H. P. PEPPER, H. C. LAM, W. M. BLOCH, J. H. GEORGE* (UNIVERSITY OF ADELAIDE, AUSTRALIA)

Biomimetic Total Synthesis of (±)-Garcibracteatone
Org. Lett. **2012**, *14*, 5162–5164.

Category

Synthesis of Natural Products and Potential Drugs

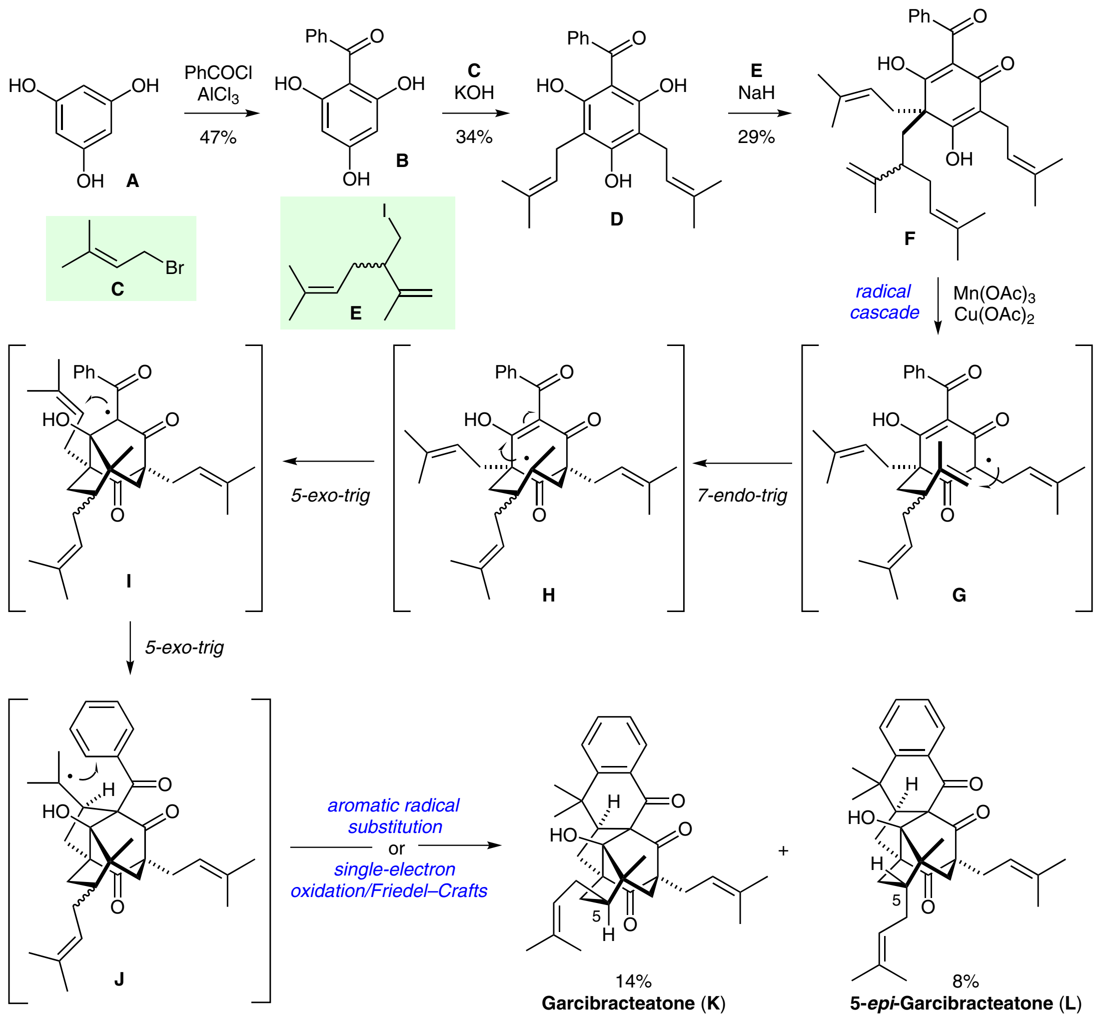
Key words

radical cascade

polyprenylated acylphloroglucinol

biomimetic synthesis

Total Synthesis (±)-Garcibracteatone



Significance: Garcibracteatone (**K**) is the structurally most complex polycyclic polyprenylated acylphlorogucinol natural product that has so far been isolated. The four-step total synthesis presented makes use of a biomimetic radical cascade reaction to build up four rings in one transformation. Additionally, the previously unknown relative stereochemistry at C-5 was assigned.

Comment: Precursor **F** for the key transformation is synthesized from phloroglucinol **A** in three steps by Friedel–Crafts acylation followed by subsequent diprenylation and alkylation with (±)-lavandulyl iodide (**E**). Oxidation of **F** by using $Mn(OAc)_3$–$Cu(OAc)_2$ initiates a radical cascade, which ultimately leads to the formation of the natural product garcibracteatone **K** (14% yield) along with its C5-epimer **L** (8% yield). This key transformation constructs four rings and five stereocenters.

SYNFACTS Contributors: Erick M. Carreira, Stefan Diethelm
Synfacts 2013, 9(1), 0001
DOI: 10.1055/s-0032-1317856; **Reg-No.:** C02812SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

oseltamivir phosphate

Tamiflu

enzymatic desymmetrization

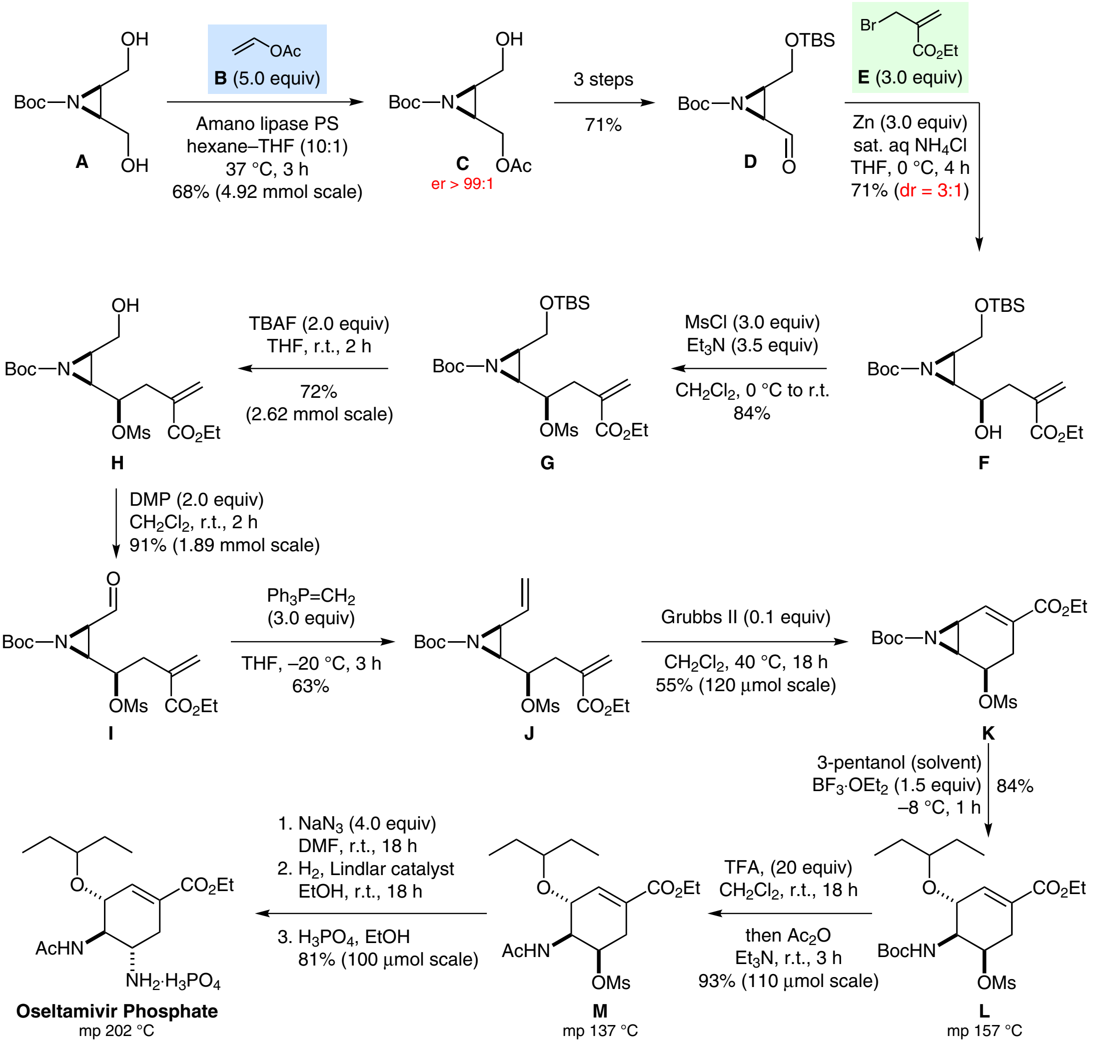
ring-closing metathesis

aziridine ring opening

H.-S. OH, H.-Y. KANG* (CHUNGBUK NATIONAL UNIVERSITY, REPUBLIC OF KOREA)

Synthesis of (–)-Oseltamivir Phosphate (Tamiflu) Starting from *cis*-2,3-Bis(hydroxymethyl)aziridine
J. Org. Chem. **2012**, *77*, 8792–8796.

Synthesis of (–)-Oseltamivir Phosphate



Significance: Oseltamivir phosphate (Tamiflu®) is a neuraminidase inhibitor that is widely prescribed for the treatment of various influenzas. The key step in this small-scale, 21-step synthesis is the enzymatic desymmetrization of the *meso*-diol **A** using Amano lipase PS. The diol **A** was prepared in six steps starting from *cis*-2-butene-1,4-diol.

Comment: For the enzymatic desymmetrization of closely related substrates, see: K. Fuji et al. *Tetrahedron Lett.* **1990**, *31*, 6663. For a closely related strategy based on epoxide opening and ring-closing metathesis, see: V. Rawat, S. Dey, A. Sudalai, *Org. Biomol. Chem.* **2012**, *10*, 3988.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0002 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317719; **Reg-No.:** K09212SF

A. K. GHOSH,* X. CHENG, B. ZHOU (PURDUE UNIVERSITY, WEST LAFAYETTE, USA)
Enantioselective Total Synthesis of (+)-Lithospermic Acid
Org. Lett. **2012**, *14*, 5046–5049.

Category

Synthesis of Natural Products and Potential Drugs

Key words

lithospermic acid

HIV integrase

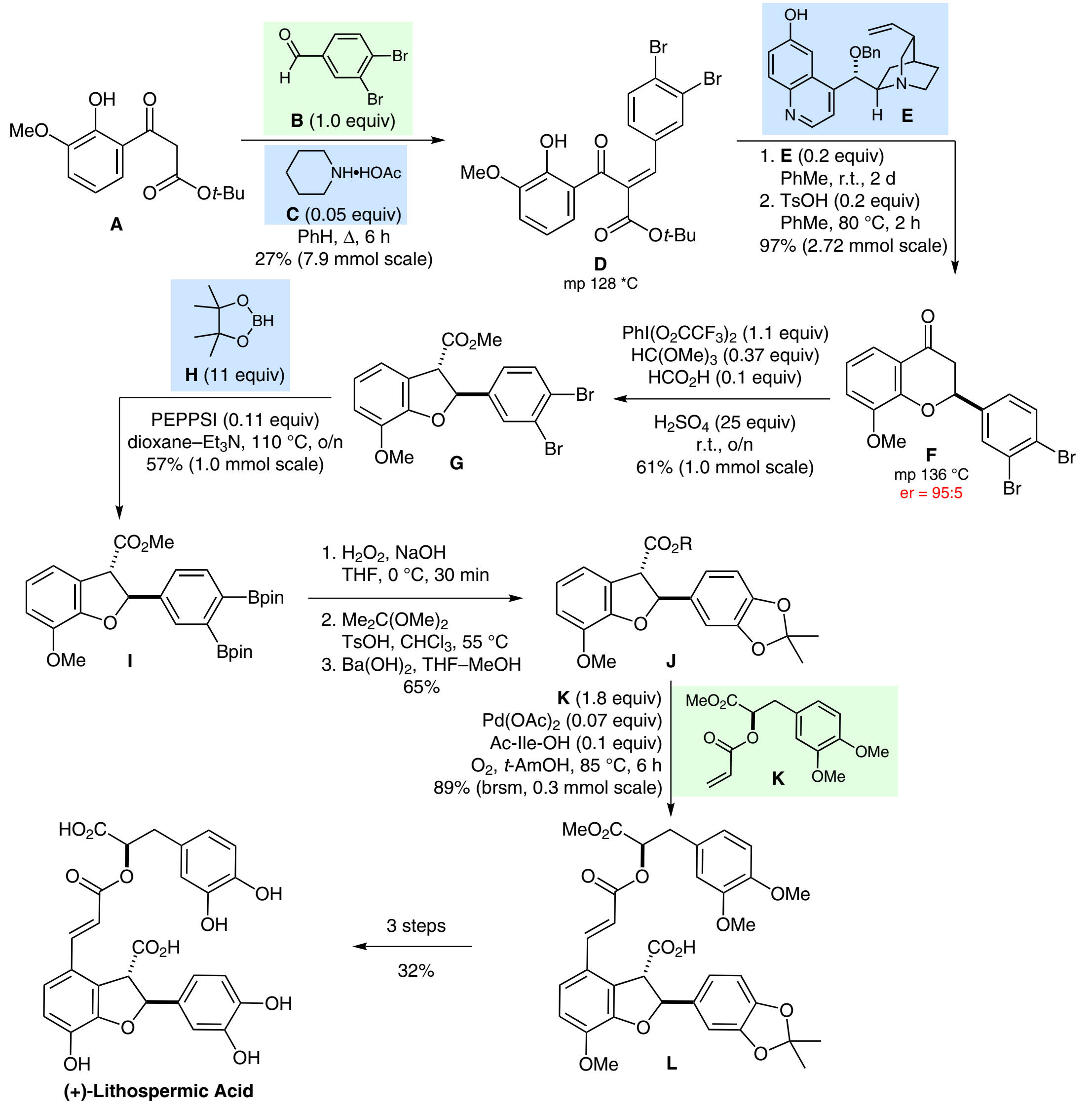
organocatalysis

asymmetric oxa-Michael reaction

oxidative ring contraction

C–H activation

Synthesis of (+)-Lithospermic Acid



Significance: This elegant synthesis of the HIV integrase inhibitor lithospermic acid features (1) an enantioselective intramolecular oxa-Michael reaction; (2) an oxidative ring contraction of the chromanone **F**; and (3) an intermolecular palladium-catalyzed C–H olefination used to append acrylate ester **K** to **J**.

Comment: The enantiomeric ratio of **F** improved to 99:1 after one recrystallization. The presence of the two electronegative bromine atoms on chromanone **F** were essential for the success of the oxidative ring contraction mediated by phenyliodonium bis(trifluoroacetate).

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0003
DOI: 10.1055/s-0032-1317722; **Reg-No.:** K09512SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

communesin F

indol-2-one

Diels–Alder cycloaddition

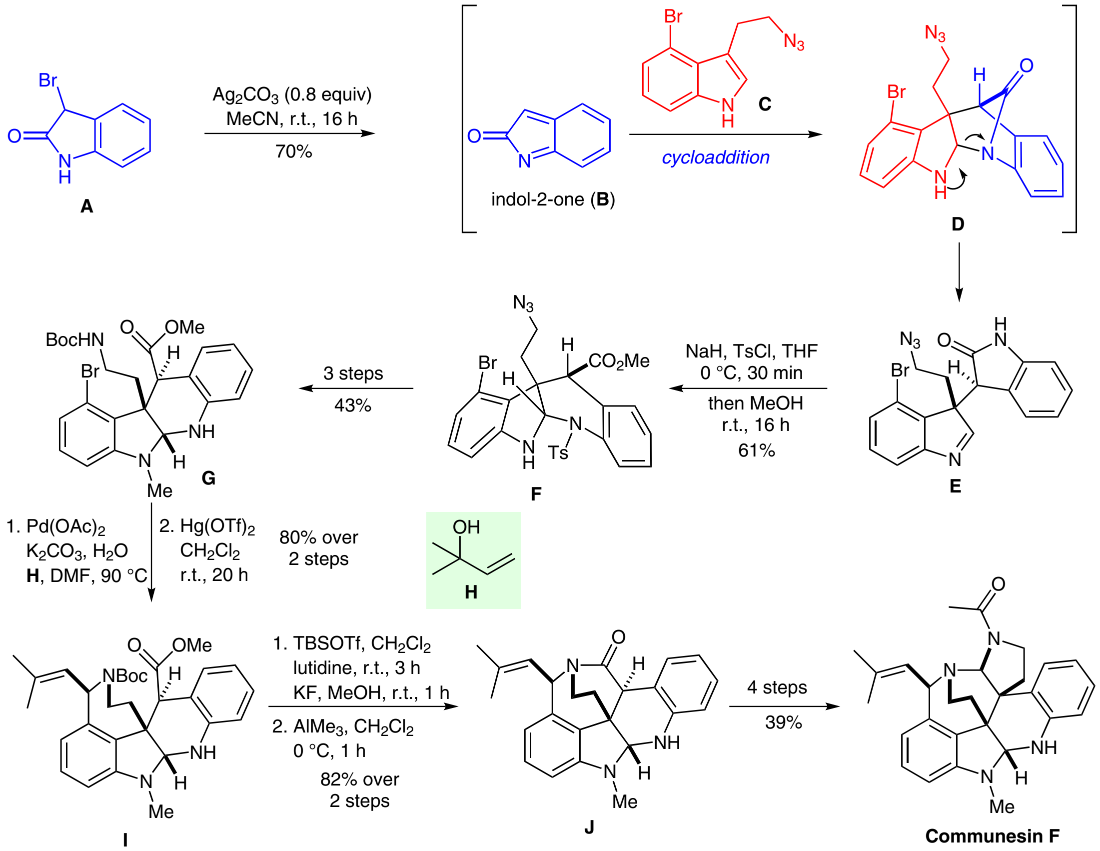
mercuric triflate

trimethyl aluminum

J. BELMAR, R. L. FUNK* (PENNSYLVANIA STATE UNIVERSITY, USA)

Total Synthesis of (±)-Communesin F via a Cycloaddition with Indol-2-one
J. Am. Chem. Soc. **2012**, *134*, 16941–16943.

Total Synthesis of Communesin F



Significance: The stereochemically complex polycyclic structure of the communesins has attracted the interest of several researchers and led to the total syntheses of communesin A, B and F. Funk and co-worker now report an elegant and concise synthesis of the moderately cytotoxic communesin F that relies on an unusual Diels–Alder cycloaddition of indol-2-one, a reaction developed by the group. Its considerable synthetic utility has previously been demonstrated in the total synthesis of perophoramidine and is now further showcased by the synthesis of communesin F in only 15 steps and an overall yield of 6.7%.

Comment: Indol-2-one **B** was generated from bromooxindole **A** and underwent smooth cycloaddition with indole **C** to afford **E** via intermediate **D**. Tosylation of the amide followed by methanolysis led to formation of aminal **F**. Advanced tetracyclic intermediate **G** was obtained in three more steps. Heck reaction of **G** with alcohol **H**, followed by a high-yielding mercuric-triflate promoted cyclization to the benzazepine gave **I**. Cyclization to the bridged lactam **J** could not be achieved under thermal conditions, but exposure to trimethyl aluminum effected the desired transformation. Synthetic communesin F was obtained after four more steps.

SYNFACTS Contributors: Erick M. Carreira, Simon Krautwald
Synfacts 2013, 9(1), 0004 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317850; **Reg-No.:** C02212SF

Z. SHI* ET AL. (BRISTOL-MYERS SQUIBB CO., NEW BRUNSWICK AND PRINCETON, USA)
Development of a Practical Synthesis of a p38 Kinase Inhibitor via a Safe and Robust Amination
Org. Process Res. Dev. **2012**, *16*, 1618–1625.

Category

Synthesis of Natural Products and Potential Drugs

Key words

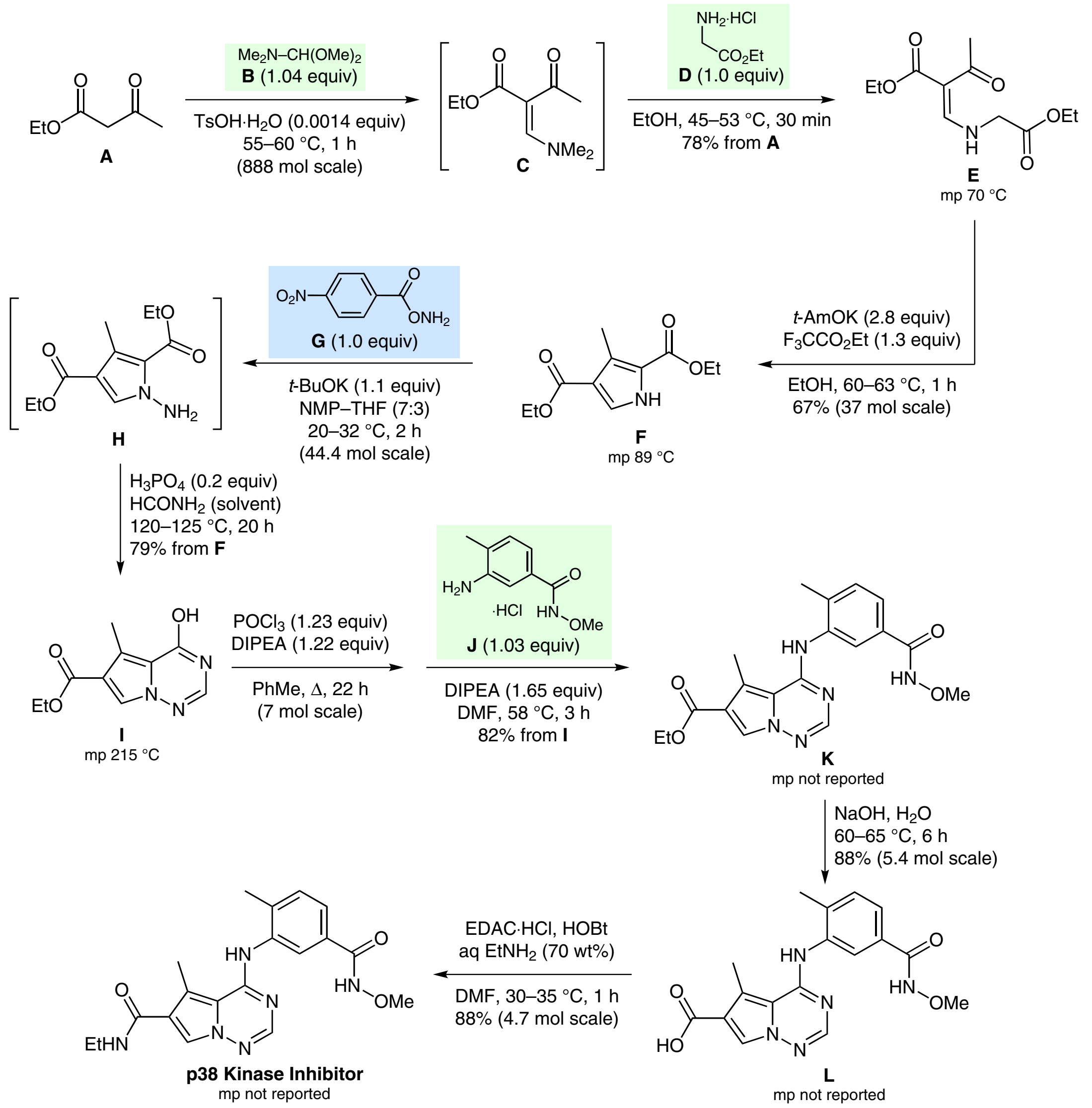
p38 kinase inhibitors

amination

***O*-(4-nitrobenzoyl)-hydroxylamine**

pyrrolotriazines

Synthesis of a p38 Kinase Inhibitor



Significance: The target pyrrolotriazine is a p38 kinase inhibitor that was a lead compound for the treatment of rheumatoid arthritis. The synthesis depicted features a safe and scalable N-amination of the pyrrole **F** using *O*-(4-nitrobenzoyl)hydroxylamine (**G**). The synthesis delivered 1.6 kg of active pharmaceutical ingredient (API) in 26% overall yield.

Comment: Competing ester hydrolysis products generated in the condensation of **E** to the pyrrole **F** were minimized by adding ethyl trifluoroacetate as a water scavenger. A large-scale process for the synthesis of the crystalline *O*-4-(nitrobenzoyl)-hydroxylamine (**G**) is described.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0005 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317723; **Reg-No.:** K09612SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

candesartan cilexetil

angiotensin II receptor antagonists

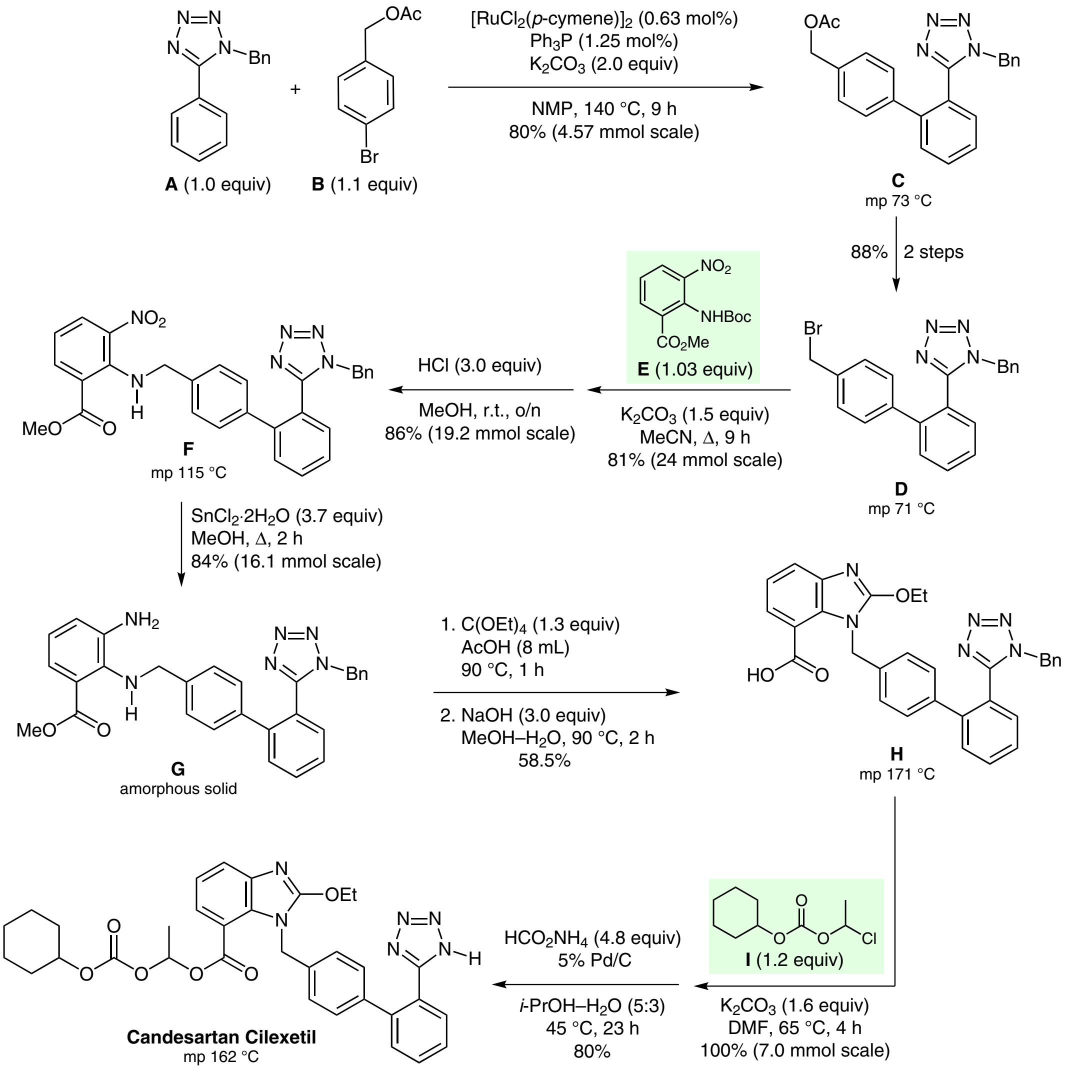
C–H arylation

ruthenium

transfer hydrogenation

M. SEKI* (MITSUBISHI TANABE PHARMA CORPORATION, OSAKA, JAPAN)
An Efficient C–H Arylation of a 5-Phenyl-1*H*-tetrazole Derivative: A Practical Synthesis of an Angiotensin II Receptor Blocker
Synthesis **2012**, *44*, 3231–3237.

Synthesis of Candesartan Cilexetil



Significance: Candesartan cilexetil (Atacand®) is an angiotensin II receptor antagonist that is prescribed for the treatment of hypertension. It is a prodrug that is hydrolyzed to candesartan in the gut. The synthesis depicted, features an efficient protocol for ruthenium-catalyzed C–H arylation of the tetrazole **A**.

Comment: A significant challenge in this small-scale synthesis was the final removal of the benzyl protecting group from the tetrazole unit using transfer hydrogenation. Best results were obtained using a 'thickshell' Pd/C catalyst from Evonik.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0006 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317726; **Reg-No.:** K09912SF

N. SHIMADA, Y. ABE, S. YOKOSHIMA, T. FUKUYAMA* (THE UNIVERSITY OF TOKYO, JAPAN)
Total Synthesis of (–)-Lycoposerramine-S
Angew. Chem. Int. Ed. **2012**, *51*, 11824–11826.

Category

Synthesis of Natural Products and Potential Drugs

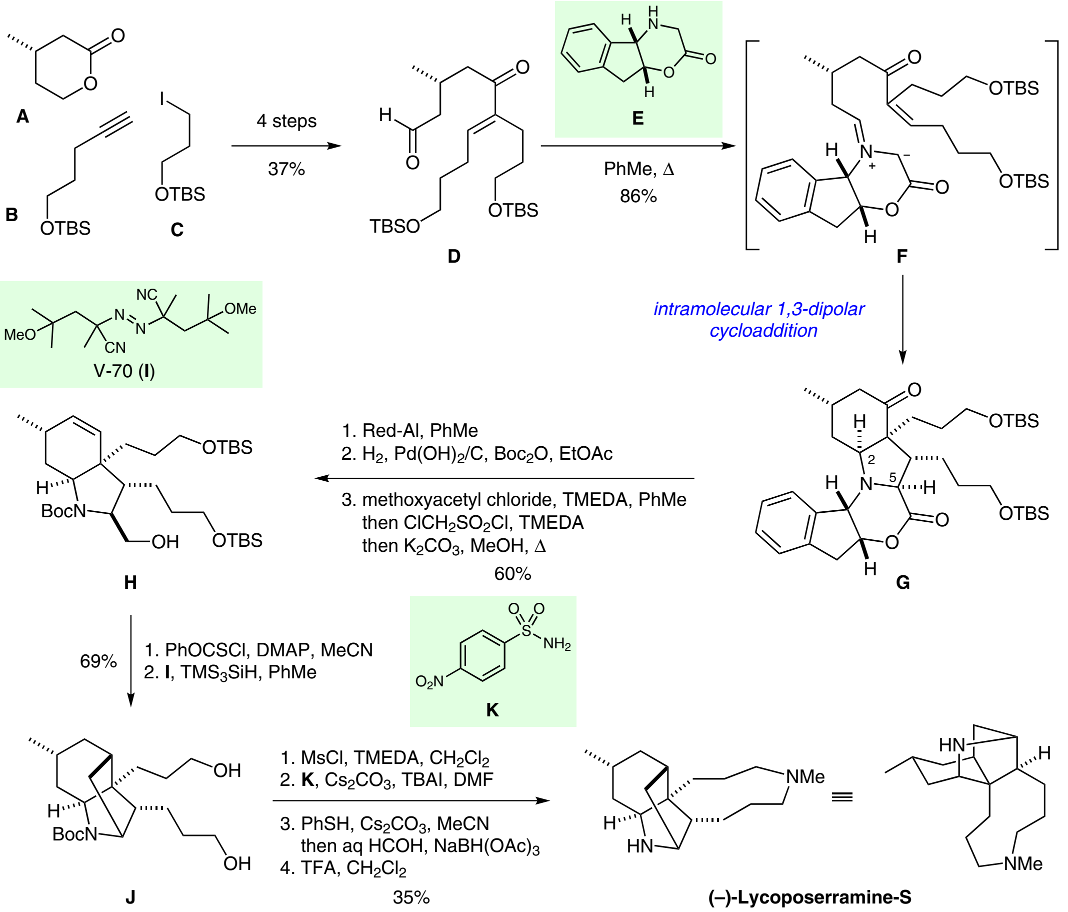
Key words

lycoposerramine-S

azomethine ylides

1,3-dipolar cycloaddition

Total Synthesis of (–)-Lycoposerramine-S



Significance: Fukuyama and co-workers report the first total synthesis of the caged tetracyclic *Lycopodium* alkaloid (–)-lycoposerramine-S. The enantioselective synthesis is centered around an impressive 1,3-dipolar cycloaddition which diastereoselectively constructs the central pentasubstituted pyrrolidine ring utilizing a chiral morpholinone. A radical cyclization and alkylative ring closure of the nine-membered ring using a 4-nitrobenzenesulfonyl amide leads to the synthesis of the natural product in only 14 steps.

Comment: In a striking intramolecular 1,3-dipolar cycloaddition, condensation of aldehyde **D** with morpholinone **E** led to the diastereoselective formation of pyrrolidine **G** containing four newly constructed contiguous stereocenters in excellent yield. The formation of the 2,5-*cis* relationship is thought to arise from preferential formation of *Z*-azomethine ylide **F**. Exhaustive reduction, selective elimination of the resulting secondary alcohol followed by a radical annulation led to tricycle **J**. Finally, the medium-sized ring was assembled by use of alkylative nosyl amide chemistry previously developed by the Fukuyama group.

SYNFACTS Contributors: Erick M. Carreira, Simon Breitler
Synfacts 2013, 9(1), 0007
DOI: 10.1055/s-0032-1317853; **Reg-No.:** C02512SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

(–)-leiodermatolide

alkyne metathesis

antitumor agents

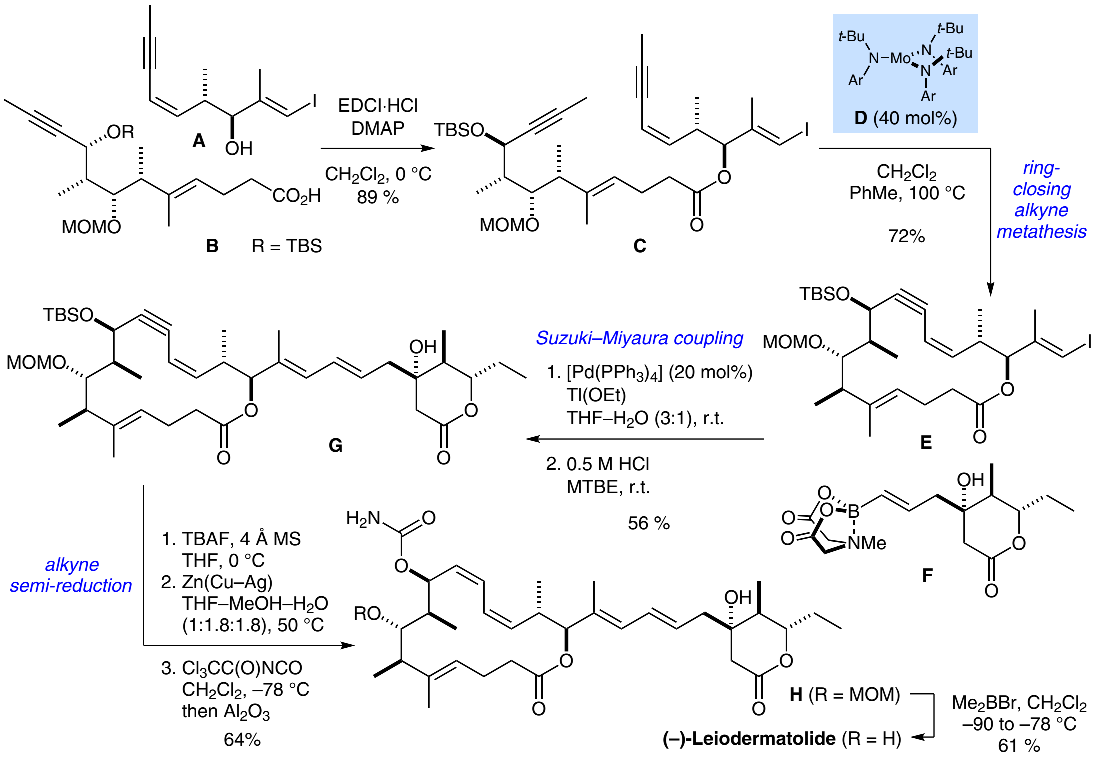
structure elucidation

molybdenum

J. WILLWACHER, N. KAUSCH-BUSIES, A. FÜRSTNER* (MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG, MÜLHEIM AN DER RUHR, GERMANY)

Divergent Total Synthesis of the Antimitotic Agent Leiodermatolide
Angew. Chem. Int. Ed. **2012**, *51*, 12041–12046.

Synthesis of (–)-Leiodermatolide



Significance: Leiodermatolide is an antimitotic macrolide isolated in 2011 from the deep-water sponge *Leiodermatium sp*. that exhibited potent and selective in vitro cytotoxicity against various human cancer cell lines ($IC_{50} < 10$ nM). Although the natural product was shown to induce cell cycle arrest at the G2/M transition, it had no effect on purified tubulin, indicating a novel mode of action. In addition to the promising biological activity, leiodermatolide posed an interesting target for synthetic studies, as the segregated stereoclusters within the macrolactone and the δ-lactone terminus could not be assigned unambiguously.

Comment: In order to address this issue, a strategy was chosen, in which the δ-lactone subunit **F** was merged with macrocycle **E** at a late stage of the synthesis, granting access to either conceivable diastereomer of the target. The assembly commenced with esterification of **A** and **B**, giving diyne **C**, which underwent efficient cyclization using molybdenum complex **D** as a catalyst precursor. Suzuki–Miyaura coupling of vinyliodide **E** and boronate **F** gave intermediate **G**, which was advanced to leiodermatolide in four further steps, including Zn(Cu–Ag)-mediated enyne semi-reduction to the corresponding *Z,Z*-configured diene. Subtle differences in the ^{1}H NMR data of the respective isomers allowed for a conclusive stereochemical assignment of the natural product.

SYNFACTS Contributors: Erick M. Carreira, Oliver F. Jeker
Synfacts 2013, 9(1), 0008 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317854; **Reg-No.:** C02612SF

Y. ZHAO* ET AL. (TAKEDA CALIFORNIA, SAN DIEGO, MILLENIUM PHARMACEUTICALS INC., CAMBRIDGE AND IRIX PHARMACEUTICALS, GREENVILLE, USA)

Process Research and Kilogram Synthesis of an Investigational, Potent MEK Inhibitor
Org. Process Res. Dev. **2012**, *16*, 1652–1659.

Category

Synthesis of Natural Products and Potential Drugs

Key words

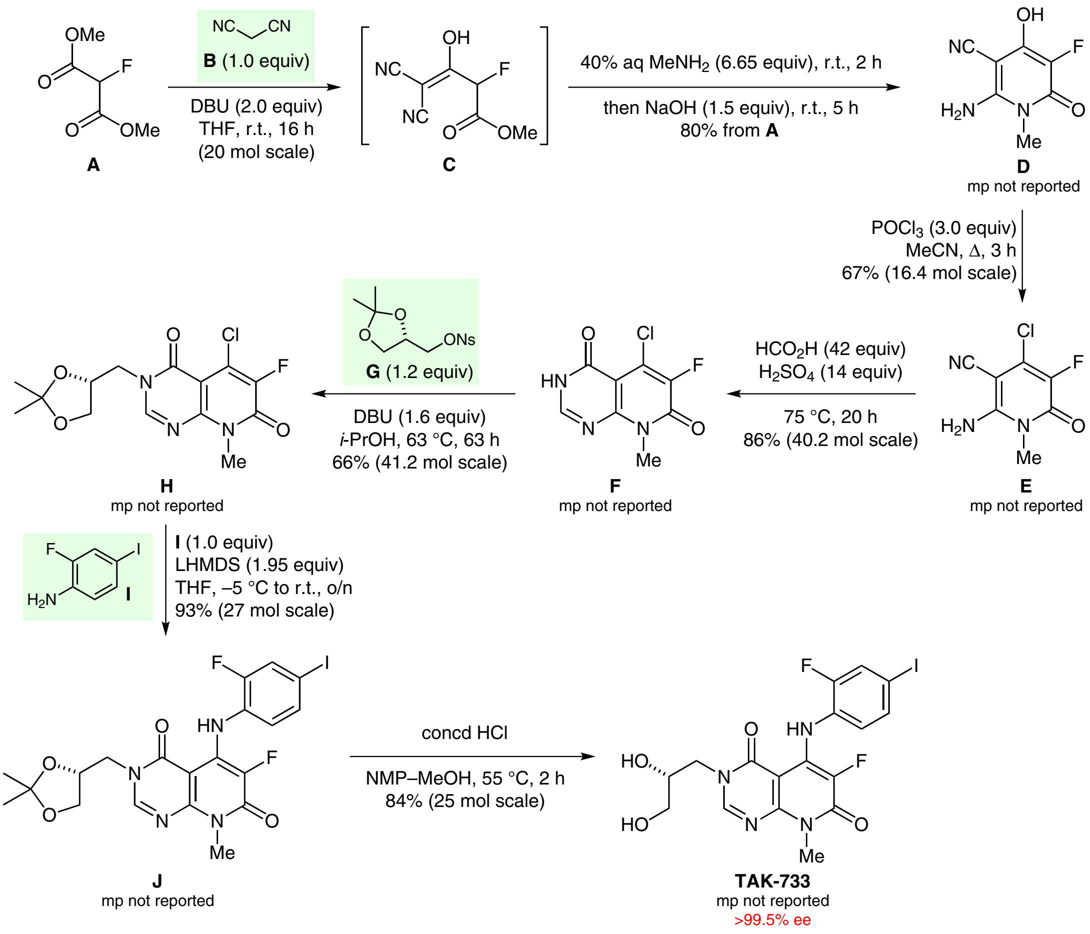
TAK-733

MEK inhibitors

3-fluoropyridone

cascade reaction

Synthesis of TAK-733



Significance: MEK kinases regulate the pathway that mediates proliferative and anti-apoptotic signaling factors that promote tumor growth and metastasis. TAK-733 is an MEK kinase inhibitor that entered phase I clinical trials for the treatment of cancer. A noteworthy feature of this short synthesis (25% yield overall) is the one-pot, three-step synthesis of the fluoropyridone **D**, in which the fluorine atom is present at the outset.

Comment: The reaction of **F** with the nosylate **G** gave a mixture of N- and O-alkylation products (8:1) from which the desired N-alkylation product was isolated by crystallization. The mixture of *N*-methyl pyrrolidine (NMP) and methanol used in the final deprotection step, helped to ensure formation of the desired polymorph. The nine-step discovery synthesis (3% overall yield) is also presented.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0009 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317725; **Reg-No.:** K09812SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

glucokinase activators

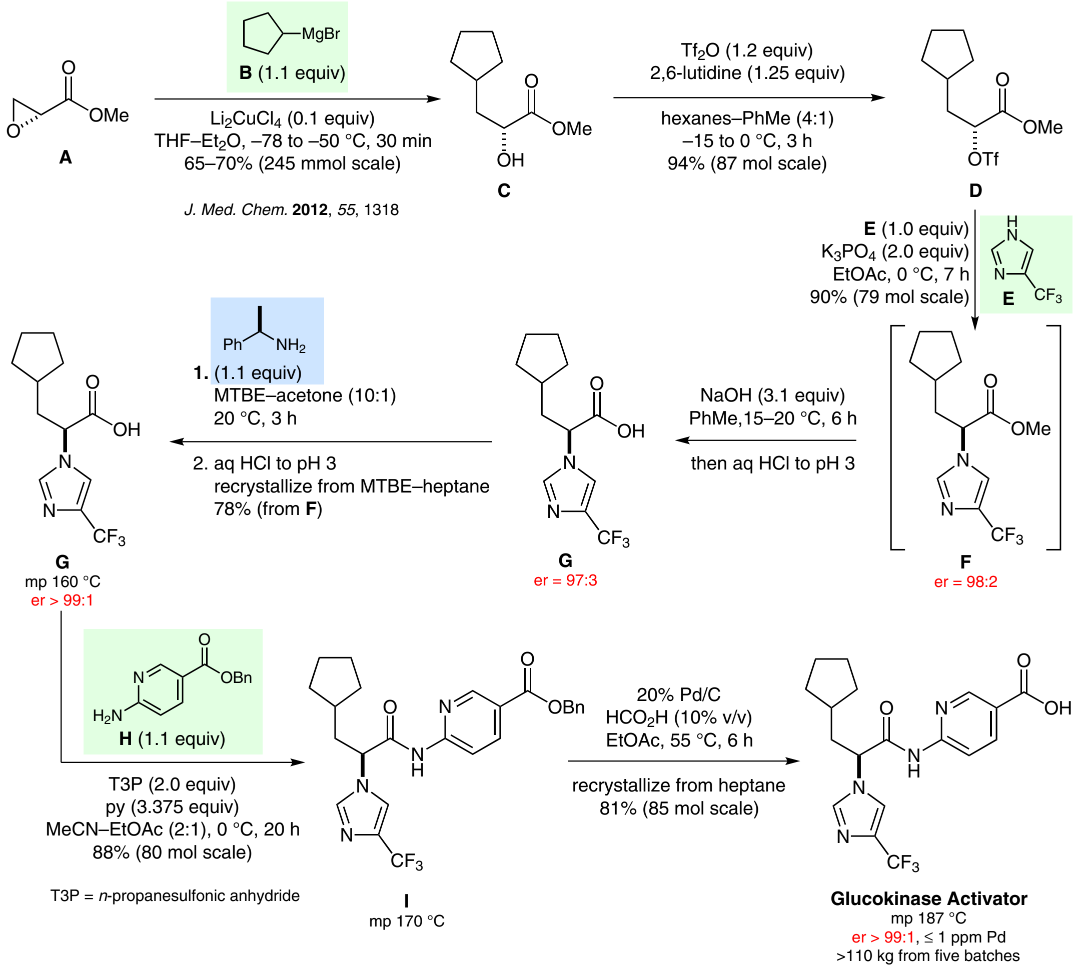
amide bond formation

***n*-propanesulfonic anhydride**

J. R. DUNETZ,* M. A. BERLINER* ET AL. (PFIZER WORLDWIDE RESEARCH AND DEVELOPMENT, GROTON, USA AND SANDWICH, UK; ASYMCHEM LIFE SCIENCE CO., TIANJIN, P. R. OF CHINA)

Multikilogram Synthesis of a Hepatoselective Glucokinase Activator
Org. Process Res. Dev. **2012**, *16*, 1635–1645.

Synthesis of a Glucokinase Activator



Significance: Glucokinase mediates glucose metabolism in the liver and insulin release in the pancreas. The target molecule selectively activates liver glucokinase with diminished risk of hypoglycemia. It is a lead for the treatment of type 2 diabetes. A major challenge in the synthesis depicted was the formation of amide **I** by the condensation of the racemization-prone carboxylic acid **G** with the weakly nucleophilic 6-aminonicotinic ester **H**. Best results were obtained using *n*-propanesulfonic anhydride (T3P) as the condensing agent.

Comment: The N-alkylation of imidazole **E** was studied extensively to achieve high regioselectivity with minimal racemization. Best results were obtained using potassium phosphate as base and ethyl acetate as solvent, in which case the regioselectivity was 96:4. The unwanted regioisomer and epimer was removed by crystallization of the salt prepared from (*R*)-α-methylbenzylamine. A further complication was the hydrolytic lability of the hard-won amide bond in **I**.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0010   Published online: 17.12.2012
DOI: 10.1055/s-0032-1317724; **Reg-No.:** K09712SF

Erratum

Synthesis of a Glucokinase Activator

J. R. Dunetz,* M. A. Berliner* et al. *Synfacts* **2013**, *9*, 10.

T3P was misrepresented. T3P is *n*-propanephosphonic acid anhydride. We apologize for this mistake.

X.-F. YANG, C.-H. DING, X.-H. LI, J.-Q. HUANG, X.-L. HOU,* L.-X. DAI, P.-J. WANG
(SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)
Regio- and Enantioselective Palladium-Catalyzed Allylic Alkylation of Nitromethane with Monosubstituted Allyl Substrates: Synthesis of (*R*)-Rolipram and (*R*)-Baclofen
J. Org. Chem. **2012**, *77*, 8980–8985.

Category

Synthesis of Natural Products and Potential Drugs

Key words

(*R*)-rolipram

(*R*)-baclofen

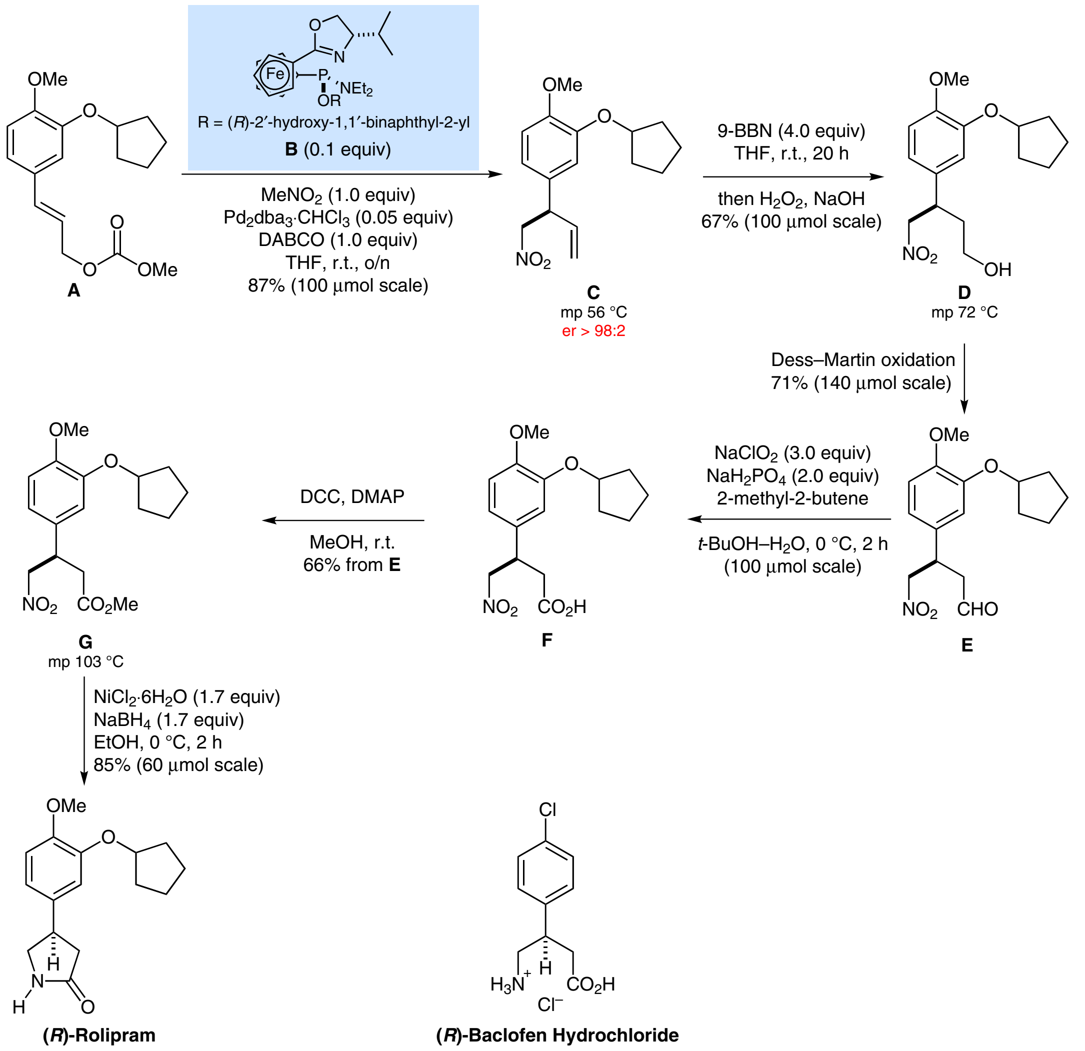
asymmetric allylic alkylation

nitromethane

allyl carbonates

palladium

Synthesis of (*R*)-Rolipram



Significance: Rolipram is a phosphodiesterase-4 (PDE-4) inhibitor that displays potentially useful anti-inflammatory, antidepressant and antipsychotic effects. The key step in the micro-scale synthesis depicted is the palladium-catalyzed asymmetric allylic alkylation of nitromethane with the allylic carbonate **A**. High regio- and enantioselectivities were observed using the ferrocene-based SIOCPhox chiral ligand **B**.

Comment: The scope of the asymmetric allylic alkylation of nitromethane was explored using eleven aryl-substituted allyl methyl carbonates giving yields of 80–92% (one exception) and enantiomeric excesses of 90–98%. The reaction was also applied to an asymmetric synthesis of the anti-spasmodic agent (*R*)-baclofen.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0011 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317720; **Reg-No.:** K09312SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

pregabalin

kainic acid

Hayashi–Miyaura asymmetric conjugate addition

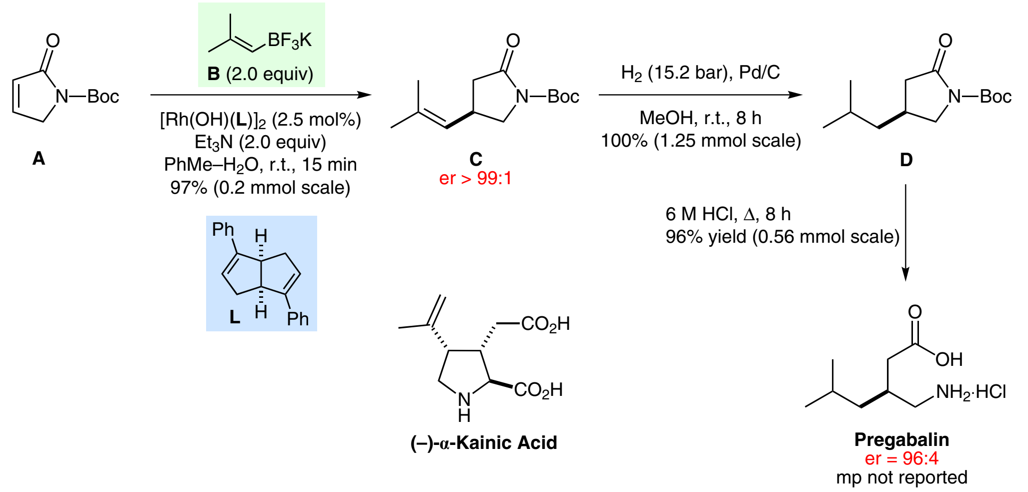
rhodium catalysis

alkenyl trifluoroborates

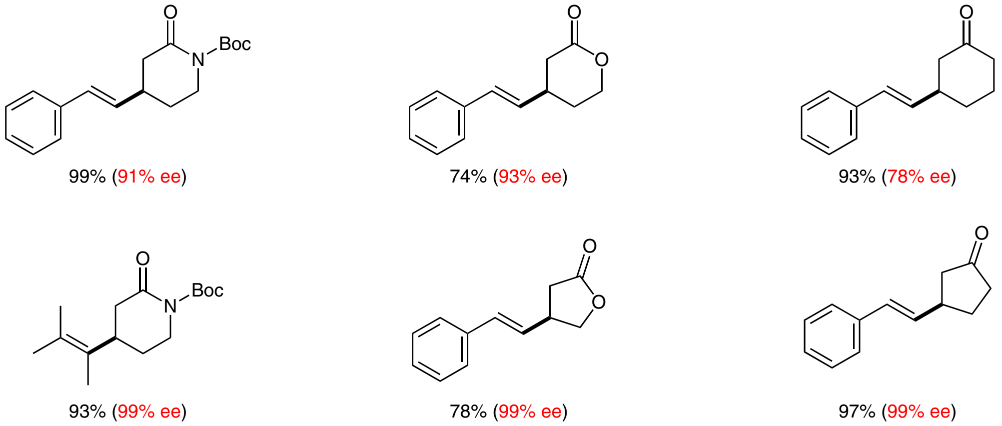
H.-J. YU, C. SHAO, Z. CUI, C.-G. FENG,* G.-Q. LIN* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)

Highly Enantioselective Alkenylation of Cyclic α,β-Unsaturated Carbonyl Compounds as Catalyzed by a Rhodium–Diene Complex: Application to the Synthesis of (*S*)-Pregabalin and (–)-α-Kainic Acid
Chem. Eur. J. **2012**, *18*, 13274–13278.

Synthesis of Pregabalin



Further examples of adducts derived from the asymmetric conjugate addition reaction:



Significance: Pregabalin (Lyrica®) is a lipophilic GABA analogue that is prescribed for the treatment of epilepsy. This short, small-scale synthesis of pregabalin features a highly enantioselective asymmetric conjugate addition of the alkenyl trifluoroborate **B** to the α,β-unsaturated lactam **A** catalyzed by a rhodium complex incorporating the chiral bicyclo[3.3.0]octa-2,5-diene ligand **L**.

Comment: A further 17 examples of this new variant of the Hayashi–Miyaura asymmetric conjugate addition reaction are reported using six α,β-unsaturated carbonyl substrates and ten alkenyl trifluoroborates. The asymmetric conjugate addition was also applied to the synthesis of the potent neuroexcitatory agent α-kainic acid (seven steps, 40% overall yield).

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0012

DOI: 10.1055/s-0032-1317717; **Reg-No.:** K09012SF

J. LI, Y. CAI, W. CHEN, X. LIU, L. LIN, X. FENG* (SICHUAN UNIVERSITY, CHENGDU, P. R. OF CHINA)
Highly Enantioselective Fluorination of Unprotected 3-Substituted Oxindoles: One-Step Synthesis of BMS 204352 (Maxipost)
J. Org. Chem. **2012**, *77*, 9148–9155.

Synthesis of Maxipost

Category

Synthesis of Natural Products and Potential Drugs

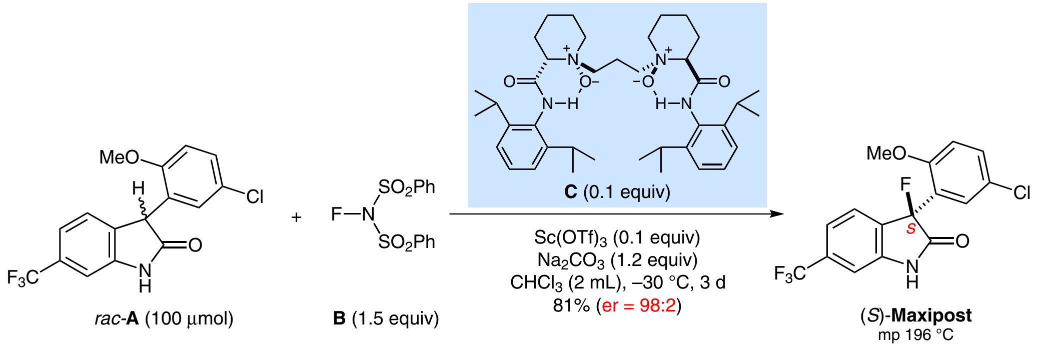
Key words

maxipost

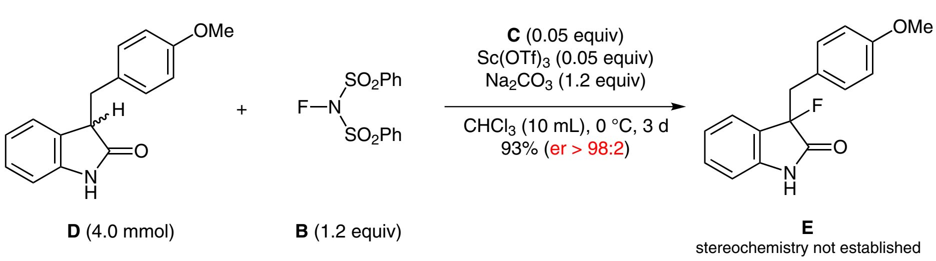
asymmetric fluorination

scandium triflate

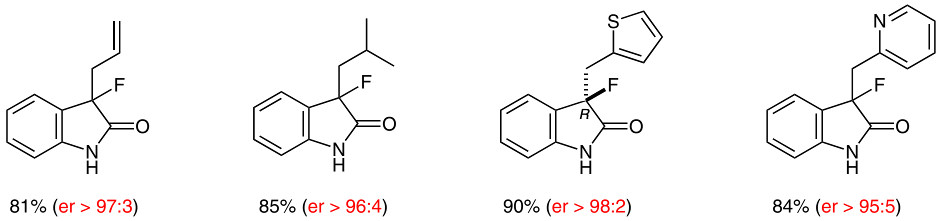
***N*-fluorobenzenesulfonimide**



Asymmetric fluorination of oxindole D on a gram scale:



Further examples of the asymmetric fluorination of oxindoles:



Significance: Maxipost is a post-stroke neuroprotective agent that acts by opening large conductance Ca^{2+}-activated (maxi-K) potassium channels. Previous syntheses of maxipost by asymmetric fluorination of oxindoles required protection of the oxindole nitrogen as the *N*-Boc derivative. The route depicted features the direct asymmetric catalytic fluorination of the oxindole **A** using *N*-fluorobenzenesulfinimide (**B**) in the presence of 10 mol% of a chiral complex derived from scandium triflate and the amine oxide ligand **C**.

Comment: Attempts to perform the maxipost synthesis on a 3.5 mmol scale resulted in decreased yield and enantioselectivity (53% yield, 86% ee) due to the low solubility of the substrate. By constrast, the asymmetric fluorinaton of oxindole **D** on a 4.0 mmol scale gave **E** in 93% yield and 97% ee. The small selection of the 29 examples described, showed that yields and enantioselectivities are generally high.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0013
DOI: 10.1055/s-0032-1317721; **Reg-No.:** K09412SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

GDC-0068

serine/threonine kinase

Akt inhibitor

Favorskii ring contraction

Noyori asymmetric transfer hydrogenation

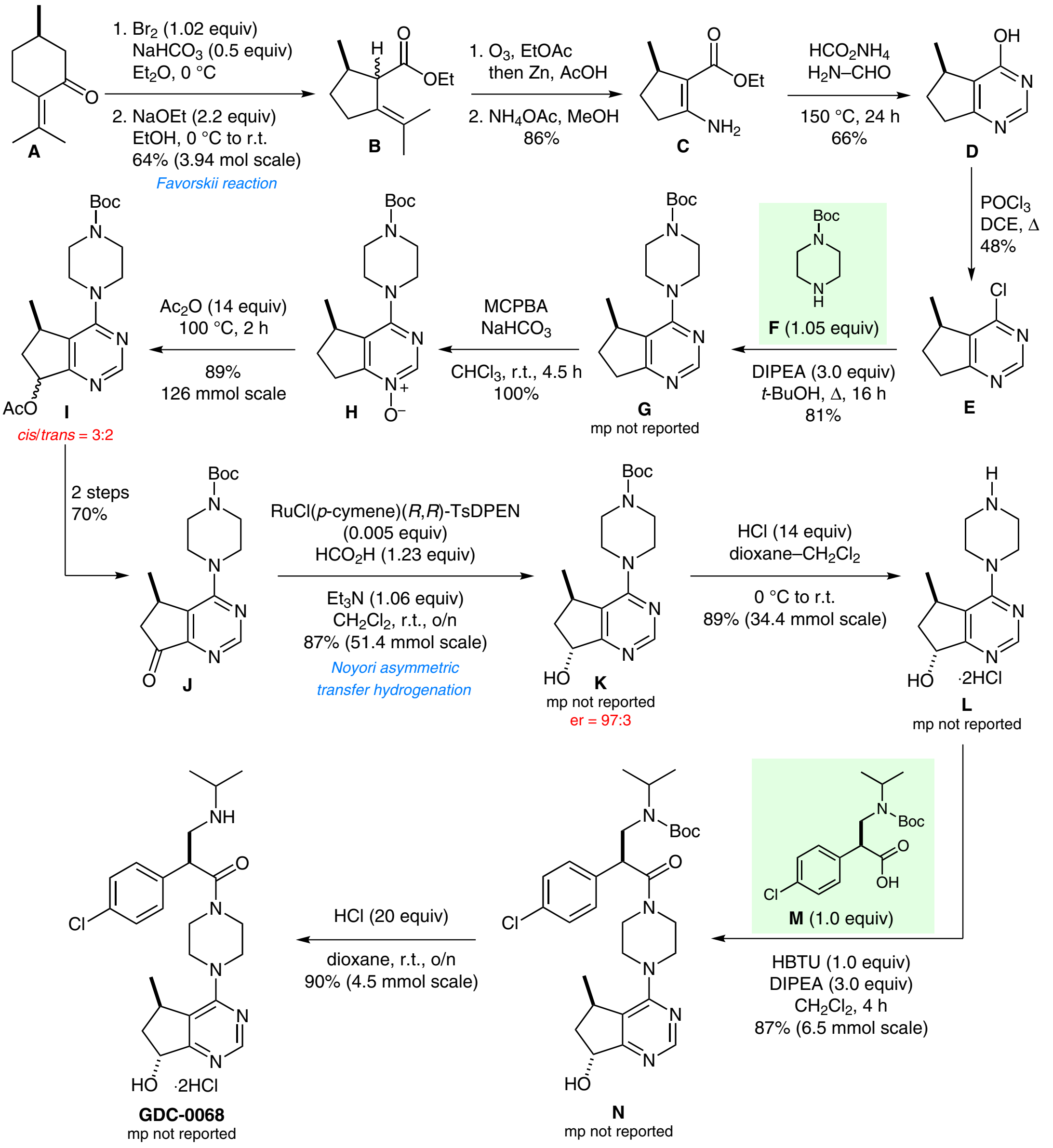
pyrimidine *N*-oxide rearrangement

J. F. BLAKE* ET AL. (ARRAY BIOPHARMA INC., BOULDER AND GENENTECH INC., SOUTH SAN FRANCISCO, USA)

Discovery and Preclinical Pharmacology of a Selective ATP-Competitive Akt Inhibitor (GDC-0068) for the Treatment of Human Tumors

J. Med. Chem. **2012**, *55*, 8110–8127.

Synthesis of Akt Inhibitor GDC-0068



Significance: Akt is a kinase that controls cellular processes by phosphorylating substrates involved in apoptosis, transcription, cell cycle progression and translation. GDC-0068 is an Akt inhibitor that is in clinical trials for the treatment of cancer.

Comment: Key steps in the synthesis depicted are (1) the use of a Favorskii ring contraction in the conversion of (*R*)-pulegone (**A**) to the ester **B** and (2) the Noyori asymmetric transfer hydrogenation of ketone **J**.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2013, 9(1), 0014
DOI: 10.1055/s-0032-1317718; **Reg-No.:** K09112SF

C. R. EDWANKAR, R. V. EDWANKAR, J. R. DESCHAMPS, J. M. COOK* (UNIVERSITY OF WISCONSIN-MILWAUKEE AND NAVAL RESEARCH LABORATORY, WASHINGTON, D. C., USA)

Nature-Inspired Stereospecific Total Synthesis of *P*-(+)-Dispegatrine and Four Other Monomeric *Sarpagine* Indole Alkaloids
Angew. Chem. Int. Ed. **2012**, *51*, 11762–11765.

Total Synthesis of the Dimeric *Sarpagine* Indole Alkaloid *P*-(+)-Dispegatrine

Category

Synthesis of Natural Products and Potential Drugs

Key words

dispegatrine

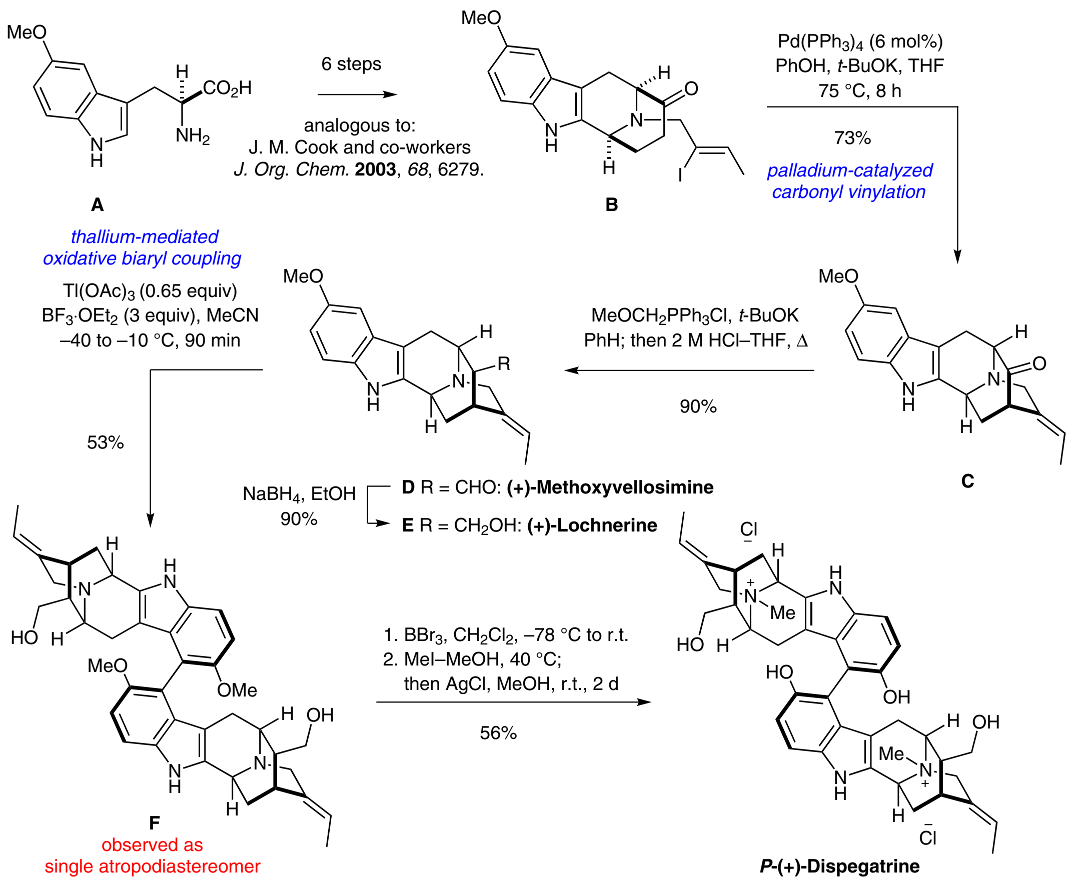
sarpagine alkaloids

carbonyl vinylation

thallium

oxidative biaryl coupling

dimerization



Significance: Reported in this work is the first total synthesis of *P*-(+)-dispegatrine, a complex dimeric *sarpagine* indole alkaloid, which has been shown to exhibit anti-hypertensive activity due to its affinity to both the α1 and α2 adrenoreceptors. In addition to an efficient asymmetric route, the synthetic efforts toward this natural product have also led to the determination of the absolute configuration around the biaryl axis, which had previously been left unassigned by the isolation group.

Comment: The most notable feature in the synthetic route presented above is a thallium-mediated oxidative dimerization of (+)-lochnerine (**E**) which regioselectively delivers the desired dimer **F**. Thereby, the rigid chiral framework of the monomer dictates atroposelection during the dimerization reaction, leading exclusively to the naturally occuring atropodiastereomer (*P*-isomer). This and similar results from an earlier semi-synthetic study led to the proposal that the biaryl coupling might closely parallel the biosynthetic route.

SYNFACTS Contributors: Erick M. Carreira, Nikolas Huwyler
Synfacts 2013, 9(1), 0015
DOI: 10.1055/s-0032-1317855; **Reg-No.:** C02712SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

bromoetherification

ring expansion

lauroxocanes

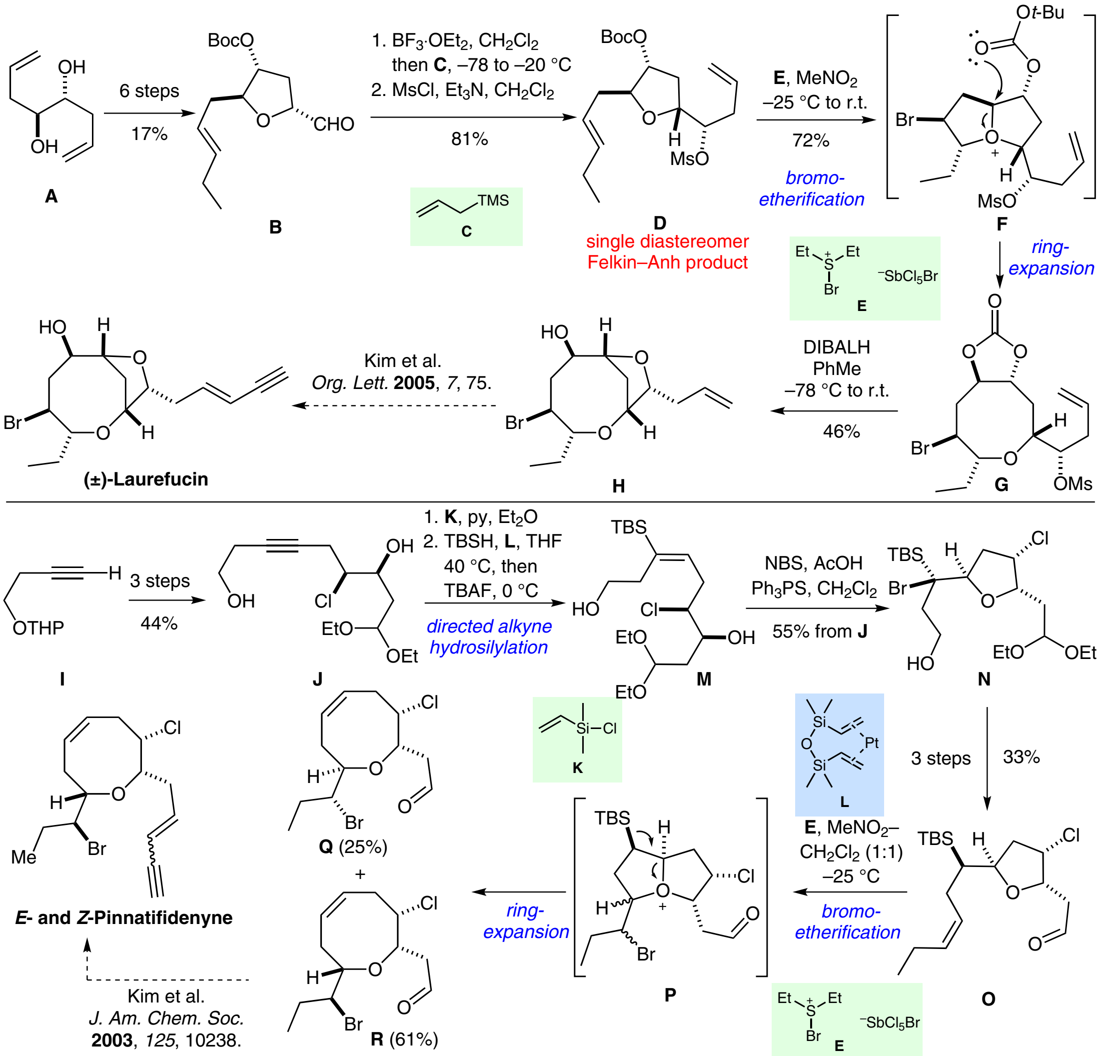
haloethers

S. A. SNYDER,* A. P. BRUCKS, D. S. TREITLER, I. MOGA (COLUMBIA UNIVERSITY, NEW YORK, USA)

Concise Synthetic Approaches for the *Laurencia* Family: Formal Total Syntheses of (±)-Laurefucin and (±)-*E*- and (±)-*Z*-Pinnatifidenyne

J. Am. Chem. Soc. **2012**, *134*, 17714–17721.

Formal Syntheses of (±)-Laurefucin and (±)-*E*- and (±)-*Z*-Pinnatifidenyne



Significance: (±)-Laurefucin and (±)-*E*- and (±)-*Z*-pinnatifidenyne are oxocanes belonging to the class of *Laurencia* haloethers. The authors implement a previously developed bromoetherification–ring-expansion sequence to obtain the stereochemically rich medium-sized rings present in the natural products.

Comment: Treatment of highly functionalized tetrahydrofuran substrates **D** and **O** with bromonium source **E**, induces a haloetherification giving oxonium intermediates **F** and **P**. Subsequent intramolecular trapping by an internal nucleophile provides previously reported cyclic ethers **G** and **R**.

SYNFACTS Contributors: Erick M. Carreira, Julian Egger
Synfacts 2013, 9(1), 0016

DOI: 10.1055/s-0032-1317851; **Reg-No.:** C02312SF

P. JAKUBEC, A. HAWKINS, W. FELZMANN, D. J. DIXON* (UNIVERSITY OF OXFORD, UK)
Total Synthesis of Manzamine A and Related Alkaloids
J. Am. Chem. Soc. **2012**, *134*, 17482–17485.

Category

Synthesis of Natural Products and Potential Drugs

Key words

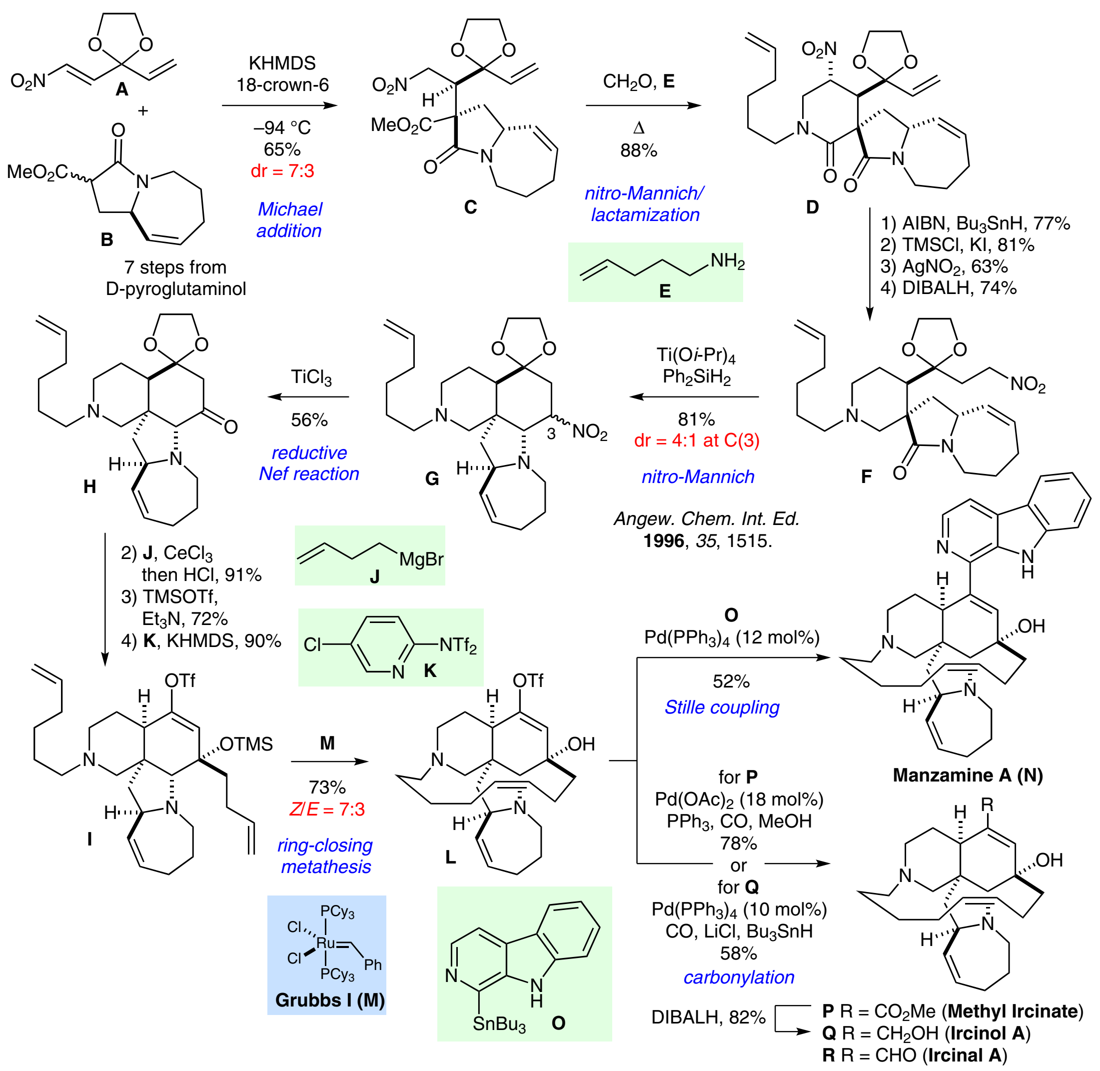
nitro-Mannich reaction

ring-closing metathesis

Michael addition

alkaloids

Total Synthesis of Manzamine A and Related Alkaloids



Significance: Manzamine A (**N**) is a highly structurally complex alkaloid with a wide range of biological activities. The total synthesis reported is the shortest to date, accessing manzamine A (**N**) in 20 linear steps from commercially available starting materials. The key feature of the synthesis is the use of nitro groups as handles to construct two rings of the manzamine core by nitro-Mannich reactions.

Comment: The total synthesis of manzamine A (**N**) starts with a Michael addition onto nitroolefin **A**. A series of two nitro-Mannich reactions delivers **I**, which undergoes ring-closing metathesis to construct the 13-membered ring incorporating a *Z*-double bond. Palladium-catalyzed coupling reactions on vinyl triflate **L** produce manzamine A (**N**) or the related alkaloids **P**–**Q**, alternatively.

SYNFACTS Contributors: Erick M. Carreira, Stefan Diethelm
Synfacts 2013, 9(1), 0017 Published online: 17.12.2012
DOI: 10.1055/s-0032-1317852; **Reg-No.:** C02412SF