Natural Product Synthesis

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A Second-Generation Total Synthesis of Spirastrellolide A Methyl Ester**

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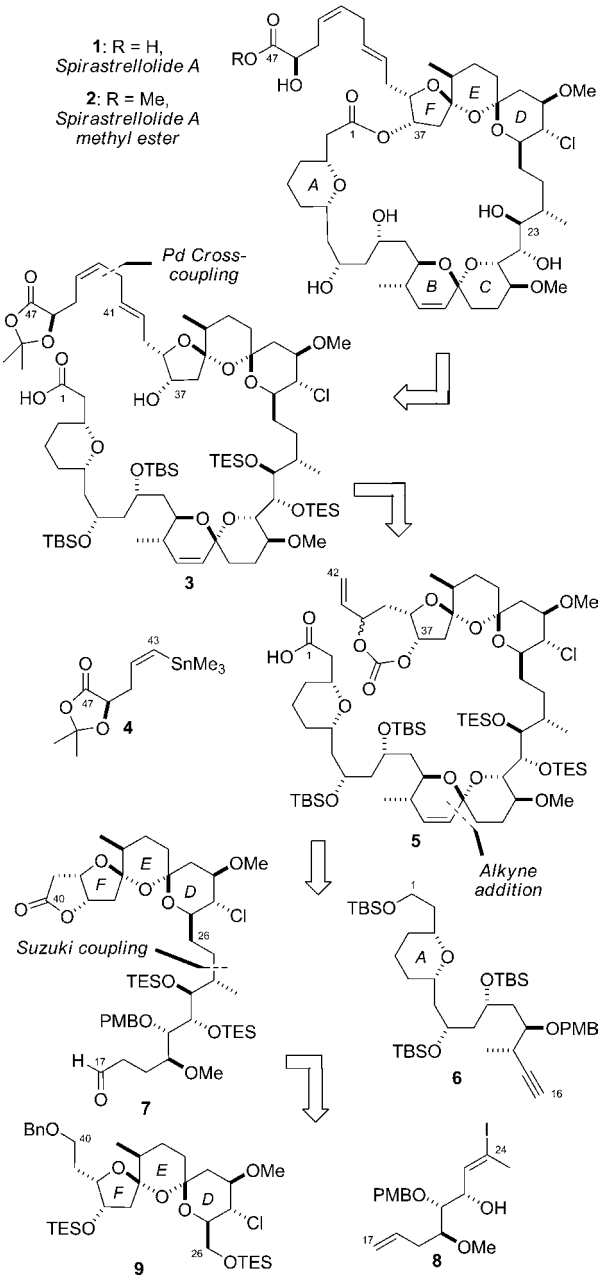
Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

Marine macrolides that selectively disrupt cell cycle events represent important lead compounds for anticancer drug discovery,[1,2] as highlighted by the recent development of Halaven (a fully synthetic analogue of the halichondrins) for the treatment of metastatic breast cancer.[3] Notable amongst this group are the spirastrellolides, a family of complex macrocyclic polyketides isolated from the Caribbean sponge *Spirastrella coccinea*, of which the first to be reported (in 2003) and most abundant member is spirastrellolide A (**1**, Scheme 1).[4] However, structural and stereochemical determination was not completed until 2007, following the identification and derivatization of six closely related congeners, spirastrellolides B–G.[5] Isolated as their methyl ester derivatives (e.g. **2**), these architecturally complex 38-membered macrolides exhibit uniformly strong activity and an unusual phenotypic response in a cell-based antimitotic assay, which has been shown to be mediated through potent and selective inhibition of protein phosphatase 2A ($IC_{50} = 1$ nM for **1**). As drugs that target the inhibition of protein phosphatases have already shown considerable therapeutic value in fields tackling cancer and other metabolic disorders,[6] the synthesis and evaluation of novel PP2A inhibitors based on the spirastrellolide scaffold is of significant current interest.

Testament to the acute challenge presented by these spiroacetal macrolides, and despite intense research efforts,[7–9] only three completed syntheses of the spirastrellolides have been reported to date: the first total synthesis of spirastrellolide A methyl ester **2** by our group,[10] and two subsequent syntheses of the 15,16-dihydro congener, spirastrellolide F methyl ester, by the Fürstner group.[11,12] Evolving alongside the structure determination studies undertaken by the Andersen group, our first-generation total synthesis of **2** tackled the double challenge of constructing the fragments whilst maintaining the flexibility required to access any of the possible spirastrellolide diastereomers. Following this synthesis and freed of such restrictions, we now report a signifi-



Scheme 1. 2nd generation retrosynthetic analysis of spirastrellolide A methyl ester. Bn = benzyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

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cantly improved second-generation total synthesis of **2** that features uniformly high levels of stereocontrol combined with more expedient fragment assembly, in which the crucial macrolactonization step is found to exhibit a critical dependence on a free C23 alcohol in the fully elaborated C1–C47 *seco* acid.

A key modification to this second-generation synthesis was simplification of side-chain attachment through preparation of the complete C1–C47 carbon backbone (**3**) prior to macrolactonization (Scheme 1).[13] The corresponding C1–C47 *seco* acid **3** would be accessed using a cross-coupling reaction between C43–C47 stannane **4** and C1–C42 cyclic carbonate **5**. This revised approach would allow for stereocontrolled installation of the required *E*,*Z* skipped diene while simultaneously freeing the C37 hydroxy group for macrolactonization, thereby reducing reliance on protecting groups.

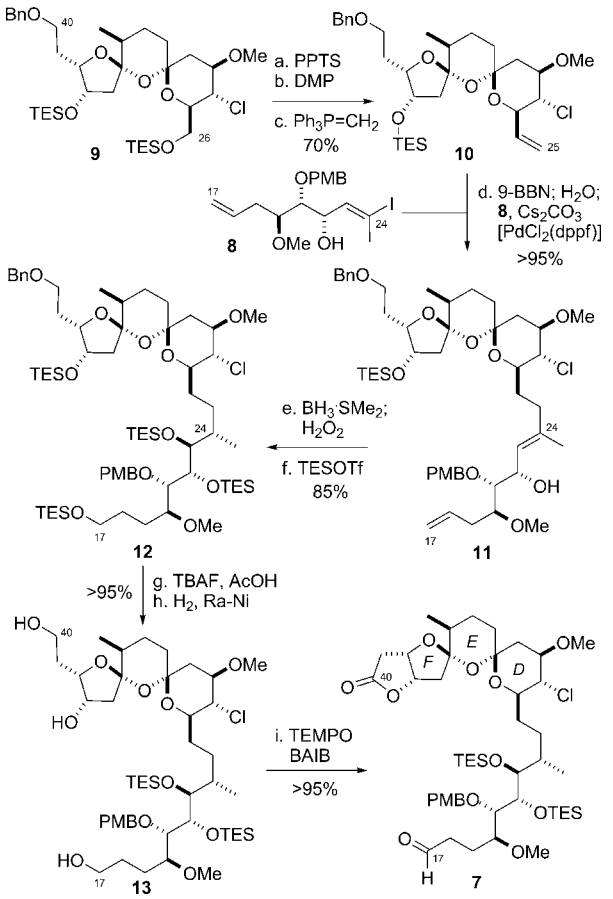
Cyclic carbonate **5** would be generated from a γ-lactone fused to the F ring. Building on our earlier studies, the BC-spiroacetal would be installed through PMB deprotection/in situ spiroacetalization of a *Z* enone arising from coupling of the C1–C16 alkyne fragment **6** and C17–C40 aldehyde **7**. Bond scission at C24/C25 then reveals two intermediates we had employed previously: the C17–C24 vinyl iodide **8**[10a] and the C26–C40 DEF-bis(spiroacetal) **9**.[8d]

As shown in Scheme 2, synthesis of C17–C40 aldehyde **7** commenced with selective desilylation of DEF-bis(spiroacetal) **9** to afford the corresponding C26 alcohol, which was then oxidized (DMP, $NaHCO_3$) and methylenated (H_3CPPh_3Br, *n*BuLi) to give the C25–C40 alkene **10** in 70% overall yield. Hydroboration of alkene **10** with 9-BBN provided the corresponding trialkylborane which was then subjected to a highly effective *B*-alkyl Suzuki coupling[14] with vinyl iodide **8**, mediated by [$PdCl_2$(dppf)], which delivered diene **11** in essentially quantitative yield.

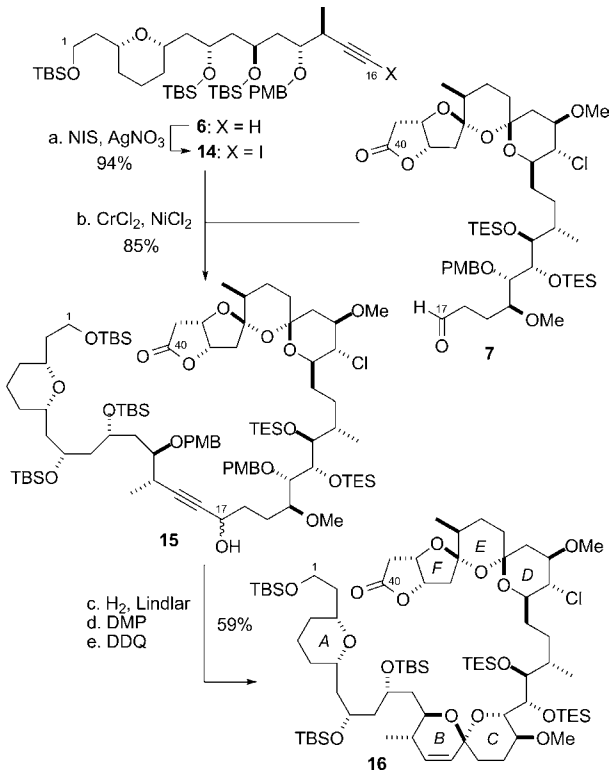
Installation of the requisite hydroxy groups at C17 and C23, with the necessary configuration at C23/C24, was then carried out through a substrate-controlled double hydroboration of diene **11**. Significant enhancement in the diastereoselectivity of this key transformation was realized by exploiting a marked substrate concentration dependence. Under optimized conditions, diene **11** was added dropwise over 2 h via syringe pump to a solution of $BH_3{\cdot}SMe_2$ in THF at 0 °C. Oxidative workup (H_2O_2, NaOH) and persilylation of the crude triol then provided the tetra-TES ether **1** in excellent yield and diastereoselectivity (85%, 10:1 d.r.). Selective deprotection to remove the more labile C17 and C37 TES ethers, followed by debenzylation, gave triol **13** in >95% yield. At this stage, completion of the targeted C17–C40 fragment **7** was conveniently and efficiently accomplished through a one-pot, triple oxidation at C17 and C40 (TEMPO/PhI$(OAc)_2$) which proceeded with concomitant lactonization.[15]

With the modified C17–C40 aldehyde **7** in hand, coupling with the C1–C16 framework was required (Scheme 3). Initial attempts involving exposure of the lithium acetylide of **6** to aldehyde **7** led predominantly to decomposition, which is thought to relate to complications arising from the γ-lactone moiety.[16] After a degree of experimentation, smooth coupling of the corresponding iodoalkyne **14** with aldehyde **7** was accomplished under Nozaki–Hiyama–Kishi conditions ($NiCl_2$, $CrCl_2$).[17] The resulting C1–C40 propargylic alcohols **15** were subjected to Lindlar reduction (H_2, Pd/$CaCO_3$/Pb, quinoline) and Dess–Martin oxidation to provide the corresponding *Z* enone in 72% yield over the two steps. Bis-PMB deprotection (DDQ, 0 °C) and in situ spiroacetalization then provided C1–C40 BC-spiroacetal **16** as a single diastereomer (82%), without accompanying deprotection of the C23 TES ether as observed previously—a seemingly minor detail which later proved to be of great consequence.[10b]

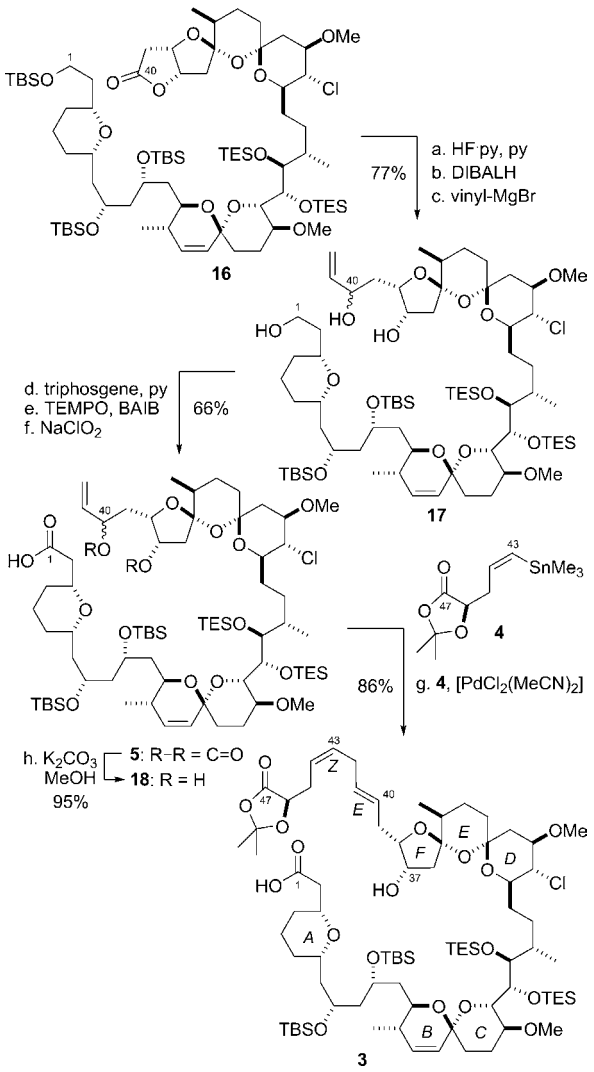
With C1–C40 heptacycle **16** in hand, our attention turned to the installation of the side chain to complete the C1–C47 carbon backbone of spirastrellolide A (Scheme 4). Accordingly, selective C1 desilylation followed by partial reduction of the γ-lactone (DIBALH) and addition of vinylmagnesium



Scheme 2. Preparation of C17–C40 aldehyde **7**. a) PPTS, CH_2Cl_2/MeOH (12:1), 0 °C, 88%; b) DMP, $NaHCO_3$, CH_2Cl_2; c) Ph_3PCH_3Br, *n*BuLi, THF, −78 °C to RT, 80% (over 2 steps); d) 9-BBN, THF; H_2O; **8**, [$PdCl_2$(dppf)], Ph_3As, Cs_2CO_3, THF/DMF (1:1), >95%; e) $BH_3{\cdot}SMe_2$, THF; MeOH, 30% H_2O_2, 1 M NaOH, 0 °C to RT; f) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 85% (over 2 steps, d.r. 10:1); g) TBAF, AcOH, THF, >95%; h) H_2, Raney-Ni, EtOH, 97%; i) TEMPO, BAIB, CH_2Cl_2/pH 7 buffer (5:1), >95%. 9-BBN = 9-borabicyclo[3.3.1]nonane, BAIB = [bis(acetoxy)iodo]benzene, DMF = *N*,*N*-dimethylformamide, DMP = Dess–Martin periodinane, dppf = 1,1′-bis(diphenylphosphanyl)-ferrocene, PPTS = pyridinium *para*-toluenesulfonate, TBAF = tetrabutylammonium fluoride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.



Scheme 3. Completion of the C1–C40 spirastrellolide A heptacycle **16**. a) NIS, $AgNO_3$, THF, 94%; b) $CrCl_2$, $NiCl_2$, THF, 85%; c) Pd/$CaCO_3$/Pb, quinoline, H_2, EtOAc; d) DMP, $NaHCO_3$, CH_2Cl_2, 72% (over 2 steps); e) DDQ, CH_2Cl_2/pH 7 buffer (9:1), 0°C, 82%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(dimethylamino)pyridine, NIS = *N*-iodosuccinimide.

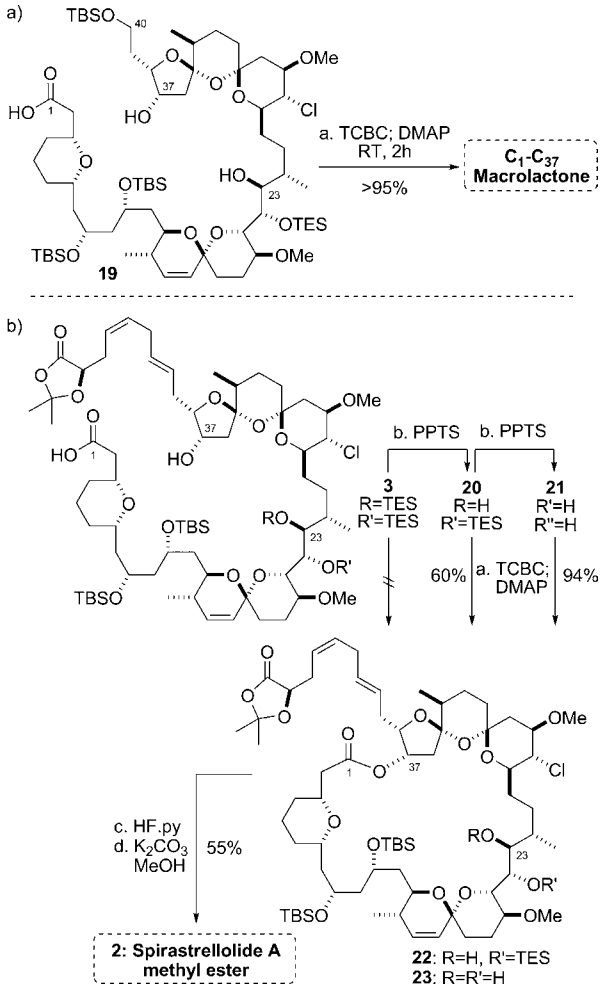


Scheme 4. Preparation of spirastrellolide A *seco* acid **3**. a) HF·py, py, THF, 89%; b) DIBALH, CH_2Cl_2, −78°C, >95%; c) vinyl-MgBr, THF, 0°C to RT, 91%; d) triphosgene, py, Et_3N, CH_2Cl_2, −78°C, 82%; e) TEMPO, BAIB, CH_2Cl_2/pH 7 buffer (5:1); f) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O/THF (1:1:1), 80% (2 steps); g) [$PdCl_2(MeCN)_2$], **4**, DMF/H_2O/THF (8:2:1), 86%; h) K_2CO_3, MeOH, 95%. DIBALH = diisobutylaluminium hydride, py = pyridine.

bromide provided allylic alcohol **17** (80% over 3 steps), as an inconsequential 3:2 epimeric mixture of C40 alcohols. Treatment of triol **17** with triphosgene to selectively generate the C37–C40 cyclic carbonate, followed by oxidation of the remaining alcohol at C1, afforded the C1–C42 carboxylic acid **5**, ready for the planned π-allyl Stille cross-coupling reaction.[18] Following optimization in model studies,[10b] we were pleased to observe the smooth coupling of **5** with the C43–C47 stannane **4** using catalytic [$PdCl_2(MeCN)_2$] in wet DMF, which afforded C1–C47 diene **3** as a single *E*,*Z* isomer in 86% yield. Notably, this protocol for assembling the full spirastrellolide side chain on a linear intermediate was found to be significantly more efficient than our earlier route using olefin cross-metathesis in the presence of the sterically demanding macrolactone core.

In our earlier synthesis, Yamaguchi macrolactonization[19a] of the corresponding C1–C40 hydroxy acid **19** (Scheme 5) had proceeded in excellent yield (>95%), which we presumed reflected a highly favorable conformational pre-organization of the (side-chain truncated) *seco* acid.[10b] Macrolactonization of **3** was therefore expected to proceed with similar facility, yet no macrocyclic products were isolated when **3** was submitted to a wide range of macrolactonization conditions (including Yamaguchi, Keck and Shiina),[19] with only degradation of the starting material observed. Similarly, the failure of the C1–C42 diol **18** (shown in Scheme 4), which contains a truncated side chain, to undergo productive macrolactonization suggested this could not be solely a consequence of structural variation in this region.[20] This frustrating outcome is particularly surprising given the structural homology of **18** to the previously successful substrate **19**, and suggested to us that these macrolactonization failures possibly arose from a subtle conformational influence from the C23 TES ether, serendipitously a free alcohol for **19**, preventing closure of the 38-membered macrocycle.

To test the hypothesis of a protecting group dependence at the C23 position located in the linker domain between the BC and DEF spiroacetal ring systems, C1–C47 carboxylic acid **3** was subjected to mildly acidic conditions (PPTS, CH_2Cl_2/MeOH). Depending on the duration of the reaction, this gave access to either diol **20** (mono-desilylation to form the C23 alcohol) or triol **21** (bis-desilylation to form the C22/C23 diol).



Scheme 5. Macrolactonization and total synthesis of spirastrellolide A methyl ester **2**. a) TCBC, Et_3N, THF; DMAP, PhH, 2 h, 0% for **3**, 60% for **20**, 94% for **21**; b) PPTS, CH_2Cl_2/MeOH (7:1); c) HF·py, py, THF, 71%; d) K_2CO_3, MeOH, 77%. TCBC = 2,4,6-trichlorobenzoyl chloride.

Gratifyingly, submission of either **20** or **21** to our standard Yamaguchi macrolactonization conditions (PhH, room temperature, 2 h) now afforded the corresponding macrocycles, **22** and **23**, in 60% and 94% yield, respectively.

The remarkable success of these reactions to construct the signature 38-membered macrolactone of the spirastrellolides not only highlights the inherent selectivity for lactonization at the C37 alcohol (rather than alcohols at C22 or C23), but also emphasizes the subtle and often unexpected conformational influence of remote functionality.[20] In retrospect, it appears highly likely that the successful macrocyclization of our first-generation substrate **19** was unknowingly dependent upon a serendipitous desilylation to give a free C23 alcohol during the (DDQ-mediated) BC-spiroacetalization step. In the present case, removal of the remaining silyl groups could then be achieved under fluorous conditions (HF·py/py), to provide the corresponding tetraol. Finally, cleavage of the dioxolanone protecting group (K_2CO_3, MeOH) afforded (+)-spirastrellolide A methyl ester in 77% yield, authenticated by detailed NMR correlation with previously recorded spectra.[10b]

In conclusion, we have achieved a much-improved total synthesis of the antimitotic marine macrolide spirastrellolide A methyl ester (**2**) that proceeds in 6% yield over 23 steps from the key DEF-bis(spiroacetal) intermediate **9**.[21] This second-generation route features a uniformly high level of stereocontrol combined with rapid fragment assembly, and should be readily amenable to the synthesis of useful quantities of this scarce anticancer agent, along with other congeners and analogues, for further biological studies. Surprisingly, a free C23 alcohol in the fully elaborated C1–C47 *seco* acid (**3**) was found to be essential for the realization of a smooth and high-yielding macrolactonization, where this hydroxy group presumably contributes to a favorable conformational pre-organization of the southern hemisphere—a finding which exemplifies the unanticipated challenges that are often faced in tackling the chemical synthesis of complex natural products.

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[20] We attribute this remarkable result to favorable conformational pre-organization of the C22–C24 linker region for alcohols **20** and **21**, not adopted by bis-TES ether **3**, which serves to direct the BC- and DEF-spiroacetals in a productive manner for closure of the 38-membered macrolactone. This effect may derive from possible hydrogen bonding of the free C23 alcohol with the C11 ether, according to that observed in the crystal structure of a macrocyclic pentaol obtained previously (Ref. [10b]). Alternatively, alleviating the steric hindrance imposed by the vicinal TES ethers may permit stereoelectronic control of the C22/C23 conformation to predominate. The forcing conditions required by Fürstner (refluxing PhMe) for Yamaguchi macrolactonization were also ascribed to a disadvantageous conformation imposed by a C22–C23 isopropylidene acetal; see Ref. [11b].

[21] In comparison, our first-generation synthesis (Ref. [10b]) proceeded in ca. 1% yield over 25 steps from **9**.

