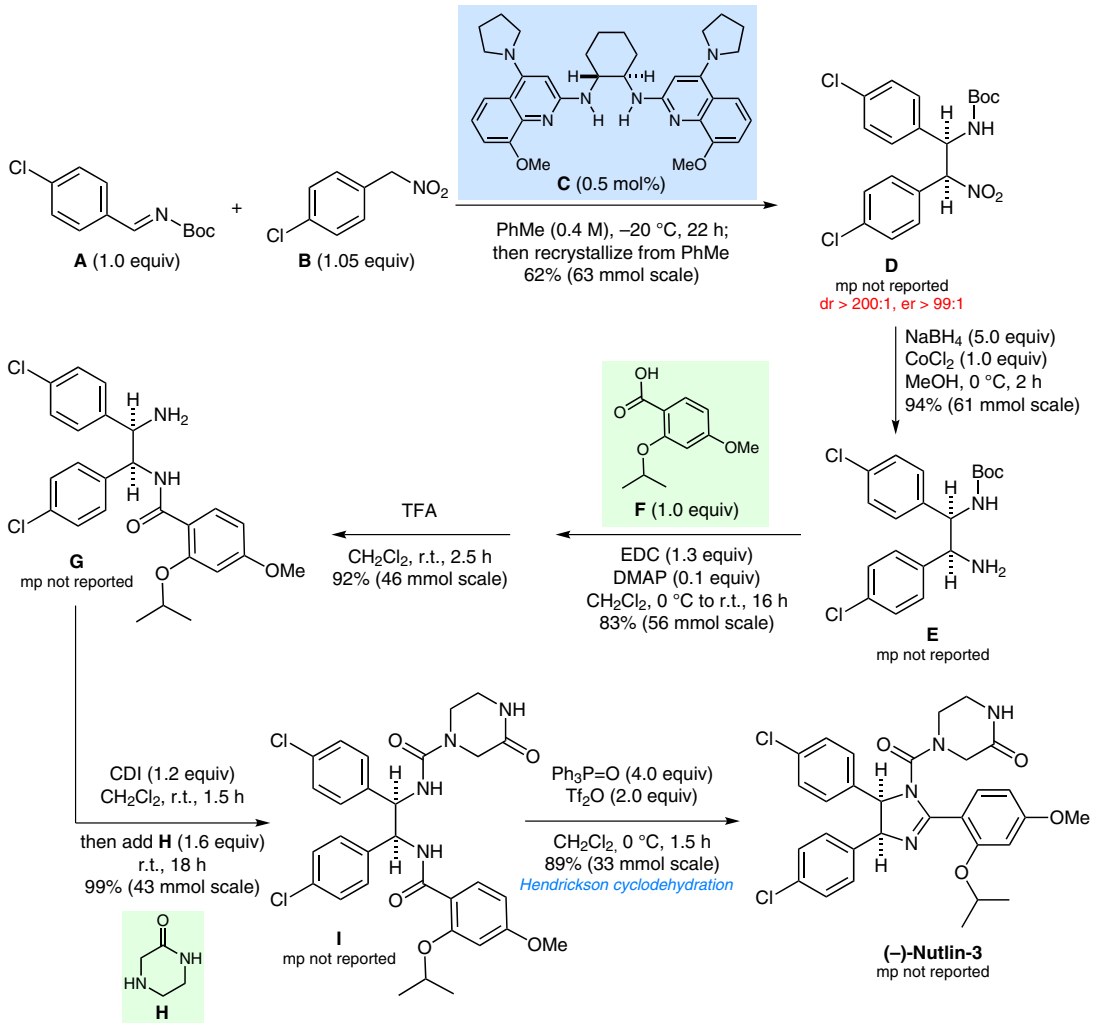
T. A. DAVIS, A. E. VILGELM, A. RICHMOND, J. N. JOHNSTON* (VANDERBILT UNIVERSITY, NASHVILLE AND VANDERBILT SCHOOL OF MEDICINE, NASHVILLE, USA)

Preparation of (–)-Nutlin-3 Using Enantioselective Organocatalysis at Decagram Scale
J. Org. Chem. **2013**, *78*, 10605–10616.

Synthesis of (–)-Nutlin-3



Significance: Nutlin-3 inhibits the interaction between proteins p53 and MDM2. It is of interest as an investigative tool in cancer biology. The key step in the decagram-scale synthesis depicted is an enantioselective aza-Henry reaction catalyzed by the novel bis(amidine) **C** that provides high enantioselectivity at higher temperatures and lower catalyst loadings than previously possible (T. A. Davis, J. Johnston *Chem. Sci.* **2011**, *2*, 1076).

Comment: The optimized conditions of the aza-Henry reaction include the following: 0.5 mol% catalyst loading, slow addition of imine (ca. 0.06 equiv aliquots over 8 h), essentially stoichiometric amounts of the two partners **A** and **B**, a relatively high reaction concentration (0.4 M in PhMe), and exclusive precipitation of the desired diastereoisomer. A 90% yield of product **D** was produced after filtration in 91% ee and a dr > 200:1.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2014, 10(1), 0001 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340328; **Reg-No.:** K07413SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

nutlin-3

***cis*-imidazolines**

organocatalysis

chiral bis(amidine) catalysts

asymmetric aza-Henry reaction

Category

Synthesis of Natural Products and Potential Drugs

Key words

chlorosulfolipids

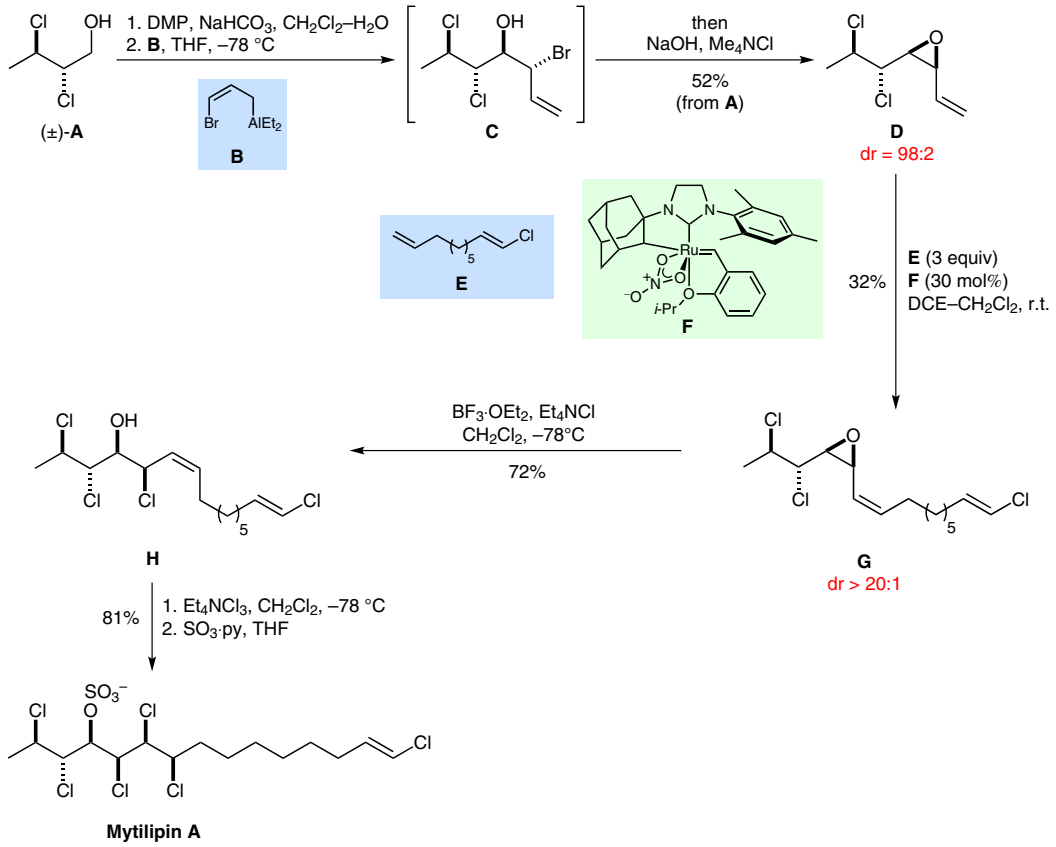
olefin metathesis

allylation

W.-J. CHUNG, J. S. CARLSON, D. K. BEDKE, C. D. VANDERWAL* (UNIVERSITY OF CALIFORNIA, IRVINE AND AMGEN, INC., SOUTH SAN FRANCISCO, USA)

A Synthesis of the Chlorosulfolipid Mytilipin A via a Longest Linear Sequence of Seven Steps
Angew. Chem. Int. Ed. **2013**, *52*, 10052–10055.

Short Total Synthesis of (±)-Mytilipin A



Significance: Mytilipin A is a member of the chlorosulfolipid family of natural products. It was isolated from the mussel *Mytilus galloprovincialis* and is associated with seafood poisoning. In addition to their previous syntheses of other polychlorinated natural products (*J. Am. Chem. Soc.* **2009**, *131*, 7570; *J. Am. Chem. Soc.* **2010**, *132*, 2542), the authors describe a short access to mytilipin A.

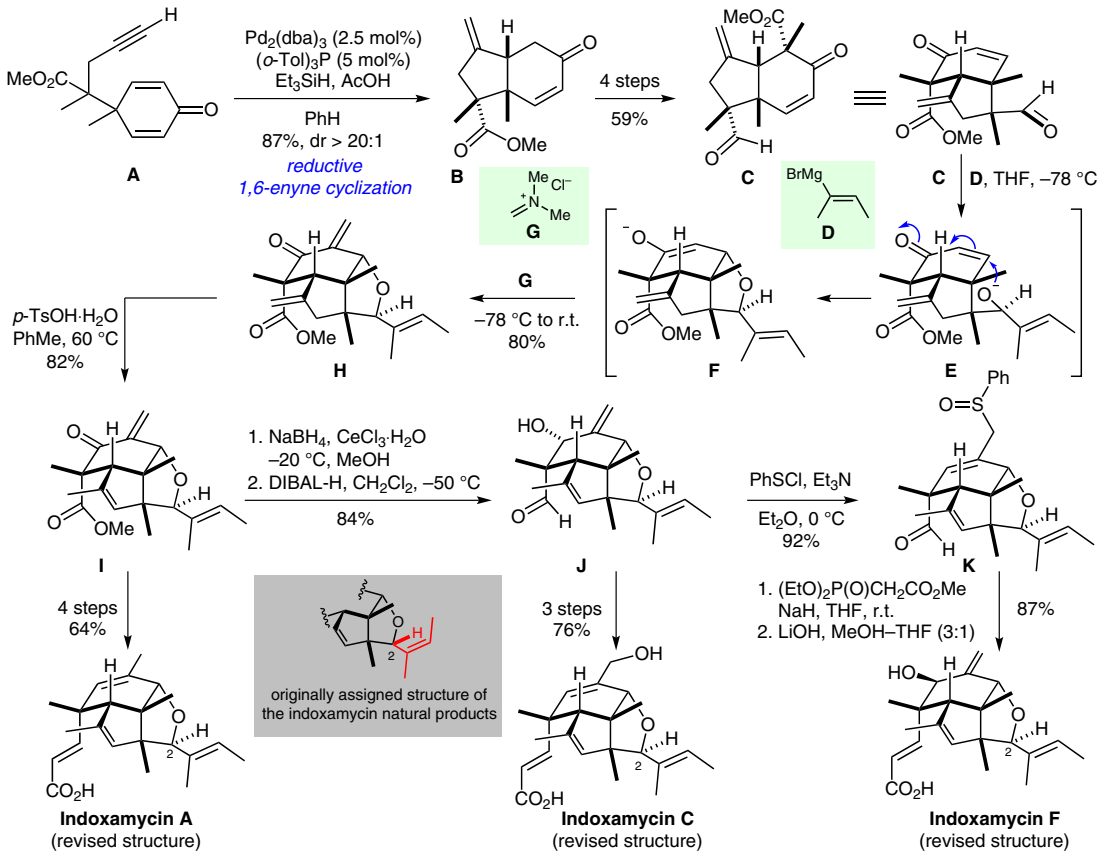
Comment: Dichloroalkohol **A** was oxidized with DMP and the sensitive aldehyde was directly subjected to a highly diastereoselective allylation with **B** to give **D** after basic work-up. *cis*-Selective metathesis with **E** yielded **G** in 30% yield but allowed the synthesis to be finished in only another three steps. In total, (±)-mytilipin A was prepared in seven linear steps and in more than 8% yield. The authors also describe a kinetic resolution of epoxide **D**, so that an enantioselective synthesis is possible with the same route.

SYNFACTS Contributors: Erick M. Carreira, Hannes F. Zipfel
Synfacts 2014, 10(1), 0002 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340355; **Reg-No.:** C07413SF

C. HE, C. ZHU, Z. DAI, C.-C. TSENG, H. DING* (ZHEJIANG UNIVERSITY, HANGZHOU, P. R. OF CHINA)

Divergent Total Synthesis of Indoxamycins A, C, and F
Angew. Chem. Int. Ed. **2013**, *52*, 13256–13260.

Total Synthesis of Indoxamycins A, C, and F



Significance: In 2009, a Japanese research group reported the isolation of a novel class of natural products, the indoxamycins. These marine-derived polyketides are characterized by a highly substituted tricyclic core, bearing six contiguous stereogenic centers, three of which are quaternary. This work describes not only the total synthesis of indoxamycin A, C, and F, but led also to a stereochemical revision. This finding is in agreement with the total synthesis and the resulting structural reassignment of another member of the family, indoxamycin B (O. F. Jeker, E. M. Carreira *Angew. Chem. Int. Ed.* **2012**, *51*, 3474; *Synfacts* **2012**, *8*, 593).

Comment: A salient feature of the presented synthesis is a highly selective palladium-catalyzed reductive 1,6-enyne cyclization to access bicycle **B** in excellent yield. After four more steps, a tandem 1,2-Grignard addition–oxa-Michael–methenylation (**C** → **H**) followed by double-bond isomerization provides rapid entry to common intermediate **I**. From this branching point, all three target molecules could be synthesized in a few transformations (3–4 steps) and high overall yield. The spectra of all three natural products matched the reported isolation data, therefore confirming the hypothesis of a stereochemical misassignment at C2 and of the double-bond geometry.

SYNFACTS Contributors: Erick M. Carreira, Christian Ebner
Synfacts 2014, 10(1), 0003 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340353; **Reg-No.:** C07213SF

Category
Synthesis of Natural Products and Potential Drugs

Key words
indoxamycins
polyketides
reductive 1,6-enyne cyclization
palladium

Category

Synthesis of Natural Products and Potential Drugs

Key words

spirotryprostatin A

Mizoroki–Heck reaction

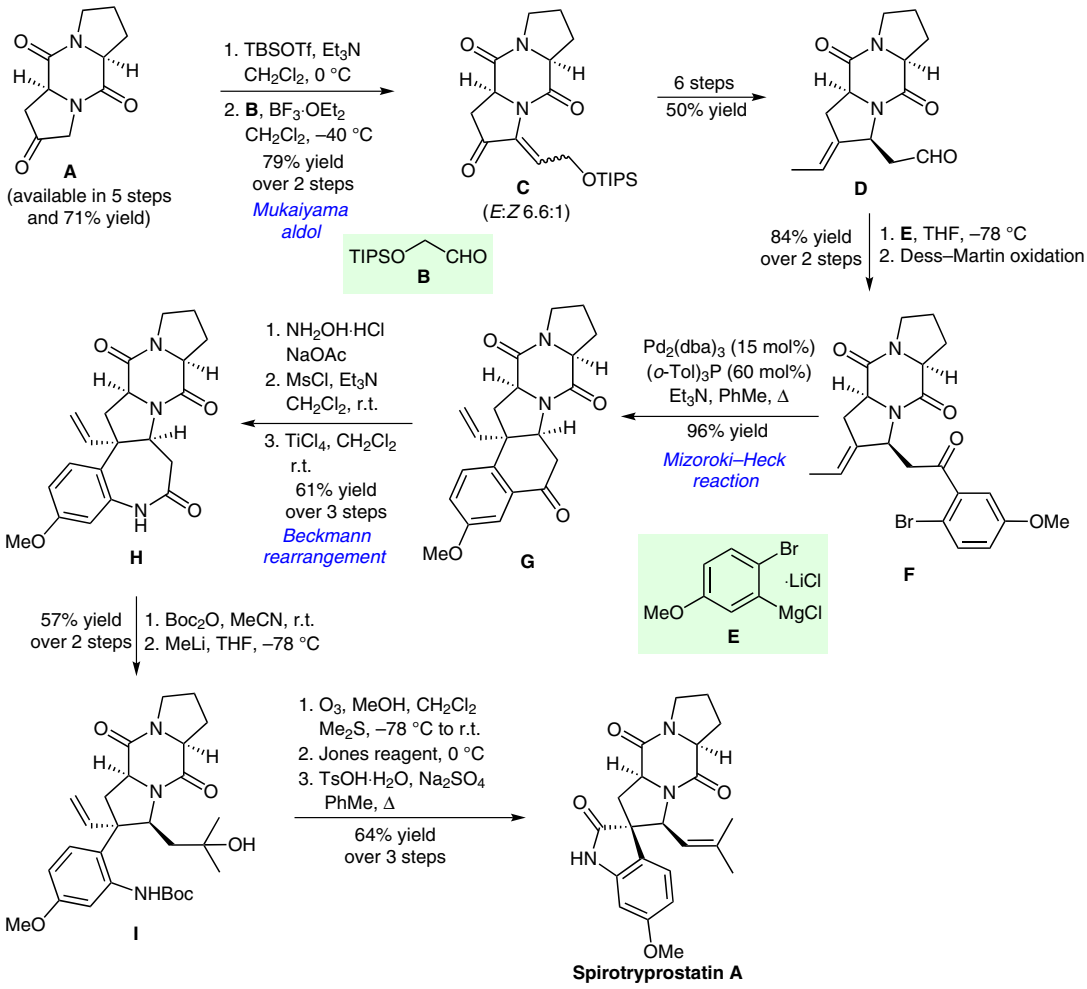
diketopiperazines

spirocycles

K. KITAHARA, J. SHIMOKAWA, T. FUKUYAMA* (THE UNIVERSITY OF TOKYO, JAPAN)

Stereoselective Synthesis of Spirotryprostatin A
Chem. Sci. **2014**, DOI: 10.1039/C3SC52525B.

Total Synthesis of Spirotryprostatin A



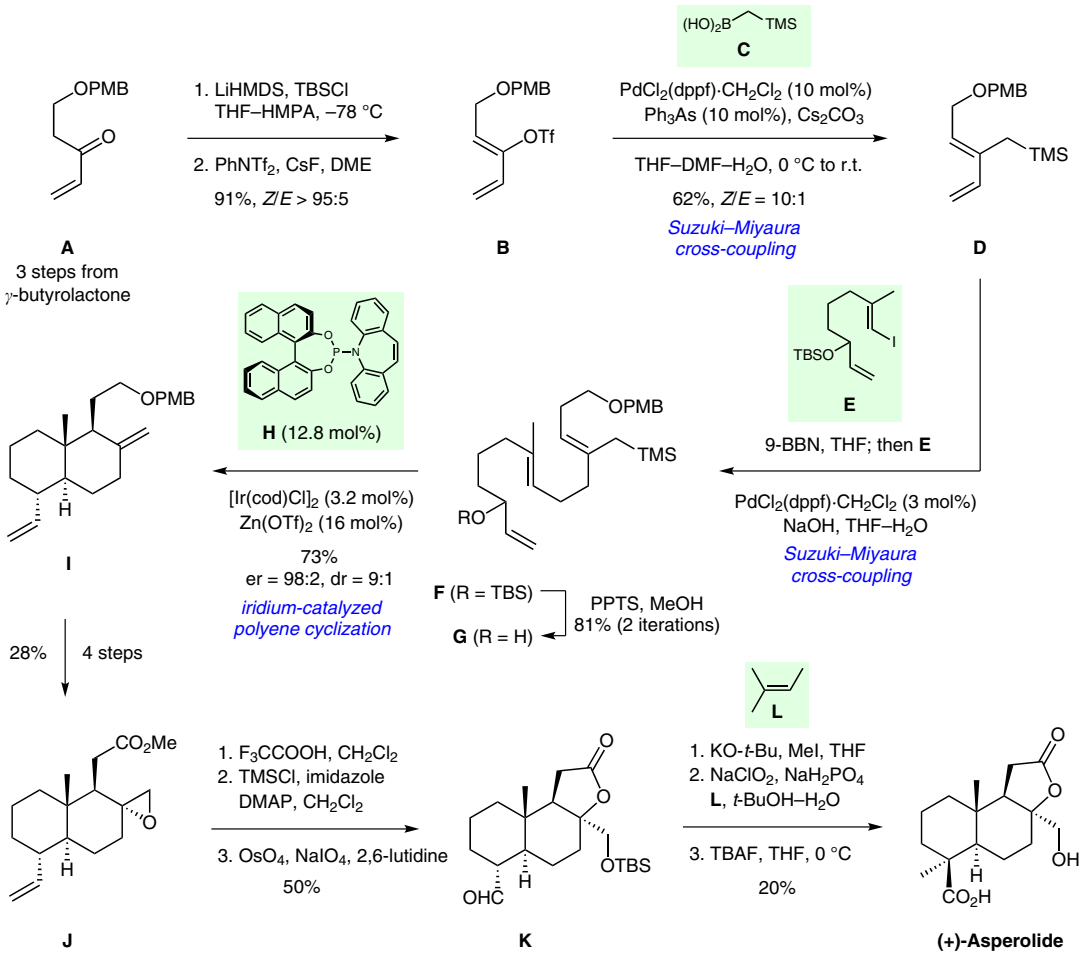
Significance: Spirotryprostatin A, a spirocyclic diketopiperazine natural product that was isolated in 1996, was found to be an inhibitor of the mammalian cell cycle in G2/M phase and thus an interesting lead in drug discovery. A number of syntheses of spirotryprostatin A have been disclosed, and Fukuyama now describes a synthetic strategy that relies on a Heck reaction for the elegant installation of the quaternary stereocenter.

Comment: A silyl enol ether derived from diketopiperazine **A** underwent a Mukaiyama aldol reaction with aldehyde **B** to afford enone **C**, which was converted into aldehyde **D** in six steps. Addition of aryl Grignard **E** followed by oxidation of the resulting secondary alcohol furnished ketone **F**, which gave spirocycle **G** in the key Heck reaction. The anilide was then introduced through Beckmann rearrangement (**G** → **H**). **H** could be advanced into the target molecule in five additional steps.

SYNFACTS Contributors: Erick M. Carreira, Simon Krautwald
Synfacts 2014, 10(1), 0004 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340358; **Reg-No.:** C07713SF

O. F. JEKER, A. G. KRAVINA, E. M. CARREIRA* (ETH ZÜRICH, SWITZERLAND)
Total Synthesis of (+)-Asperolide C by Iridium-Catalyzed Enantioselective Polyene Cyclization
Angew. Chem. Int. Ed. **2013**, *52*, 12166–12169.

Total Synthesis of (+)-Asperolide C



Significance: The first total synthesis of (+)-asperolide C, a tetranorlabdane diterpenoid isolated from the endophytic fungal strain *Aspergillus wentii* EN-48, is reported including the first thorough characterization of this natural product which previously could only be obtained as an inseparable mixture with another related terpene. The synthetic strategy, which delivers the desired target in 18 steps for the longest linear sequence, could thereby potentially also be used to access other members of the labdane class and related terpenes.

Comment: The key element of the synthesis is the use of an iridium-catalyzed, enantioselective polyene cyclization in which the cationic cascade is terminated by an allyl silane to forge a properly substituted decaline scaffold with the required exocyclic double bond in excellent stereoselectivity. This process, which resembles the currently accepted mechanism for the biogenesis of these terpenes, in fact represents one of only three examples to date applying an asymmetric polyene cyclization cascade in a natural product synthesis.

SYNFACTS Contributors: Erick M. Carreira, Nikolas Huwyler
Synfacts 2014, 10(1), 0005 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340356; **Reg-No.:** C07513SF

Category
Synthesis of Natural Products and Potential Drugs

Key words
asperolide C
polyene cyclization
iridium
Suzuki–Miyaura cross-coupling

Category

Synthesis of Natural Products and Potential Drugs

Key words

atorvastatin

enantioselectivity

oxa-Michael reaction

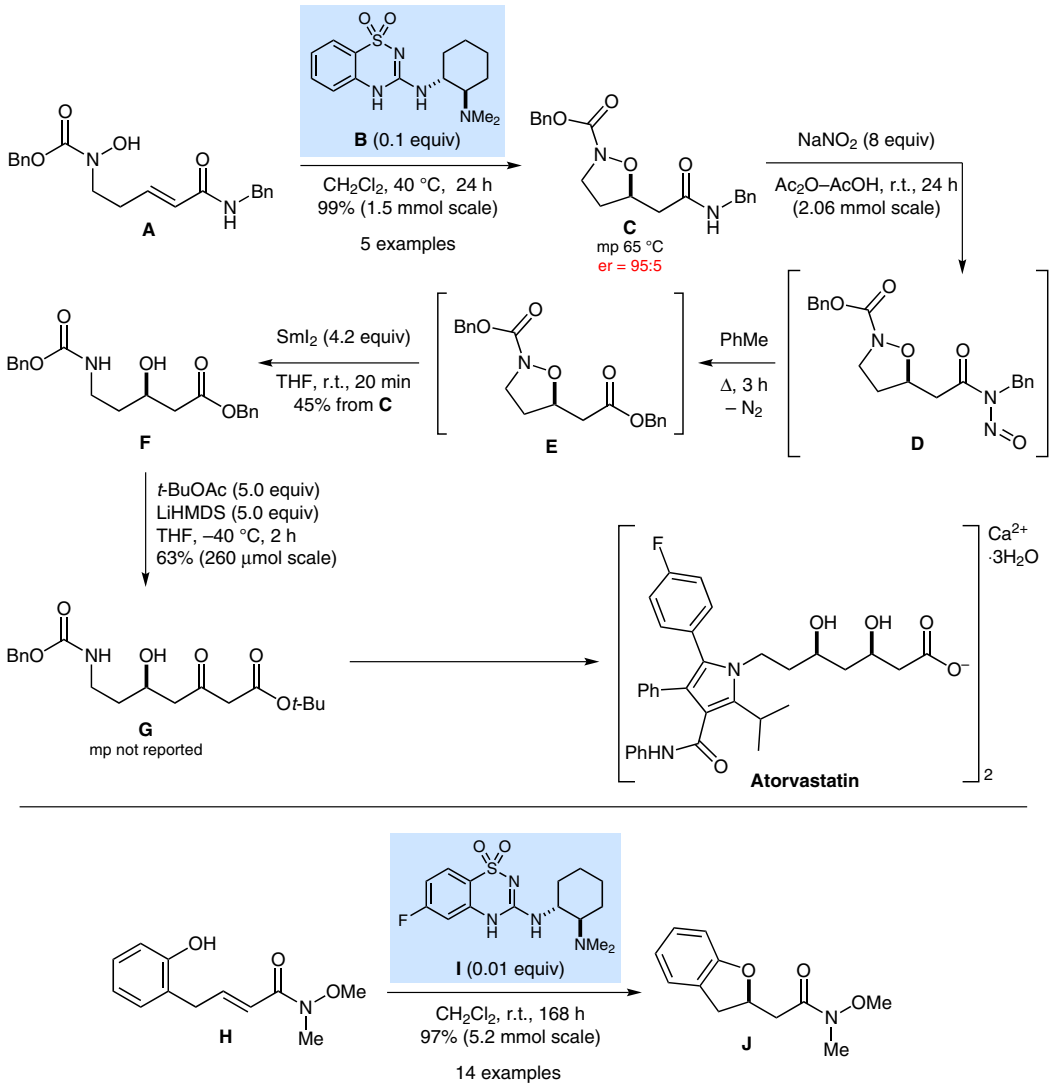
organocatalysis

Y. KOBAYASHI, Y. TANIGUCHI, N. HAYAMA, T. INOKUMA, Y. TAKEMOTO* (KYOTO UNIVERSITY, JAPAN)

A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters

Angew. Chem. Int. Ed. **2013**, *52*, 11114–11118.

A Formal Synthesis of Atorvastatin



Significance: The key step in this formal synthesis of atorvastatin (Lipitor®) is the enantioselective intramolecular oxa-Michael reaction of **A** mediated by 10 mol% of benzothiadiazine catalyst **B**. Methods for converting **G** and its relatives into atorvastatin have been summarized by Y. Kawato et al. (*Chem. Eur. J*. **2013**, *19*, 3802; see also references therein).

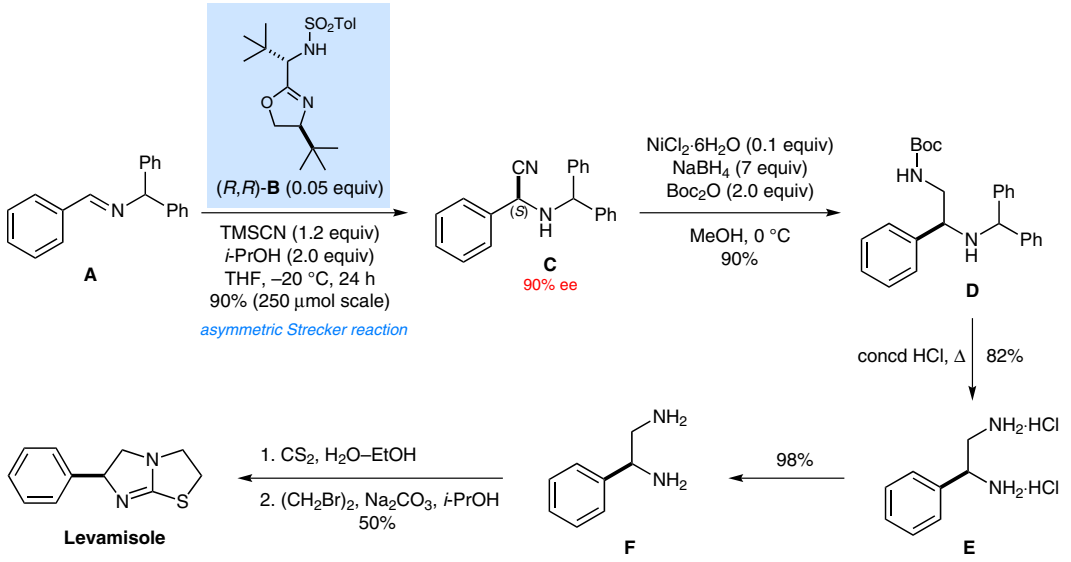
Comment: For the conversion of *N*-nitrosamides into esters (e.g., **D** → **E**), see: D. T. Glatzhofer, R. R. Roy, K. N. Cossey *Org. Lett*. **2002**, *4*, 2349. Phenolic nucleophiles (14 examples) also participate in the oxa-Michael reaction, and in the case of **H** only 1 mol% of catalyst **I** is required.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2014, 10(1), 0006 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340325; **Reg-No.:** K07113SF

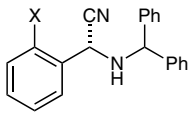
A. SADHUKHAN, D. SAHU, B. GANGULY,* N. H. KHAN,* R. I. KURESHY, S. H. R. ABDI, E. SURESH, H. C. BAJAJ (CENTRAL SALT & MARINE CHEMICALS RESEARCH INSTITUTE, BHAVNAGAR, INDIA)

Oxazoline-Based Organocatalyst for Enantioselective Strecker Reactions: A Protocol for the Synthesis of Levamisole
Chem. Eur. J. **2013**, *19*, 14224–14232.

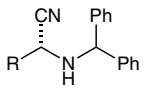
Synthesis of Levamisole



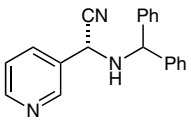
Scope of the substrates in the asymmetric Strecker reaction catalyzed by (*S*,*S*)-B:



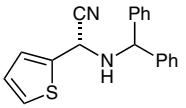
X	Yield (%)	ee (%)
Me	90	94
OMe	93	96
F	78	91
Cl	90	82
Br	93	80
NO_2	90	82



R	Yield (%)	ee (%)
Bn	90	91
CH_2Bn	90	87
t-Bu	91	93
i-Bu	94	90
Hex	90	71
CH=CHPh	93	90



85% (60% ee)



94% (82% ee)

Significance: Levamisole (Ergamisol®) is an antihelminthic that is currently used to treat worm infestations in livestock. The synthesis of levamisole depicted features an asymmetric Strecker reaction of *N*-benzhydryl aldimine **A** with trimethylsilyl cyanide catalyzed by oxazoline (*R*,*R*)-**B** (5 mol%) as the key step. The chiral α-aminonitrile intermediate **C** was generated in 90% yield and 90% ee.

Comment: A study of the scope of the asymmetric Strecker reaction (18 examples) revealed that both alkyl and aryl *N*-benzhydryl aldimines participate in the reaction to give the corresponding α-aminonitriles in good yield and generally >80% ee with some exceptions being shown in the box above. For a previous synthesis of levamisole based on asymmetric diamination of styrenes, see: C. Röben et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 9478.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2014, 10(1), 0007 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340326; **Reg-No.:** K07213SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

levamisole

asymmetric Strecker reaction

α-aminonitriles

organocatalysis

1,2-diamines

Category

Synthesis of Natural Products and Potential Drugs

Key words

fusarisetin A

intramolecular Pauson–Khand reaction

cobalt

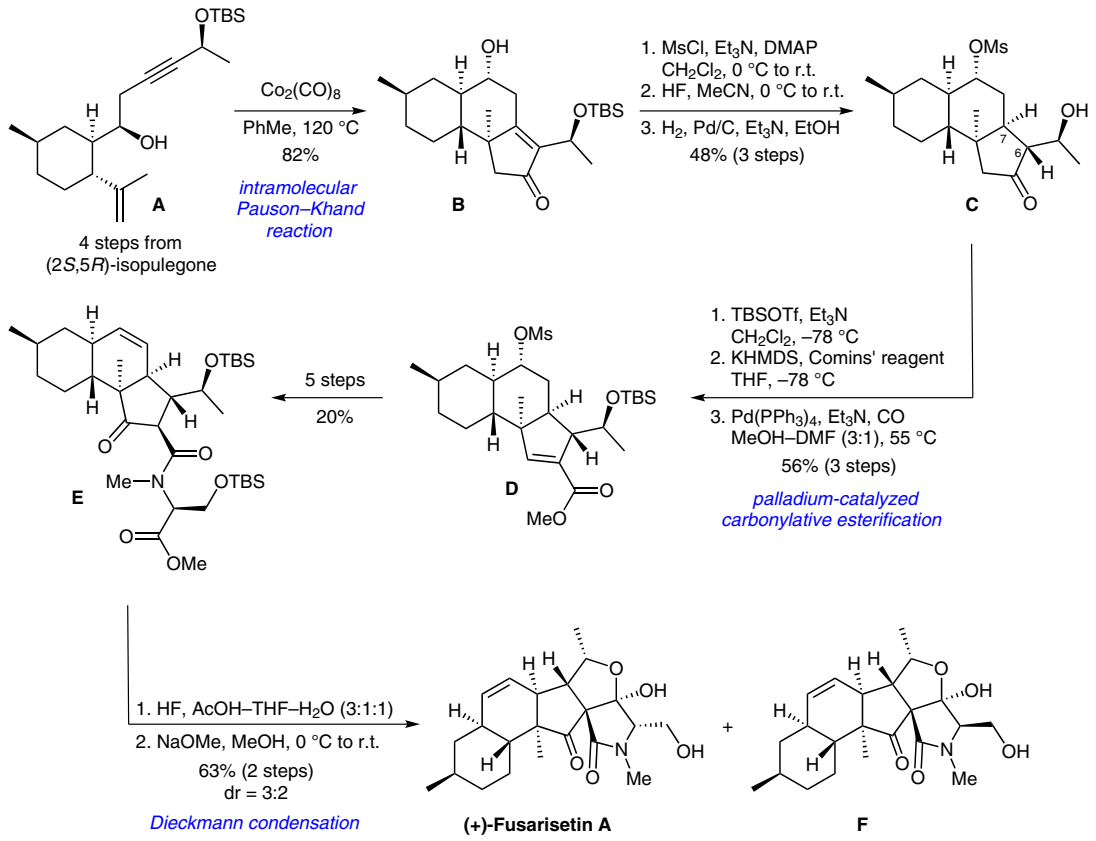
Dieckmann condensation

J. HUANG, L. FANG, R. LONG, L.-L. SHI, H.-J. SHEN, C.-C. LI,* Z. YANG* (PEKING UNIVERSITY SHENZHEN GRADUATE SCHOOL AND PEKING UNIVERSITY, BEIJING, P. R. OF CHINA)

Asymmetric Total Synthesis of (+)-Fusarisetin A via the Intramolecular Pauson–Khand Reaction

Org. Lett. **2013**, *15*, 4018–4021.

Synthesis of (+)-Fusarisetin A



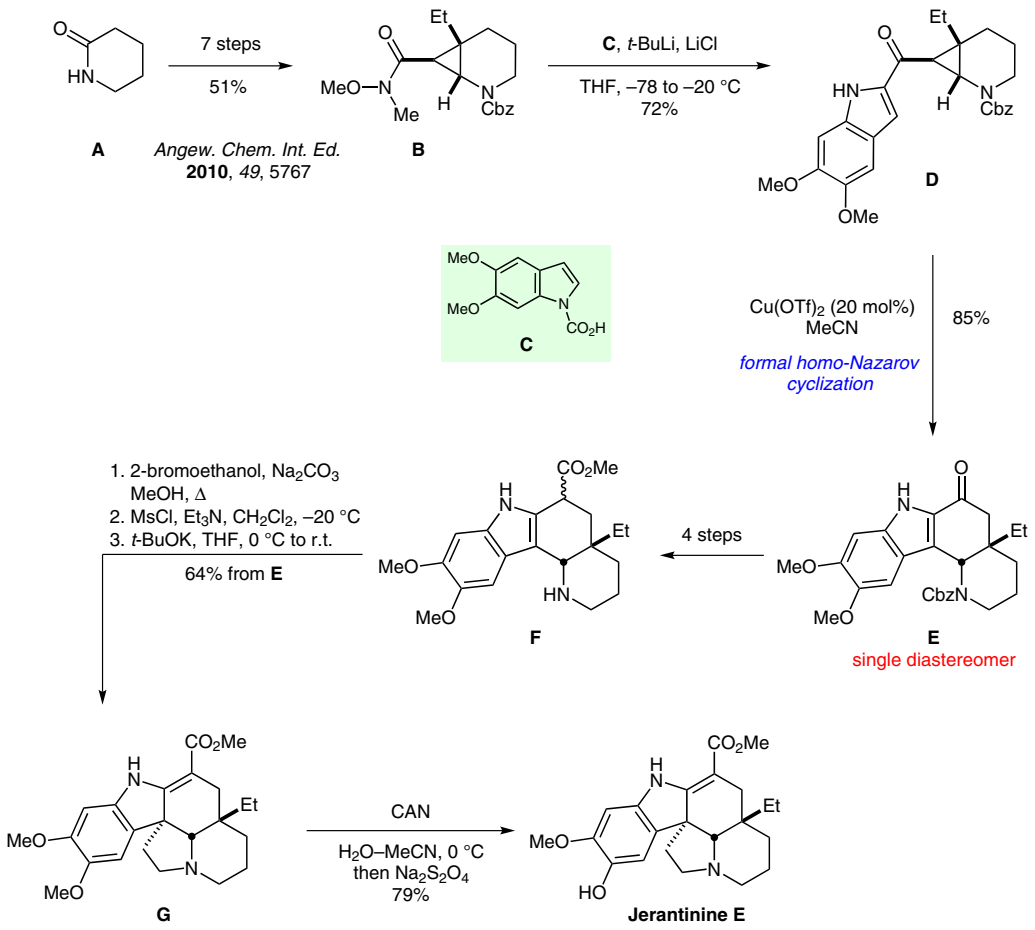
Significance: Isolated in 2011 from the soil fungus *Fusarium* sp. FN080326, fusarisetin A has gained considerable attention because of its unprecedented molecular structure and its striking bioactivity. Fusarisetin A exhibits a complex 6,6,5,5,5-fused pentacyclic ring system containing ten stereocenters. Moreover, this natural product displays potent inhibition of acinar morphogenesis, cell migration, and invasion in MDA-MB-231 breast cancer cells, without apparent cytotoxicity. Li, Yang, and co-workers report a total synthesis of (+)-fusarisetin A based on a stereoselective intramolecular Pauson–Khand reaction for the construction of the 6,6,5-tricyclic moiety.

Comment: After screening of conditions, the authors identified the $Co_2(CO)_8$-mediated Pauson–Khand reaction as the most efficient method for the stereoselective formation of cyclopentenone **B**. Stereoselective reduction of **B** proved to be challenging. Thus, installation of a mesylate group followed by desilylation was crucial to access ketone **C** with the correct configuration at C6 and C7. Carbonylative esterification afforded ester **D**, which was further elaborated into amide **E**. Finally, Dieckmann condensation followed by hemiacetalization furnished (+)-fusarisetin A along with the separable diastereoisomer **F** (dr = 3:2).

SYNFACTS Contributors: Erick M. Carreira, Adrien Joliton
Synfacts 2014, 10(1), 0008 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340357; **Reg-No.:** C07613SF

R. FREI, D. STAEDLER, A. RAJA, R. FRANKE, F. SASSE, S. GERBER-LEMAIRE, J. WASER*
(ECOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, SWITZERLAND AND HELMHOLTZ CENTRE FOR INFECTION RESEARCH, BRAUNSCHWEIG, GERMANY)
Total Synthesis and Biological Evaluation of Jerantinine E
Angew. Chem. Int. Ed. **2013**, *52*, 13373–13376.

Synthesis of Jerantinine E



Significance: Jerantinine E was isolated in 2008 from *Tabernaemontana corymbosa.* This *Aspidosperma* alkaloid shows potent cytotoxic activity against human KB cells. The authors report the first synthesis of racemic jerantinine E. Separation of (+)- and (–)-jerantinine E allowed for further biological evaluation. Additionally, investigations into the mode of action revealed potent inhibition of tubulin polymerization.

Comment: The synthesis commenced with an organo-lithium addition to Weinreb amide **B**. Treatment of the resulting ketone **D** with copper (II) triflate resulted in a formal homo-Nazarov cyclization, which gave tetracyclic intermediate **E** as a single diastereomer. A double-alkylation sequence of **F** followed by selective demethylation of **G** afforded jerantinine E in 17 steps from **A** and 16% overall yield.

SYNFACTS Contributors: Erick M. Carreira, Mathias J. Jacobsen
Synfacts 2014, 10(1), 0009 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340354; **Reg-No.:** C07313SF

Category
Synthesis of Natural Products and Potential Drugs

Key words
jerantinine E
aspidosperma alkaloids
formal homo-Nazarov cyclization

Category

Synthesis of Natural Products and Potential Drugs

Key words

I-BET762

GSK525762

1,4-benzodi-azepines

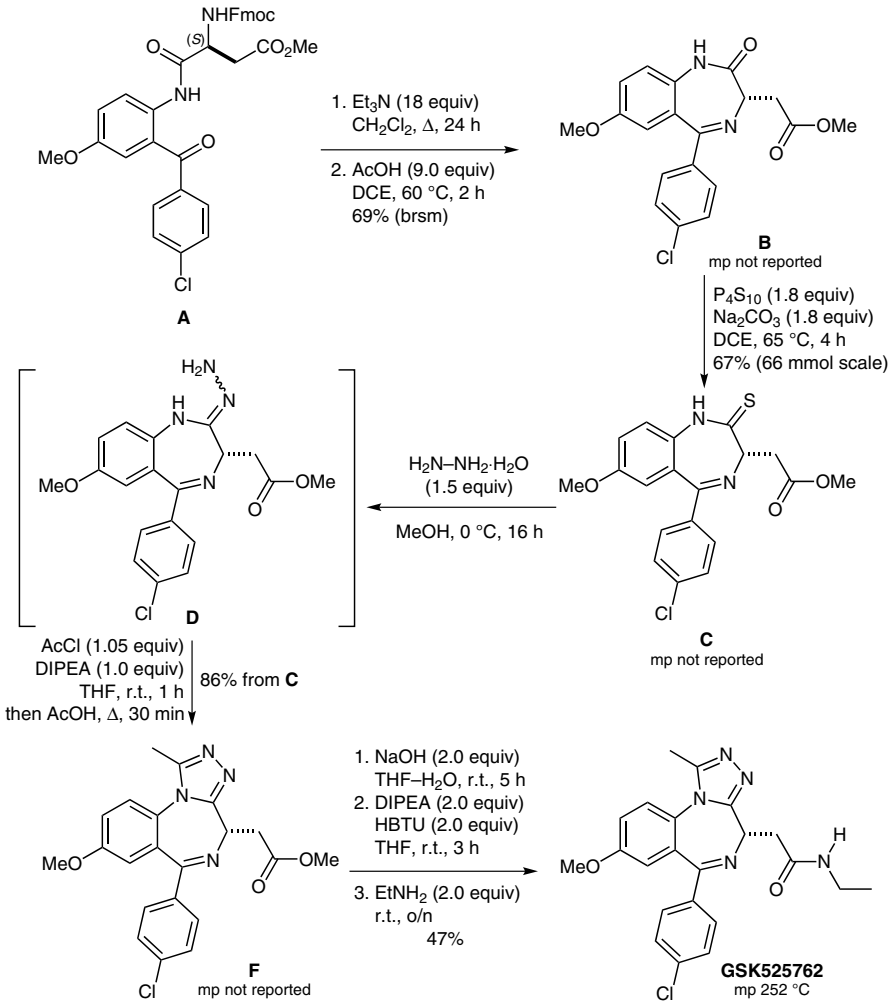
1,2,4-triazoles

O. MIRGUET,* N. PARR* ET AL. (GLAXOSMITHKLINE R&D, VILLEBON-SUR-YVETTE, FRANCE AND STEVENAGE, UK)

Discovery of Epigenetic Regulator I-BET762: Lead Optimization to Afford a Clinical Candidate Inhibitor of the BET Bromodomains

J. Med. Chem. **2013**, *56*, 7501–7515.

Synthesis of Epigenetic Regulator I-BET762 (GSK525762)



Significance: I-BET762 (GSK525762) has entered phase I/II clinical trials for the treatment of the aggressive NUT midline carcinoma and other cancers. It disrupts the function of the bromodomain and extra-terminal domain (BET) family of proteins. The synthesis depicted features the construction of the 1,4-benzodiazepine skeleton with incorporation of an (*S*)-aspartic acid moiety.

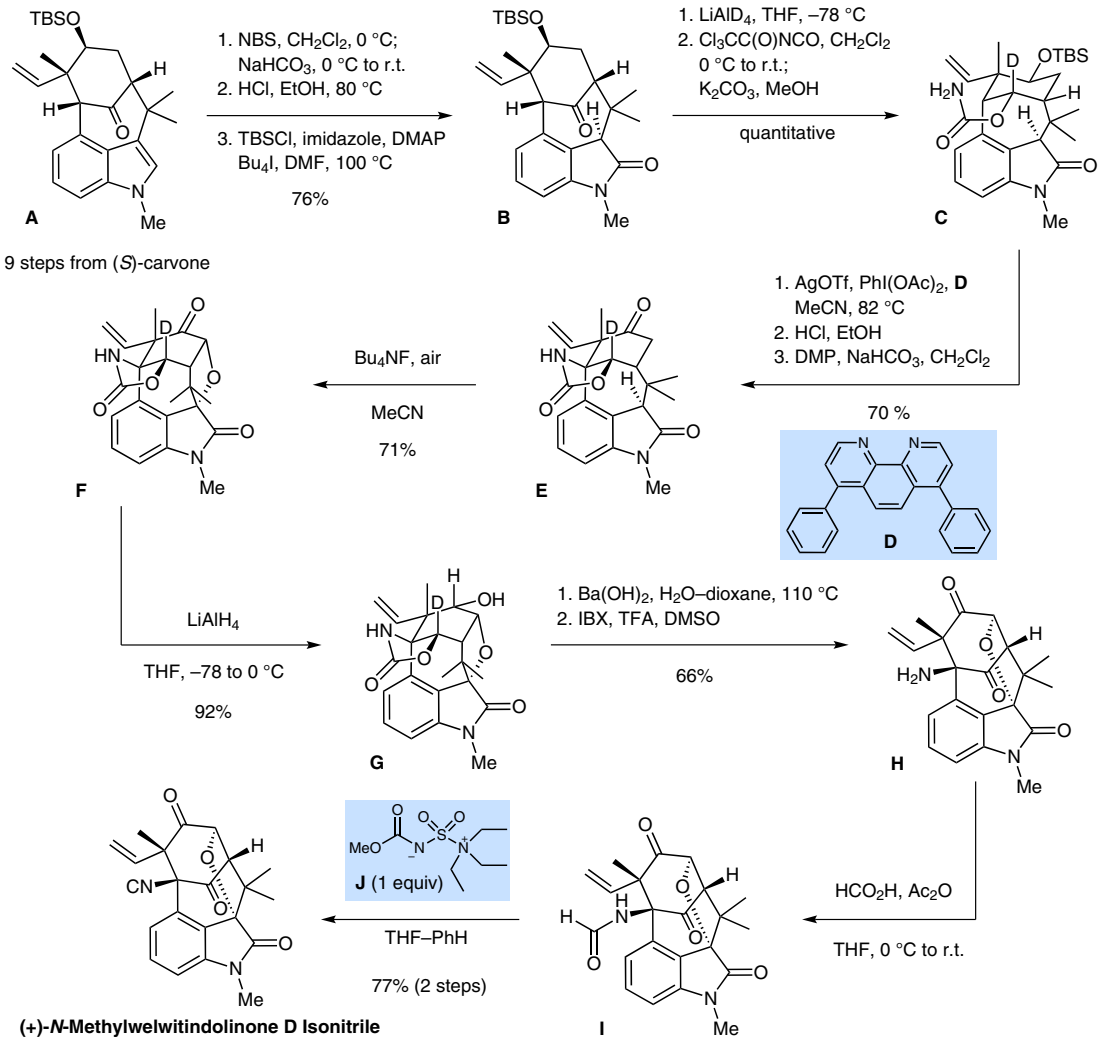
Comment: For a synthesis of benzophenone **A**, see: C.-w. Chung et al. *J. Med. Chem.* **2011**, *54*, 3827. The easy epimerization of the stereogenic center that occurs in the thionation reaction (**B** → **C**) was suppressed by conducting the reaction in the presence of sodium carbonate. The (*R*)-enantiomer is biologically inactive as a BET inhibitor.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2014, 10(1), 0010 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340327; **Reg-No.:** K07313SF

E. D. STYDUHAR, A. D. HUTERS, N. A. WEIRES, N. K. GARG* (UNIVERSITY OF CALIFORNIA, LOS ANGELES, USA)

Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile
Angew. Chem. Int. Ed. **2013**, *52*, 12422–12425.

Synthesis of (+)-*N*-Methylwelwitindolinone D Isonitrile



Significance: The welwitindolinones display interesting biological properties such as antifungal activity and microtubule depolymerization in human carcinoma cells. The challenging architecture of the target compound features an oxidized bicyclo[4.3.1]decane motif. The additional tetrahydrofuran ring was efficiently introduced by a double functionalization using air.

Comment: **A** was converted into deuterium-containing indolinone **C**. As described earlier by the authors, exploitation of the isotope effect during nitrene insertion afforded **E** in good yield. Oxidation to **F** was affected using tetra-*n*-butylammonium fluoride (TBAF) and air. Since hydrolysis of **F** led to decomposition, **H** was prepared by a reduction–hydrolysis–oxidation sequence. Formylation and dehydration yielded the target.

SYNFACTS Contributors: Erick M. Carreira, Matthias Westphal
Synfacts 2014, 10(1), 0011 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340352; **Reg-No.:** C07113SF

Category
Synthesis of Natural Products and Potential Drugs

Key words
welwitindolinone D
isotope effect
nitrene insertion
C–H functionalization
aerobic oxidation

Category

Synthesis of Natural Products and Potential Drugs

Key words

SIRT1 inhibitor

[3,3]-sigmatropic rearrangement

Cope rearrangement

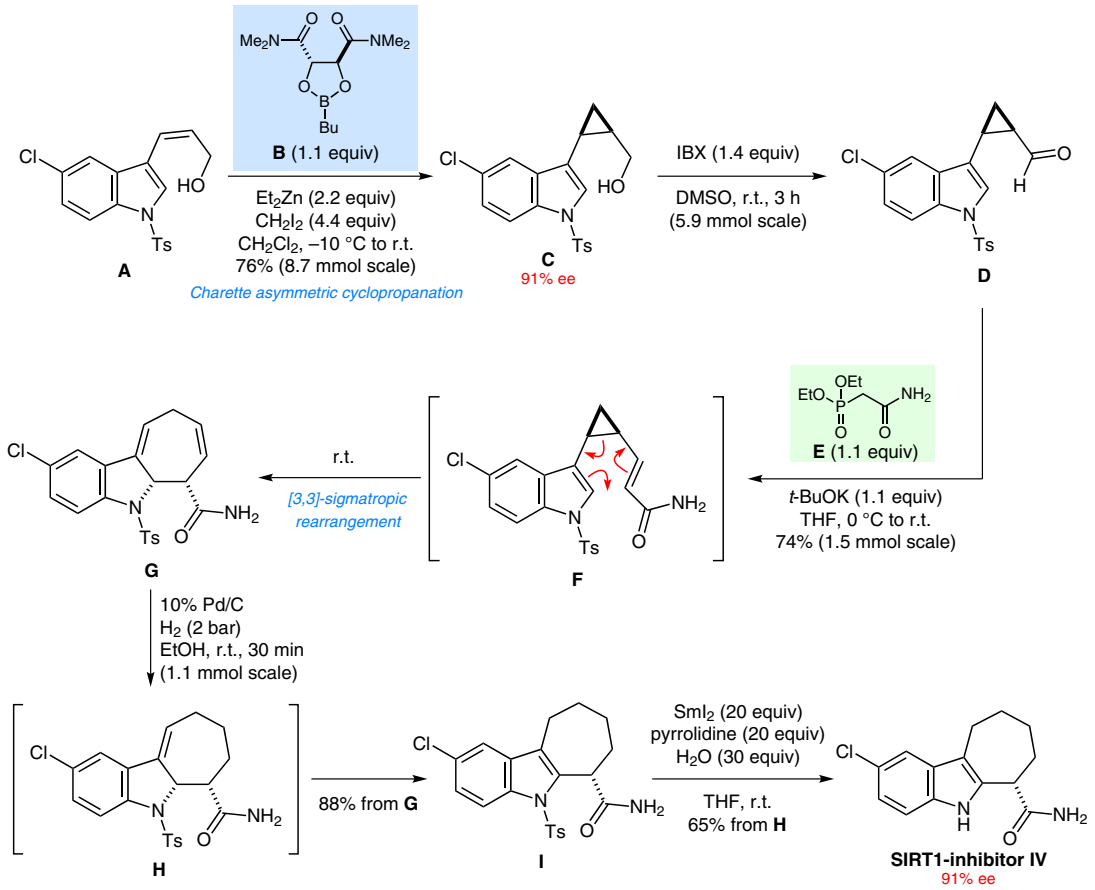
asymmetric cyclopropanation

cascade reaction

P. J. GRITSCH, E. STEMPEL, T. GAICH* (LEIBNIZ UNIVERSITY, HANNOVER, GERMANY)

Enantioselective Synthesis of Cyclohepta[*b*]indoles: Gram-Scale Synthesis of (*S*)-SIRT1-Inhibitor IV
Org. Lett. **2013**, *15*, 5472–5475.

Synthesis of a SIRT1 Inhibitor



Significance: SIRT1 deacetylates the p53 tumor suppressor protein, a key transcriptional regulator of genes involved in cell cycle regulation, apoptosis, and DNA repair. The target molecule is a potent SIRT1 inhibitor. The key step in the synthesis of the (*S*)-eutomer depicted is the stereospecific [3,3]-sigmatropic rearrangement of the divinylcyclopropane intermediate **F** derived from aldehyde **D** via a Horner–Wadsworth–Emmons (HWE) reaction.

Comment: Twelve examples of the HWE–[3,3]-sigmatropic rearrangement cascade leading to cyclohepta[*b*]indoles are described. The temperature required for the [3,3]-sigmatropic rearrangement varies from room temperature to 140 °C, depending on the structure of the indole divinylcyclopropane. For an earlier synthesis of the racemic target and its chiral HPLC resolution, see: A. D. Napper et al. *J. Med. Chem.* **2005**, *48*, 8045.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2014, 10(1), 0012 Published online: 13.12.2013
DOI: 10.1055/s-0033-1340329; **Reg-No.:** K07513SF