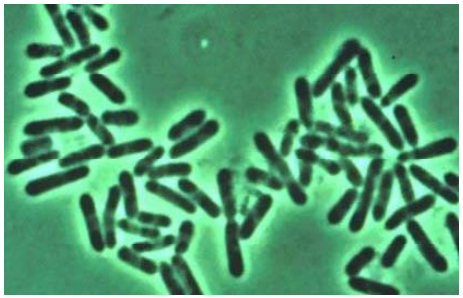
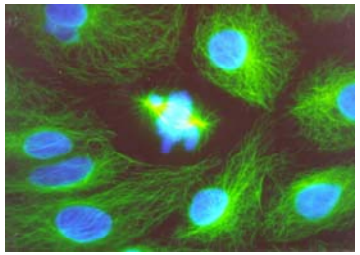
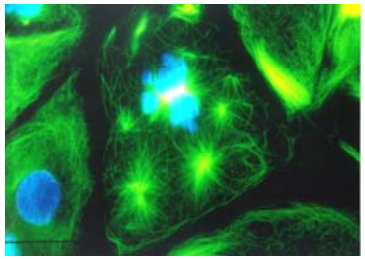
Partial Reduction of Activity

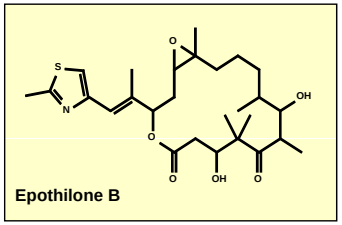


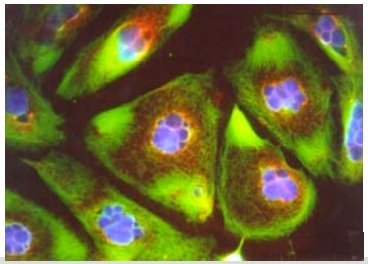
Targets: **Tubulin** (Synthesis)
Actin (Genetics and Synthesis)

Target: Tubulin cytoskeleton



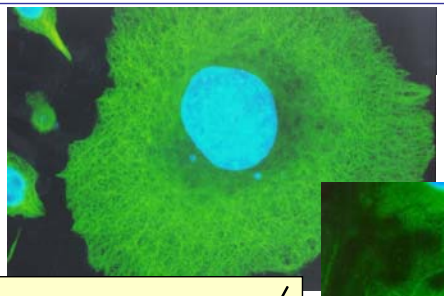




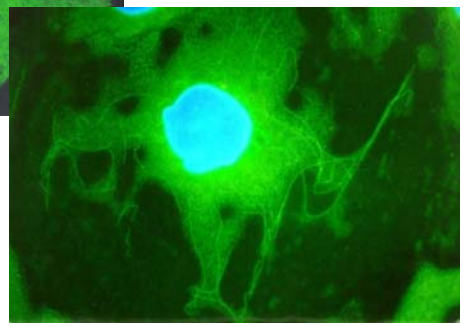


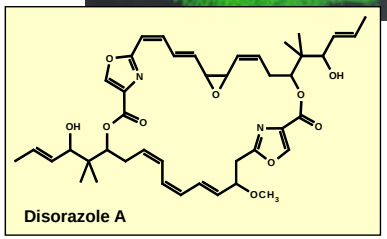
Epothilone induces microtubule polymerisation

Target: Tubulin cytoskeleton



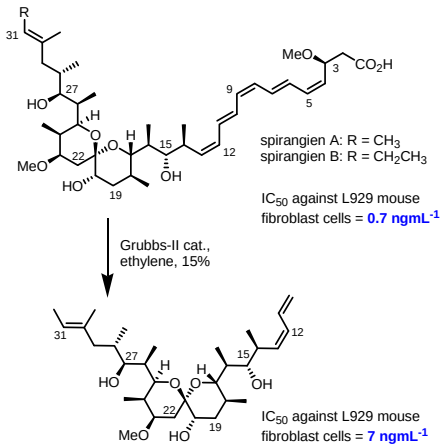
IC_{50} = 2 - 8 pg/ml

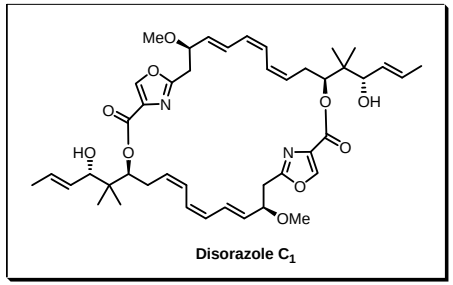




Disorazoles inhibit tubulin polymerisation

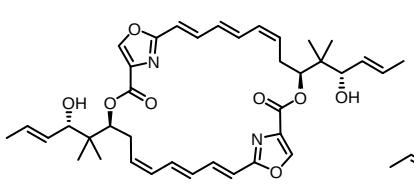
How to simplify Natural Products?



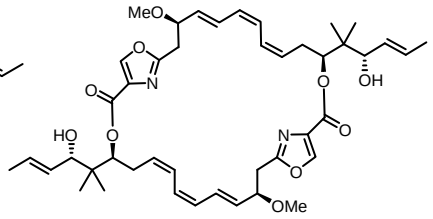


J. Niggemann, N. Bedorf, U. Flörke, H. Steinmetz, K. Gerth, H. Reichenbach, G. Höfle, *Eur. J. Org. Chem*. **2005**, 5013.

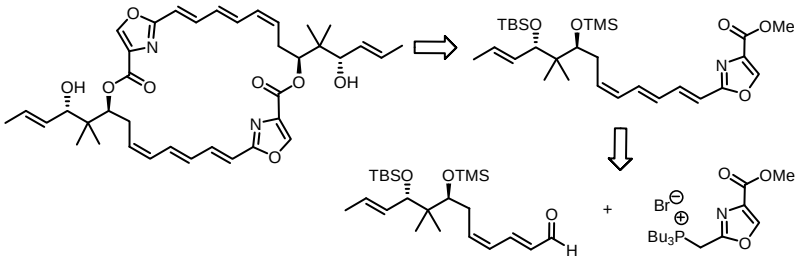
P. Wipf, T.H. Graham *J. Am. Chem. Soc*. **2004**, *126*, 15346.
M.C. Hillier, A.T. Price, A.I. Meyers *J. Org. Chem.* **2001**, *66*, 6037.
I.V. Hartung, B. Niess, L.O. Haustedt, H.M.R. Hoffmann *Org. Lett.* **2002**, *4*, 3239.



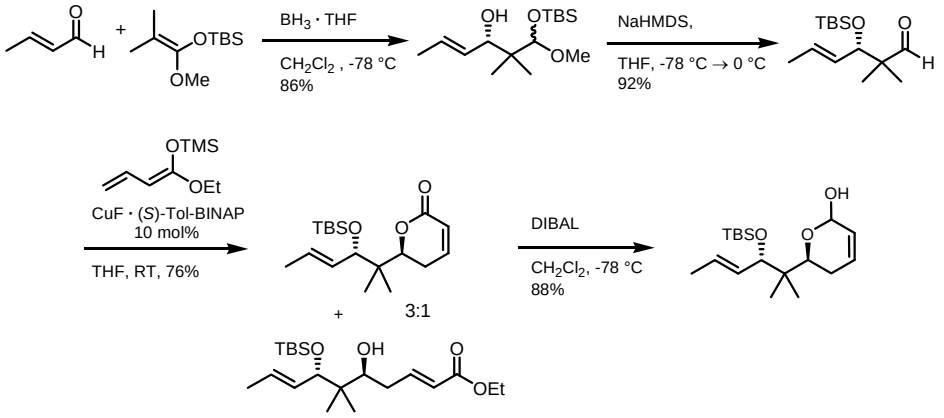
"Short Disorazole"



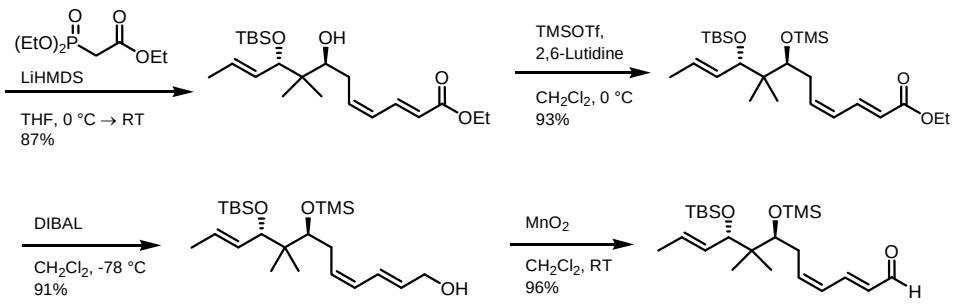
Disorazole C_1



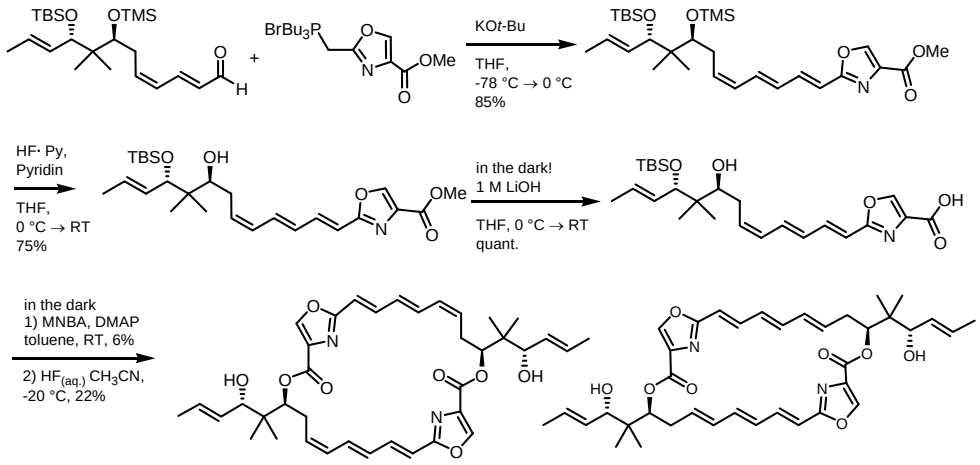
Romy Schäckel, Bruce Melancon*, Coura Diene* (*Taylor group)



Romy Schäckel



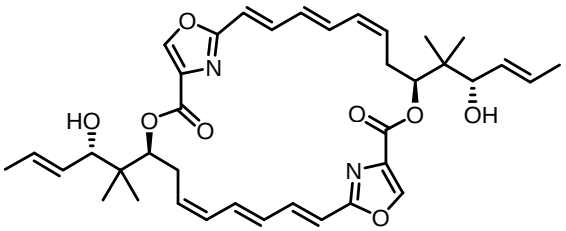
Romy Schäckel



Romy Schäckel

Summary:

Simplified disorazoles are still active in the low nM-range

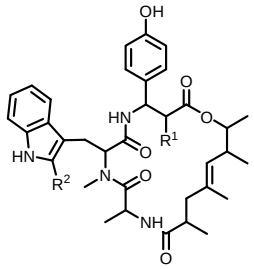


Disorazole 1

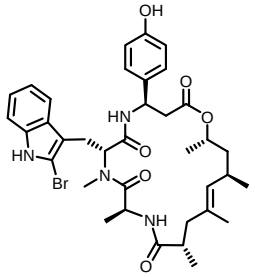
IC_{50} against L929 mouse fibroblast cells = 3.2 ngmL^{-1}

Romy Schäckel

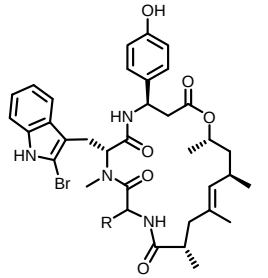
Chondramides induce the polymerizatrion of g-actin



Chondramide:
A (1) : R^1 = OMe, R^2 = H
B (2) : R^1 = OMe, R^2 = Cl
C (3) : R^1 = H, R^2 = H
D (4) : R^1 = H, R^2 = Cl

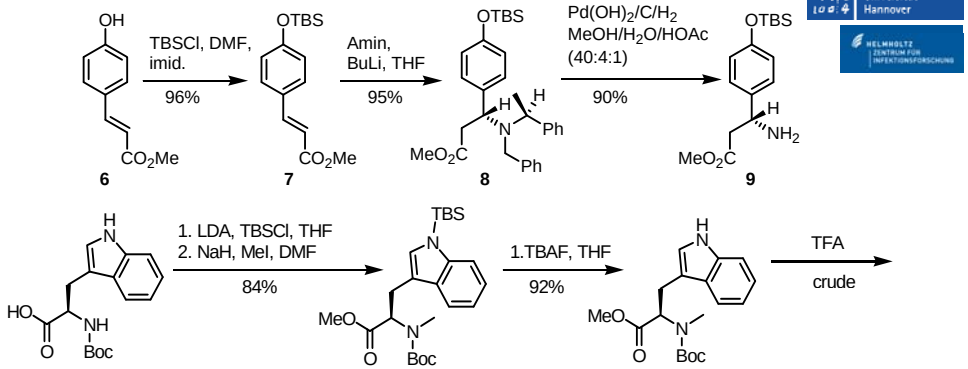


Jaspamid (Jasplakinolid) (5)



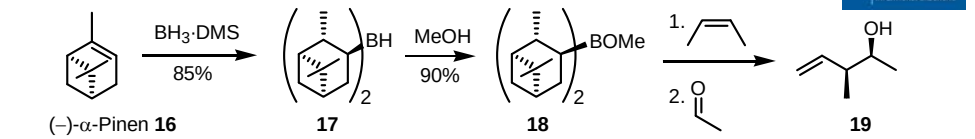
Jaspamid D R = CH_2CH_3
Jaspamid E R = CH_2OH

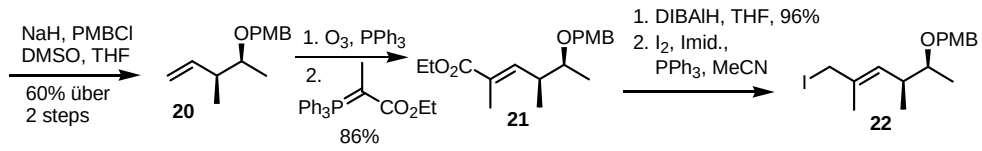
F. Sasse, B. Kunze, T. M. A. Gronewold, H. Reichenbach *J. Nat. Cancer Inst.* **1998**, *90*, 1559. R. Jansen, B. Kunze, H. Reichenbach, G. Höfle *Liebigs Ann.* **1996**, 285-290.

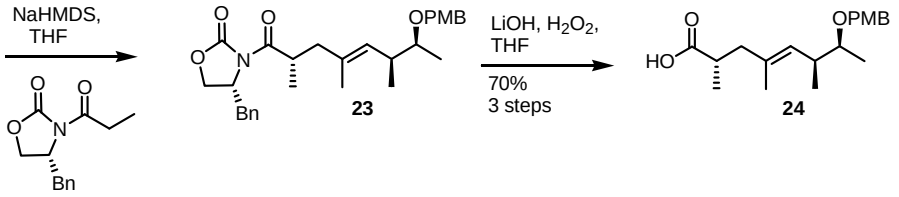


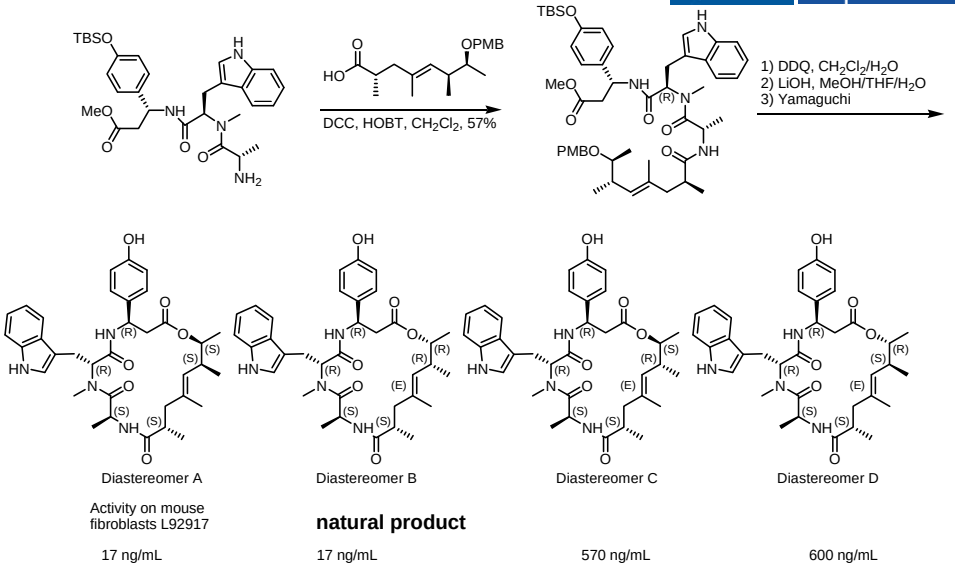
P. Ashworth, B. Broadbelt, P. Jankowski, P. Kocienski *Synthesis* **1995**, 199.

Synthesis of the polyketide segment







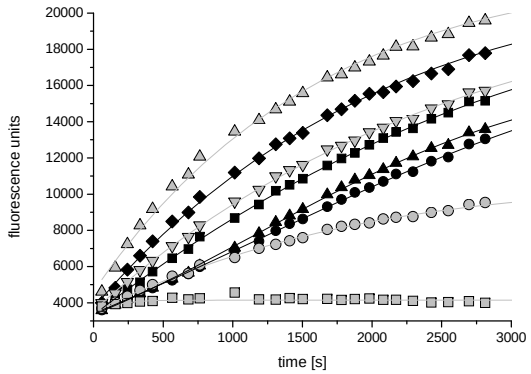


Antiproliferative activity of isomer **A**, **B**, **C** and **D** on different mammalian cell lines.

Cell line	Origin	A	B	C	D
		IC_{50}[a] [nM]			
L-929	Murine connective tissue fibroblasts	55 ± 24	81 ± 6	16 ± 70 ± 390	2400 ± 115
A-431	Human epidermoid carcinoma	55 ± 5	49 ± 3	620 ± 280	1200 ± 45
A-498	Human kidney carcinoma	24 ± 3	32 ± 2	500 ± 130	920 ± 270
A-549	Human lung carcinoma	26 ± 5	23 ± 2	510 ± 195	930 ± 60
SK-OV-3	Human ovary adenocarcinoma	16 ± 5	19 ± 2	320 ± 60	1040 ± 160

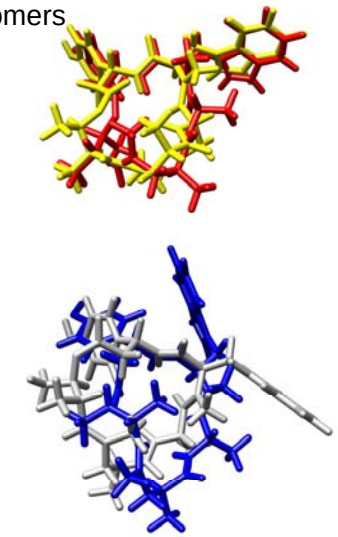
[a] data are means ± standard deviations of two independent IC_{50} value determinations

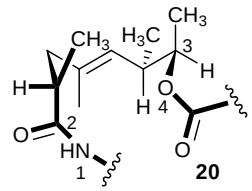
Induction of G-actin polymerization by chondramide



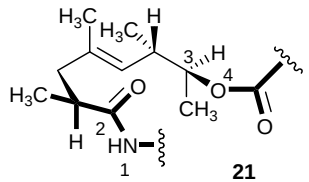
Induction of G-actin polymerization by chondramide. Pyrene-actin in a non-polymerizing buffer was incubated with chondramide C diastereomers and actin polymerization monitored by measuring increasing fluorescence. Every diastereomer was applied at 10 µM concentration (depicted by black symbols: diamonds **20**, squares **21**, uptriangles **22,** and circles **23**). With chondramide C the induction efficacy at additional concentrations is shown (grey symbols: uptriangles 40 µM, downtriangels 5 µM, and circles 1 µM; grey squares: methanol only).

Superimposition of the chondramide C isomers

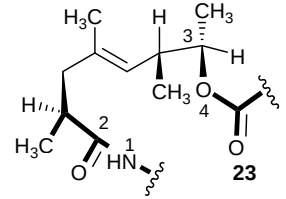




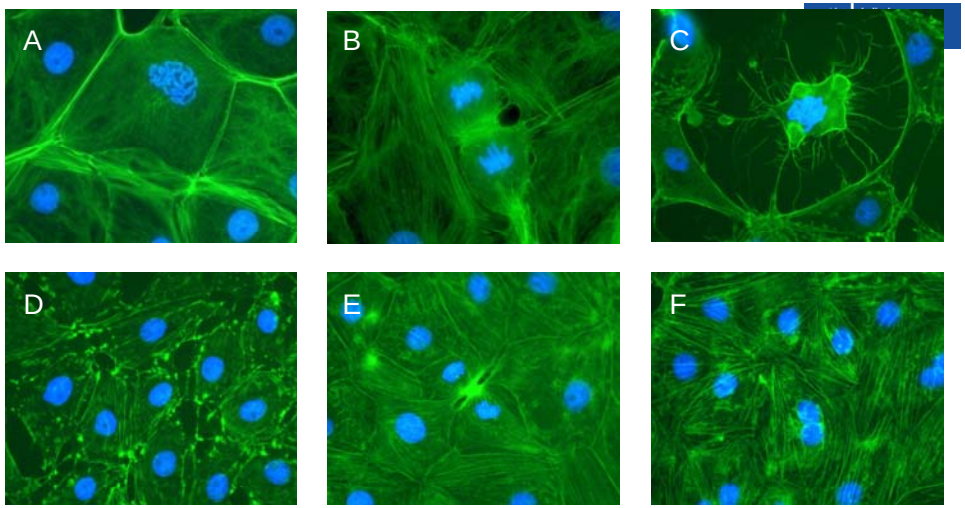
N(1)-O(5) distance = 4.5A
Torsion angle N(1)C(2)C(3)(O4) = -64.1°



N(1)-O(5) distance = 4.2A
Torsion angle N(1)C(2)C(3)(O4) = -74.6°

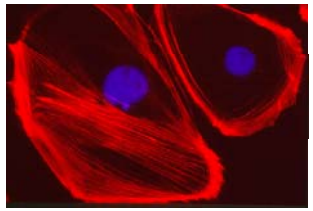


N(1)-O(5) distance = 4.8A
Torsion angle N(1)C(2)C(3)(O4) = 33.2°

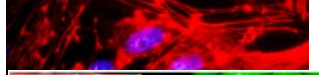


Influence of chondramide C (**30**) on the actin cytoskeleton of A-498 kidney cancer cells after different incubation times. **A, B;** control cells with a dividing cell in the center, in metaphase (**A**), and in telophase (**B**). Cells that were incubated with chondramide (100 ng/ml) showed abnormal metaphase cells (**C**, after 2 hours), and a strengthened contractile ring in late telophase (**E**, after 18 hours). Spots of F-actin became visible especially at focal adhesion points (**D**, after 4 hours), stress fibers became stronger and flakes of actin appeared (**E** and **F**, after 18 hours).

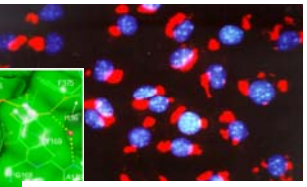
Target: Actin cytoskeleton

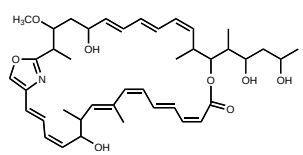


stabilizer of actin polymerization

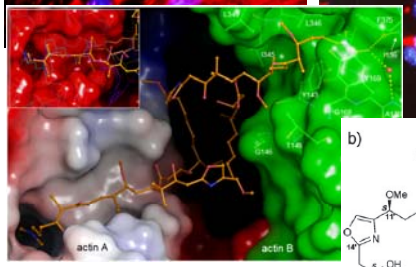


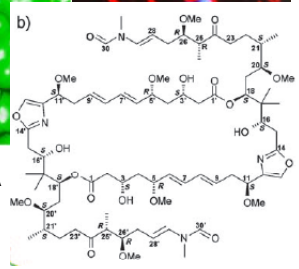
Chondramide B





Chivosazol

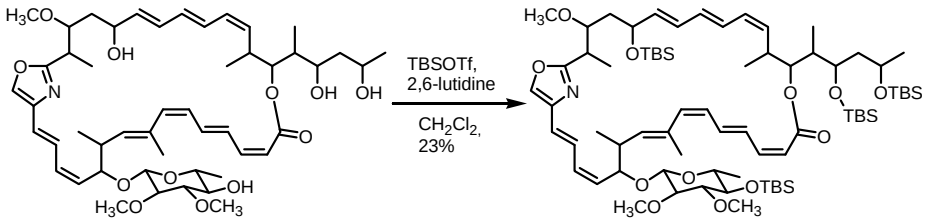


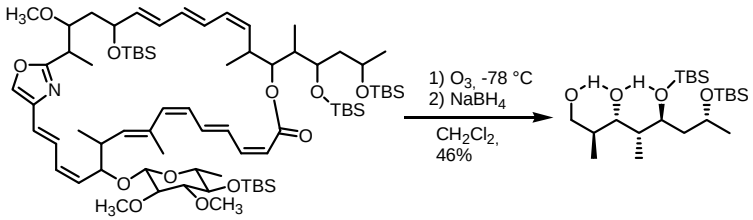


Rhizopodin A

inhibitor of actin polymerization

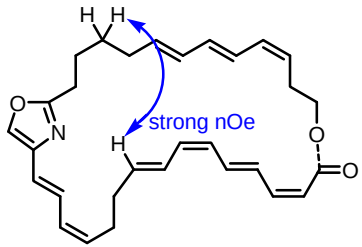
Configurational Assignment of Chivosazol





Dominic Janssen

New Strategy for the Configurational Assignment of Polyketides



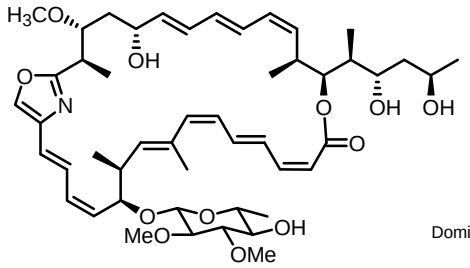
Monte Carlo
Conformational analysis
using nOe as restrain

↓

Structures were clustered

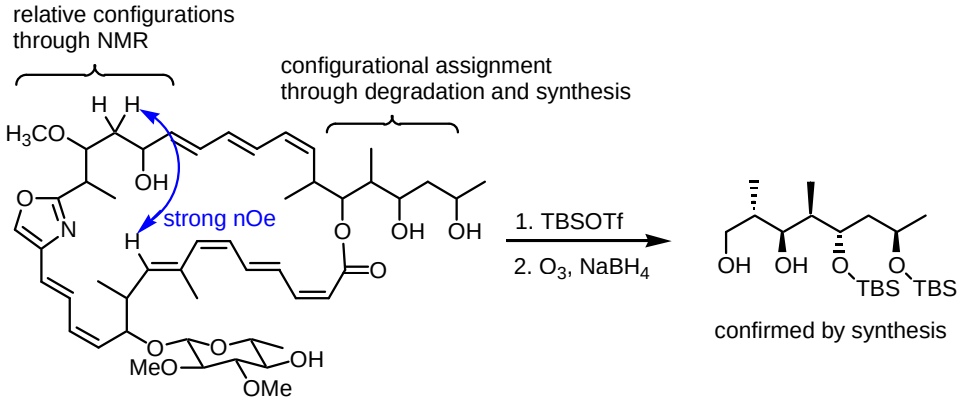
↓

Substituents were introduced
based on their coupling constants



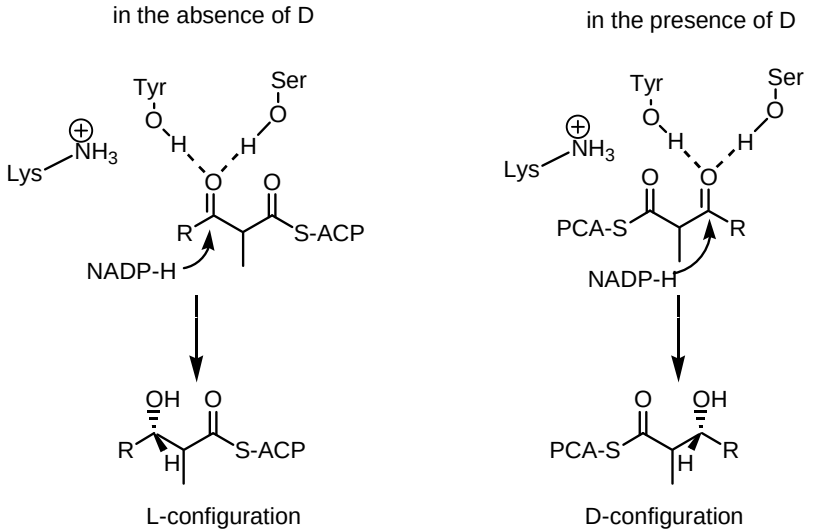
Dominic Janssen

New Strategy for the Configurational Assignment of Polyketides



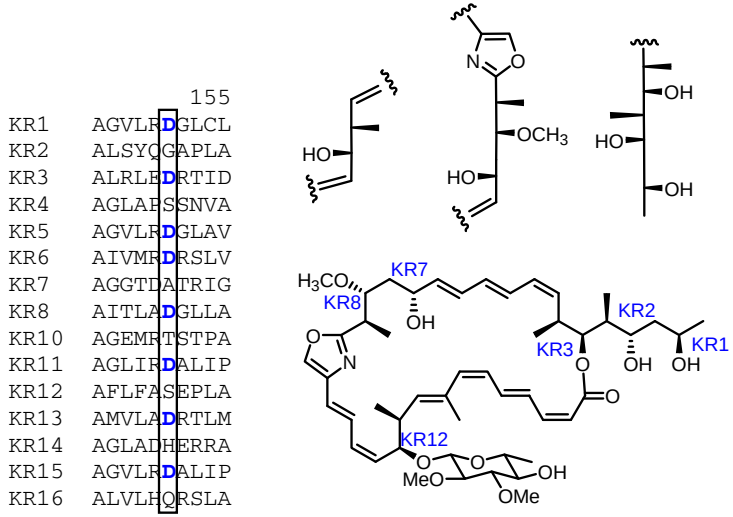
Dominic Janssen

Configurational Assignment of Chivosazol



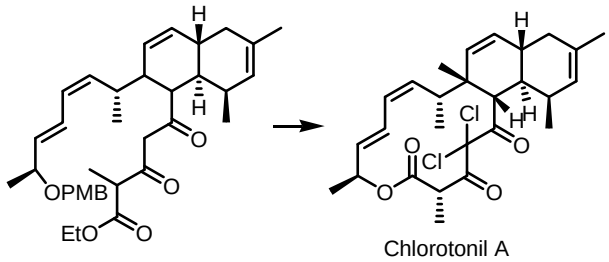
Dominic Janssen

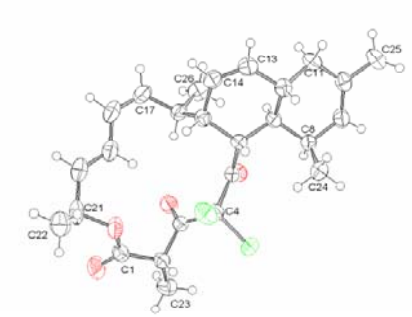
Configurational Assignment of Chivosazol



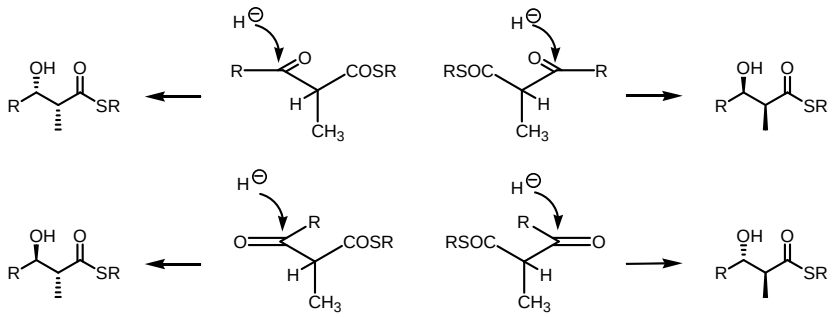
A. Kirschning et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 2308.
D. Menche et al. *J. Am. Chem. Soc.* **2008**, *130*, 14234.

Dominic Janssen





Nicola Rahn

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LD_Borrelidin_4_KR_1            LLDTDAEETAAVLRAKSAGARNLHELLDD----VDAFVLFSSGAGVWGSSAQGAYAAANAYLDALAEQRRGQG-RPATSVAWGAW
LD_Epothilon_4_KR_1             LAETDEALLESVLRPKVAGSWLLHRLLRDR--PLDLFVLFSSGAAVWGGKGQGAYAAANAFLDGLAHHRRAHS-LPALSLAWGLW
LD_Erythromycin_1_KR_2          INDMDEAAFDEVVAAKAGGAVHLDELCS----DAELFLLFSSGAGVWGSARQGAYAAANALDAFAHRRRGRG-LPATSVAWGLW
LD_Erythromycin_3_KR_1          LDDLTEAEFTEIADVKVRGTVNLDELCP----DLDAFVLFSSNAGVWGSPGLASYAAANAFLDGFARRRRSEG-APVTSIAWGLW
LD_Erythromycin_3_KR_2          LHEIG--ELESVCAAKVTGARLLDELCP----DAETFVLFSSGAGVWGSANLGAYSAANAYLDALAHRRAEG-RAATSVAWGAW
LD_Geldanamycin_1_KR_3          LSKMTLAEFADIGQAKIAGARHLDDLLGER--ELDAFVLFSSGAAAWGSGGQSAYAAGNAYLDGLAQRRRARG-LAATSVAWGAW
LD_Geldanamycin_Hydroxylymalonyl VTEVTTEEFAAVTGAKVRGALVLDELVGDR--ELDAFVLFSSGAGVWGSGGQAPYAAGNAFLDGLAARRRAHG-LAATAVAWGGW
LD_Herbimycin_1_KR_3            LSKMTLAEFADIGRAKIAGARHLDDLLGER--ELDAFVLFSSGAAWGSGGQSAYAAGNAYLDGLAQRRRARG-LAATSVAWGAW
LD_Herbimycin_Hydroxymalonyl    VTEVTAEEFAAVTGAKVRGALVLDQLVGDR--QLDAFVLFSSGAGVWGSGGQAPYAAGNAFLDGLAARRRAHG-LAATSVAWGGW
LD_Lankamycin_1_KR_2            VREMTREEFRTVLAAKVDGARNLAHACP----GLSLFLLFSSGAAVWGSAQGGAYAAGNAFLDAFAQHRRRAG-LAATSVAWGLW
LD_Lankamycin_3_KR_1            LEAITEEEFTRVTAAKITGTAHLDELCP----DADTFVLFSSNAGVWGASRAGAYAAANAFLDGFAHRRRRRG-LPALSVAWGLW
LD_Lankamycin_3_KR_2            LTDLDPDELARVTRVKTVGARLLDELCP----DAETFVLFSSGAGLYGSGLLGAYAAGNAFLDALAHRRRAAG-KPATSIAWGAW
LD_Megalomycin_1_KR_2           LTDMDPADLADVVAVKVDGAVHLADLCP    EAELFLLFSSGAGVWGSARQGAYAAGNAFLDAFARHRRDRG LPATSVAWGLW
LD_Megalomycin_3_KR_1           VQELTESEFTEITDAKVRGTANLAELCP----ELDALVLFSSNAAVWGSPGLASYAAGNAFLDAFARGRRSG-LPVTSIAWGLW
LD_Megalomycin_3_KR_2           LDRID--ELESVSAAKVTGARLLDELCP----DADTFVLFSSGAGVWGSANLGAYAAANAYLDALAHRRRQAG-RAATSVAWGAW
LD_Monensin_7_KR_1              IGDLTTARLGEVLGSKSDAAWNLHELTRDL--DLSAFVMFSSGAGVWGSGQQGAYGAANHFLDALAEHRRAQG-LPATSIAWGPW
LD_Monensin_8_KR_1              LGDVSGAELDEVLRPKALAAHHLHELTREL--PLSAFVMFSSGAGVWGSGQQGAYGAANHFLDALAEHRRAEG-LPATSIAWGPW
LD_Nystatin_2_KR_2              AADLTLDQLDALLRAKLTAAHHLHELTAPL--DLDAFVLFSSGAAVWGSGGQPGYAAANAYLDALAAHRRSLD-LPGASVAWGTW
LD_Oleandomycin_1_KR_2          LAEISVQEAADVMAAKVAGAVNLGELVDPC--GLEAFVLFSSNAGVWGSGGQAVYAAANAFLDALAVRRRGVG-LPATSVAWGMW
LD_Oleandomycin_3_KR_1          LAEISVQEAADVMAAKVAGAVNLGELVDPC--GLEAFVLFSSNAGVWGSGGQAVYAAANAFLDALAVRRRGVG-LPATSVAWGMW
LD_Oleandomycin_3_KR_2          LAEISVQEAADVMAAKVAGAVNLGELVDPC--GLEAFVLFSSNAGVWGSGGQAVYAAANAFLDALAVRRRGVG-LPATSVAWGMW
LD_Oligomycin_1_KR_2            VRELDLADLDAQMAAKTLGARHLDELTTERGLELDAFVVFSSGAAIWGSAGNGGYAAANAYLDALAWDRRARG-LAATSVSWGGW
LD_Oligomycin_7_KR_1            VRELDLADLDAQMAAKTLGARHLDELTTERGLELDAFVVFSSGAAIWGSAGNGGYAAANAYLDGLAWDRRARG-LAATSVSWGGW
LD_Phoslactomycin_5_KR_1        LEDMTADEFQEVVAAKVDGARVLDELLGDT--ELDAFVVFSSIAAVWGSSRSGAYAAGNASLDALVEQRRARA-AAGTSVAWGFW
LD_Pikromycin_3_KR_1            LDVTGPEDIARILGAKTSGAEVLDDLLRGT--PLDAFVLYSSNAGVWGSGQSVYAAANAHLDALAARRRARG-ETATSVAWGLW
LD_Rifamycin_2_KR_2             IETLDRDRLATVFAPKVDAVRHLDELTRDR--LDDAFVVYSSVSAVFMGAGSGSYAAANAFLDGLMANRRAAG-LPGLSLAWGLW
LD_Soraphen_2_KR_3              LAATSMEDLAEVVSGKVQGARHLHDLLGSR--PLDAFVLFSSGAVWGSGGQQGSYAAANAFLDALAEQRRSLG-LTATSVAWGVW
LD_Spinosad_3_KR_1              LAETDQNGLAEICAAKVRGAQVLDELCDST--DLDAFVLFSSGAGVWGSGGQAGYAAANAFLDTLAEQRRARG-LPATSISWGSW
LD_Spirangien_SpiE_KR_3         IAATDIADLADAVAGKAAGARHLDELFGDR--ALDAFVLFSSGAAVWGSGGQQGAYAAANAFLDALAERRARG-LAATSVAWGAW
LD_Spirangien_SpiG_KR_8         VAAMRVEELADAIAAKARGAQHLHDVFAQR--PLDAFVLFSSGAGVWGGRQGAYAAANAFLDALAEARRADG-LAATSIAWGAW
LD_Stigmatellin_4_KR_1          LADLDAEGLQAIFRSKAEGSWALHRVLEGT--PLDFFVFFSSGSALMSSPLLGGYAAANAFMDALAHTRRAQG-LPALSINWGFW
LD_Tylacton_4_KR_1              FTALDETTTAGVYGGKVLGARHLDELTRELGIGLDAFVLFSSGAAVWGSGGQTAYGAANAALDALAERRRAAG-LPATSVAWGLW
LL_Chivosazol_ChiE_KR_12        LAAMSPERFLELLGAKLWGSRALAAALAEH-APGFLVFFSSIQSSSRDKGQAAYAAGSVFQDALGASLARSAGYPVKVVNWGYW

LL_Amphotericin_2_KR_1          LADTTVDAFADVVHAKVTGARILDELLDDE--ELDDFVLYSSTAGMWGSGVHAAYVAGNAYLSALAEQRRARG-ARATSIHWGKW
LL_Amphotericin_4_KR_3          LDATTLDDFDRVLAAKVTGAQILDELLDDE--ELDDFVLYSSTAGMWGSGAHAAYVAGNAYLAALAEHRRARG-LTALSLSWGIW
LL_Aurafuron_AufD_KR_2          IVNQSWEAFERVLRPKVRGAWHLHRNAR----DLDFFVHFSSASSLLGPHGQASYAAANAFLDALAYHQRAHH-TPAVTINWGPW
LL_Chivosazol_ChiB_KR_2         LASMDTDTFARVLSPKVQGSVALYRALADE--PLDFLVFFSSIQSFTGDKSQSNYAAGCAFKDAFADHLRARAPFPVKTINWGYW
LL_Concanamycin_3_KR_1          LSDTDPDEFADTLYAKVAGAENLDAVFDRD--DLDTFVLFSSISGVWGSGDHGAYAAANAHLDALADRRRARG-RTATSVVWGIW
LL_Concanamycin_5_KR_1          VRDENPASMAATLAAKVQGAANLDAVLADT--DLDAFVLYSSVSGVWGSADHAAYVAGNAYLDALAAHRRGRG-LAATSVVWGIW
LL_Concanamycin_5_KR_2          LDDTPLDAFAEVVAAKAEGARHLDELLDR---DLDAFVLSSVAGVWGSSNHAAYTAGNAYLDALAEHRRAAG-LSATTVDWGVW
LL_Myxalamide_2_KR_1            LENMDLAAMTAMMRPKVLGSWVLHEVTREA--ELDFFVMFSSTSTLWGASGLAHYAAGNQFLEALAHHRRAQG-LPATTIHWGTW
LL_Nystatin_2_KR_1              LADTTVAEFADVVHAKVTGARILDELLDDA--ELDDFVLYSSTAGMWGSGVHAAYVAGNAYLSALAEQRRARG-LRTTSIHWGKW
LL_Nystatin_4_KR_3              LDATTLADFDRVLHAKVTGAQVLAELLDDE--ELDDFVLYSSTAGMWGSGAHAAYVAGNAYLAALAEHRRANG-LPALSLSWGIW
LL_Oligomycin_2_KR_2            LAEAGPDDLAEAMAAKVTGIAHLEAALDPE--QLDAVVYFSSISASWGAGDHGVYAAANGVLDARAEARSAAG-VHTVSLAWAPW
LL_Pimaricin_3_KR_3             LDETTLDDFAKVMDAKVIGARHLDELLGD---DLDAFVLYSSTAGMWGSGAHAAYVAGNAYLNALAEHRRARG-ARATAVSWGIW
LL_Rifamycin_3_KR_1             TGALTRERLAKVFAPKVDAANHLDELTRDL--DLDAFIVYSSASSIFMGAGSGGYAAANAYLDGLMAARRAAG-LPGLSLAWGPW
AA_Sorapen_2_KR_5_silent        LGAMSLERIDRVFAPKIDAAWHLHQLTQDK--PLAAFILFSSVAGVLGSSGHSNYAAASAFLDALAHHRRAQG-LPASSLAWSHW
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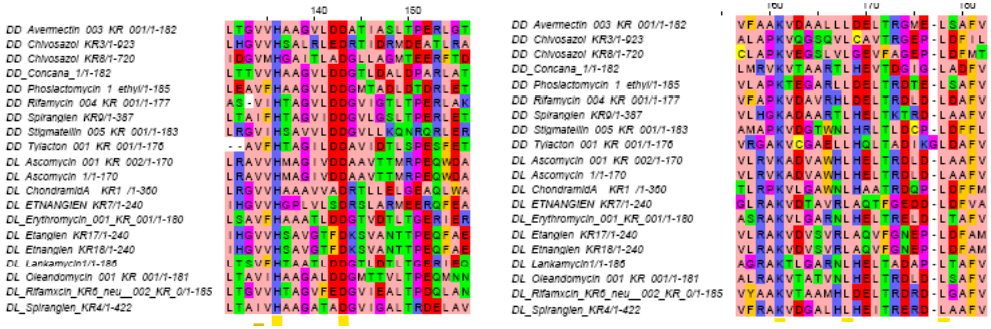
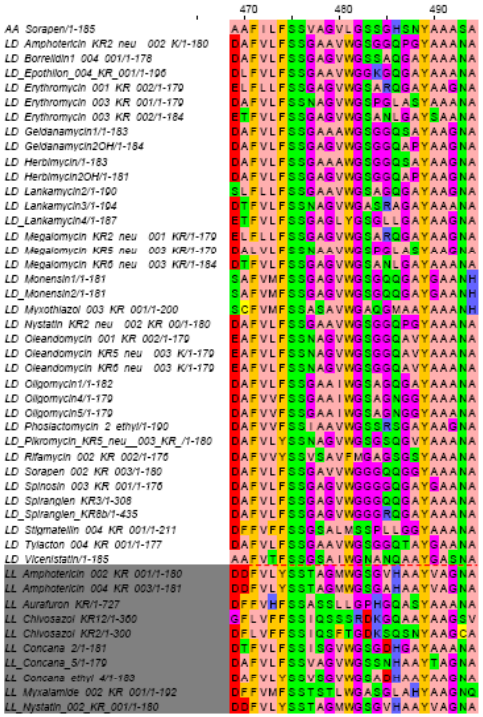
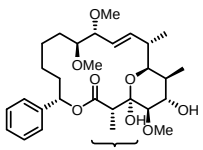


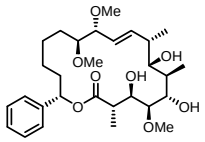


Soraphen

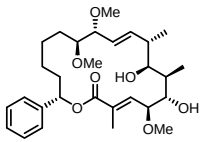


modul has a silent KR and DH

"Genetic Soraphen I"



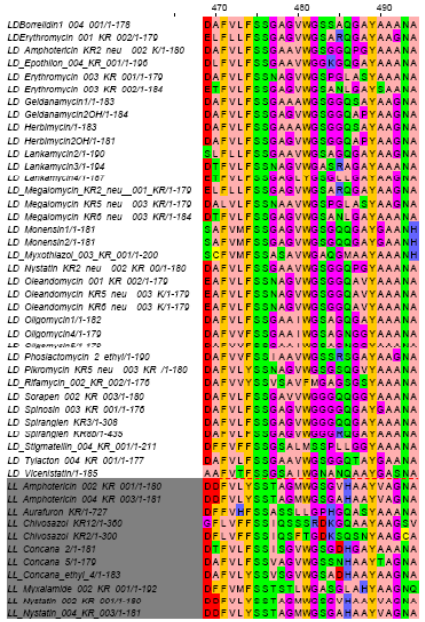
"Genetic Soraphen II"

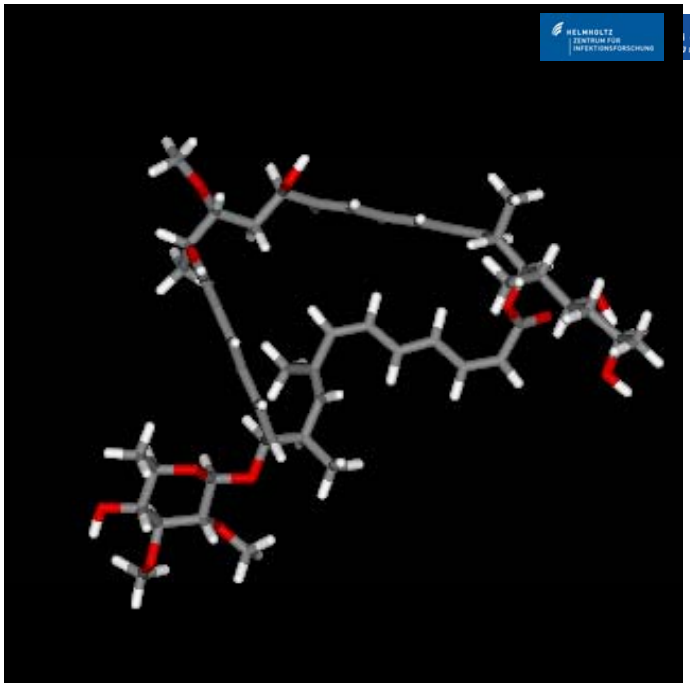


it is an "LL" ketoreductase

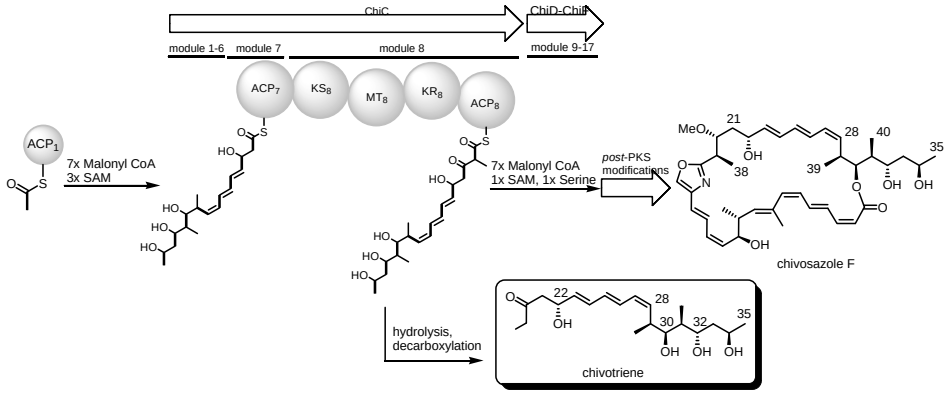
Summary:

The configuration at methyl branches can be predicted from the keto reductase amino acid sequence

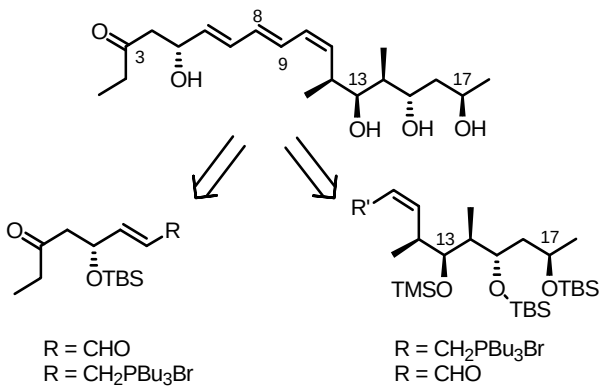




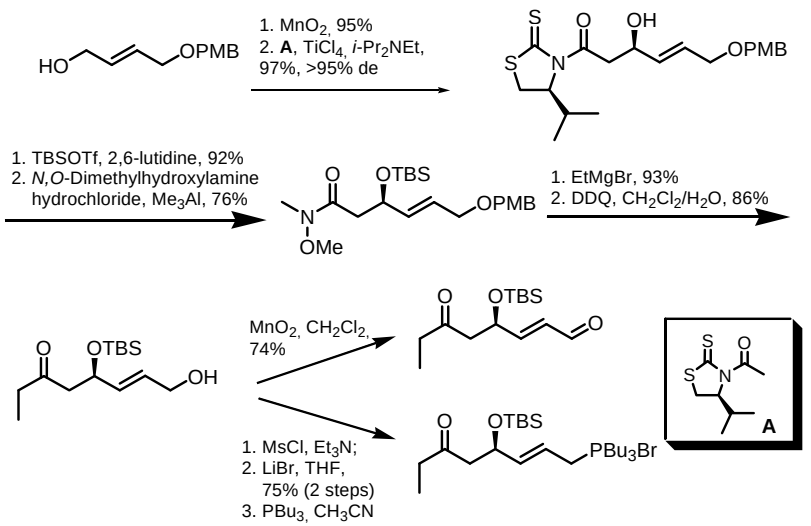
Chivotriene, a Chivosazole Shunt Product from *Sorangium cellulosum*



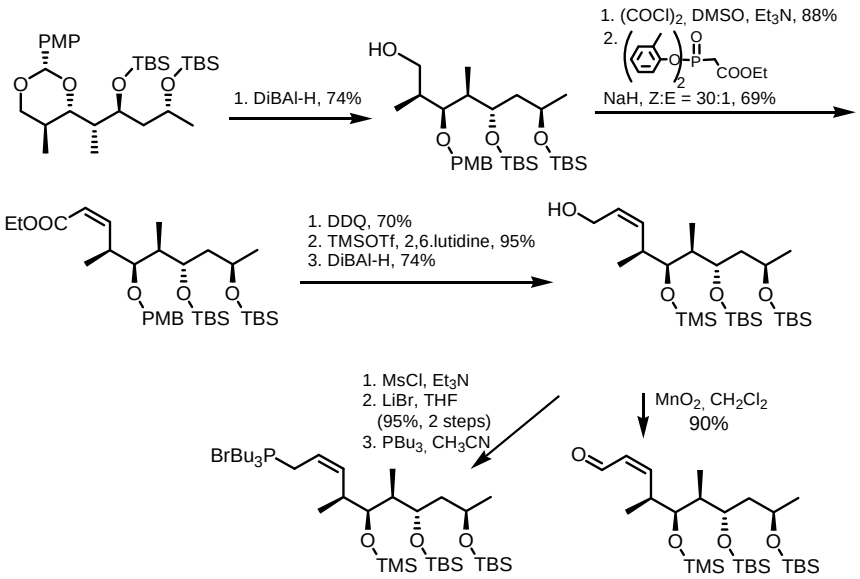
Chivotriene, a Chivosazole Shunt Product from *Sorangium cellulosum*

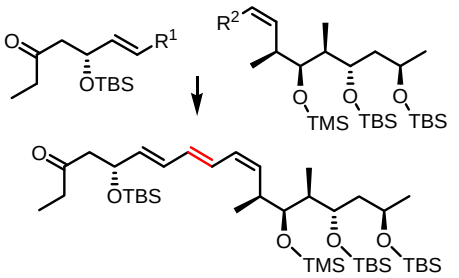


Chivotriene, a Chivosazole Shunt Product from *Sorangium cellulosum*



Chivotriene, a Chivosazole Shunt Product from *Sorangium cellulosum*

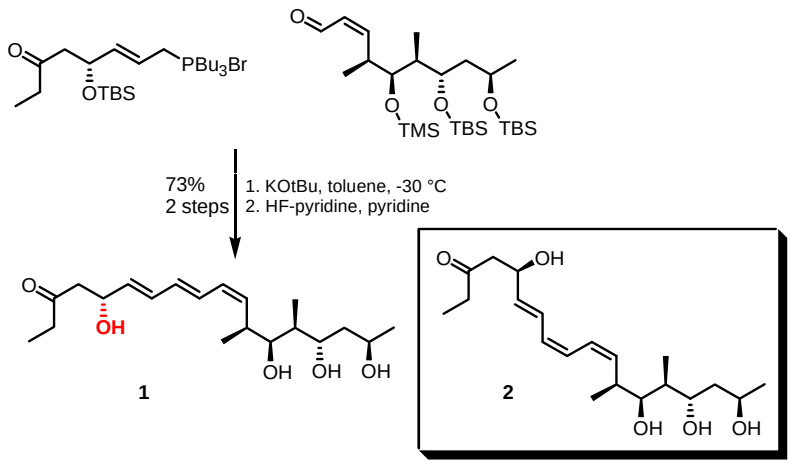




entry	base	R^1	R^2	*E:Z*	temp.	Yield[a]
1	KOtBu	CHO	CH_2PBu_3Br	1:1	0 ° C	57% 36%[b]
2	KOtBu	CHO	CH_2PBu_3Br	2:1	- 30 ° C	78%
3	LiOtBu	CHO	CH_2PBu_3Br	2:1	- 30 ° C	71%
4	LiHMDS	CHO	CH_2PBu_3Br	2:1	- 30 ° C	80%
5	KOtBu	CH_2PBu_3Br	CHO	**7:1**	- 30 ° C	73%

[a]calculated over two steps from the corrresponding allyl bromide; [b]elimination product

Chivotriene, a Chivosazole Shunt Product from *Sorangium cellulosum*

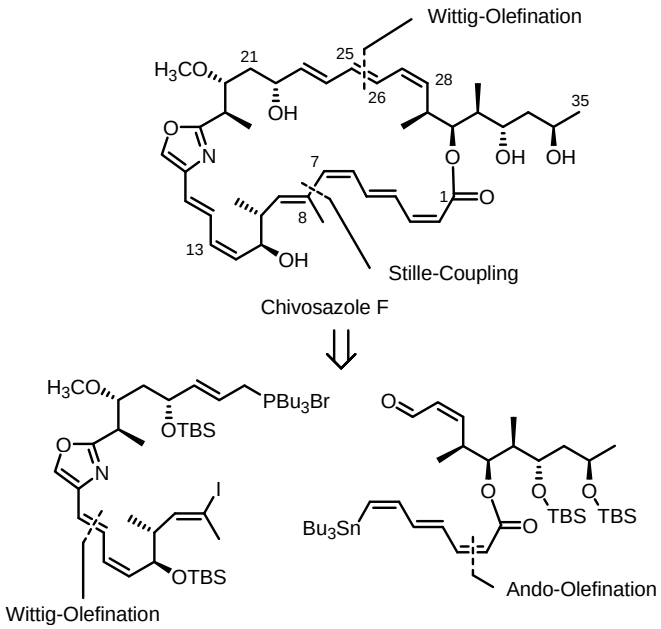


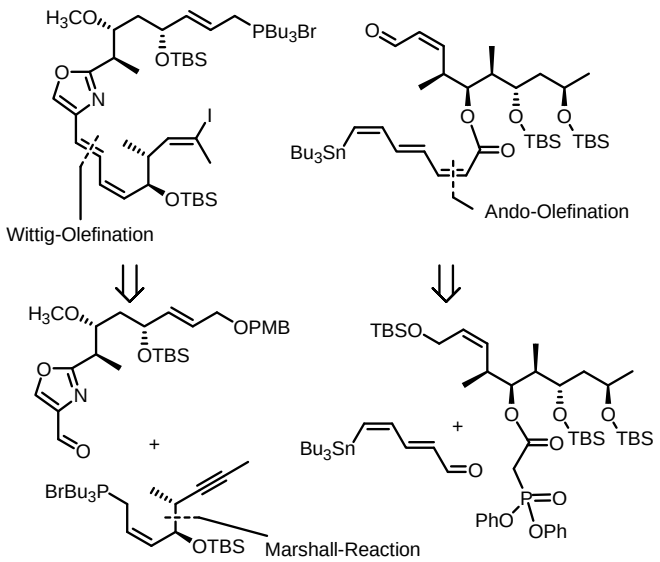
Chivotriene, a Chivosazole Shunt Product from *Sorangium cellulosum*

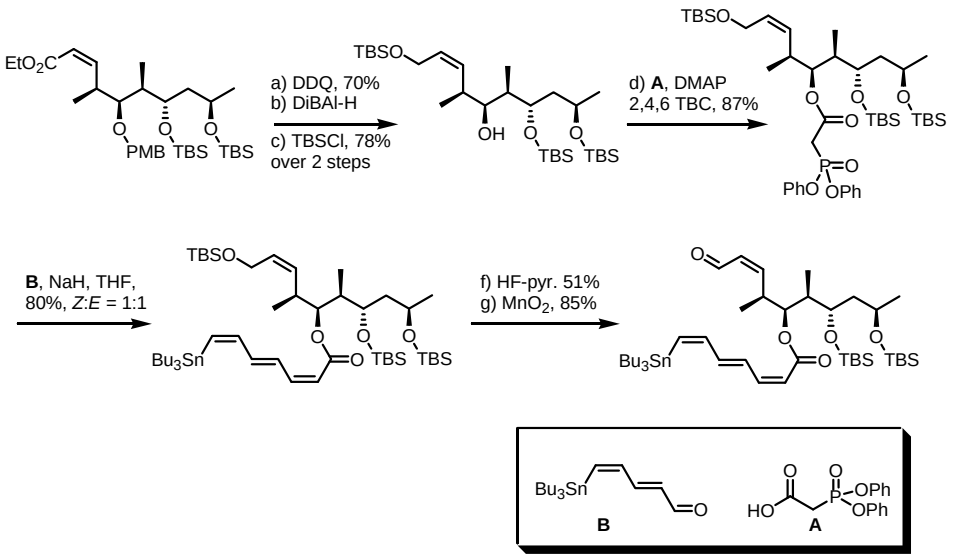
-Isomer **17** is more active than the shunt product itself.
-By staining F-actin of treated PtK2 potooroo and L929 mouse cells no specific interference with actin filament stability could be detected.

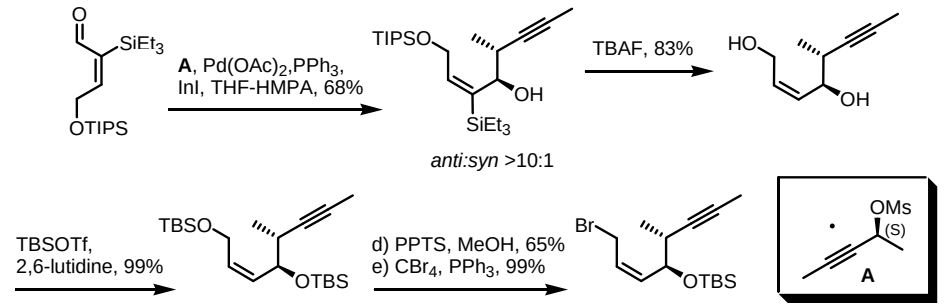
Cell line	Origin	1	2
L-929	murine connective tissue	50	23
KB-3-1	human cervix carcinoma	>100	>100
PC-3	human prostate carcinoma	100	>100
U-937	human lymphoma	n.d.	25
HUVEC	human umbilical vein endothelial cells	100	25

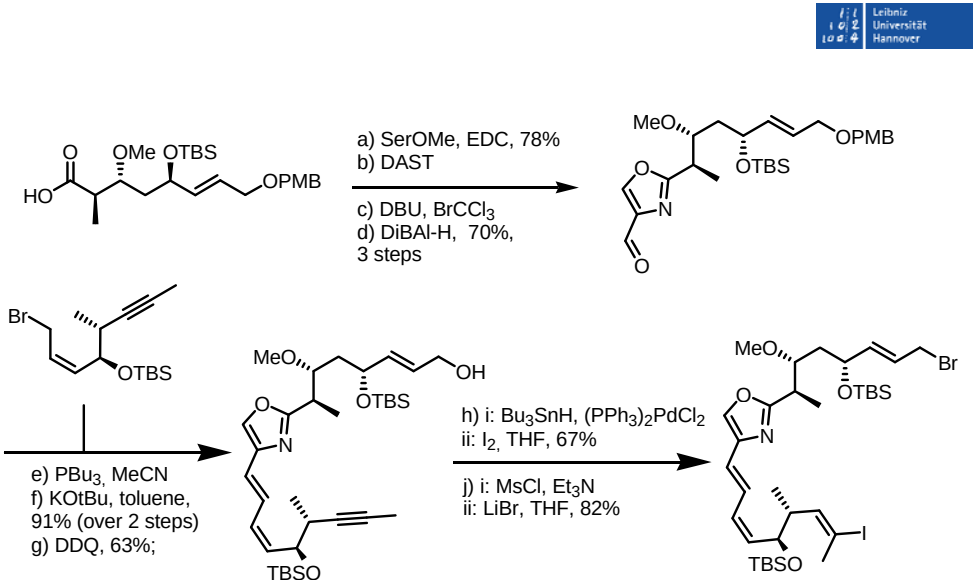
Antiproliferative activity IC_{50} [µg/mL] of **1** and **17**. Values are means of two determinations in parallel.

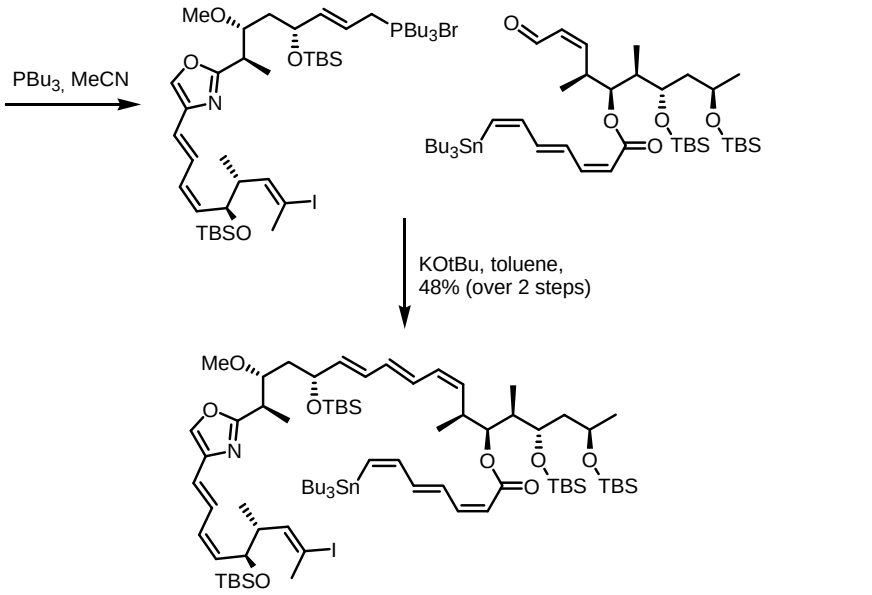


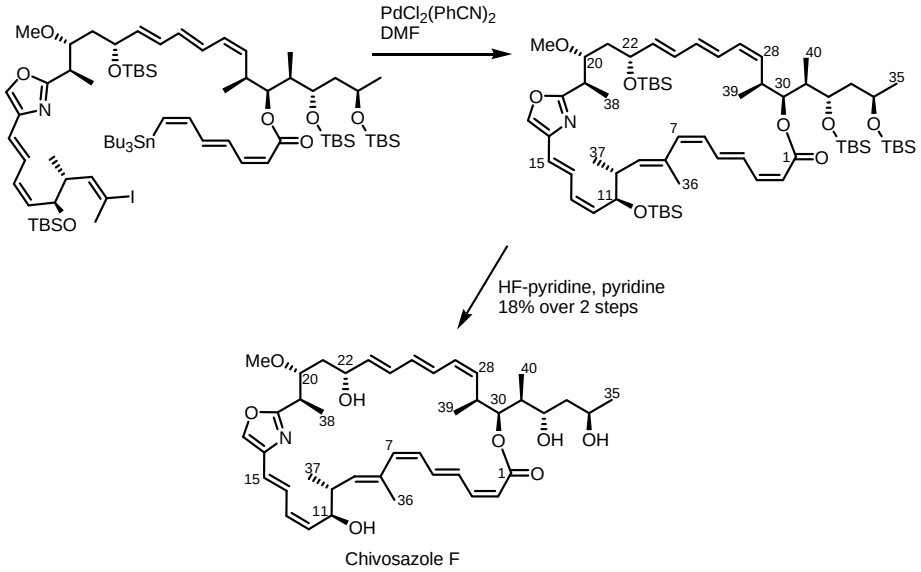


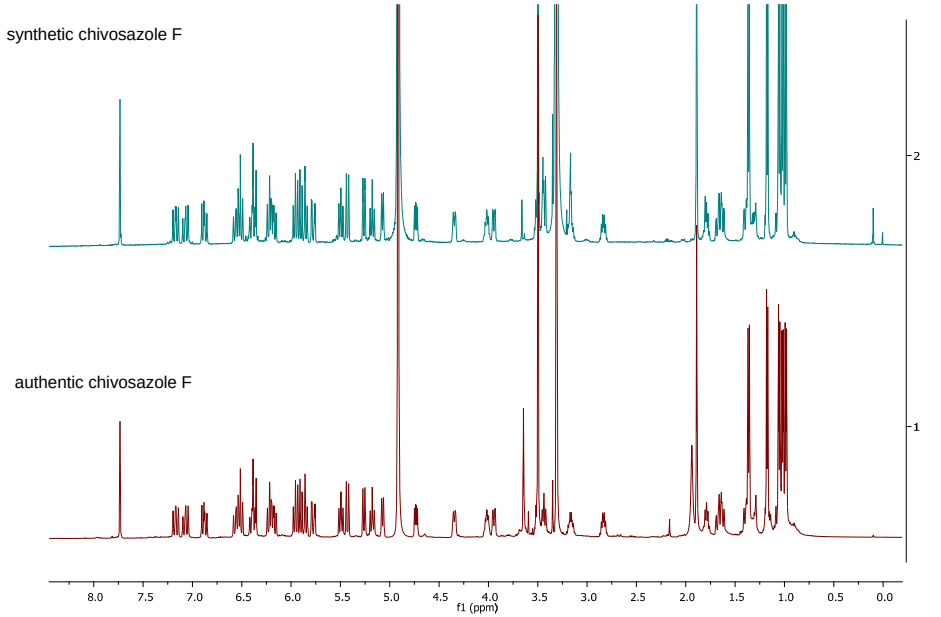

EtO2C
PMB TBS TBS
a) DDQ, 70%
b) DiBAl-H
c) TBSCl, 78%
over 2 steps
TBSO
OH
TBS TBS
d) A, DMAP
2,4,6 TBC, 87%
TBS TBS
PhO OPh
B, NaH, THF,
80%, Z:E = 1:1
Bu3Sn
f) HF-pyr. 51%
g) MnO2, 85%
B
A


SiEt3
OTIPS
A, Pd(OAc)2,PPh3,
InI, THF-HMPA, 68%
TIPSO
OH
SiEt3
anti:syn >10:1
TBAF, 83%
HO
TBSOTf,
2,6-lutidine, 99%
TBSO
OTBS
d) PPTS, MeOH, 65%
e) CBr4, PPh3, 99%
Br
OMs
(S)
A


HO
OMe OTBS
OPMB
a) SerOMe, EDC, 78%
b) DAST
c) DBU, BrCCl3
d) DiBAl-H, 70%,
3 steps
MeO
OTBS
Br
e) PBu3, MeCN
f) KOtBu, toluene,
91% (over 2 steps)
g) DDQ, 63%;
OH
TBSO
h) i: Bu3SnH, (PPh3)2PdCl2
ii: I2, THF, 67%
j) i: MsCl, Et3N
ii: LiBr, THF, 82%
I


PBu3, MeCN
MeO
OTBS
PBu3Br
TBSO
I
Bu3Sn
TBS TBS
KOtBu, toluene,
48% (over 2 steps)


PdCl2(PhCN)2
DMF
HF-pyridine, pyridine
18% over 2 steps
Chivosazole F


synthetic chivosazole F
authentic chivosazole F
f1 (ppm)