The Total Synthesis of Discodermolide

The Journey from 7 mg to 60 g

Outline of Topics for Discodermolide

I. Introduction:
   a. Structure and Bioactivity
   b. Historical Outline
II. Smith Synthesis
   a. First-Generation Route
   b. Second-Generation Route
   c. Third-Generation Route
III. Paterson Synthesis
   a. First-Generation Route
   b. Second-Generation Route
IV. Novartis Synthesis
   a. Hybrid Smith-Paterson Approach
V. Conclusion

Partial Bibliography:

Reviews:
Chemtracts 2000, 13, 229-36.
C&E News 2004, 82(9), 33-35.
The Structure of Discodermolide

- Structure determined by extensive spectroscopic studies as well as single-crystal X-ray.
- Linear propionate chain containing 13 stereocenters, 6 of which bear hydroxyls, remaining 7 bear methyls.
- Contains a tetrasubstituted δ-lactone, two di- and one trisubstituted (Z)-alkene.
- Contains a carbamate moiety and a terminal (Z)-diene.
- Discodermolide adopts a U-shaped conformation, where the internal (Z)-alkenes act as conformational locks by minimizing A(1,3) strain and syn-pentane interactions along the backbone.
- The δ-lactone is held in a boat-like conformation.

Why is Total Synthesis of Discodermolide Important?

Bioactivity:
- Initial studies revealed that (+)-discodermolide was an apparent immunosuppressant.
- Later studies revealed that Discodermolide stabilizes microtubules faster and more potently than any of the other known MTS agents, and is a potent inhibitor of tumor cell growth in vitro including Taxol-resistant cells. It is also more water soluble than Taxol.
- Promising synergy observed when used in combination with Taxol.
- Licensed by Novartis in 1998 to develop it as a new-generation anticancer drug. Currently, in Phase I Clinical Trials.

Production:
- From deep-water marine sponge, Discodermia dissoluta, which must be harvested by manned submersibles off the Bahamas at a depth in excess of 33 m.
- Natural material is scarce: 0.002% w/w from frozen sponge (7 mg isolated from 454 g of crude)
- Fermentation has not been successful to date.
Discodermolide "Highlights" Timeline

Harbor Branch Oceanographic Institution, Inc., FL


A. B. Smith. Gram-Scale Synthesis.

S. Schreiber. First Total Synthesis.

Licensed by Novartis.


Amos B. Smith, III: First Generation Approach

The absolute stereochemistry was unknown when they began the synthesis.

Denotes the repeating stereochemical triad.

Amos B. Smith, III: Constructing the Common Precursor

1. PMBOO
   PPTS, CH2Cl2/Cyclohexane
2. LIAH4, THF
3. Swern [O]
4. TMSS(CH2)3STMS, ZnCl2, Et2O
5. HN(Me)OMe-HCl, AlMe3, THF

(59% overall)

Common Precursor
Can be executed on 50g scale

This was Schreiber's SM as well.

PMB =

+---+---+---+---+---+---+
|   |   |   |   |   |   |
+---+---+---+---+---+---+

Amos B. Smith, III: Constructing Fragment A

1. TBSOTf, 2,6-lut., CH2Cl2
2. H2, Pd(OH)2/C, EtOH
3. SO3•Py, Et3N, DMSO
4. TMSS(CH2)3STMS, ZnCl2, Et2O

(71%)

1. DIABAL, THF
2. MeOH, CH(O)Me3
3. t-BuLi, THF, HMPA

(71%)

1. Ph(CF3-CO)2
2. Me2NBH(OAc)3
3. EtSH, MgBr2, Et2O
4. Swern [O]

(87%)

(78%)

anomers were separable, but carried forward
anomers separated at the thioacetal stage

TBSOMe
Amos B. Smith, III: Constructing Fragment B

1. TBSOTf, 2,6-lut., CH2Cl2
2. DIBAL, THF (88%)

1. IPh3P+Et
   NaHMDS, THF
   (Z:E = 6:1, 41%)

2. Br, Ph3P, CO2Et, PhH, Δ
3. MsCl, Et3N, CH2Cl2
4. LiBH4, PhH
   (Z:E = 8.5:1, 64%)

olefin geometry checked by halogen-metal exchange, only t-BuLi in Et2O completely prevented a retro-[1,5]-Brook rearrangement.

Amos B. Smith, III: Constructing Fragment C

1. DDQ, CH2Cl2
2. LiAIH4, THF (62%)

1. TBSOTf, 2,6-lut., CH2Cl2
2. LiBH4, EtOH, THF
3. Ph3P, I2, Imid., PhH/Et2O (77%)

(80%)
Amos B. Smith, III: Fragment Coupling B and C

Postulated that a mixed tert-butyl-alkyl zinc intermediate is reactive in the process.

Amos B. Smith, III: Fragment Coupling BC and A

(2 steps, 67% Z:E >49:1)

(87% for DDQ, 37% for next 2 steps)

Yamamoto Olefination
Amos B. Smith, III: Completion (First Generation)

\[
\text{Kokovsky Protocol} \quad \begin{align*}
1. & \quad \text{Cl}_3\text{CCONCO, DCE} \\
2. & \quad \text{K}_2\text{CO}_3, \text{MeOH} \\
3. & \quad 48\% \text{HF/MeCN (1:9)} \\
& \quad (53\%) 
\end{align*}
\]

\[\text{(-)-Discodermolide}\]

(note: opposite enantiomer pictured)

Amos B. Smith, III: Second Generation Approach

New Goals:
- Prepare 1 g of Discodermolide
- Use Similar Strategy

Problems from G1 Synthesis:
- Long Synthesis of A
- Poor Yield on Phosphonium Salt

Denotes the repeating stereochemical triad.

Amos B. Smith, III: Constructing the Common Precursor

1. TBSOTf, 2,6-lut., CH₂Cl₂
2. LiAlH₄, THF
3. Swern [O]
4. n-Bu₂BOTf, Et₃N, CH₂Cl₂

"Roche Ester"

[Chemical structures and reactions]

Amos B. Smith, III: Constructing Fragment A

1. TBSOTf, 2,6-lut., CH₂Cl₂
2. H₂, Pd(OH)₂/C, EtOH
3. SO₃•Py, i-PrNEt₂, DMSO

55% yield, 4 steps
highly crystalline adduct (confirmed with X-ray)

Common Precursor
Can be executed on 60-70g scale

Changed chiral auxiliary to eliminate the need for chromatography at this stage.

"Roche Ester"

PMBONHCCl₃PPTS, ... was easily recovered (80-90%)

Changed chiral auxilliary to eliminate the need for chromatography at this stage.

Amos B. Smith, III: Constructing Fragment A

1. TBSOTf, 2,6-lut., CH₂Cl₂
2. H₂, Pd(OH)₂/C, EtOH
3. SO₃•Py, i-PrNEt₂, DMSO

(85-93%)

crystalline

ds > 20:1

K-Selectride
PhMe/THF
(dr 9:1; 50-79%)

crystalline

carried through directly as the lactone

Amos B. Smith, III: Constructing Fragment A

1. TiCl₄, CH₂Cl₂
2. OTMS
3. TFA/Hexanes, rt

(70-77%)

note: allylmatal addition followed by asymmetric dihydroxylation failed to give higher than 3:1 selectivity.

Me₄NB(OAc)₃H also gave a 3:1 ratio

1. TBSCI, Imid., CH₂Cl₂
2. O₃, CH₂Cl₂; Ph₃P

(80-82%)

* 7 Steps Eliminated from First-Generation Route!
Amos B. Smith, III: Constructing Fragment B

1. TBSOTf, 2,6-lut., CH₂Cl₂
2. DIBAL, THF
3. NaHMDS, -23 °C
4. Add substrate, -33 °C

40-46% overall, ds 8-17:1

* Single Chromatography Required

Amos B. Smith, III: Constructing Fragment C

1. DDQ, CH₂Cl₂
2. LIAH₄, THF
3. Ph₃P, I₂, Imid., PhH/Et₂O

60-71%, 3 steps

(69-78%)
Amos B. Smith, III: Fragment Coupling B and C

1. ZnCl₂ (1.15 eq.), Et₂O
2. tBuLi (3 eq.), Et₂O, -78 °C
then 5% Pd(PPh₃)₃, Et₂O, rt

1.5 eq. (usually 1.5 eq. required)

Amos B. Smith, III: Fragment Coupling B and C

1. DDQ
2. TrCl · DMAP, Py
3. DIBAL, 0 °C
4. DMP [O], NaHCO₃

Yamamoto Olefination done on BC fragment, vs. fully coupled core (Z:E = 4:1)

Amos B. Smith, III: Fragment Coupling BC and A

1. NaHMDS, THF, -20 °C

1. PPh₃, I₂, PhH/ Et₂O
2. PPh₃, t-Pr₃NEt, PhH/Tol

Dauben’s High-Pressure Method: 185,000 psi
10-14 days, 2 g max!

reported to be unstable – just residue from CDCl₃
(+)-Discodermolide

(note: DDQ cycloaddition takes care of other olefin isomer?)
Ian Paterson: Retrosynthetic Analysis

[Chemical diagram showing the retrosynthetic analysis process]

Ian Paterson: Fragment A Construction

[Chemical diagram showing the synthesis process of Fragment A]

Ian Paterson: Fragment B Construction

1. PMBO(=NH)CCl₃, cat. TfOH, Et₂O (83%)
   2. i-PrMgCl, HN(Me)OMe • HCl, THF (83%) at reflux
   3. 2,6 dimethylphenol, DCC, DMAP, CH₂Cl₂ (95%)

Ian Paterson: Fragment C Construction

1. PMBO(=NH)CCl₃, cat. TfOH, Et₂O (65%) 3 steps
   2. NaI, NaHCO₃, MeOH, H₂O (65%)

(97%)
Ian Paterson: Elaboration of the BC fragment

Ian Paterson: Coupling B and C
Ian Paterson: Completion of the Synthesis

1. (±)-IPC$_2$BCl, Et$_3$N, Et$_2$O
2. H$_2$O$_2$ (30% aq.), MeOH, 0 °C
This step generates an 85:15 mixture of open chain/lactone form which is carried on.

1. Me$_3$NBH(OAc)$_2$, MeCN, AcOH
2. HF • Py, THF
(84%)

Second Generation Approach:
- Reduce Number of Steps
- Eliminate Chiral Reagents and Auxiliaries

Ian Paterson: Common Precursor

- "Roche Ester"
  - 3 steps (84%)
- PMBO
  - 1. DDQ, CH₂Cl₂, pH 7 buffer
  - 2. Swern [O] (2 steps, 90%)
- NaBH₂(OAc)₃
  - THF, AcOH (2 steps, 62%)
- 95:5 dr

Ian Paterson: Fragment A Construction

- PMBO
  - 1. NaClO₂
  - 2. MeI, K₂CO₃
  - TBSOTf, 2,6-lut.
- MeOMeOTBSMe
  - 95% (4 steps)

- Ph(OAc)₂
  - PMBO
  - 1. c-Hex₂BCl, Et₃N, Et₂O
  - 2. H₂O₂ (30%)
- TEMPO
  - 90% (2 steps)

- MeO
  - 1. DDQ, CH₂Cl₂, pH 7 buffer
  - 2. Swern [O] (2 steps, 90%)
Ian Paterson: Fragment B Construction

1. DIBAL
2. I₂, Imidazole, PPh₃ (90%)

1. 18-Cr-6, KHMDSPF₃CCH₂OOF₃CCH₂O
2. TBSOTf, 2,6-lut. (3 steps, 72%)

Ar = MeO

Ian Paterson: Fragment C Construction

1. TBSCI, Imidazole
2. DDQ, mol. sieves (82%)

1. CSA (cat.) MeOH, CH₂Cl₂
2. Dess-Martin [O] (84%)

Ar = MeO

CrCl₂, THF; then, KH (84%)
Ian Paterson: Coupling B and C

1. TEMPO, PhI(OAc)₂, CH₂Cl₂  
2. 18-Cr-6, K₂CO₃, F₃CC₂H₂O₂, F₃CC₂H₂O₂  
(12:1 Z:E, 90%)

1. LIAH₂, THF  
2. TBSOTf, Et₃N, CH₂Cl₂  
3. DDQ
(83%)

Ian Paterson: Endgame (2nd Generation)

1. AcOH, aq. THF  
2. K-Selectride, PhMe, THF  
3. HCl, MeOH  
(97:3 dr, 66%)

(+)-Discodermolide

- Boron-Aldol works on gram scale
- Li-enolate produces opposite config.  
  (Felkin-Anh induction from aldehyde)
Novartis Process Group: Scale-Up Route (Phase I Clinical Trial Campaign)


Novartis Process Group: Scale-Up Route

Hybrid Novartis-Smith-Paterson Route

1. PMBO
   PPTS, CH2Cl2/Cyclohexane (100%)
2. LiBH4, THF/EtOH (100%)
3. TEMPO/Bleach, CH2Cl2 (100%)

-replaced LIAIH4 with LiBH4 (slow filtration)
-replaced Swern with TEMPO/Bleach (DMS not environmentally friendly)
-not stable for extended storage - subjected to syn-aldol without further purification

29-50 g, 75%
29-25 kg, 46-55%

Quality of Bu3BOTf is really important.

AlMe3 could not be used (process safety) so a mixed-anhydride approach was employed.
Novartis: Constructing Fragment A

1. TBSOTf, 2,6-lut., toluene
2. H2, Pd/C, t-BuOH
3. TEMPO, PhI(OAc)2

(Novartis: Constructing Fragment B

1. MeMgBr
2. SO3, Py, DMSO

(66% for 5-step sequence, 'routine several kg scale')
Novartis: Constructing Fragment C

\[ \text{Scheme: Constructing Fragment C} \]

1. DDQ, 4ÅMS, Toluene (61%)
2. LiAlH₄, THF (91%)

1. TBSOTf, 2,6-lut., CH₂Cl₂
2. LiBH₄, EtOH, THF
3. Ph₃P, I₂, Imid., Toluene (50%)

light sensitive

Novartis: Key Suzuki Coupling

\[ \text{Scheme: Key Suzuki Coupling} \]

1. t-BuLi, 9-MeOBBN, THF, -78 °C
2. Cs₂CO₃, DMF, Pd(dppf)₂Cl₂, 20 °C

(73%; some des-iodo of SM obs. also)

Marshall’s Suzuki approach was superior, as the Negishi coupling (Smith) resulted in the formation of some inseparable side products.

1. DIBAL (92%)
2. SO₂/Py, DMSO (93%)

1. CrCl₃, Br, TMS
2. KOH (81%)

Paterson’s Protocol:
Nozaki-Hiyama-Kishi (2 diastereomers), then Peterson syn-elimination
Novartis: Further Elaboration

Novartis: Critical Endgame Maneuvers

- Quality of commercial DIP-Cl was "capricious".
  Solved by using 70% DIP-Cl in hexane
- 4:1 epimer mixture at 250 mg scale (45%), but 23% on 50g! The problem was identified as the direct reduction of the aldehyde.
- They determined the cause of reduction was incomplete enolization. Changing to 24 hrs worked better on small scale (50% yield), but again disaster on larger scale.
- They determined that the workup (peroxide, silica gel) were lowering the yield. A quick aqueous workup was performed instead, and purification by reverse-phase silica gel led to reproducible 50-55% yields.
- Epimer can be recycled and used to make the final product.
Novartis: The Grand Finale!

Panic broke out on the final step when they realized that the > 99% HPLC pure final product in solution registered an impurity around 8% after crystallization!

Discodermolide, 60 g!

Totals:
43 chemists
17 chromatographic purifications
20 months to complete
(~1 step / 2 weeks)

The Afterglow of the Novartis Synthetic Campaign

Ian Paterson  Amos Smith, III  Stuart Schreiber

"Spectacular...It's probably the best piece of synthetic work from an industrial company"
-Steven Ley (Cambridge, UK)

"Some 3,000 kg of the sponge, a quantity that probably does not exist, would have been needed to deliver 60 g"
-Stuart Mickel

"Clearly, the Novartis synthesis is a wonderful accomplishment, demonstrating that if a new drug candidate is sufficiently valuable, synthetic chemists will rise to the challenge of developing a viable synthetic approach no matter how complex the structure"
-Amos Smith, III

"On a positive note, this project was a first for Novartis, and its progress was avidly followed by the entire department who were all interested in the disco".
-Novartis
What Makes A Great Total Synthesis?

Amos B. Smith, III:
- Clever Use of 'Common Precursor'
- Prepared 1 g as proof-of-concept

Paterson:
- Common Precursor Approach (G2)
- Effective use of boron aldol reaction to assemble molecule
- Substrate-controlled creation of stereocenters (no auxiliaries)

Novartis:
- Preparation of 60 grams!

Smith G1:
A: 14%, 19 steps
B: 19%, 8 steps
C: 22%, 11 steps
Common Steps: 11
Total for Fragments: 27
Finish: 3%, 13 steps

Smith G2:
A: 25%, 13 steps
B: 24%, 8 steps
C: 30%, 11 steps
Common Steps: 11
Total for Fragments: 21
Finish: 20%, 13 steps

Paterson G1:
A: 46% 10 steps
B: 43%, 10 steps
C: 43% 12 steps
Common Steps: 0
Total for Fragments: 32
Finish: 21%, 13 steps

Paterson G2:
A: 40%, 11 steps
B: 24%, 11 steps
C: 28%, 13 steps
Common Steps: 11
Total for Fragments: 24
Finish: 19%, 12 steps

Novartis:
A: 22%, 11 steps
B: 6%, 9 steps
C: 8%, 12 steps
Common Steps: 12
Total for Fragments: 20
Finish: 7%, 15 steps