A Second-Generation Total Synthesis of Spirastrellolide A Methyl Ester

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Introduction of Spirastrellolide A

Isolation: A complex polyketide macrolide that was isolated as its methyl ester derivative in 2003 from the Caribbean sponge *Spirastrella coccinea*; Family numbers of Spirastrellolide: A-G; Biological Activity: selective inhibition of protein phosphatase 2A
Structural Elucidation of Spirastrellolide A

Published 2003
13 undefined stereocenters, omitted F-ring, C28 chlorination

Published 2004
C46 stereocenter, the stereochemical relationship between three macrocyclic stereoclusters (C3-C7, C9-C24, and C27-C38)
possible 16 diastereomers

Published 2007
1: R = H, Spirastrellolide A
1*: R = Me, Spirastrellolide A methyl ester
**Retrosynthetic Analysis**

![Chemical Diagram]

The diagram illustrates a retrosynthetic analysis of a complex organic molecule, highlighting key steps in its synthesis:

1. **Stille cross coupling**
2. **Macrolactonisation**
3. **Alkyne addition BC-spirocyclisation**
4. **Suzuki coupling /hydroboration**
5. **Double AD**
6. **HWE**

The steps are represented by arrows indicating the direction of synthesis from the final product back to the starting materials. Each reaction is labeled with relevant chemical modifications and reagents, such as TBSO, TESO, PMBO, and OTBS, which are common protecting groups in organic chemistry.
Synthesis of the fragment 8

1) LiAlH₄, THF
2) DMP, DCM

9 \[\rightarrow\] 10

86%, dr > 20:1

1) TBSOTf, 2,6-lutidine, DCM
2) NaBH₄, MeOH then K₂CO₃, NaIO₄, THF-pH 7 buffer

11 \[\rightarrow\] 12 \[\rightarrow\] 13

86%

1) Ba(OH)₂, THF:H₂O (40:1); 14
2) [(PPh₃)CuH]₆, PhMe:H₂O (200:1)
3) MeCN-HCl
4) DMP, DCM

8 \[\rightarrow\] 15

47%

1) CSA (cat.), MeOH
2) DMP, NaHCO₃, DCM
3) (MeO)₂POCH₂Li, THF, -78 °C; DMP, DCM

14 \[\rightarrow\] 15

53%

11
Synthesis of the fragment 7

[Chemical reaction diagram]
Synthesis of the fragment 5

1) BH₃.SMe₂, H₂O
   NaOH (dr 10:1)
2) TESOTf
3) PPTs
4) DMP
   53%, 4 steps

1) MeNH(OMe).HCl, AlMe₃, TESOTf
2) AllylMgBr
3) Zn(BH₄)₂ (dr > 20:1)
4) Me₂OBF₄
5) PPTs
   66%, 5 steps

18

21

24

17

24

25

6
Synthesis of the fragment 4

1) $O_3$; PPh$_3$
2) (-)-ipc$_2$BAlyl
71% 2 steps

1) LiAlH$_4$
2) TBSCI
3) $O_3$; PPh$_3$
88% 3 steps

1) Me$_4$NBH(OAc)$_3$
(dr > 20:1)
2) DDQ
3) TBSOTf
4) BH$_3$ SMe$_2$
42% 4 steps

1) DMP
2) CBr$_4$, PPh$_3$, Et$_3$N
3) HF/py/py
4) PMBTCA
5) n-BuLi
73% 5 steps
Synthesis of the fragments 2

1) n-BuLi;
2) H₂, Pd/CaCO₃/Pb
3) DMP, NaHCO₃

82%

DDQ, pH7 buffer

58%

2,4,6-trichlorobenzoyl chloride, Et₃N; DMAP

99%

TEMPO, BAIB, NaClO₂

29: X = H, H; R = TES
30: X = O; R = TES, 88%
2: X = O; R = H, 64% (brsm)
Synthesis of the fragments 1
Retrosynthetic Analysis
Synthesis of Fragment 41

1) PPTS
2) DMP
3) Ph₃P=CH₂
70%

9-BBN; H₂O; 6, Cs₂CO₃
[PdCl₂(dpff)]
>95%

1) BH₃·SMe₂; H₂O₂
2) TESOTf
85%

1) TBAF, AcOH
2) H₂, Ra-Ni
>95%

TEMPO, BAIB
>95%
Synthesis of fragment 49
Synthesis of fragment 38

1) HF py, py
2) DIBALH
3) vinyl-MgBr

77%

1) triphosgene, py
2) TEMPO, BAIB
3) NaClO

66%

K₂CO₃, MeOH
R-R = C = O
95%

R = H

93%
Conclusion

The first total synthesis:
Over 0.55% yield over the longest linear sequence of 36 steps; ca. 1% yield over 25 steps from the key DEF-bis(spiroacetal) intermediate.

The second-generation synthesis:
6% yield over 23 steps from the key DEF-bis(spiroacetal) intermediate.

Key modification
Challenges and Highlights

- HWE reaction; Stryker’s reagent; Sharpless reaction
- Evans aldol reaction; Weinreb amide; Chelation-controlled reduction (Zn(BH₄)₂)
- Wittig-Grubbs; Stille cross coupling; Wulff-Stille process
- Brown allylation; Boron aldol reaction; Corey-Fuchs alkylation
- Alkyne addition; BC-spirocyclisation; NHK reaction
- Suzuki coupling/ hydroboration
Ian Paterson received his B.Sc. in Chemistry in 1976 from St. Andrews University. In 1979, he obtained his Ph.D. from Cambridge University, working with Professor Ian Fleming. After a one-year stay as a NATO Postdoctoral Research Fellow with Professor Gilbert Stork at Columbia University, New York, he joined the faculty at University College London. In 1983, he moved back to Cambridge, where he is now Professor of Organic Chemistry and a Fellow of Jesus College. His research interests are centered on the development of novel synthetic methods for the control of stereochemistry and the total synthesis of bio-active natural products, particularly anticancer agents.

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<th>Compound</th>
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Marine macrolides that selectively disrupt cell cycle events represent important lead compounds for anticancer drug discovery, as highlighted by the recent development of Halaven (a fully synthetic analogue of the halichondrins) for the treatment of metastatic breast cancer. 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. However, structural and stereochemical determination was not completed until 2007, following the identification and derivatization of six closely related congeners, spirastrellolides B–G. Isolated as their methyl ester derivatives, 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 spirastrellolide A). As drugs that target the inhibition of protein phosphatases have already shown considerable therapeutic value in fields tackling cancer and other metabolic disorders, the synthesis and evaluation of novel PP2A inhibitors based on the spirastrellolide scaffold is of significant current interest.
In conclusion, we have achieved a much-improved total synthesis of the antimitotic marine macrolide spirastrellolide A methyl ester that proceeds in 6% yield over 23 steps from the key DEF-bis(spiroacetal) intermediate. 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 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.
Thanks!