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Total Synthesis of Spirastrellolide A Methyl Ester—Part 1: Synthesis of an Advanced C17–C40 Bis-spiroacetal Subunit**

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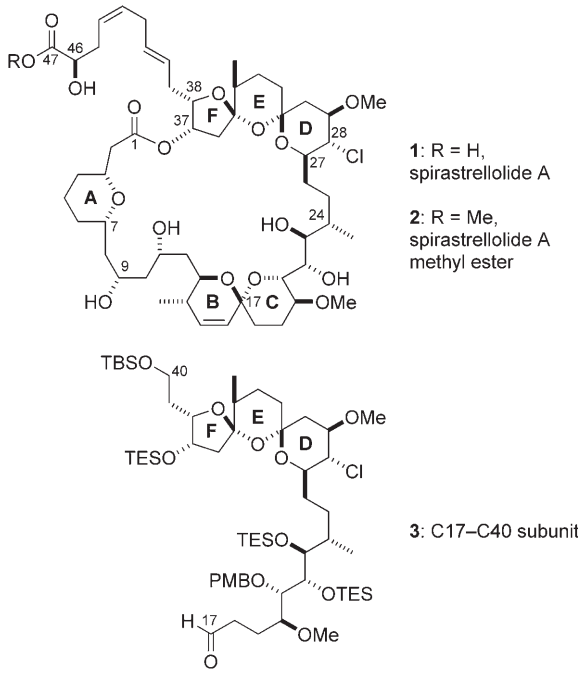
Spirastrellolide A (**1**, Scheme 1) and its methyl ester derivative **2** were isolated in 2003 by Andersen and co-workers from the Caribbean marine sponge *Spirastrella coccinea*.[1] The spirastrellolides are potent, highly selective inhibitors of protein phosphatase 2A ($IC_{50} = 1$ nM for **1**), causing premature cell entry into mitosis.[1b] Protein phosphatases play a vital role in the regulation of many cellular processes, interference of which has been implicated in the onset of several diseases including cancer and Alzheimer's.[2] Therefore, the identification of selective inhibitors of protein phosphatases may afford both valuable molecular probes for cell biology, as well as promising lead compounds for the development of novel therapeutic agents.[3]



Scheme 1. Spirastrellolide A (**1**), its methyl ester (**2**), and the advanced C17–C40 subunit **3**. PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

From a structural perspective, spirastrellolide A consists of a 47-carbon backbone with 21 stereocenters, of which 20 are included within a 38-membered macrocycle that also comprises three cyclic ether subunits (A, BC, and DEF rings). The intriguing structure (Scheme 1), coupled with the potent biological profile, has inspired us[4] and other research groups[5] to initiate studies towards a total synthesis. Herein we report the stereocontrolled synthesis of the advanced C17–C40 bis-spiroacetal subunit **3**, by following two complementary routes that are based on different fragment-coupling strategies. In the accompanying communication, we report its elaboration to incorporate the BC spiroacetal domain, and the subsequent macrocyclization and attachment of the side chain, which has culminated in the first total synthesis of spirastrellolide A methyl ester.

At the outset of our work, the relative and absolute configuration of spirastrellolide A was undefined.[1a] Despite extensive NMR studies,[1b] the relative stereochemistry between four principle regions of the molecule (C3–C7, C9–C24, C27–C38, and the remote C46 stereocenter) remained unknown. Only in 2007 was the structural ambiguity resolved, with the isolation of spirastrellolide B (lacking both the chlorine substituent at C28 and the C15–C16 alkene), and the X-ray crystal structure of a derivative,[1c] followed by the assignment at C46 through chemical degradation studies.[1d]

As outlined in Scheme 2, we envisaged a late-stage attachment of the side chain by employing stannane **4** (or its enantiomer), after macrolactonization of an appropriate seco acid **5**. The next key disconnection involves unraveling the BC ring spiroacetal, and implementation of an alkyne addition/Lindlar reduction sequence using the alkyne **6**, a tactic that had proven robust in earlier studies.[4b,c,e] In contrast, the scission of the pivotal C17–C40 fragment into two stereochemically discrete subunits was uncharted territory, and led us to explore two alternative strategies. In Strategy A, a disconnection between C25 and C26 in **7** was envisaged by using a modified Julia olefination[6] between sulfone **8** and aldehyde **9**, the latter being directly available from our previous work.[4d] This strategy benefits from the installation of the required C20–C24 stereopentad before olefination, and provides a fully functionalized C17–C40 subunit **7**. The choice of a C40 benzyl ether in **7** would enable rapid assessment of the validity of this approach, as this

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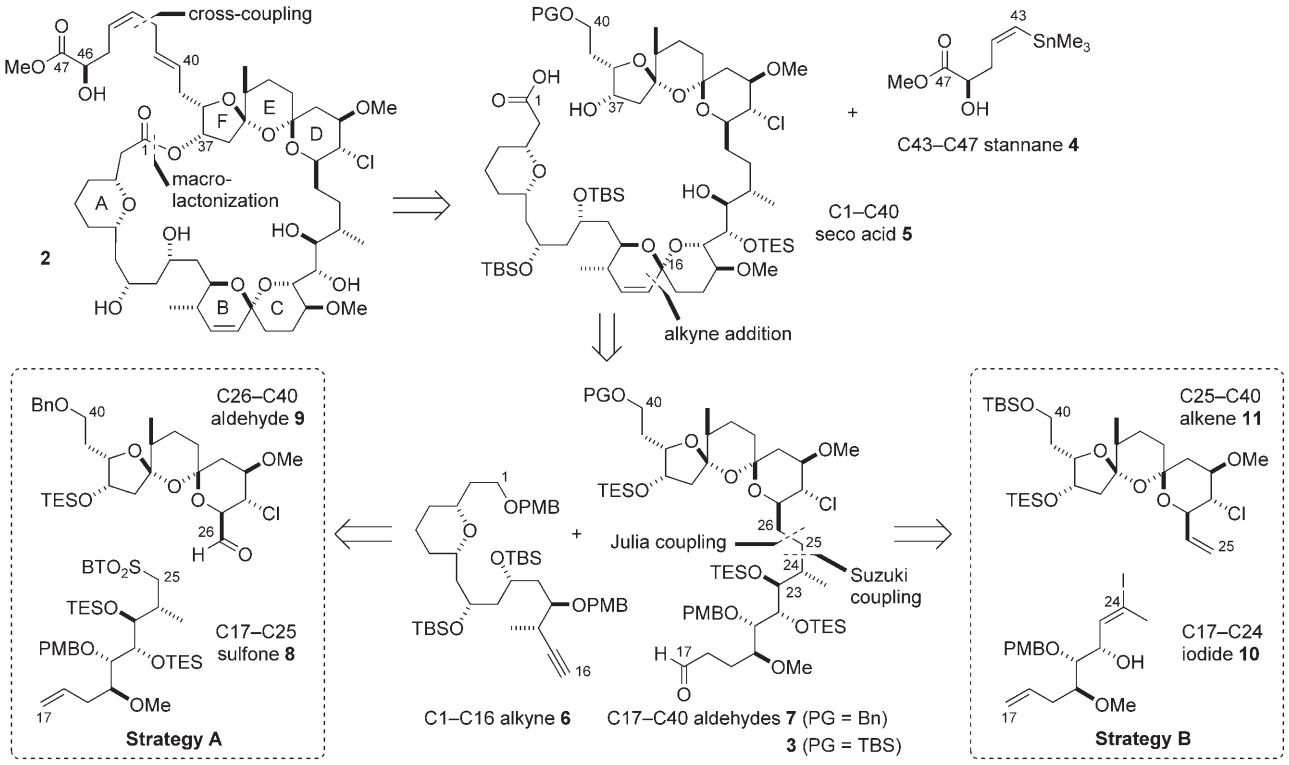

Scheme 2. Retrosynthetic analysis of spirastrellolide A methyl ester (**2**) based on Julia (Strategy A) and Suzuki (Strategy B) fragment coupling reactions to construct the pivotal C17–C40 subunit. Bn = benzyl, BT = benzothiazole, PG = protecting group.

protecting group is already present in aldehyde **9**. Nevertheless, in anticipation of the challenges we might face with such a hindered olefination, we also contemplated Strategy B, in which the C24–C25 bond would be forged using an ambitious sp^2–sp^3 Suzuki cross-coupling reaction[7] involving the C17–C24 iodide subunit **10** and alkene **11**. A subsequent double hydroboration of the resulting diene might then install the requisite stereocenters at C23 and C24 as well as oxygenation at C17 and C23, thus enabling conversion into the required aldehyde functionality in **3**. In practice, we elected to pursue both these strategies, mindful also of the potential benefits of structural correlation of advanced intermediates common to both routes.

Strategy A commenced with synthesis of the C17–C25 sulfone **8** (Scheme 3). Based on the work of Seebach and Warmuth[8a] and others[8b,9] the chelated lithium enolate of the methyl ester **12** of (*S*)-malic acid was methylated to afford **13** (d.r. 90:10),[8] followed by transformation into the aldehyde **14**[9] in readiness for an Evans glycolate aldol coupling reaction. As our BC-spiroacetalization strategy called for a PMB ether at C21, this required the use of the imide **15**.[10] Pleasingly, reaction of the (*Z*)-dibutylboron enolate of **15** with aldehyde **14** in toluene provided the *syn*-aldol adduct **16**, thus installing the C21 and C22 stereocenters (76%, d.r. 95:5). Assembly of the full C20–C24 stereopentad was completed following the stepwise conversion of **16** into the ketone **17** through addition of allylmagnesium bromide to the intermediate Weinreb amide **18**.[11] Treatment of **17** with zinc borohydride (diethyl ether, −10°C) effected a chelation-controlled reduction to afford the C20 alcohol **19** (78%, d.r. 95:5). Following formation of the methyl ether (**20**), a sequence involving acetal cleavage, persilylation of the resulting triol with TESOTf, and selective desilylation gave the primary alcohol **21** (71%). Completion of the targeted sulfone **8** required introduction of the benzothiazolylsulfone functionality, which was achieved from **21** by sulfide formation under Mitsunobu conditions and oxidation with $[(NH_4)_6Mo_7O_{24}]$ (69%, over 2 steps). Overall, the C17–C25 sulfone **8** was prepared in 16 steps and 6.4% yield from ester **12**.

The C26–C40 DEF bis-spiroacetal aldehyde **9** could be readily prepared from the acyclic diene **22** by using our tandem double-Sharpless asymmetric dihydroxylation/spirocyclization tactic (Scheme 4).[4d] Taking into consideration the need for scale-up, we improved the route towards diene **22**. This commenced with the Oehlschlager–Brown chloroallylation[12] of aldehyde **23**[13] (with in situ acetal cleavage), and subsequent methyl ether formation, to give the ketone **24** (d.r. > 95:5, 92% *ee*) with installation of the C28 and C29 stereocenters. Addition of the dicyclohexylboron enolate of **24** ($cHex_2BCl$, Et_3N) to aldehyde **25**[4d] gave a mixture of epimeric aldol adducts which underwent clean elimination (MsCl, Et_3N). This robust sequence enabled the rapid and facile preparation of triene **26** on a 10-g scale. The elaboration of **26** to the targeted tricyclic DEF subunit was accomplished by a four-step sequence of enone/ketone reduction,[14] silyl ether cleavage, and Swern oxidation of the resulting diol to afford diene **22** (68%).[15] By following our previous route,[4d] **22** underwent efficient double Sharpless asymmetric dihydroxylation[16]/cyclization to afford the C26–C40 DEF bis-

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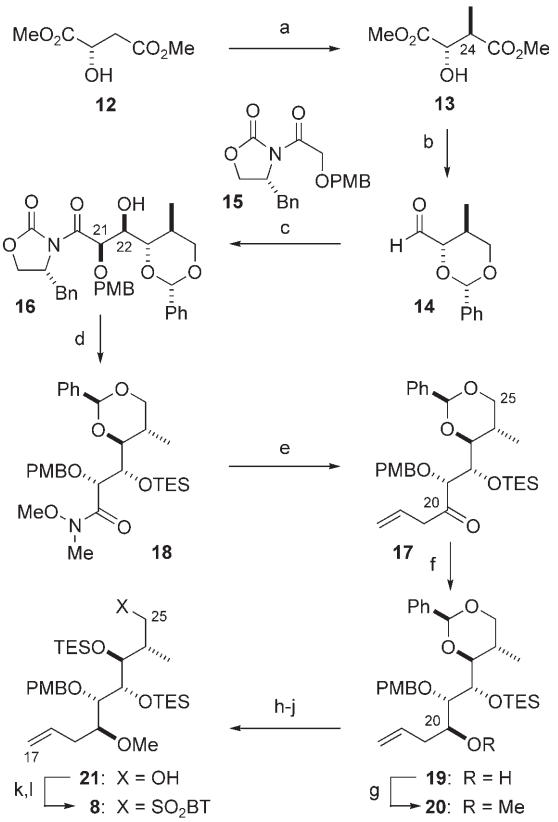
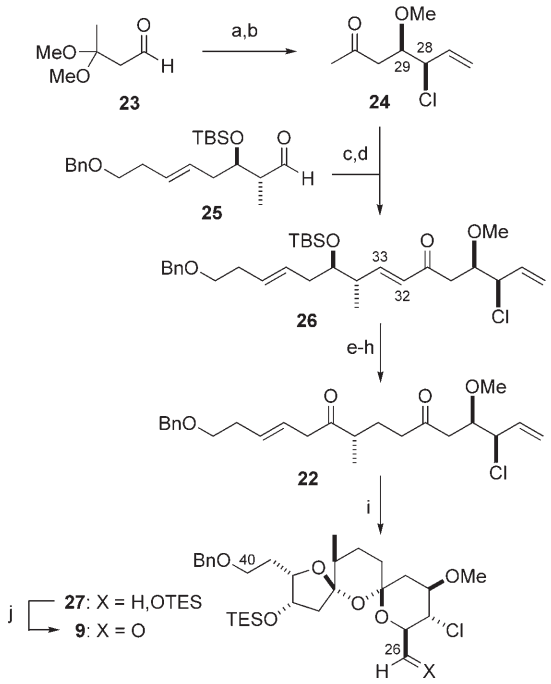


Scheme 3. Preparation of the C17–C25 sulfone **8**. a) LDA, THF, HMPA, −78 °C to RT, 61 %; b) $LiAlH_4$, THF, RT; $PhCH(OMe)_2$, TsOH, CH_2Cl_2, Et_3N, RT; DMP, CH_2Cl_2, RT, 53 % (over 3 steps); c) **15**, nBu_2BOTf, Et_3N, toluene, −50 °C; **14**, −50 °C to −30 °C, 76 % (d.r. 95:5); d) $AlMe_3$, MeNH(OMe)·HCl, THF, −20 °C to RT; TESOTf, 2,6-lutidine, CH_2Cl_2, 72 %; e) $CH_2{=}CHCH_2MgBr$, THF, −20 °C, 95 %; f) $Zn(BH_4)_2$, Et_2O, −10 °C, 78 %; g) Me_3OBF_4, proton sponge, CH_2Cl_2, 94 %; h) TsOH, MeOH, 94 %; i) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100 %; j) HF·Py/Py (1:3), THF, 0 °C to RT, 80 %; k) BTSH, PPh_3, DEAD, THF, 99 %; l) $[(NH_4)_6Mo_7O_{24}]$, 30 % H_2O_2, EtOH, RT, 70 %. BTSH = 2-mercaptobenzothiazole, DEAD = diethylazodicarboxylate, DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, HMPA = hexamethyl phosphoramide, PMB = *para*-methoxybenzyl, proton sponge = 1,8-bis(dimethylamino)naphthalene, Py = pyridine, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.



Scheme 4. Improved route to form the C26–C40 aldehyde **9**. a) $CH_2{=}CHCH_2Cl$, $cHex_2NLi$, (−)-Ipc_2BOMe, THF, Et_2O, −95 °C; $BF_3{\cdot}Et_2O$; **23**, −95 °C to −78 °C; 30 % H_2O_2, pH 7 buffer; b) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 °C, 39 % (over 2 steps); c) $cHex_2BCl$, Me_2NEt, Et_2O, 0 °C; **25**, −78 °C, 88 %; d) MsCl, Et_3N, 0 °C to RT, 83 %; e) $[\{(Ph_3P)CuH\}_6]$, $PhSiH_3$, toluene, 90 %; f) DIBALH, CH_2Cl_2, −78 °C; g) 1 N HCl, MeCN, RT; h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 75 % (over 3 steps); i) see Ref. [4d], 65 %; j) PPTS, CH_2Cl_2/MeOH (6:1), 0 °C; DMP, $NaHCO_3$, CH_2Cl_2, 78 %. cHex = cyclohexyl, DIBALH = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, Ipc = isopinocampheyl, Ms = methanesulfonyl, PPTS = pyridinium *para*-toluenesulfonate.

spiroacetal **27** (65 %). After selective cleavage of the C26 TES ether, **27** was converted into the aldehyde **9**[5i] by using Dess–Martin periodinane.

With a scalable route to the aldehyde **9** established, the feasibility of the Julia-type coupling in Strategy A could now be explored (Scheme 5). After extensive experimentation, we found that generation of the lithium anion of sulfone **8** (LHMDS, −78 °C, THF) followed by the addition of aldehyde **9** and warming the reaction to ambient temperature afforded the C17–C40 alkene **28** in 32 % yield. Despite the modest yield, Strategy A was validated by selective hydroboration of the terminal olefin to give the primary alcohol, followed by reduction of the internal double bond with diimide to afford **29** (81 %, over 2 steps). Finally, Dess–Martin oxidation of **29** delivered the C17–C40 aldehyde **7** (84 %), which was primed to undergo coupling with the C1–C16 alkyne **6** and complete the assembly of the C1–C40 framework. Nevertheless, it was clear that Strategy A had not performed to our expectations, not least because of the rather lengthy synthesis of the sulfone **8** and the disappointing yield of the key fragment coupling step, presumably as a result of steric hindrance imposed by the bis-spiroacetal for reaction at the C26 position of aldehyde **9**.

We next turned to Strategy B (Scheme 2), involving an ambitious sp^2–sp^3 Suzuki coupling reaction to assemble the C17–C40 aldehyde **3**. This alternative route would benefit from moving the key bond scission from C25–C26 to C24–C25, thus potentially counteracting the perceived steric encumbrance that had plagued the Julia coupling approach. At this point, the protecting group at C40 was switched to a TBS ether, which should be more easily cleaved in the presence of the C15–C16 dpuble bond compared to cleavage of a benzyl ether. Preparation of the C25–C40 alkene **11** (Scheme 6) began from the C26–C40 intermediate **27**[4d] by debenzylation, formation of the TBS ether, and selective manipulations at C26 (cleavage of the TES ether, oxidation to the aldehyde, and Wittig methylenation). This sequence provided the alkene **11**, destined for a Suzuki cross-coupling reaction, on a multigram scale (46 % from **27**). Similar quantities of the vinyl iodide partner **10** could be prepared starting from the aldehyde **30**[17] by using an Evans glycolate aldol reaction analogous to that employed for sulfone **8**.[10]

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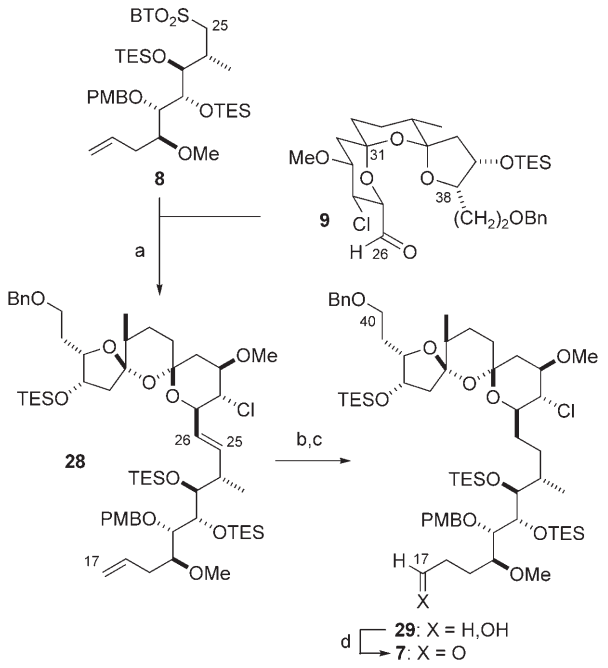
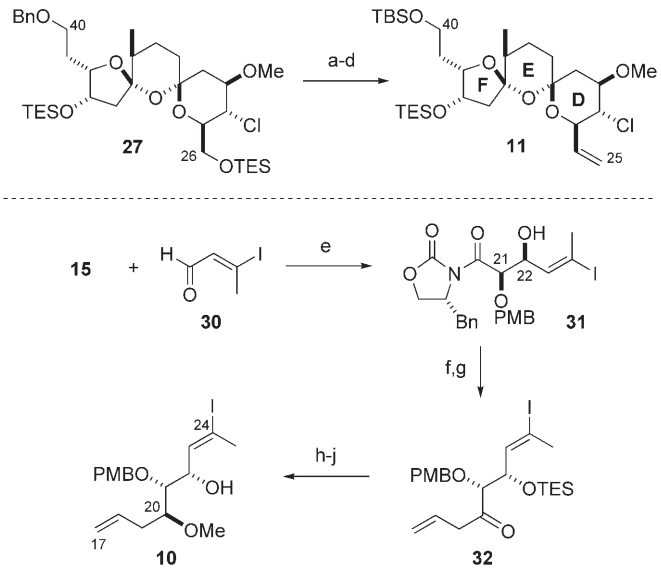


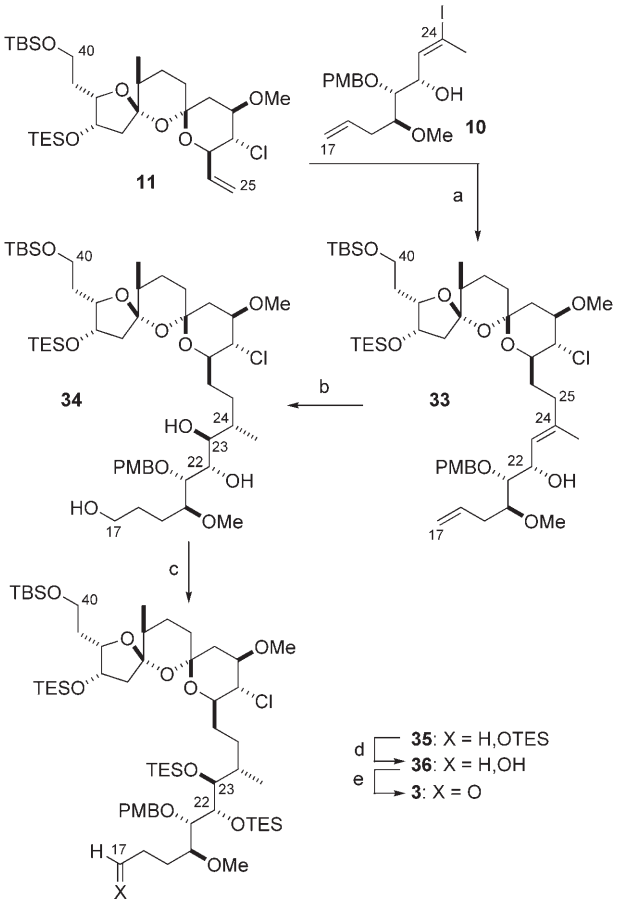
Scheme 5. Modified Julia olefination to form the C17–C40 subunit **7**. a) **8**, LHMDS, THF, −78 °C; **9**, −78 °C to RT, 32%; b) $BH_3{\cdot}SMe_2$, THF, 0 °C; 30% H_2O_2, pH 7 buffer; c) $(NCO_2K)_2$, AcOH, Py, MeOH, 81% (over 2 steps); d) DMP, $NaHCO_3$, CH_2Cl_2, 84%. LHMDS = lithium hexamethyldisilazide.



Scheme 6. Preparation of the C25–C40 alkene **11** and the C17–C24 vinyl iodide **10**. a) H_2, Raney-Ni, EtOH; TBSCl, imidazole, CH_2Cl_2, 86%; b) PPTS, CH_2Cl_2/MeOH (7:1), 0 °C; c) DMP, $NaHCO_3$, CH_2Cl_2; d) $Ph_3P{=}CH_2$, THF, −78 °C to RT, 53% (over 3 steps); e) $n$$Bu_2BOTf$, Et_3N, toluene, −50 °C; **30**, −50 °C to −30 °C, 79% (d.r. 95:5); f) $AlMe_3$, MeNH(OMe)·HCl, THF, −20 °C to RT; TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 86%; g) $CH_2{=}CHCH_2MgBr$, THF, −78 °C to 0 °C, 93%; h) $Zn(BH_4)_2$, Et_2O, −50 °C, 90% (d.r. > 95:5); i) Me_3OBF_4, proton sponge, CH_2Cl_2, 93%; j) PPTS, MeOH, 99%.

Once again, this reaction selectively installed the required C21 and C22 stereocenters (79%, d.r. 95:5). Subsequent cleavage of the auxiliary, and allylation of the intermediate Weinreb amide[11] yielded ketone **32** (80%). The remaining C20 stereocenter was established as before by using a chelation-controlled reduction of **32** with zinc borohydride (d.r. > 95:5), and two further steps provided the desired vinyl iodide **10** (83%). Notably, this sequence represents a substantial improvement over the earlier synthesis of sulfone **8**, as it is accomplished in just six steps from aldehyde **30** (52% yield).

We were now faced with the challenging union of the complex subunits **10** and **11** (Scheme 7). Gratifyingly, hydroboration of the alkene **11** by using 9-BBN, followed by addition of the iodide **10** and a catalytic amount of [$PdCl_2$(dppf)], led to a smooth sp^2–sp^3 Suzuki coupling reaction and formation of the trisubstituted (23*E*)-alkene **33** in 83% yield.[18] The completion of the targeted C17–C40 subunit **3** required the installation of stereocenters at C23 and C24, for which we planned to use a substrate-controlled hydroboration. Although such hydroborations have good precedence for delivering 1,3-diols from other allylic alcohol systems,[19] this particular alkene substitution pattern has not been used to afford 1,2-diols, and therefore the stereochemical outcome



Scheme 7. Suzuki coupling reaction of alkene **11** and iodide **10**: formation of the fully functionalized C17–C40 aldehyde **3**. a) 9-BBN, THF; H_2O; **10**, [$PdCl_2$(dppf)], Ph_3As, Cs_2CO_3, THF/DMF (1:1), 83%; b) $BH_3{\cdot}SMe_2$, THF; MeOH, 30% H_2O_2, 1 M NaOH, 0 °C to RT; c) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 67% (over 2 steps, d.r. 75:25); d) PPTS, CH_2Cl_2/MeOH (12:1), 0 °C, 98%; e) DMP, $NaHCO_3$, CH_2Cl_2, 80%. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMF = *N*,*N*-dimethylformamide, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

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was uncertain. In the event, we found the double hydroboration reaction required an unprotected alcohol at C22, and that this substrate **33** gave a 3:1 ratio of diastereomers (which proved difficult to separate) in favor of the desired C22,C23-*anti* isomer **34**. Configurational assignment was performed on a closely related system[20] by chemical correlation with intermediate **29** (Scheme 5), NOE studies of a derivative,[21] and was confirmed by an X-ray crystal structure of a more advanced intermediate.[22] Finally, aldehyde **3** was attained by silylation of the crude triol **34** to give **35**, followed by selective cleavage of the TES ether at C17 to generate the alcohol **36** and Dess–Martin oxidation (44%, over 4 steps from **11**). Overall, this expedient Suzuki/hydroboration route is clearly superior to the alternative Julia olefination sequence (Scheme 5) and, importantly, proved readily amenable to providing gram quantities of aldehyde **3**.[23]

In conclusion, we have completed the stereocontrolled preparation of the fully functionalized C17–C40 DEF bis-spiroacetal subunits **7** and **3**, by using independent Julia and Suzuki coupling strategies, respectively. The scalable and efficient synthesis of aldehyde **3** forms the cornerstone of our campaign towards the total synthesis of spirastrellolide A methyl ester, which is reported in the following communication.[22]

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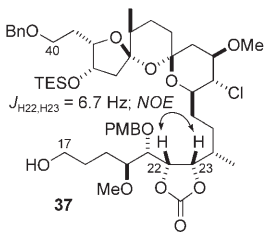
[20] The C40 benzyl ether analogue of diene **33** gave a similar mixture of triols upon hydroboration, the ^{1}H NMR spectra of which correlated closely with that of **34**. The triols were converted into intermediate **29** (Scheme 5) by persilylation (TESOTf) and selective C17 deprotection, thus confirming the configurations at C23 and C24.

[21] The major triol formed in the corresponding benzyl ether series was also converted into the *cis*-carbonate **37**.



[22] I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas, C. Moessner, *Angew. Chem.* **2008**, DOI: 10.1002/ange.200705566; *Angew. Chem. Int. Ed.* **2008**, DOI: 10.1002/anie.200705566.

[23] See the Supporting Information.

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