Organic Syntheses Published in Nature

and Why

(2005-2010)

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First published November 4, 1869
Published by Alexander Macmillan
Started by Joseph Norman Lockyer
Nature

- 2009 Impact factor: 34.48
- Comparable to Science in all statistics
- Far fewer chemistry articles not related to chemical biology or biochemistry
Nature

Criteria for publication (Articles and Letters)

Report original scientific research

Are of outstanding scientific importance

Reach a conclusion of interest to an interdisciplinary readership

About 10,000 articles submitted/year

Only about 800 are accepted (8%)

Decision about broad interest made solely by Nature editors, not referees
Why Nature?

- Concepts
- Methodology
- First Synthesis
- Family
- Biological Activity

Broad Interest
Nature

 Papers not covered in this talk

"Synthesis and structural analysis of 2-quinuclidonium tetrafluoroborate"

"Highly efficient molybdenum-based catalysts for enantioselective alkene metathesis"

"Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions"

"Scaleable catalytic asymmetric Strecker syntheses of unnatural a-amino acids"

"Umpolung reactivity in amide and peptide synthesis"
Total synthesis of marine natural products without using protecting groups

(+) - welwitindolinone

(+) - ambiguine H

(-) - fischerindole I

(-) - hapalindole U

Protecting Group Free Syntheses: General Concept

"Standard"

Ambiguine H

Baran

Biological

Protecting groups needed

"Caged reactivity"

Enzymes necessary

No enzymes

No protecting groups
(-)-Hapalindole U

8 steps, 7.61% yield (from commercially available materials)

Previous: 20 steps, racemic (Natsume, 1990)
(+)-Ambiguine H

(-)-Hapalindole U

10 steps, 2.88% yield by RSM (from commercially available materials)

No previous syntheses
(-)-Fischerindole I

7 steps, 2.14% yield by RSM
13% without first two steps

Previous: Baran, JACS 2005, 1.14%, 7 steps
(+)-Welwitindolinone

(−)-fischerindole I

\[ \text{XeF}_2, \text{H}_2\text{O} \]

8 steps, 0.94% yield by RSM

5.7% without first two steps (listed in *Nature*)

Baran, *JACS* 2005: 0.28% overall
Marine natural products overview

- Protecting group free syntheses
- Shorter route = faster optimization

Rules for effective synthesis
"Gram-scale"

Direct indole coupling
XeF₂ initiated cyclization
Norrish-like fragmentation cascade

First Synthesis
- (-)-hapalindole U
- ambiguine H
- welwitindolinone A, (-)-fischerindole I

Methodology

Biological Activity
- Anti-fungal, -bacterial -mycotic, -cancer
- Activities of some comparable to streptomycin, pura

Family
- Members of four families
- Stigonemataceae family of cyanobacteria

Concepts
Total synthesis of bryostatin 16 using atom-economical and chemoselective approaches

Bryostatin 16: Retrosynthetic Analysis

Cationic Au
Pd-catalyzed alkyne macrocyclization

Carbonylation
Bryostatin 16: Retrosynthetic Analysis

Tandem alkene-alkyne coupling/
Michael addition

- Convergent and "atom economical"
- Incorporates new methodologies
- Adaptable to analogue syntheses

commercially available
Bryostatin 16

1) (Ipc)_2B(allyl) 67%, 94% ee
2) NaH, PMB-Br 90%

OsO_4, NaIO_4
H_2O, dioxane 87%

8 steps

Previous route 16 steps from

t-BuLi, ZnMe_2 97%

1) In, InF_3 (10 mol %)
2) Dess-Martin
3) (S)-CBS (5%)
61%, 90% ee, three steps
Bryostatin 16

1) CpRu(MeCN)₃PF₆, 13%
   34%, 80% by RSM

2) NBS
   98%

1) CSA, MeOH
   93%

2) PdCl₂(MeCN)₂, dpff
   CO (1 atm), MeOH
   83%, 93% by RSM
Bryostatin 16

D-glactonic acid 1,4-lactone

5 steps, PG/FG switching
49%, 55% by RSM

Nature starting material

7 steps
53%

3 steps
67%
Bryostatin 16

(2,4,6-Cl₃Ph)CH₂Cl, Et₃N; then acid, DMAP

92%

DDQ, pH 7.0 buffer
46% diol, 58% mono-PMB

Resubject mono-PMB
75% overall
Bryostatin 16

Longest linear: 26 steps, 0.09%
- By RSM: 0.27%
- 35 total steps
- From commercial: 45 steps

1) AuCl(PPh₃) (20 mol%)
   AgSbF₆ (20 mol%)
   73%
2) Piv₂O, DMAP
3) TBAF
   32%, last two steps
Bryostatin 16 overview

Concepts
- Chemoselectivity
- Atom economy
- Adaptability to analogues
- Testing of methodologies

Methodology
- Tandem Ru coupling/Michael
- Pd-catalyzed alkyne-alkyne macrocyclization
- Au-catalyzed dihydropyran formation

Family
- Only one synthesized
- Analogues and other bryostatins accessible

First Synthesis
- First bryostatin 16 synthesis
- Failed metathesis attempts
- Fourth bryostatin synthesis

Biological Activity
- Significant anticancer potential during in vivo trials
- Suggested potential for cognitive impairments
The total synthesis of (−)-cyanthiwigin F by means of catalytic enantioselective alkylation

(--)-Cyanthiwigin F: Retrosynthetic Analysis

Pd-cuprate enol triflate coupling → Radical acylation → Vinyl borate CM, [O] → RCM

Methylation → Enantioselective double allylation → Negishi enol triflate coupling

Claisen-Dieckmann
\(-\)-Cyanthiwigin F

\[ \text{allyl alcohol, NaH} \quad \text{toluene, reflux} \]

\[ \text{K}_2\text{CO}_3, \text{Mel} \quad 51\%, \text{two steps} \]

\[ \begin{array}{c}
\text{meso} \\
\text{14\% yield}
\end{array} \]

\[ \begin{array}{c}
\text{(R,R)} \\
\text{64\% yield, 99\% ee}
\end{array} \]

\[ \begin{array}{c}
\text{Pd(dmba)}_2 (5 \text{ mol\%}) \\
\text{1:1 racemic:meso}
\end{array} \]

- Sets all key stereochemistry in one step
- Guides selective formation of other stereocenters
(-)-Cyanthiwigin F

(R, R) 25%

(R, S) 50%

(S, R) (R, S) (R, S) (S, S) (S, S)
(-)-Cyanthiwigin F

\[ (R, R) \rightarrow (R) \rightarrow (R, R) \]
\[ (S, R) \rightarrow (S) \rightarrow (S, S) \]
\[ meso (R, S) \rightarrow (S, S) \rightarrow meso (R, S) \]
\[ (S) \rightarrow meso (R, S) \]

81% 18% <1%
(-)-Cyanthiwigin F

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {$(R)$};
\node (2) at (1,1) {$(R, R)$};
\node (3) at (-2,1) {$(R, R)$};
\node (4) at (-2,-1) {$(S, S)$};
\node (5) at (-1,-1) {$(R)$};
\node (6) at (0,-2) {$(S)$};
\node (7) at (1,-2) {$(R, S)$};
\node (8) at (2,-1) {$(R, R)$};
\node (9) at (2,0) {$(R)$};
\node (10) at (2,2) {$(R, S)$};

\draw[->,blue] (1) edge (2);
\draw[->,blue] (2) edge (3);
\draw[->,blue] (3) edge (1);
\draw[->,blue] (3) edge (5);
\draw[->,blue] (5) edge (4);
\draw[->,blue] (5) edge (1);
\draw[->,blue] (5) edge (8);
\draw[->,blue] (8) edge (9);
\draw[->,blue] (9) edge (3);
\draw[->,blue] (9) edge (7);
\draw[->,blue] (7) edge (5);
\draw[->,blue] (7) edge (6);
\draw[->,black] (6) edge (4);
\draw[->,black] (6) edge (1);
\end{tikzpicture}
\end{center}

\begin{itemize}
\item $ meso (R, S)$ \quad 18\%
\item $ meso (R, S)$ \quad 81\%
\item $ (S, S)$ \quad <1\%
\end{itemize}
(-)-Cyanthiwigin F

1) KHMDS, PhN(Tf)₂
2) Zn, TMS-Cl, Pd(PPh₃)₄

57%, two steps

10% Hoveyda-Grubbs II
then NaBO₃, THF/H₂O

51%

9 steps from diallyl succinate

2.06% yield, 99% ee, single diastereomer
Cyanthiwigin overview

- Double enantioselective alkylation
- Enantioselective
- Tandem RCM/CM
- First synthesis of F
- Third cyanthiwigin synthesis
- Concepts
- Key step guides stereochemistry
- Only one synthesized
- Suggests applicability to other cyanthiwigins
- Cytotoxic against human tumor cells (3.1 \(\mu\)M)
- Other cyanthins is...
Total synthesis of a chlorosulpholipid cytotoxin associated with seafood poisoning

hexachlorosulpholipid

Hexachlorosulpholipid: Retrosynthetic Analysis

Takai-Utimoto, [O]  
chlorination

Wittig, [O]  
Anti-epoxide opening

bis-hydroxylation, epoxidation

germination

reduction

Me=CH_2CO_2Et
Hexachlorosulpholipid: First Route

1) Tf$_2$O, DABCO
   75 %, (96% by RSM)
2) CSA, MeOH
   98%

1) Swern
2) n-BuLi
62%, two steps
4.2:1 Z:E

Diastereoselective installation of chlorides
Forms cis epoxide for chloride opening
Wittig sets olefin geometry for chlorination
Hexachlorosulpholipid: First Route

1) DAIB, TEMPO
2) CrCl₂, CHCl₃

49%, two steps

1) Et₄NCl₃
2) CSA, MeOH

41%, two steps

39% major
4% minor, 31% RSM

27% (66% RSM)
Hexachlorosulpholipid: First Route

- (±)-single diastereomer
- natural product

- 2D $^1$H NMR and $^1$H-heteronuclear coupling experiments determine relative configuration

- Similar analysis of synthesized allylic chloride revealed 4,5-anti configuration
Hexachlorosulpholipid: Initial Route
Hexachlorosulpholipid: Revised Route

- Shortens previous route by 3 steps
- Improved Z-selectivity in Wittig
- Sets trans epoxide and utilizes anchimeric assistance to from chlorohydrin
Hexachlorosulpholipid: Revised Route

1) Et₄NCl₃ (10:1 dr)
2) CSA, MeOH

91%, two steps
83% desired diastereomer

SO₃·Pyr

99%

1) DAIB, TEMPO
2) CrCl₂, CHCl₃

47%, two steps

Identical NMR to natural product

10 steps from ethyl scorbate

1.15% of desired diastereomer (3.21% based on RSM)
Hexachlorosulpholipid overview

**Concepts**
- Contributes to NMR database
- Use of anchimeric assistance
- Scaleable synthesis
- Facilitates biological studies

**Methodology**
- Selective chlorination via cyclic chloronium
- J-based configurational analysis

**First Synthesis**
- First chlorosulpholipid

**Family**
- Only one synthesized
- Suggests framework for other syntheses

**Biological Activity**
- Shown to inhibit cell growth
- Related compounds show anti-microbial activity
Total synthesis of eudesmane terpenes by site-selective C-H oxidations

Terpene Syntheses: General Concept

- Terpene biosynthesis

\[
\text{geranylgeranyl pyrophosphate} \xrightarrow{\text{cyclase phase}} \text{taxadiene} \xrightarrow{\text{oxidation phase}} \text{paclitaxel}
\]

- Two phase total synthesis approach

\[
\text{simple commercial starting materials} \xrightarrow{\text{cyclase phase}} \text{3-deactyl-baccatin III} \xrightarrow{\text{oxidation phase}} \text{4-epiajanol} \xrightarrow{\text{oxidation phase}} \text{eudesmanol}
\]
Dihydrojunenol

1) $\text{Ph}^+\text{N}^-$, 5 mol% $\rightarrow$ 63%, 89% ee

2) LiOH, $i$-PrOH $\rightarrow$ 99%

1) $\text{MgBr}$, PCC, MS $\rightarrow$ 74%, two steps

9 steps, 21%, single diastereomer

Previous route: 9 steps, 8%, 3 isomers

"Gram quantities" for oxidation studies
Eudesmane terpenes

- 12 steps each, 17 and 9% from commercial
- Reassigned dihydroxyeudesmane
- Structures verified by X-ray
Eudesmane terpenes

13 steps, 9% from commercial

Previously unsynthesized
Eudesmane terpenes

Methyl propionate (CH₃CO₂Br) and 100 W sunlamp

LiOH

87% H₂SO₄

90% NaOH

15 steps, 4% from commercial

Previously unsynthesized
"...linear C-H activation strategy featuring multiple site selective oxidations in total synthesis"
Eudesmane terpenes overview

- Two-phase synthesis approach
- Adaptable to new syntheses

- "Retrosynthesis pyramid"
- "Gram-scale"

Methodology
- Trifluoroethyl carbamate directing group
- TFDO selective oxidation predicted by $^{13}$C NMR

First Synthesis
- Four unsynthesized
- One improved intermediate
- One new analogue

Family
- Six Eudesmane terpenes

References the terpene family (taxol)

Biological Activity
- Related to taxol
Why Nature?

- Concepts
- Methodology
- Family
- First Synthesis
- Biological Activity

Broad Interest