Highlights in Polyquinane Natural Product Synthesis

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Evans Group Afternoon Seminar
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Overview of Polyquinane Seminar

Leading References

Comprehensive coverage of syntheses and methodology


Methodology reviews

• Trost, B.M. Chem Soc. Rev. 1982, 11, 141
• Ramaiah, M. Synthesis 1984, 529
• Hudlicky, T.; Price, J. D. Chem. Rev. 1989, 89, 1467

Overview of Seminar

Introduction
Polyquinane Skeletal Motifs
Biosynthetic Pathways

Representative Syntheses
Diquinanes: Pentalenolactone E Methyl Ester
Linear Triquinanes: Capnellene, Corolin
Angular Triquinanes: Siliphinene, Pentalenene
Propellanes: Modhephene
Polyquinane Nomenclature

Diquinanes

Linear Triquinanes

cis

cis-anti-cis

cis-syn-cis

cis-anti-trans

Angular Triquinaes

Tetraquinanes

cis-anti-cis

* Highly strained ring systems which are not commonly found in polyquinane natural products
Polyquininane Structural Motifs: Diquinanes

Albene

Cedrene

Pentalenolactone E Methyl Ester

Magellanine

Quadrone

Modhephene
Polyquininane Structural Motifs: Higher Quinanes

**Linear Triquinanes**
- Hirsutene
- Coriolin
- Hirsutic Acid-C
- Capnellene

**Angular Triquinanes**
- Silphinene
- Pentalenene
- Laurenene
- Retigeranic Acid

**Tetraquinane**
- Crinipellin-B
Diquinanes: The Pentalenolactone Family

• Pentalenolactones A, B, D, E, F, G, H, O, and P have been isolated and characterized from *Streptomyces* strains. They differ in placement of the methyl groups (gem-dimethyl vs. 1,2-stereochemistry) and unsaturation in ring A, and in having a methylene, epoxide or cyclopropyl group alpha to the lactone. Cane, D. E. et al. *J. Org. Chem.* 1992, 57, 845 and references therein.

• Members of the pentalenolactone family have shown antibacterial, antiviral, and enzyme inhibitor properties. Cane D. E. et al. *Arch. Biochem. Biophys.* 1989, 270, 50 and references therein.
Retrosynthetic Analysis of (±)-Pentalenolactone E Methyl Ester

Taber: intramolecular C-H insertion

Marino: [3+2] annulation

Linder et al.: [3+2] annulation
(±)-Pentalenolactone E Methyl Ester: Intramolecular C-H Insertion

1. trisyl azide, KOH  
2. hυ, MeOH  
3. LiOH, DME  
1. (COCl)$_2$; LiCH$_2$CO$_2$Me  
2. TsN$_3$, Et$_3$N  
87% y.

NaBH$_4$, MeOH; dicyclohexyl-carbodiimide, Cu$_2$Cl$_2$, THF  
40% y.

CrO$_3$, HOAc  
22% y.

Rh$_2$(OAc)$_4$, CH$_2$Cl$_2$, rt  
91% y.

(A was obtained as a 30% y. of a 3:1 mix of carbonyl diastereomers)

08-Taber pent'lactone 1/26/99 1:18 PM
(±)- Pentalenolactone E Methyl Ester: base-induced [3+2] annulation

1. Me₃SiCl, Et₃N Δ

2 eq. PhS₋PPh₃⁺
5 eq KF, 0.1 eq 18-crown-6, 95% y.

2. 4 eq N₂CHCO₂Et, CuSO₄
65% y., 2 steps

RhCl(PPh₃)₃
Et₃SiH

2.5 eq N₂CHCO₂-t-Bu
CuSO₄, PhH

Et₃NHF
70% y., 3 steps

PhS PPh₃⁺BF₄⁻

(1:1 cis:trans)
(±)- Pentalenolactone E Methyl Ester: base-induced [3+2] annulation

1. NaOH H₂O/MeOH
2. ClCO₂Et, Et₃N; NaBH₄,
3. TFA 43% y.

1. p-TSA, 2. ClCO₂Me

1. NaCNBH₃, MeOH, HCl
2. MCPBA; K₂CO₃
60% y., 4 steps

A

13 steps to A, 11% overall yield

(-) - Pentalenolactone E Methyl Ester: Pd-catalyzed [3+2] annulation

\[\text{pig liver esterase} \quad 95\% \text{ y.}, \ 98\% \text{ ee}\]

\[\text{8 steps} \quad 33\% \text{ overall y.}\]

\[\text{3 mol\%Pd(OAc)}_2 \quad 3 \text{ mol\% } \text{P(Pr)}_3 \quad \text{THF, reflux} \quad 75\% \text{ y.}\]

1. ZnEt\textsubscript{2}, CH\textsubscript{2}I\textsubscript{2}, 94\% y.
2. H\textsubscript{2}, Pt, AcOH 99\% y.

1. O\textsubscript{3}, DMS 85\% y.
2. WOCl\textsubscript{4}, 2 eq. MeI 97\% y.

51\% isolated + 2 other isomers
(-) - Pentalenolactone E Methyl Ester: Pd-catalyzed [3+2] annulation

(±)- Pentalenolactone E Methyl Ester: Methylenation

1. MeOMgOCO₂Me
2. HCHO, Et₂NH, HOAc, NaOAc
   27% yield

- Use of Eschenmoser's salt in place of formalin/Et₂NH solution resulted in 40-50% yield in methylenation: Marino, J. P. *J. Org. Chem.* 1987, 52, 4140

- On (−)-A, methylation according to Paquette protocol proceeded in 73% yield: Mori, K. *Tetrahedron* 1988, 44, 2835

Linear Triquinanes: Coriolin and Capnellene

- Both Capnellene and Coriolin are members of the hirsutane structure class of linear triquinanes.


Retrosynthetic Analysis of Capnellene

Oda: 1,2 alkyl shift

Shibasaki: asymmetric Heck and radical 5-exo-trig cyclization

Singh: oxa-di-π-methane rearrangement
(±)-Capnellene: TMSI-based 1,2-alkyl shift

3.5 eq. TMSCl
3.5 eq. NaI
52% y.

(CO₂Et)₂, NaH
89% y.

CO₂Et
Et₃N 76% y.

Me₂CuLi
88% y.

Ph₃P=CH₂

Capnellene

• Methylenation of B previously performed by Paquette, L. A. Tet. Lett. 1981, 22, 4393

5 steps to B, 22% overall y.

(±)-Capnellene: Oxa-Di-π-Rearrangement

1. NaIO$_4$  
2. Oz  
85% y.

1. Zn, NH$_4$Cl, Δ  
2. NaH, MeI  
89% y.

1. SeO$_2$  
2. KH$_2$PO$_4$  
63% y.  
2. Jones oxid. 78% y.

1. H$^+$, HO OH  
2. hv  
64% y.

1. NaBH$_4$  
2. Jones oxid. 68% y.
(±)-Capnellene: Oxa-Di-π-Rearrangement

1. H₂, Pd/C
   85% y.

1. NaBH₄  90%
2. NaH, CS₂, MeI
   imidazole, 90% y.

1. Bu₃SnH
   AIBN, Δ
   76% y.

Singh, V.  J. Org. Chem. 1998, 63, 4011
(-)-Capnellene: Annulation via Asymmetric Heck Reaction

1. Bu₃SnH, AIBN
2. NaOH, MeOH
96% yield

1. Et₂Zn, CH₂I₂ 95%
2. H₂, PtO₂, AcOH 80%

1. o-NO₂PhSeCN, PPh₃, pyridine
2. H₂O₂, K₂CO₃
78% yield

20 steps, 20% overall yield

Retrosynthetic Analysis of Coriolin

Wender: [4+4] Cycloaddition

Curran: Tandem Radical Cyclization
(±)-Coriolin: [4+4] cycloaddition

CO₂Me → \( \text{CHO} \) → Momo → Momo

1. Li, 9-BBN, H₂O₂, NaOH 64% 2. PDC 80%

1. MOMCl, KH 77% 2. PDC 80%

200 °C, 12 h 60% y., 2 steps
(±)-Coriolin: [4+4] cycloaddition

1. B2H6, THF; H2O2, NaOH 79% y.
2. PDC 90% y.

1. MsCl, Et3N 80% y.
2. 6N HCl/THF/H2O (1:2:1) 66% y.

• C taken on to Coriolin by Ikegami, S. Tetrahedron 1981, 37, 4411

13 steps to C, 3.6% overall yield

Wender, P. A. J. Am. Chem. Soc. 1987, 109, 2523
(±)-Coriolin: Tandem Radical Cyclization

1. TBSO\(\rightarrow\)Br
2. LAH
90% y., 2 steps

1. PCC
2. Li\(\rightarrow\)TMS
98% y.

1. PCC
2. (CHOH)\(\rightarrow\), H\(+\)
3. Bu\(_4\)NF
53% y., 3 steps
(±)-Coriolin: Tandem Radical Cyclization

1. SmI₂, THF/HMPA 20/1
2. pTSA, acetone 60% y.

LDA; TBSCI, THF/DMPU 89% y.

D has been taken on to coriolin by Danishefsky, S. J. Am. Chem. Soc. 1981, 103, 3460

(±)-Coriolin: Final Oxygenation Strategies

1. LDA, PhSeBr
2. 30% H2O2, AcOH
3. H2O:AcOH:THF (3:1:1) 50% y., 3 steps

1. MCPBA
2. DBU 21% y., 3 steps

1. VO(acac)2, t-BuOOH 65% y.
2. CrO3, pyridine 40% y.

1. VO(acac)2, t-BuOOH
2. CrO3, pyridine

Step C → D performed by Ikegami, S. *Tetrahedron* 1981, 37, 4411


Final CrO3 oxidation performed by Umezawa, S. *J. Antibiot.* 1980, 33, 404

Coriolin
(±)-Coriolin: Tandem Radical Cyclization of Oxygenated Precursor

1. MCPBA 85% y.
2. K$_2$CO$_3$ 98% y.
1. Hg(OAc)$_2$; NaBH$_4$/MeOH 70% y.
2:1 eno:exo

1. NaSePh; H$_2$O$_2$ 77% y.
2. Cl$_3$C-CN-OMPM
PPTS 91% y.

1. MsCl, Et$_3$N quant.
2. pyridine 45% y.

64% y. of desired epoxide

8 steps to H, 5.8% overall y.

- Enantioselective synthesis of H allowed for elaboration to F via Curran's methodology

Angular Triquinanes: Silphinene and Pentalenene

Propellanes: Modhephene


- Pentalenene, first isolated in 1980 from *Streptomyces griseochromongenes* by Seto and co-workers, has been shown to be the parent of the pentalenolactone family of antibiotics. Pentalenene synthase has been isolated and extensively studied to determine the biosynthetic origins of polyquinane natural products. Seto, H.; Yonehara, H. *J. Antibiot.* 1980, 33, 92. Cane, D. E. *et al.* *Bioorg. Chem.* 1984, 12, 312.

- Modhephene was isolated from the goldenrod plant *Isocoma wrightii* in 1978 and was the first natural product found to have the [3.3.3]-propellane skeleton. Zalkow, L. H. *et al.* *J. Chem. Soc. Chem. Commun.* 1978, 420.
Silphinene: Retrosynthetic Analysis

Franck-Neumann: [2+2] Cycloaddition & Nazarov Reaction

Wender: Arene-Olefin meta-Photocycloaddition
(±)-Silphinene: [2+2] cycloaddition and Nazarov cyclization

1. TBAF
2. 10% H$_2$SO$_4$
3. quant.

1. ThexylMe$_2$SiOTf
2. SeO$_2$
3. 70% y.

1. BnOCNHCCl$_3$
cat. TFA 80% y.

1. ThexylMe$_2$SiOTf
2. 92% y.

1. TMSOTf, Et$_3$N
2. Me$_2$N$_2$
3. h$_\nu$ 70% y.

1. ZrCl$_4$, rt
2. 90% y.
(±)-Silphinene: [2+2] cycloaddition and Nazarov cyclization

1. BrMg(CH=CH)SiMe₃  
   80% yield

2. MnO₂  
   85% yield

1. TBAF quant.
2. Swern 89% yield

1. anhyd. N₂H₄
   KOH, Δ 46% yield

1. LDA, HMPT; CH₃I 63% yield
2. Me₂CuLi  
   78% yield

(±)-Silphinene: Arene-Olefin meta-Cycloaddition

1. Li (1%Na)
2. Δ

NH₃, -78 °C → -33 °C; NH₄Cl 87% y.

Vycor filtered Hg arc lamp 70% y.

3 steps, 20% overall y.

• For theoretical studies on arene-olefin meta-cycloaddition, see Houk, K. Pure App. Chem. 1982, 54, 1633

Wender, P. A. Tet. Lett. 1985, 26, 2625
Pentalenene: Retrosynthetic Analysis

Pattenden: Grob Fragmentation & Transannular Cyclization

Lange: Radical Fragmentation

MeO₂C

Δ
(±)-Pentalenene: Cationic Transannular Cyclization

\[
\text{HO}_2\text{C} \quad \text{CH}_2=\text{CHLi} \quad 66\% \text{ y.} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} ; \quad \text{NaCl, DMSO, H}_2\text{O, } \Delta \quad 80\% \text{ y.}
\]

\[
\text{MeO}_2\text{C} \quad \text{K}^+ \quad \text{t-Bu} \quad 98\% \text{ y.}
\]

\[
\text{HO} \quad \text{O} \quad \text{OTBS} \quad \text{Me}_3\text{CuLi}_2 \quad 82\% \text{ y.}
\]

\[
\text{H} \quad \text{Me}_3\text{CuLi}_2 \quad 1. \text{ TBSCI, Et}_3\text{N} \quad 99\% \text{ y.}
\]

\[
\text{HO} \quad \text{O} \quad \text{OTBS} \quad \text{Me}_3\text{CuLi}_2 \quad 2. \text{ h}_\nu \quad 81\% \text{ y.}
\]
(±)-Pentalenene: Cationic Transannular Cyclization

1. PPh₃=CH₂ 82% y.
2. RhCl₃•3H₂O 51% y.

BF₃•Et₂O

25-35% y

Pentalenene

38% y.

11 steps, 4% overall yield

(±)-Pentalenene Precursor: Radical Fragmentation

For other syntheses of H, see Helquist, P. *Tet. Lett.* 1991, 32, 5753

(±)-Modhephene: Carbocation Rearrangements

\[ \text{Acetone} \xrightarrow{\text{KO-}t\text{-Bu}} \text{Cl}_2\text{C}=\text{C}=\text{O} \xrightarrow{81\% \ y.} \rightarrow \rightarrow \xrightarrow{\text{Zn, HOAc}} \xrightarrow{85\% \ y.} \rightarrow \rightarrow \text{Cl}_2\text{C}=\text{C}=\text{O} \rightarrow \rightarrow \rightarrow \xrightarrow{\text{MCPBA}} \xrightarrow{91\% \ y.} \rightarrow \rightarrow \]

\[ \text{BF}_3\cdot\text{Et}_2\text{O} \xrightarrow{54\% \ y.} \rightarrow \rightarrow \xrightarrow{\text{MCPBA}} \xrightarrow{91\% \ y.} \rightarrow \rightarrow \]
(±)-Modhephene: Carbocation Rearrangements

\[ \text{O} \quad \text{1. LDA} \quad \text{O} \quad \text{1. LDA} \quad \text{CH}_3\text{Li} \]
\[ \text{2. CH}_3\text{I} \quad 90\% \ y. \quad 2. \text{aq. Na}_2\text{SO}_4 \quad 66\% \ y. \quad 69\% \ y. \]

- Longer reaction times (6 h) resulted in 6 products forming (only 6% was modhephene), indicating that the formation of modhephene was under kinetic control.