1587 (m), 1496 (s), 1467 (m), 1385 (w), 1366 (w), 1327 (w), 1301 (w), 1241 (s), 1172 (m), 1138 (m), 1079 (m), 1039 (s), 912 (w), 881 (w), 752 (s), 690 (s), 614 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 2 H, H-9), 6.96–6.88 (m, 3 H, H-8, H-10), 4.37 (tt, ^3J = 6.6 Hz, ^5J = 1.8 Hz, 1 H, H-14), 3.98 (dd, ^2J = 9.4 Hz, ^3J = 5.8 Hz, 1 H, H-6a), 3.90 (dd, ^2J = 9.4 Hz, ^3J = 5.6 Hz, 1 H, H-6b), 3.67 (d, ^5J = 1.8 Hz, 2 H, H-11), 3.16–3.03 (m, 2 H, H-2, H-5a), 2.73–2.62 (m, 1 H, H-5b), 2.07–1.94 (m, 1 H, H-3a), 1.92–1.70 (m, 3 H, H-3b, H-4), 1.69–1.58 (m, 2 H, H-15), 1.58–1.49 (m, 1 H, H-18), 1.49–1.38 (m, 2 H, H-16), 1.24–1.14 (m, 2 H, H-17), 0.87 (d, ^3J = 6.6 Hz, 6 H, H-19, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0 (C-7), 129.5 (C-9), 120.9 (C-10), 114.6 (C-8), 86.3 (C-12), 80.3 (C-13), 70.9 (C-6), 62.7 (C-14), 60.2 (C-2), 53.7 (C-5), 42.4 (C-11), 38.7 (C-17), 38.4 (C-15), 28.7 (C-18), 28.1 (C-3), 23.2 (C-4, C-16), 22.7 (C-19), 22.7 (C-19′).

MS (ESI): *m*/*z* (%) = 330.25 (100) $[M + H]^+$, 352.24 (19) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{31}NNaO_2^+$: 352.2252; found: 352.2245.

(*R*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-yn-4-yl (*R*)-2-Acetoxy-2-phenylacetate [(4*R*)-18c] and (*S*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-yn-4-yl (*R*)-2-Acetoxy-2-phenylacetate [(4*S*)-18c]

N,*N*′-Dicyclohexylcarbodiimide (46.0 mg, 0.223 mmol, 2.1 equiv), 4-(dimethylamino)pyridine (12.8 mg, 0.104 mmol, 1.0 equiv) and (*R*)-*O*-acetylmandelic acid (42.3 mg, 0.218 mmol, 2.1 equiv) were added to the diastereomeric mixture of (4*R*/*S*)-alcohols **17b** (34.4 mg, 0.104 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL). The mixture was stirred for 2 d at room temperature. After dilution with CH_2Cl_2 (10 mL) and washing with aqueous $NaHCO_3$ (10 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether, 1:4) to afford a diastereomeric mixture of esters (4*R*)-**18c** and (4*S*)-**18c** (48.6 mg, 96.0 µmol, 92%) as a yellow oil. Purification via HPLC (Nucleosil 50-5, EtOAc/hexane 1:4, 60 mL/min, 63 bar) afforded (4*R*)-**18c** (22.1 mg, 43.7 µmol, 42%) and (4*S*)-**18c** (26.5 mg, 52.3 µmol, 50%).

(4*R*)-18c

$[\alpha]_D^{23}$ –52.3 (*c* 1.00, CH_2Cl_2); R_f = 0.18 (EtOAc/petroleum ether, 1:4; ninhydrin, UV).

HPLC: t_0 = 1.28 min, k = 5.25 (Nucleosil 50-5, EtOAc/hexane 1:4, 2 mL/min, 109 bar).

IR (thin film): 3035 (w), 2954 (m), 2869 (m), 1751 (s), 1601 (m), 1587 (w), 1497 (m), 1457 (m), 1371 (m), 1327 (w), 1233 (vs), 1206 (s), 1174 (s), 1082 (m), 1052 (m), 967 (w), 913 (w), 753 (s), 693 (m), 657 (w), 628 (w), 618 (w), 602 (w), 584 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.46 (m, 2 H, H-26), 7.40–7.33 (m, 3 H, H-25, H-27), 7.30–7.23 (m, 2 H, H-9), 6.93 (tt, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1 H, H-10), 6.90–6.86 (m, 2 H, H-8), 5.91 (s, 1 H, H-21), 5.41 (tt, ^3J = 6.6 Hz, ^5J = 1.8 Hz, 1 H, H-14), 3.86 (dd, ^2J = 9.3 Hz, ^3J = 5.7 Hz, 1 H, H-6a), 3.81 (dd, ^2J = 9.3 Hz, ^3J = 5.6 Hz, 1 H, H-6b), 3.56 (dd, ^2J = 2.6 Hz, ^5J = 1.8 Hz, 2 H, H-11), 3.02–2.93 (m, 1 H, H-2), 2.88 (ddd, ^2J = 9.0 Hz, ^3J = 7.0 Hz, ^3J = 2.3 Hz, 1 H, H-5a), 2.50 (ddd, ^2J = 9.0 Hz, ^3J = 6.9 Hz, ^3J = 6.9 Hz, 1 H, H-5b), 2.20 (s, 3 H, H-23), 1.95–1.83 (m, 1 H, H-3a), 1.82–1.61 (m, 5 H, H-3b, H-4, H-15), 1.59–1.47 (m, 1 H, H-18), 1.47–1.37 (m, 2 H, H-16), 1.23–1.14 (m, 2 H, H-17), 0.87 (d, ^3J = 6.7 Hz, 6 H, H-19, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4 (C-22), 168.0 (C-20), 159.1 (C-7), 133.5 (C-24), 129.5 (C-9), 129.3 (C-27), 128.8 (C-25), 127.8 (C-26), 120.8 (C-10), 114.6 (C-8), 81.7 (C-12), 81.4 (C-13), 74.6 (C-21), 70.9 (C-6), 65.9 (C-14), 59.7 (C-2), 53.3 (C-5), 42.0 (C-11), 38.4 (C-17), 35.0 (C-15), 28.7 (C-3), 27.9 (C-18), 23.3 (C-4), 22.9 (C-16), 22.6 (C-19), 22.6 (C-19′), 20.8 (C-23).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{31}H_{40}NO_5^+$: 506.2901; found: 506.2898.

(4*S*)-18c

$[\alpha]_D^{22}$ –123.1 (c 1.00, CH_2Cl_2); R_f = 0.18 (EtOAc/petroleum ether, 1:4; ninhydrin, UV).

HPLC: t_0 = 1.28 min, k = 7.10 (Nucleosil 50-5, EtOAc/hexane 1:4, 2 mL/min, 109 bar); t_0 = 1.68 min, k = 6.67 (*S*,*S*-Whelk-O 1, *i*PrOH/hexane 2:98, 2 mL/min, 29 bar).

IR (thin film): 3064 (w), 3038 (w), 2953 (m), 2870 (m), 1747 (s), 1600 (m), 1497 (m), 1456 (w), 1371 (m), 1336 (m), 1291 (w), 1228 (vs), 1172 (s), 1110 (w), 1081 (w), 1041 (s), 964 (w), 925 (w), 753 (s), 693 (s), 654 (w), 626 (w), 612 (w), 598 (w), 586 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.44 (m, 2 H, H-26), 7.41–7.33 (m, 3 H, H-25, H-27), 7.31–7.23 (m, 2 H, H-9), 6.96–6.88 (m, 3 H, H-8, H-10), 5.94 (s, 1 H, H-21), 5.39 (tt, ^3J = 6.6 Hz, ^5J = 1.8 Hz, 1 H, H-14), 3.94 (dd, ^2J = 9.4 Hz, ^3J = 5.7 Hz, 1 H, H-6a), 3.87 (dd, ^2J = 9.4 Hz, ^3J = 5.5 Hz, 1 H, H-6b), 3.67 (dd, ^5J = 1.8 Hz, ^2J = 1.6 Hz, 2 H, H-11), 3.14–2.99 (m, 2 H, H-2, H-5a), 2.67 (ddd, ^2J = 9.3 Hz, ^3J = 9.3 Hz, ^3J = 7.2 Hz, 1 H, H-5b), 2.19 (s, 3 H, H-23), 2.03–1.91 (m, 1 H, H-3a), 1.90–1.66 (m, 3 H, H-3b, H-4), 1.65–1.56 (m, 2 H, H-15), 1.45–1.33 (m, 1 H, H-18), 1.28–1.09 (m, 2 H, H-16), 1.09–0.98 (m, 2 H, H-17), 0.78 (d, ^3J = 6.6 Hz, 3 H, H-19), 0.78 (d, ^3J = 6.6 Hz, 3 H, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2 (C-22), 168.0 (C-20), 159.1 (C-7), 133.9 (C-24), 129.5 (C-9), 129.4 (C-27), 128.9 (C-25), 127.8 (C-26), 120.8 (C-10), 114.6 (C-8), 81.9 (C-12), 81.7 (C-13), 74.6 (C-21), 70.8 (C-6), 65.7 (C-14), 60.0 (C-2), 53.5 (C-5), 42.3 (C-11), 38.2 (C-17), 35.0 (C-15), 28.6 (C-3), 27.9 (C-18), 23.3 (C-4), 22.6 (C-16), 22.6 (C-19), 22.5 (C-19′), 20.8 (C-23).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{31}H_{40}NO_5^+$: 506.2901; found: 506.2908.

8-Methyl-1-((*S*)-(2-phenoxymethyl)pyrrolidin-1-yl)non-2-yn-4-one (19b)

MnO_2 (296.8 mg, 3.414 mmol, 10.0 equiv) was added to the diastereomeric mixture of (*R*/*S*)-alcohols (4*R*)-**17b** and (4*S*)-**17b** (112.3 mg, 0.341 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 3 d at room temperature. Then, another portion of MnO_2 (297.4 mg, 3.421 mmol, 10.0 equiv) was added and stirring was continued for a further 3 d. The solids were removed by filtration through a silica pad and the solid residues were rinsed with EtOAc (100 mL). The combined organic layers were dried ($MgSO_4$) to afford ketone **19b** (89.7 mg, 0.274 mmol, 80%) as a yellow oil.

$[\alpha]_D^{22}$ –96.5 (c 1.00, CH_2Cl_2); R_f = 0.41 (EtOAc/petroleum ether, 1:4; ninhydrin, UV).

HPLC: t_0 = 2.60 min, k = 4.00 (Nucleosil 50-5, *i*PrOH/hexane 1:99, 2 mL/min, 41 bar).

IR (thin film): 2954 (m), 2871 (m), 2210 (m), 1675 (s), 1600 (m), 1587 (m), 1498 (s), 1468 (m), 1366 (w), 1301 (w), 1243 (vs), 1153 (m), 1039 (m), 754 (s), 691 (m), 618 (w), 605 (w), 587 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2 H, H-9), 6.94 (tt, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1 H, H-10), 6.92–6.87 (m, 2 H, H-8), 3.92 (d, ^3J = 5.6 Hz, 2 H, H-6), 3.84 (d, ^2J = 9.2 Hz, 2 H, H-11), 3.17–3.11 (m, 1 H, H-2), 3.08 (ddd, ^2J = 9.3 Hz, ^3J = 6.7 Hz, ^3J = 2.8 Hz, 1 H, H-5a), 2.74–2.66 (m, 1 H, H-5b), 2.51 (dd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, 2 H, H-15), 2.08–1.97 (m, 1 H, H-3a), 1.91–1.77 (m, 2 H, H-4), 1.76–1.70 (m, 1 H, H-3b), 1.70–1.61 (m, 2 H, H-16), 1.60–1.48 (m, 1 H, H-18), 1.23–1.15 (m, 2 H, H-17), 0.88 (d, ^3J = 6.6 Hz, 6 H, H-19, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.1 (C-14), 158.9 (C-7), 129.6 (C-8), 121.0 (C-10), 114.6 (C-9), 88.8 (C-12), 84.6 (C-13), 71.2 (C-6), 60.1 (C-2), 53.9 (C-5), 45.9 (C-15), 42.4 (C-11), 38.3 (C-17), 28.5 (C-3), 27.9 (C-18), 23.3 (C-4), 22.6 (C-19, C-19′), 22.1 (C-16).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{30}NO_2^+$: 328.2276; found: 328.2268.

(*R*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-yn-4-ol [(4*R*)-17b]

R-Alpine-Borane (142 mg, 0.550 mmol, 2.0 equiv, 0.5 M in THF) was added to neat ketone **19b** (90.1 mg, 0.275 mmol, 1.0 equiv). The mixture was stirred for 3 d at room temperature. After cooling to 0 °C, 2 M aqueous NaOH (0.35 mL) was added dropwise. After stirring for 5 min, aqueous H_2O_2 solution (0.23 mL, 35%) was added dropwise and stirring was continued for 5 min. The cooling bath was removed and the reaction mixture was heated to 40 °C for 4 h. After cooling to room temperature and dilution with Et_2O (10 mL), 2 M aqueous NaOH (4 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether, 1:1) to afford a diastereomeric mixture of alcohols (4*R*)-**17b** and (4*S*)-**17b** (62.4 mg, 0.19 mmol, 69%) as a yellow oil. The diastereomers were separated by HPLC [Nucleosil OH (Diol), EtOAc/hexane 15:85 + 1% Et_3N, 60 mL/min, 105 bar] to afford (4*R*)-**17b** (56.9 mg, 0.173 mmol, 63%) and a remaining 2:3 mixture of the diastereomeric alcohols (4*R*)-**17b** and (4*S*)-**17b** (5.5 mg, 0.017 mmol, 6%). Overall, a diastereomeric ratio of 95:5 of major (4*R*)-**17b** (59.1 mg, 0.18 mmol, 65.3%) and minor (4*S*)-**17b** (3.3 mg, 0.010 mmol, 3.7%) was found. For spectroscopic data, see above.

(*R*,*E*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-en-4-ol [(4*R*)-20]

$LiAlH_4$ (12.6 mg, 0.332 mmol, 11.3 equiv) was added to alkyne (4*R*)-**18c** (14.8 mg, (0.029 mmol, 1.0 equiv) in THF (3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 19 h. At 0 °C, water (0.1 mL), 3 M aqueous NaOH (0.1 mL) and water (0.3 mL) were successively added dropwise. The mixture was warmed to room temperature and stirred for 30 min. Then, $MgSO_4$ was added. After stirring for 30 min, the mixture was filtered through a pad of Celite and rinsed with Et_2O (50 mL). The organic layer was washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo to afford (*R*)-alcohol (4*R*)-**20** (9.6 mg, 0.029 mmol, 99%) as a yellow oil.

$[\alpha]_D^{29}$ –58.4 (*c* 1.01, CH_2Cl_2); R_f = 0.11 (EtOAc/petroleum ether, 2:3; vanillin, UV).

HPLC: t_0 = 1.17 min, *k* = 10.64. (Remark: preparative column.)

IR (thin film): 3366 (m, br), 2952 (s), 2927 (s), 2868 (m), 1600 (s), 1496 (s), 1468 (m), 1365 (w), 1300 (w), 1242 (s), 1172 (w), 1078 (s), 1039 (s), 974 (m), 912 (w), 883 (w), 753 (s), 691 (s), 640 (w), 617 (w), 606 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 2 H, H-9), 6.96–6.87 (m, 3 H, H-8, H-10), 5.82–5.73 (m, 1 H, H-13), 5.69–5.61 (m, 1 H, H-12), 4.11–4.04 (m, 1 H, H-14), 4.00 (dd, ^2J = 9.3 Hz, ^3J = 5.3 Hz, 1 H, H-6a), 3.85 (dd, ^2J = 9.3 Hz, ^3J = 6.3 Hz, 1 H, H-6b), 3.57 (dd, ^2J = 13.3 Hz, ^3J = 5.8 Hz, 1 H, H-11a), 3.15–3.02 (m, 2 H, H-11b, H-5a), 2.95–2.87 (m, 1 H, H-2), 2.38–2.29 (m, 1 H, H-5b), 2.07–1.95 (m, 1 H, H-3a), 1.85–1.71 (m, 3 H, H-3b, H-4), 1.57–1.40 (m, 3 H, H-15, H-18), 1.40–1.24 (m, 2 H, H-16), 1.20–1.14 (m, 2 H, H-17), 0.86 (d, ^3J = 6.6 Hz, 6 H, H-19, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0 (C-7), 136.4 (C-12), 129.5 (C-9), 128.3 (C-13), 120.8 (C-10), 114.6 (C-8), 72.7 (C-14), 71.1 (C-6), 62.4 (C-2), 57.0 (C-11), 54.6 (C-5), 38.9 (C-17), 37.5 (C-15), 28.7 (C-3), 28.0 (C-18), 23.4 (C-16), 23.1 (C-4), 22.7 (C-19), 22.7 (C-19′).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{34}NO_2^+$: 332.2590; found: 332.2597.

(*S*,*E*)-8-Methyl-1-((*S*)-2-(phenoxymethyl)pyrrolidin-1-yl)non-2-en-4-ol [(4*S*)-20]

Alkyne (4*S*)-**18c** (21.7 mg, 0.0429 mmol, 1.0 equiv) was reduced with $LiAlH_4$ (18.6 mg, 0.490 mmol, 11.4 equiv) according to the procedure described above to afford (*S*)-alcohol (4*S*)-**20** (14.2 mg (0.043 mmol, >99%) as a yellow oil.

$[\alpha]_D^{29}$ –58.1 (*c* 1.02, CH_2Cl_2); R_f = 0.13 (EtOAc/petroleum ether, 3:2; vanillin, UV).

HPLC: t_0 = 1.17 min, *k* = 14.18. (Remark: preparative column.)

IR (thin film): 3354 (m, br), 2951 (s), 2927 (s), 2868 (m), 1600 (s), 1496 (s), 1467 (m), 1384 (w), 1300 (w), 1243 (s), 1172 (w), 882 (w), 753 (s), 691 (s), 652 (w), 633 (w), 616 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 2 H, H-9), 6.96–6.87 (m, 3 H, H-8, H-10), 5.84–5.74 (m, 1 H, H-13), 5.68 (ddt, ^3J = 15.4 Hz, ^3J = 6.5 Hz, ^4J = 1.1 Hz, 1 H, H-12), 4.13–4.05 (m, 1 H, H-14), 4.00 (dd, ^2J = 9.5 Hz, ^3J = 5.3 Hz, 1 H, H-6a), 3.84 (dd, ^2J = 9.3 Hz, ^3J = 6.4 Hz, 1 H, H-6b), 3.55 (dd, ^2J = 13.4 Hz, ^3J = 5.9 Hz, 1 H, H-11a), 3.18–3.06 (m, 2 H, H-11b, H-5a), 2.99–2.88 (m, 1 H, H-2), 2.41–2.31 (m, 1 H, H-5b), 2.07–1.94 (m, 1 H, H-3a), 1.87–1.69 (m, 3 H, H-3b, H-4), 1.57–1.41 (m, 3 H, H-15, H-18), 1.41–1.21 (m, 2 H, H-16), 1.20–1.09 (m, 2 H, H-17), 0.85 (d, ^3J = 6.7 Hz, 6 H, H-19, H-19′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0 (C-7), 136.5 (C-12), 129.5 (C-9), 128.0 (C-13), 120.8 (C-10), 114.6 (C-8), 72.6 (C-14), 71.0 (C-6), 62.3 (C-2), 56.9 (C-11), 54.6 (C-5), 39.0 (C-17), 37.6 (C-15), 28.8 (C-3), 28.0 (C-18), 23.3 (C-16), 23.1 (C-4), 22.7 (C-19), 22.7 (C-19′).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{34}NO_2^+$: 332.2590; found: 332.2598.

(*S*)-1-((*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-8-methylnon-2-en-1-yl)-2-(phenoxymethyl)pyrrolidine [(4*R*)-21]

2,6-Lutidine (0.16 mL, 0.15 g, 1.4 mmol, 2.2 equiv) and TBSOTf (0.30 mL, 0.35 g, 1.3 mmol, 2.1 equiv) were added dropwise to (*R*)-alcohol (4*R*)-**20** (210.5 mg, 0.635 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred for 20 h at room temperature. After dilution with CH_2Cl_2 (20 mL) and washing with aqueous $NaHCO_3$ (40 mL), the remaining aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether, 1:10) to afford silyl ether (4*R*)-**21** (254.9 mg, 0.572 mmol, 90%) as a yellow oil.

$[\alpha]_D^{31}$ –43.5 (*c* 0.99, CH_2Cl_2); R_f = 0.53 (EtOAc/petroleum ether, 1:5; ninhydrin, UV).

HPLC: t_0 = 1.00 min, *k* = 4.00 (Nucleosil 50-5, EtOAc/hexane 1:4, 2 mL/min, 103 bar).

IR (thin film): 2953 (s), 2929 (s), 2857 (m), 2791 (w), 1692 (w), 1601 (m), 1587 (m), 1496 (m), 1469 (m), 1362 (w), 1300 (w), 1245 (s), 1171 (w), 1079 (m), 1039 (m), 1007 (w), 973 (m), 937 (w), 835 (s), 775 (s), 752 (s), 690 (m), 616 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 2 H, H-9), 6.96–6.88 (m, 3 H, H-8, H-10), 5.73–5.57 (m, 2 H, H-12, H-13), 4.11–4.05 (m, 1 H, H-14), 4.04–3.96 (m, 1 H, H-6a), 3.83 (dd, ^2J = 9.2 Hz, ^3J = 6.7 Hz, 1 H, H-6b), 3.54 (dd, ^2J = 13.3 Hz, ^3J = 5.3 Hz, 1 H, H-11a), 3.15–3.03 (m, 2 H, H-11b, H-5a), 2.96–2.86 (m, 1 H, H-2), 2.41–2.30 (m, 1 H, H-5b), 2.06–1.95 (m, 1 H, H-3a), 1.86–1.71 (m, 3 H, H-3b, H-4), 1.58–1.49 (m, 1 H, H-18), 1.48–1.37 (m, 2 H, H-15), 1.37–1.17 (m, 2 H, H-16), 1.17–1.08 (m, 2 H, H-17), 0.88 (s, 9 H, H-22), 0.84 (d, ^3J = 6.6 Hz, 6 H, H-19, H-19′), 0.04 (s, 3 H, H-20), 0.02 (s, 3 H, H-20′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1 (C-7), 137.0 (C-12), 129.5 (C-9), 126.8 (C-13), 120.7 (C-10), 114.6 (C-8), 73.3 (C-14), 71.2 (C-6), 61.9 (C-2), 57.0 (C-11), 54.4 (C-5), 39.0 (C-17), 38.7 (C-15), 28.9 (C-3), 28.1 (C-18), 26.1 (C-22), 23.3 (C-16), 23.2 (C-4), 22.7 (C-19), 22.7 (C-19′), 18.4 (C-21), –4.1 (C-20), –4.6 (C-20′).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{48}NO_2Si^+$: 446.3449; found: 446.3455.

(*S*)-1-((*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-8-methylnon-2-en-1-yl)-2-(phenoxymethyl)pyrrolidine [(4*S*)-21]

2,6-Lutidine (0.69 mL, 0.64 g, 6.0 mmol, 2.2 equiv) and TBSOTf (1.25 mL, 1.43 g, 5.4 mmol, 2.0 equiv) were added dropwise to (*S*)-alcohol (4*S*)-**20** (899.4 mg, 2.713 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for 20 h at room temperature. After dilution with CH_2Cl_2 (20 mL) and washing with aqueous $NaHCO_3$ (40 mL), the resulting aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified via column chromatography (EtOAc/petroleum ether, 1:10) to afford silyl ether (4*S*)-**21** (1.007 g, 2.259 mmol, 83%) as a yellow oil.

$[\alpha]_D^{30}$ –52.7 (*c* 1.02, CH_2Cl_2); R_f = 0.47 (EtOAc/petroleum ether, 1:5; ninhydrin, UV).

HPLC: t_0 = 1.00 min, k = 4.50 (Nucleosil 50-5, EtOAc/hexane 1:4, 2 mL/min, 103 bar).

IR (thin film): 2954 (s), 2927 (s), 2858 (m), 2794 (w), 1746 (w), 1601 (m), 1497 (m), 1469 (m), 1388 (w), 1362 (w), 1300 (w), 1245 (s), 1171 (w), 1081 (m), 1039 (m), 974 (m), 835 (s), 775 (s), 752 (s), 690 (m), 664 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 2 H, H-9), 6.96–6.88 (m, 3 H, H-8, H-10), 5.73–5.57 (m, 2 H, H-12, H-13), 4.11–4.05 (m, 1 H, H-14), 4.04–3.96 (m, 1 H, H-6a), 3.83 (dd, ^2J = 9.2 Hz, ^3J = 6.7 Hz, 1 H, H-6b), 3.54 (dd, ^2J = 13.3 Hz, ^3J = 5.3 Hz, 1 H, H-11a), 3.15–3.03 (m, 2 H, H-11b, H-5a), 2.96–2.86 (m, 1 H, H-2), 2.41–2.30 (m, 1 H, H-5b), 2.06–1.95 (m, 1 H, H-3a), 1.86–1.71 (m, 3 H, H-3b, H-4), 1.58–1.49 (m, 1 H, H-18), 1.48–1.37 (m, 2 H, H-15), 1.37–1.17 (m, 2 H, H-16), 1.17–1.08 (m, 2 H, H-17), 0.88 (s, 9 H, H-22), 0.84 (d, ^3J = 6.6 Hz, 6 H, H-19, H-19′), 0.04 (s, 3 H, H-20), 0.02 (s, 3 H, H-20′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1 (C-7), 137.0 (C-12), 129.5 (C-9), 126.9 (C-13), 120.8 (C-10), 114.6 (C-8), 73.4 (C-14), 71.1 (C-6), 62.2 (C-2), 57.1 (C-11), 54.5 (C-5), 39.0 (C-17), 38.7 (C-15), 28.9 (C-3), 28.1 (C-18), 26.1 (C-22), 23.2 (C-4, C-16), 22.8 (C-19), 22.7 (C-19′), 18.4 (C-21), –4.1 (C-20), –4.6 (C-20′).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{48}NO_2Si^+$: 446.3449; found: 446.3447.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610770.

References

(1) (a) Corre, C.; Son, L.; O'Rouke, S.; Chater, K. F.; Challis, G. L. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 17510. (b) Takano, E. *Curr. Opin. Microbiol.* **2006**, *9*, 287. (c) Bibb, M. J. *Curr. Opin. Microbiol.* **2005**, *8*, 208.

(2) (a) Zou, Z.; Du, D.; Zhang, Y.; Zhang, J.; Niu, G.; Tan, H. *Mol. Microbiol.* **2014**, *94*, 490. (b) Willey, J. M.; Gaskell, A. A. *Chem. Rev.* **2011**, *111*, 174. (c) Kitani, S.; Doi, M.; Shimizu, T.; Maeda, A.; Nihira, T. *Arch. Microbiol.* **2010**, *192*, 211. (d) Shikura, N.; Yamamura, J.; Nihira, T. *J. Bacteriol.* **2002**, *184*, 5151. (e) Kawachi, R.; Akashi, T.; Kamitani, Y.; Sy, A.; Wangchaisoonthorn, U.; Nihira, T.; Yamada, Y. *Mol. Microbiol.* **2000**, *36*, 302. (f) Waki, M.; Nihira, T.; Yamada, Y. *J. Bacteriol.* **1997**, *179*, 5131. (g) Horinouchi, S.; Beppu, T. *Proc. Jpn. Acad., Ser. B* **2007**, *83*, 277.

(3) (a) Kleiner, E. M.; Pliner, S. A.; Soifer, V. S.; Onoprienko, V. V.; Balasheva, T. A.; Rozynov, B. V.; Khokhlov, A. S. *Bioorg. Khim.* **1976**, *2*, 1142. (b) Anisova, N. L.; Blinova, I. N.; Efremenkova, O. V.; Koz'min, L. P.; Onoprienko, V. V. *Izv. Akad. Nauk SSSR, Ser. Biol.* **1984**, 98.

(4) VB Factors: (a) Georgousaki, K.; Tsafantakis, N.; Gumeni, S.; Gonzalez, I.; Mackenzie, T. A.; Reyes, F.; Lambert, C.; Trougakos, I. P.; Genilloud, O.; Fokialakis, N. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126952. (b) Kondo, K.; Higuchi, Y.; Sakuda, S.; Nihira, T.; Yamada, Y. *J. Antibiot.* **1989**, *42*, 1873. (c) Yamada, Y.; Sugamura, K.; Kondo, K.; Yanagimoto, M.; Okada, H. *J. Antibiot.* **1987**, *40*, 496. (d) Gräfe, U.; Reinhardt, G.; Schade, W.; Eritt, I.; Fleck, W. F.; Radics, L. *Biotechnol. Lett.* **1983**, *5*, 591.

(5) SCB Factors: (a) Sidda, J. D.; Poon, V.; Song, L.; Wang, W.; Yang, K.; Corre, C. *Org. Biomol. Chem.* **2016**, *14*, 6390. (b) Sato, K.; Nihira, T.; Sakuda, S.; Yanagimoto, M.; Yamada, Y. *J. Ferment. Bioeng.* **1989**, *68*, 170. (c) Gräfe, U.; Schade, W.; Eritt, I.; Fleck, W. F.; Radics, L. *J. Antibiot.* **1982**, *35*, 1722. For further SCB-1 derivatives displaying additional hydroxyl groups within the side chain, see: (d) Mu, Y.; Yu, X.; Zheng, Z.; Liu, W.; Li, G.; Liu, J.; Jiang, Y.; Han, L.; Huang, X. *Magn. Reson. Chem.* **2019**, *57*, 1150.

(6) SAR: (a) Hsiao, N.-H.; Nakayama, S.; Merlo, M. E.; de Vries, M.; Bunet, R.; Kitani, S.; Nihira, T.; Takano, E. *Chem. Biol.* **2009**, *16*, 951. (b) Nihira, T.; Shimizu, Y.; Kim, H. S.; Yamada, Y. *J. Antibiot.* **1988**, *41*, 1828.

(7) Syntheses. A-factor: (a) Morin, J. B.; Adams, K. L.; Sello, J. K. *Org. Biomol. Chem.* **2012**, *10*, 1517. (b) Crawforth, J. M.; Fawcett, J.; Rawlings, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1721. (c) Mori, K.; Yamane, K. *Tetrahedron* **1982**, *38*, 2919. (d) Parsons, P. J.; Lacrouts, P.; Buss, A. D. *J. Chem. Soc., Chem. Commun.* **1995**, 437. (e) Posner, G. H.; Weitzberg, M.; Jew, S.-S. *Synth. Commun.* **1987**, *17*, 611. SCB-1: (f) Takano, E.; Nihira, T.; Hara, Y.; Jones, J. J.; Gershater, C. J. L.; Yamada, Y.; Bibb, M. *J. Biol. Chem.* **2000**, *275*, 11010. SCB-2: (g) Sarkale, A. M.; Kumar, A.; Appayee, C. *J. Org. Chem.* **2018**, *83*, 4167. IM-2: (h) Mizuno, K.; Sakuda, S.; Nihira, T.; Yamada, Y. *Tetrahedron* **1994**, *50*, 10849. VB-D: (i) Elsner, P.; Jiang, H.; Nielsen, J. B.; Pasi, F.; Jørgensen, K. A. *Chem. Commun.* **2008**, 5827. VB-C: (j) Takabe, K.; Mase, N.; Matsumura, H.; Hasegawa, T.; Iida, Y.; Kuribayashi, H.; Adachi, K.; Yoda, H.; Ao, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2295.

(8) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1990**, 31.

(9) Sakuda, S.; Yamada, Y. *Tetrahedron Lett.* **1991**, *32*, 1817.

(10) The zwitterionic aza-Claisen rearrangement is described as a two-step process. After addition of a tertiary allylamine to an intermediately formed Lewis acid activated ketene, a zwitterionic *N*-acylammonium enolate is generated, which then undergoes a Claisen-type rearrangement with charge neutralization and high stereoselectivities. For a review, see: (a) Nubbemeyer, U. *Synthesis* **2003**, 961. Substrate control: (b) Nubbemeyer, U. *J. Org. Chem.* **1995**, *60*, 3773. (c) Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677. (d) Heescher, C.; Schollmeyer, D.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2013**, 4399. Auxiliary control: (e) Laabs, S.; Münch, W.; Nubbemeyer, U.; Bats, J.-W. *Tetrahedron* **2002**, *58*, 1317. (f) Zhang, N.; Nubbemeyer, U. *Synthesis* **2002**, 242. (g) Friedemann, N. M.; Härter, A.; Brandes, S.; Groß, S.; Gerlach, D.; Münch, W.; Schollmeyer, D.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2012**, 2346.

(11) (a) Gosh, A. K.; Gong, G. *Org. Lett.* **2007**, *9*, 1437. (b) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664.

(12) (a) Kanegusuku, A. L.; Castanheiro, T.; Ayer, S. K.; Roizen, J. L. *Org. Lett.* **2019**, *21*, 6089. (b) Tate, D. J.; Anemian, R.; Bushby, R. J.; Nanan, S.; Warriner, S. L.; Whitaker, B. J. *Beilstein J. Org. Chem.* **2012**, *8*, 120. (c) Zhang, X.; Da, S.; Zhang, C.; Xie, Z.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 507.

(13) Avoiding use of the expensive starting material 5-methylhexanoic acid (**1**): (a) List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Job, A.; Rios Torres, R. *Tetrahedron* **2006**, *62*, 476. (b) Debarge,

S.; McDaid, P.; O'Neill, P.; Frahill, J.; Wong, J. W.; Carr, D.; Burrell, A.; Davies, S.; Karmilowicz, M.; Steflik, J. *Org. Process Res. Dev.* **2014**, *18*, 109. (c) Rigoli, J. W.; Moyer, S. A.; Pearce, S. D.; Schomaker, J. M. *Org. Biomol. Chem.* **2012**, *10*, 1746. (d) Graham, S. M.; Prestwich, G. D. *J. Org. Chem.* **1994**, *59*, 2956.

(14) (a) Widianti, T.; Hiraga, Y.; Kojima, S.; Abe, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1881. (b) Xu, D.; Luo, S.; Yue, H.; Wang, L.; Liu, Y.; Xu, Z. *Synlett* **2006**, 2569. (c) Liu, F.; Wang, S.; Wang, N.; Peng, Y. *Synlett* **2007**, 2415.

(15) (a) Lochead, A. W.; Proctor, G. R.; Canton, M. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2477. (b) Gómez, C.; Huerta, F. F.; Yus, M. *Tetrahedron* **1998**, *54*, 6177. (c) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114. (d) Xu, H.-D.; Wu, H.; Jiang, C.; Chen, P.; Shen, M.-H. *Tetrahedron Lett.* **2016**, *57*, 2915. (e) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959. (f) Hughes, T. E.; Vath, J. E. PCT Int. Appl WO 201471368, **2014**.

(16) (a) Waterhouse, R. N.; Collier, T. L.; O'Brien, J. C. *J. Labelled Compd. Radiopharm.* **1996**, *38*, 215. (b) Rhoden, J. B.; Bouvet, M.; Izenwasser, S.; Wade, D.; Lomenzo, S. A.; Trudell, M. L. *Bioorg. Med. Chem.* **2005**, *13*, 5623.

(17) (a) Caubere, P. *Bull. Soc. Chim. Fr.* **1964**, 148. (b) Guijarro, A.; Yus, M. *Tetrahedron* **1994**, *50*, 13269.

(18) (a) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, *53*, 16449. (b) Fischer, F.; Jungk, P.; Weding, N.; Spannenberg, A.; Ott, H.; Hapke, M. *Eur. J. Org. Chem.* **2012**, 5828. (c) Mlostoń, G.; Wróblewska, A.; Obijalska, E.; Heimgartner, H. *Tetrahedron: Asymmetry* **2013**, *24*, 958.

(19) (a) Osorio-Nieto, U.; Chamorro-Arenas, D.; Quintero, L.; Höpfl, H.; Sartillo-Priscil, F. *J. Org. Chem.* **2016**, *81*, 8625. (b) Bohland, F.; Erlin, I.; Platte, L.; Schröder, M.; Schollmeyer, D.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2014**, 6272. (c) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3304.

(20) (a) Lizarzaburu, M. E.; Shuttleworth, S. *Tetrahedron Lett.* **2003**, *44*, 4873. (b) Sonawane, R. P.; Mueck-Lichtenfeld, C.; Froehlich, R.; Bergander, K.; Hoppe, D. *Chem. Eur. J.* **2007**, *13*, 6419. (c) Dehmlow, E. V.; Klauck, R.; Duettmann, S.; Neumann, B.; Stammler, H.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 2235.

(21) (a) Monnier, F.; Taillefer, M. *Angew. Chem.* **2009**, *121*, 7088. (b) Toumi, M.; Rincheval, V.; Young, A.; Gergeres, D.; Turos, E.; County, F.; Mignotte, B.; Evano, G. *Eur. J. Org. Chem.* **2009**, 3368. (c) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, L. S. *Org. Lett.* **2002**, *4*, 973.

(22) (a) Hedenström, E.; Andersson, F.; Hjalmarsson, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1513. (b) Lee, D.; Long, S. A.; Murray, J. H.; Adams, J. L.; Nuttall, M. E.; Nadeau, D. P.; Kikly, K.; Winkler, J. D.; Sung, C.-M.; Ryan, M. D.; Levy, M. A.; Keller, P. M.; DeWolf, W. E. Jr. *J. Med. Chem.* **2001**, *44*, 2015. (c) Fischer, H.; Podschadly, O.; Roth, G.; Herminghaus, S.; Klewitz, S.; Heck, J.; Houbrechts, S.; Meyer, T. *J. Organomet. Chem.* **1997**, *541*, 321. (d) Tsuo, H.-R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, F. E.; Greenberger, L. M.; Wang, Y.-F.; Wissner, A. *J. Med. Chem.* **2001**, *44*, 2719.

(23) (a) Unterhalt, B.; Middelberg, C. *Arch. Pharm.* **1994**, *327*, 119. (b) Unterhalt, B.; Middelberg, C. *Sci. Pharm.* **1994**, *62*, 51. Catalytic control: (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (d) Silhankova, A.; Hoscovec, M.; Liboska, R.; Ferles, M. *Collect. Czech. Chem. Commun.* **1989**, *54*, 1067. (e) Trost, B. M.; Ryan, M. C.; Rao, M.; Marcovic, T. Z. *J. Am. Chem. Soc.* **2014**, *136*, 17422. (f) Pennell, M. N.; Turner, P. G.; Sheppard, T. D. *Chem. Eur. J.* **2012**, *18*, 4748. (g) Thiede, S.; Wosniok, P. R.; Herkommer, D.; Debnar, T.; Tian, M.; Wang, T.; Schremp, M.; Menche, D. *Chem. Eur. J.* **2017**, *23*, 3300. (h) Shrekhar, V.; Reddy, D. K.; Reddy, S. P.; Prabhakar, P.; Venkatesvarlu, Y. *Eur. J. Org. Chem.* **2011**, 4460.

(24) Toshima, K.; Ohishi, K.; Tomishima, M.; Matsumura, S. *Heterocycles* **1997**, *45*, 851.

(25) (a) Müller, P.; Bon, V.; Senkovska, I.; Nguyen, K. D.; Kaskel, S. *Polyhedron* **2019**, *159*, 382. Epimerization: (b) Abad, J.-L.; Camps, F. *Tetrahedron* **2004**, *60*, 11519. (c) Hartwig, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1952.

(26) (a) Bartholomäus, R.; Bachmann, J.; Mang, C.; Haustedt, L. O.; Harms, K.; Koert, U. *Eur. J. Org. Chem.* **2013**, 180. (b) Candy, M.; Durand, T.; Galano, J.-M.; Oger, C. *Eur. J. Org. Chem.* **2016**, 5813. (c) McNeill, A. H.; Thomas, E. J. *Synthesis* **1994**, 322. (d) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3202. (e) Jung, M. E.; Min, S.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10834. (f) Du, Y.; Turlington, M.; Zhou, X.; Pu, L. *Tetrahedron Lett.* **2010**, *51*, 5024.

(27) (a) Nuin, E.; Gómez-Mendoza, M.; Andreu, I.; Marin, M. L.; Miranda, M. A. *Org. Lett.* **2013**, *15*, 298. (b) Kutner, A.; Martynow, J.; Chodynski, M.; Szelejewski, W.; Fitak, H.; Kupra, M. PCT Int. Appl WO 2003087048, **2003**.

(28) (a) Guy, A.; Oger, C.; Heppekausen, J.; Signorini, C.; Defelice, C.; Fürstner, A.; Durand, T.; Galano, J.-M. *Chem. Eur. J.* **2014**, *20*, 6374. (b) Ogawa, S.; Morikawa, T. *Eur. J. Org. Chem.* **2000**, 1759. (c) Steel, P. G.; Mills, O. S.; Parmee, E. R.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 391.

(29) (a) Yoshino, T.; Ng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 14185. (b) Friest, J. A.; Broussy, S.; Chung, W. J.; Berkowitz, B. B. *Angew. Chem.* **2011**, *123*, 9057. (c) Bär, A.; Bär, S. I.; Schobert, R. *Org. Biomol. Chem.* **2020**, *18*, 7565. (d) Ref. 22d; with acid chloride. (e) Jepsen, T. H.; Glibstrup, E.; Crestey, F.; Jensen, A. A.; Kristensen, J. L. *Beilstein J. Org. Chem.* **2017**, *13*, 988. (f) D'Hooghe, M.; Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 2703.

(30) (a) Manikanta, G.; Nagaraju, T.; Radha Krishna, P. *Synthesis* **2016**, *48*, 4213. (b) Schömberg, F.; Zi, Y.; Vilotijevic, I. *Chem. Commun.* **2018**, *54*, 3266. (c) Oonishi, Y.; Hosotani, A.; Yokoe, T.; Sato, Y. *Org. Lett.* **2019**, *21*, 4120.

(31) (a) Yang, F.; Ji, K.-G.; Zhao, S.-C.; Ali, S.; Ye, Y.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Eur. J.* **2012**, *18*, 6470. (b) Hashimoto, T.; Okabe, A.; Mizuno, T.; Izawa, M.; Takeuchi, R. *Tetrahedron* **2014**, *70*, 8681. (c) Jacobi, P. A.; Craig, T. A.; Walker, D. B.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

(32) (a) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371. (b) Liron, F.; Knochel, P. *Chem. Commun.* **2004**, 304. (c) Lunkwitz, R.; Zab, K.; Tschierske, C. *J. Prakt. Chem./Chem.-Ztg.* **1998**, *340*, 662.

(33) (a) Trost, B. M.; Tometzki, G. B. *Synthesis* **1991**, 1235. (b) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. (c) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330. (d) Sabitha, G.; Reddy, T. R.; Srinivas, C.; Yadav, J. S. *Helv. Chim. Acta* **2011**, *94*, 224.

(34) (a) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem.* **1998**, *63*, 6952. (b) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. (c) Compostella, F.; Franchini, L.; Giovenzana, G. B.; Panza, L.; Prosperi, D.; Ronchetti, F. *Tetrahedron: Asymmetry* **2002**, *13*, 867.

(35) (a) Brodmann, T.; Janssen, D.; Sasse, F.; Irschik, H.; Jansen, R.; Müller, R.; Kalesse, M. *Eur. J. Org. Chem.* **2010**, 5155. (b) Altendorfer, M.; Raja, A.; Sasse, F.; Irschik, H.; Menche, D. *Org. Biomol. Chem.* **2013**, *11*, 2116. (c) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149.

(36) The diastereomerically pure alcohols (4*R*)-**20** and (4*S*)-**20** with unknown absolute configuration were converted into the corresponding esters with (*R*)- and (*S*)-Mosher acid. The anisotropic shielding effect of the aryl group causes a more intensive upfield shift of adjacent protons upon comparison of the ^{1}H NMR spectra of both esters. Adopting favorable conformations of the carbon backbone (zigzag chain with minimized repulsive interactions), the Newman projections presented in the Supporting Information indicate the proximity of R^1 and R^2 of the carbinol and the Mosher ester substituents Ph and OMe. For details, see the Supporting Information. Also see: (a) Hoye, T. R.; Jeffrey, C. S.; Sao, F. *Nat. Protoc.* **2007**, *2*, 2451. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. G.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.