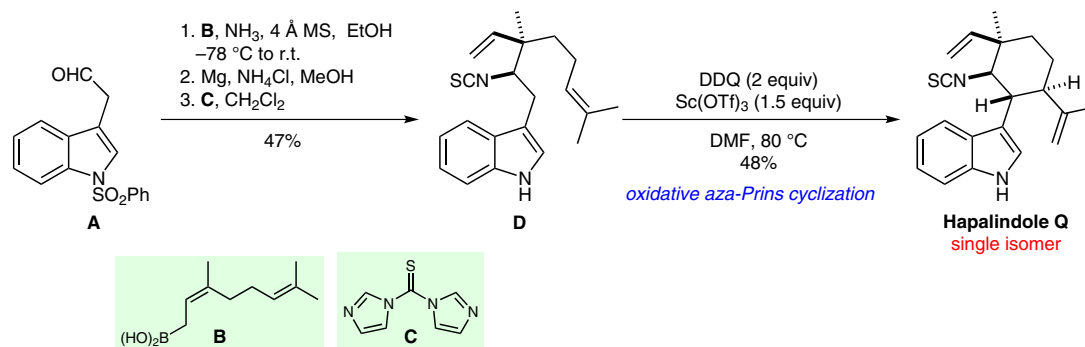
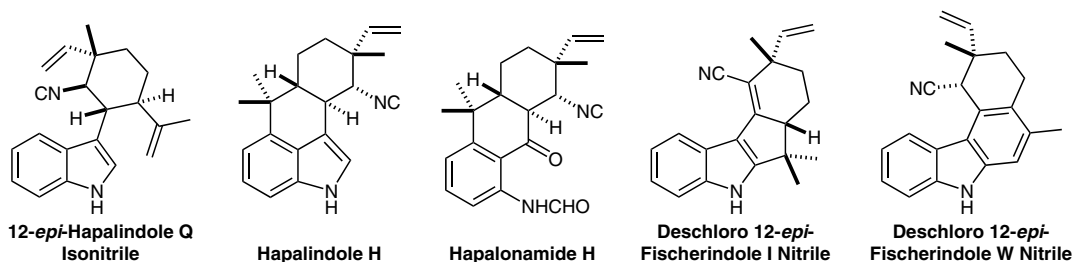


Syntheses of Hapalindole-Type Alkaloids



Other alkaloids successfully synthesized with the same strategy:

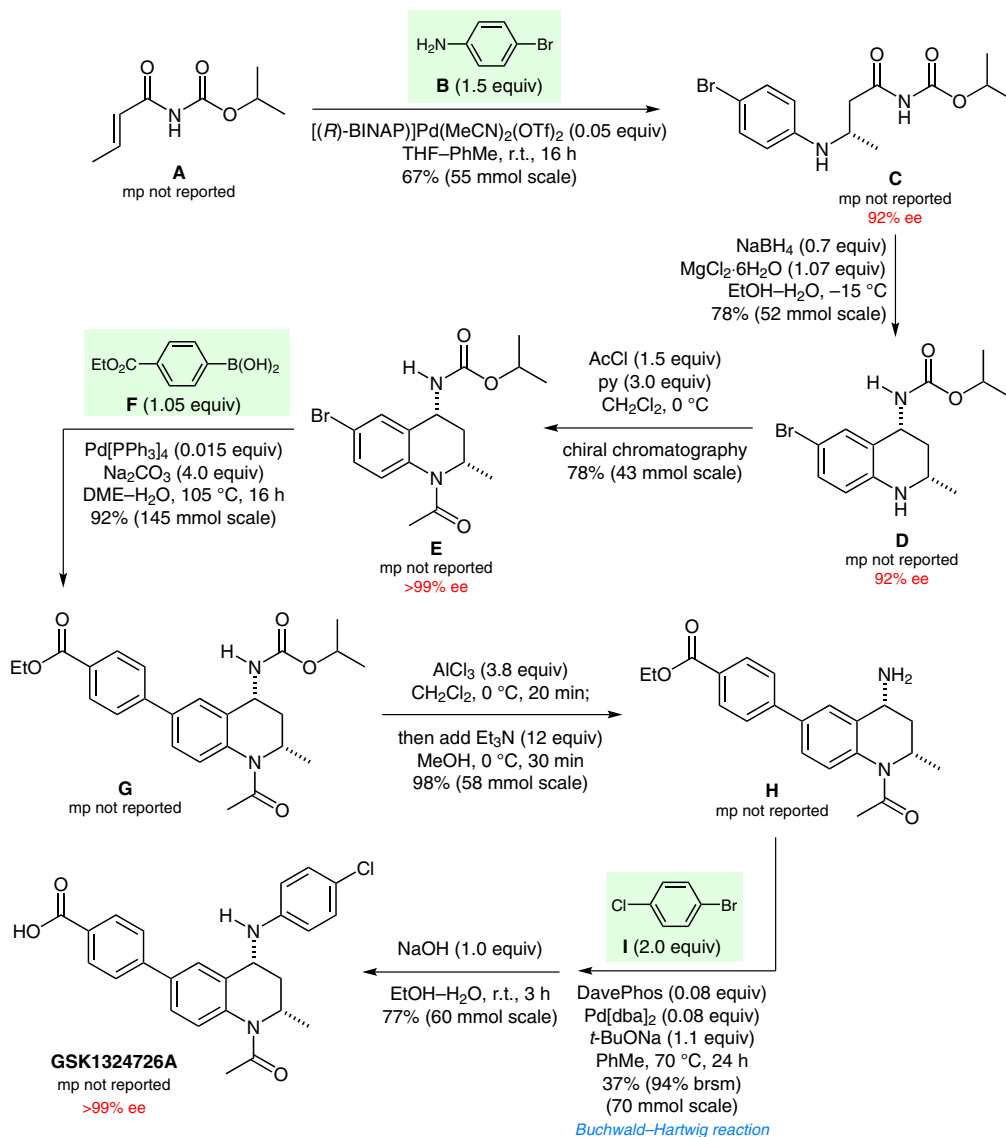


Significance: Members of the hapalindole alkaloid family have attracted considerable attention from the synthetic community due to their intriguing molecular architectures. In 1994, Moore et al. proposed that the biosynthesis of these alkaloids involves a cationic cyclization sequence to form the highly substituted cyclohexane. Inspired by this hypothesis, Li and co-workers report their successful implementation of such a strategy to access several hapalindole-type natural products.

Comment: Cyclization precursor **D** was obtained by a three-step sequence from indole **A** by allylation of an in situ generated imine. When **D** was subjected to oxidative conditions under Lewis acid activation with scandium(III) triflate, an oxidative aza-Prins cyclization yielded hapalindole **Q** in 48% yield as the only isomer. Similarly, five other naturally occurring alkaloids of this family were synthesized by application of this elegant strategy.

P. BAMBOROUGH,* R. K. PRINJHA* ET AL. (GLAXOSMITHKLINE R&D, VILLEBON-SUR-YVETTE, FRANCE AND STEVENAGE, UK)
The Discovery of I-BET726 (GSK1324726A), a Potent Tetrahydroquinoline ApoA1 Up-Regulator and Selective BET Bromodomain Inhibitor
J. Med. Chem. **2014**, *57*, 8111–8131.

Synthesis of GSK1324726A



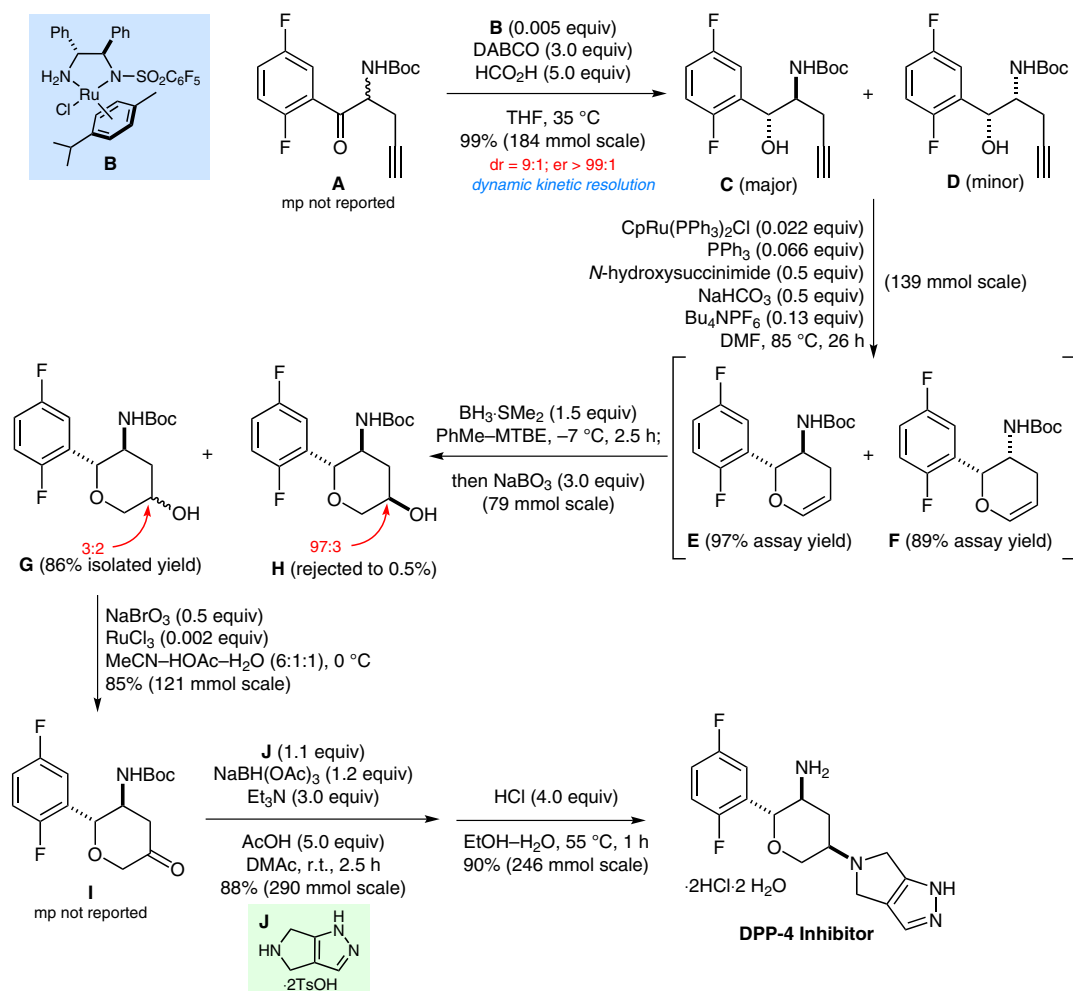
Significance: The BET family of bromodomain-containing proteins regulates expression of multiple genes including those involved in tumor cell growth and inflammation. GSK132476A is a BET bromodomain inhibitor that displays significant antiproliferative and anti-inflammatory effects.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2015, 11(1), 0002 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379642; **Reg-No.:** K05614SF

Comment: Key steps in the synthesis depicted are (1) the Pd-catalyzed asymmetric aza–Michael addition of 4-bromoaniline to (*E*)-isopropyl but-2-enoyl-carbamate (**A**) and (2) a diastereoselective cyclization of an immonium ion generated by reduction of **C** to generate the tetrahydroisoquinoline **D**.

F. XU,* M. J. ZACUTO,* Y. KOHMURA, J. ROSEN, A. GIBB, M. ALAM, J. SCOTT,
D. TSCHAEN (MERCK RESEARCH LABORATORIES, RAHWAY, USA AND MERCK SHARP &
DOHME RESEARCH LABORATORIES HODDESDON, UK)
Asymmetric Synthesis of Highly Functionalized Tetrahydropyran DPP-4 Inhibitor
Org. Lett. **2014**, *16*, 5422–5425.

Asymmetric Synthesis of a DPP-4 Inhibitor



Significance: The target tetrahydropyran DPP-4 inhibitor was of interest for the treatment of type 2 diabetes. The synthesis depicted features three tandem ruthenium-catalyzed reactions: (1) an asymmetric transfer hydrogenation of ketone **A** with dynamic kinetic resolution (2) a cycloisomerization to form a dihydropyran ring and (3) an oxidation. The overall yield of the synthesis is 25%.

Comment: Extensive optimization of the asymmetric transfer hydrogenation established that significant contributors to the yield, dr and er included the use of the pentafluoro-substituted DAIPEN catalyst **B**, DABCO as the base and THF as the solvent. The reductive amination of ketone **I** with NaBH(OAc)₃ dramatically improved (dr = 19:1) using DMAc as solvent when the bis(tosylate) salt **J** was neutralized with Et₃N followed by pH buffering with HOAc.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2015, 11(1), 0003 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379643; Reg-No.: K05714SF

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Category

Synthesis of Natural Products and Potential Drugs

Key words

DPP-4 inhibitors

asymmetric transfer hydrogenation

dynamic kinetic resolution

cycloisomerization

reductive amination

SYNFACTS
of the month

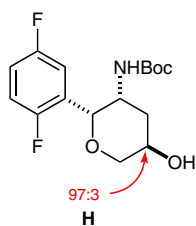
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Erratum

Asymmetric Synthesis of a DPP-4 Inhibitor

F. Xu,* M. J. Zacuto,* Y. Kohmura, J. Rosen, A. Gibb, M. Alam, J. Scott, D. Tschäen *Synfacts* **2015**, *11*, 3.

The NHBoc group of compound **H** should be pointing down. The correct structure is shown below. We apologize for this error.

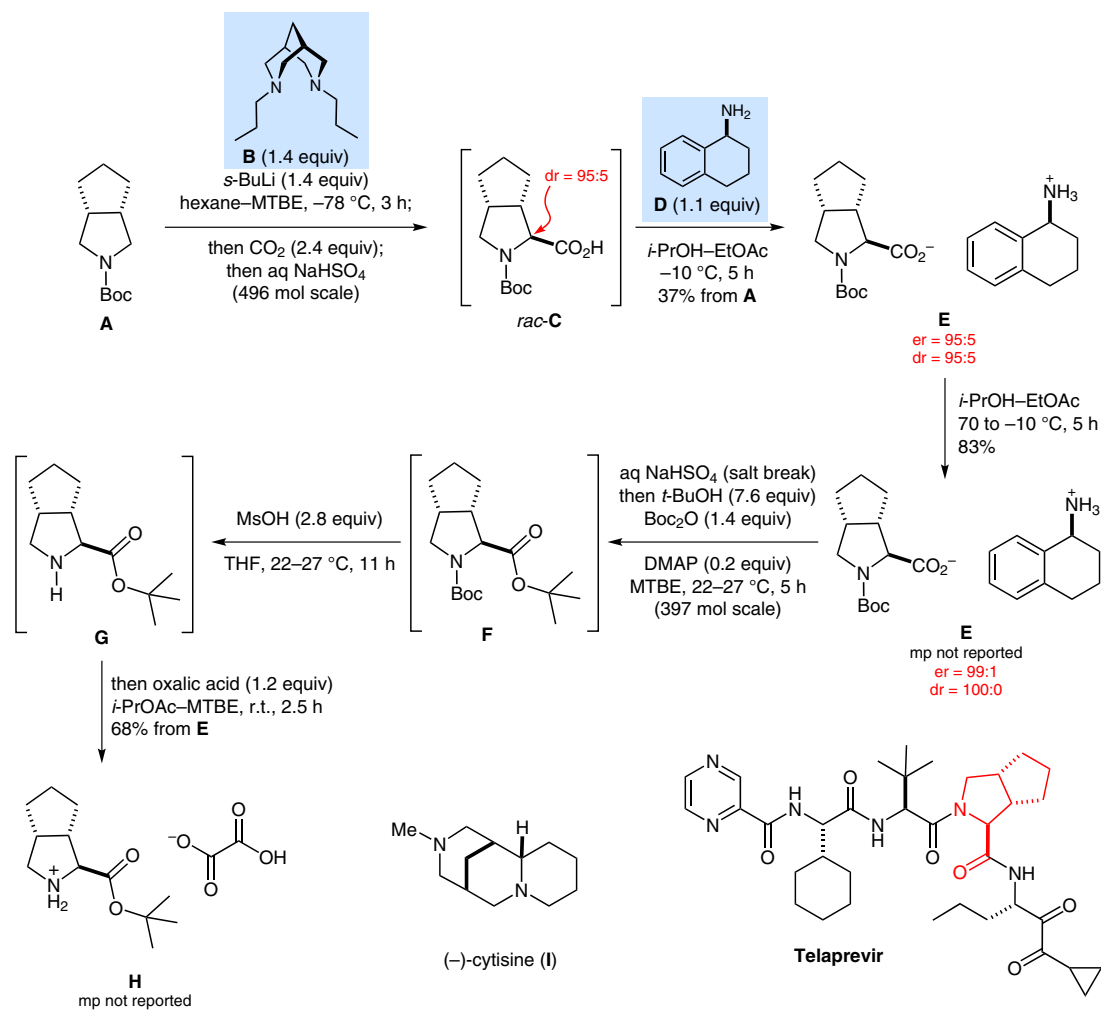


G. J. TANOURY,* M. CHEN, Y. DONG, R. FORSLUND, V. JURKAUSKAS, A. D. JONES,
D. BELMONT (VERTEX PHARMACEUTICALS, BOSTON, USA)

Stereoselective Lithiation and Carboxylation of Boc-Protected Bicyclopyrrolidine: Synthesis of a Key Building Block for HCV Protease Inhibitor Telaprevir

Org. Process Res. Dev. **2014**, *18*, 1234–1244.

Synthesis of a Key Building Block for HCV Protease Inhibitor Telaprevir



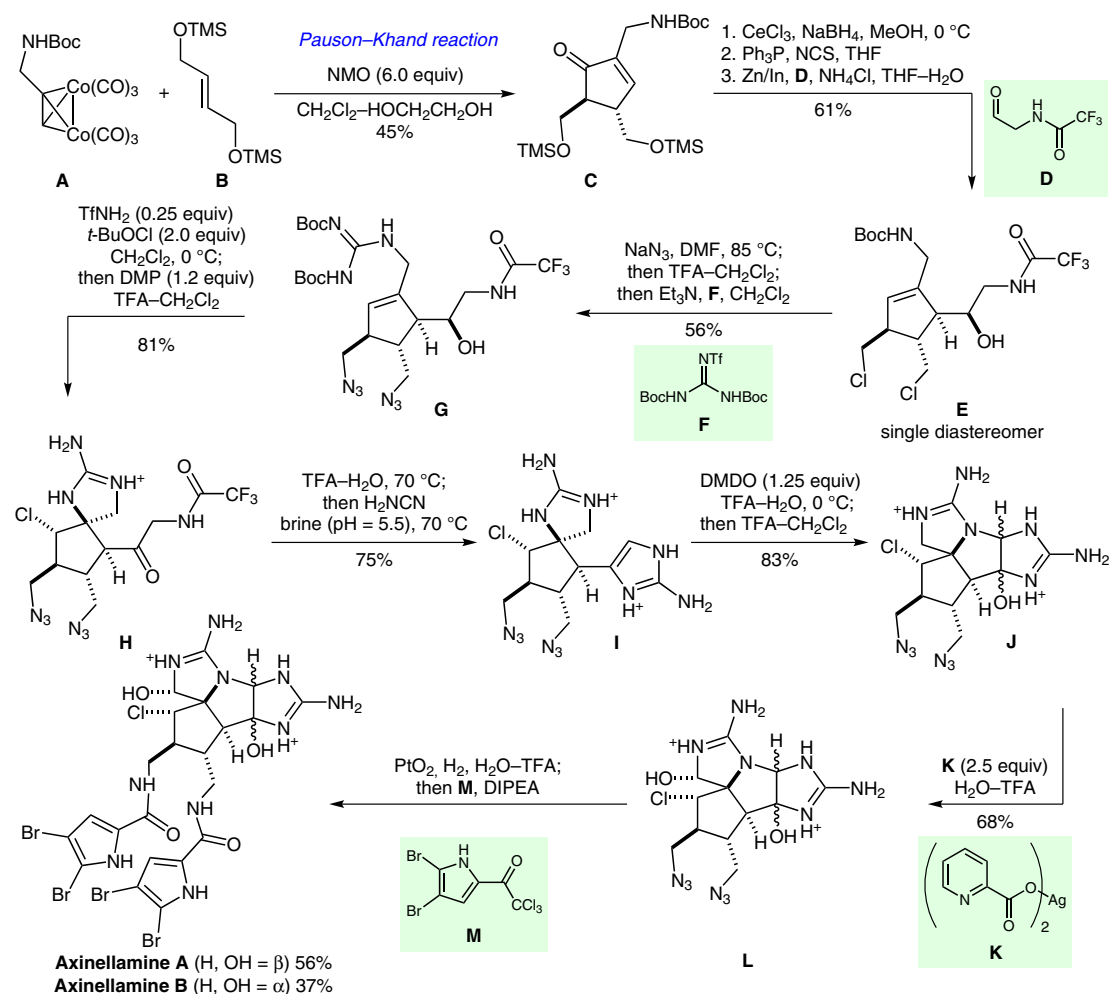
Significance: The target molecule **H** is a fragment of the HCV protease inhibitor telaprevir. A large-scale process for the synthesis of **H** entails a stereoselective lithiation–carboxylation of **A** to give *rac*-**C** followed by a resolution with (S)-1,2,3,4-tetrahydronaphthalen-1-amine (**D**). Two hundred kilograms of the target molecule **H** were manufactured in 27% overall yield by this route.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2015, 11(1), 0004 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379645; **Reg-No.:** K05914SF

Comment: An enantioselective synthesis of **C** via asymmetric lithiation–carboxylation using a variety of chiral diamine ligands was also investigated. For example the chiral diamine ligand (–)-cystisine developed by O’Brien and co-workers (*J. Am. Chem. Soc.* **2002**, *124*, 11870) provided *ent*-**C** in 44% yield and er > 99:1 after crystallization. However, this route was not pursued owing to the high cost and uncertain supply of (–)-cystisine.

R. A. RODRIGUEZ, D. B. STEED, Y. KAWAMATA, S. SU, P. A. SMITH, T. C. STEED, F. E. ROMESBERG,* P. S. BARAN* (THE SCRIPPS RESEARCH INSTITUTE, LA JOLLA, RQX PHARMACEUTICALS, LA JOLLA, AND UNIVERSITY OF CALIFORNIA, SAN DIEGO, USA)
Axinellamines as Broad-Spectrum Antibacterial Agents: Scalable Synthesis and Biology
J. Am. Chem. Soc. **2014**, *136*, 15403–15413.

Synthesis and Biology of Axinellamines A and B



Significance: Pyrrole-imidazole alkaloids are a class of complex natural products with intriguing biological activities, isolated from marine sponges. The authors present a full account of their synthetic efforts to derive substantial quantities of racemic axinellamines A and B. In addition, valuable follow-up biological studies showing antibiotic activity against Gram-positive and -negative bacteria are presented.

SYNFACTS Contributors: Erick M. Carreira, Matthias Westphal
Synfacts 2015, 11(1), 0005 Published online: 15.12.2014

DOI: 10.1055/s-0034-1379679; **Reg-No.:** C07714SF

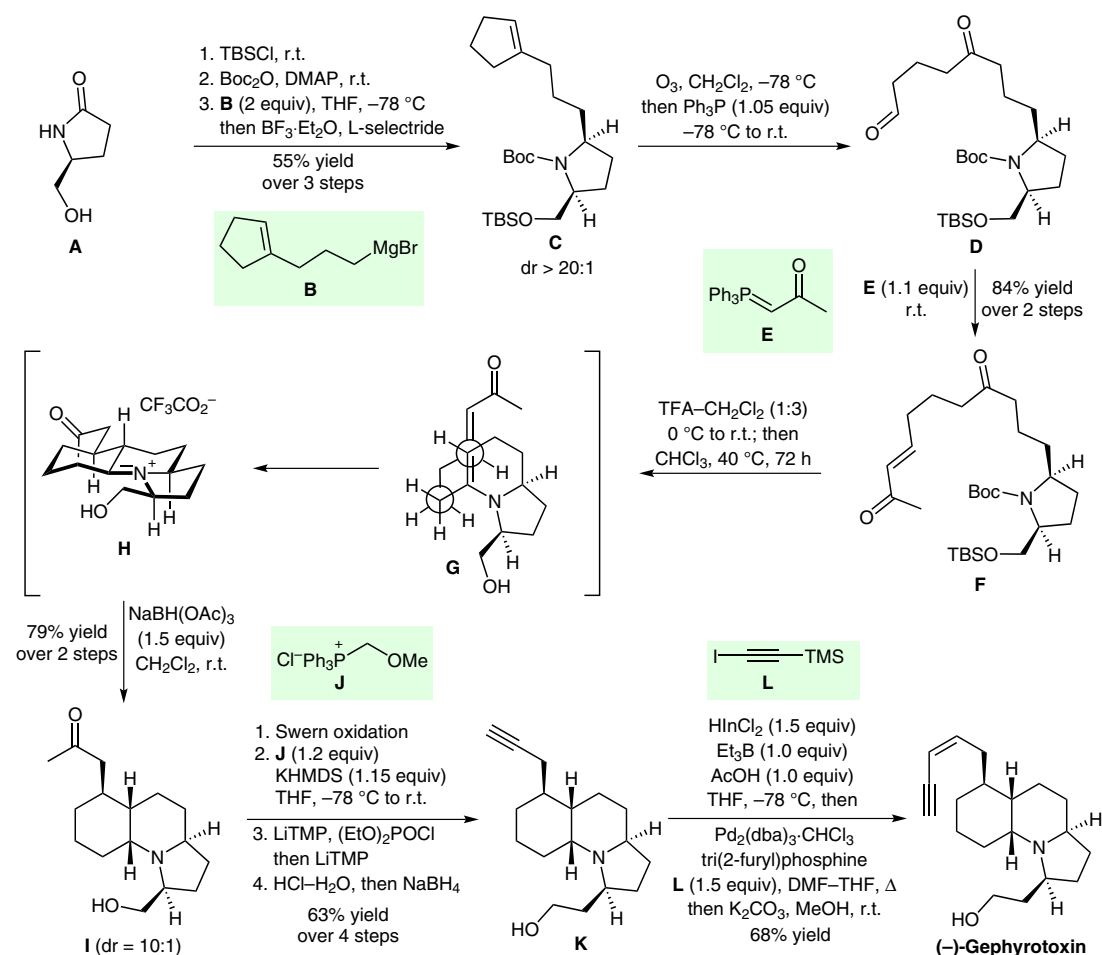
Comment: The authors disclose details of recent work directed towards the efficient synthesis of axinellamines A and B (*J. Am. Chem. Soc.* **2011**, *133*, 13922). A Pauson-Khand reaction afforded cyclopentene **C**, which could be efficiently converted into diazide **G**. Oxidative cyclization, deprotection, and imidazole formation followed by a dihydroxylation-dehydration sequence led to **J**. Silver(II)-mediated oxidation, azide reduction, and amidation afforded the two targets.

S. CHU, S. WALLACE, M. D. SMITH* (UNIVERSITY OF OXFORD, UK)

A Cascade Strategy Enables a Total Synthesis of (–)-Gephyrotoxin

Angew. Chem. Int. Ed. **2014**, *53*, 13826–13829.

Total Synthesis of (–)-Gephyrotoxin



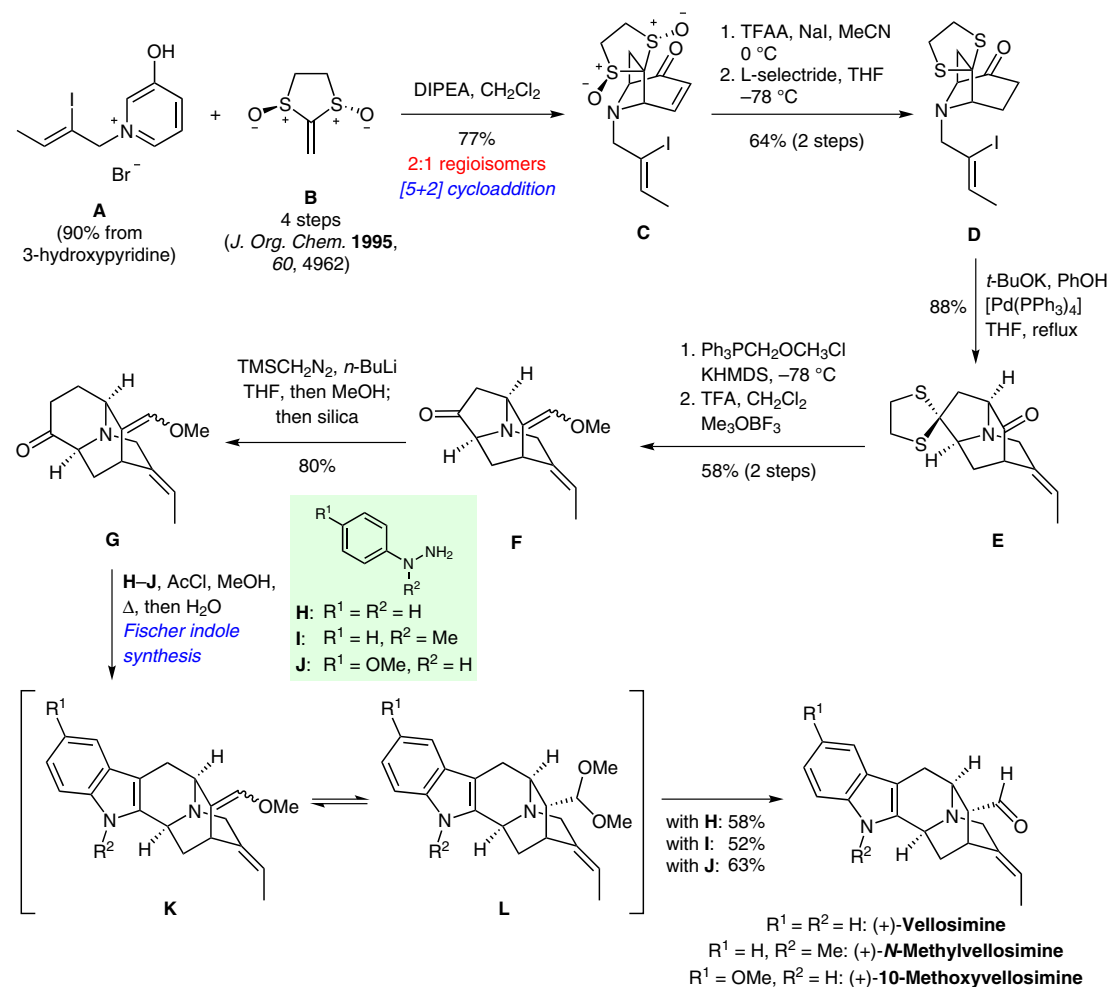
Significance: Gephyrotoxin is a relatively non-toxic dendrobatid alkaloid with an unusual neurological profile. Its properties and complex structure have made it the subject of numerous synthetic studies. Total syntheses have been reported by Kishi, Hart, Overman, as well as Sato and Chida, and a number of formal syntheses have been described. Smith and co-workers now report an elegant and concise synthesis of gephyrotoxin that relies on an intramolecular enamine/Michael cascade to access the tricyclic scaffold of the natural product.

Comment: The synthesis commenced with L-pyrroglutaminol (**A**), which was converted into key intermediate **F** in five simple steps. Deprotection of **F** was achieved by treatment with TFA, and warming to 40 °C in chloroform led to formation of iminium salt **H**, which in turn underwent hydroxyl-directed reduction to give **I** in 79% yield. A few functional-group interconversions then led to **K**. Cross-coupling with alkyne **L** followed by deprotection furnished synthetic gephyrotoxin.

SYNFACTS Contributors: Erick M. Carreira, Simon Krautwald
Synfacts 2015, 11(1), 0006 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379676; **Reg-No.:** C07414SF

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Synthesis of Sarpagine Alkaloids



Significance: The authors report the enantioselective total synthesis of three sarpagine indole alkaloids which were isolated from the plant family *Apocynaceae*. The route relies on a common intermediate **G**, which is impressively accessed using key features such as a [5+2] oxidopyridinium cycloaddition and a ring expansion. The three natural products were synthesized in only eight steps starting from known materials (12 steps from commercially available compounds).

Comment: The synthesis commenced with a [5+2] cycloaddition between oxidopyridinium salt **A** and Aggarwal's chiral ketene equivalent **B**, thus yielding the desired regioisomer **C** in a 2:1 ratio. Next, ketone **G** was accessed through an intramolecular palladium-catalyzed enolate coupling of **D**, followed by Wittig reaction, deprotection of the dithiolane, and ring expansion. The indole was introduced in the last step by a Fischer indole synthesis using phenylhydrazines with different substitution patterns to afford the three targets.

rasagiline

monoamine oxidase B inhibitors

dynamic kinetic resolution

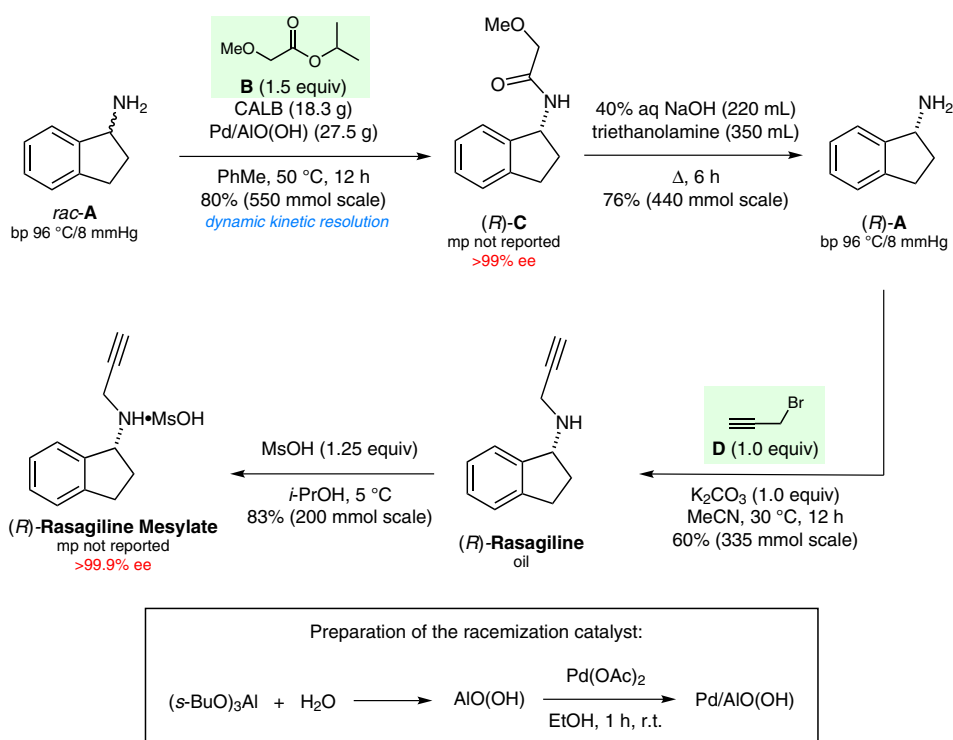
racemization

Candida antarctica lipase B

hydrogen borrowing

G. MA, Z. XU, P. ZHANG, J. LIU, X. HAO, J. OUYANG, P. LIANG, S. YOU,* X. JIA*
 (SHENYANG PHARMACEUTICAL UNIVERSITY, P. R. OF CHINA)
 Novel Synthesis of Rasagiline via a Chemoenzymatic Dynamic Kinetic Resolution
Org. Process Res. Dev. **2014**, *18*, 1169–1174.

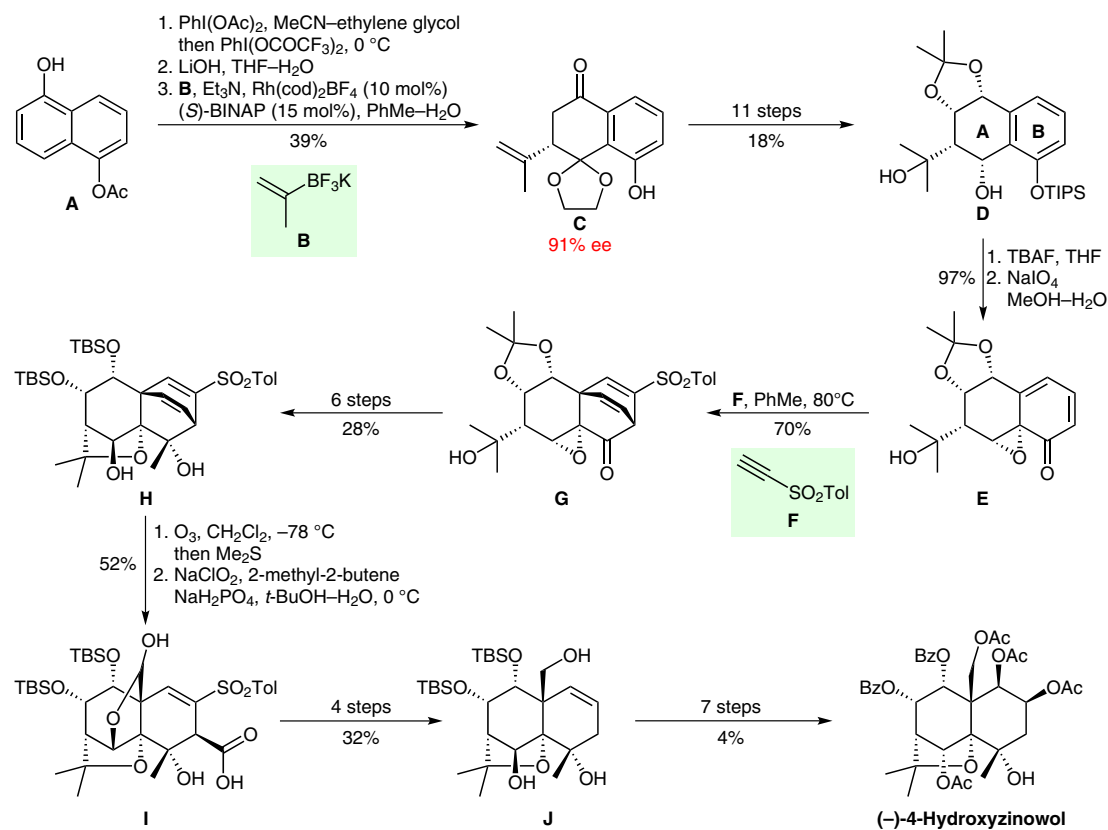
Synthesis of (*R*)-Rasagiline via Dynamic Kinetic Resolution



Significance: Rasagiline mesylate (Azilect®) is a selective monoamine oxidase B inhibitor that is administered as initial monotherapy in early Parkinson's disease and as adjunct therapy to levodopa in moderate-to-advanced disease. The key step in the synthesis depicted is the dynamic kinetic resolution of racemic 1-aminoindan **A** catalyzed by immobilized *Candida antarctica* lipase B (CALB) together with a palladium racemization catalyst – a process that could be conducted in a concentration of up to 200 g/L.

Comment: The palladium nanocatalyst Pd/AIO(OH) racemizes the amine via an imine intermediate (hydrogen borrowing). Racemization was complete in four hours using only 0.5 mol% of palladium in toluene at 70 °C. The catalyst was prepared as palladium nanoparticles entrapped in aluminum hydroxide according to the procedure of Y. Kim et al. (*Tetrahedron Lett.* **2010**, *51*, 5581). The chemoenzymatic catalyst system could be recycled 5–6 times.

Synthesis of (-)-4-Hydroxyzinowol



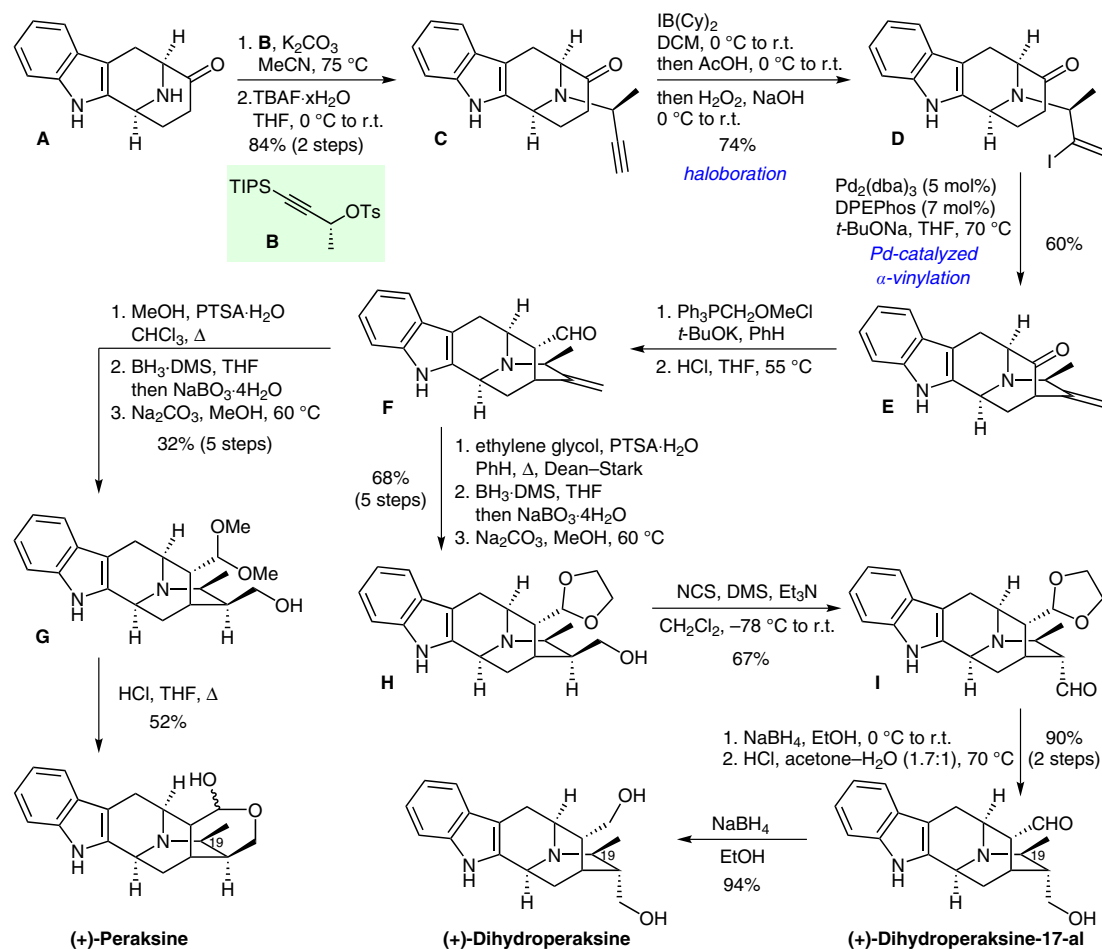
Significance: 4-Hydroxyzinowol is a highly oxidized sesquiterpenoid of the dihydro- β -agarfuran family. Following its isolation from the plant *zino-wiewia Costaricensis*, it was found to be a potent inhibitor of a daunorubicin related MDR transporter. Thus, 4-hydroxyzinowol is considered to be a potential lead structure for the treatment of cancers with acquired multi-drug resistance. In this work, the authors disclose the first total synthesis of this promising natural product.

Comment: Starting from naphthol **A**, oxidative dearomatization and asymmetric 1,4-addition of tetrafluoroborate **B** gave phenol **C** with good enantioselectivity. Further steps completed the oxidation state adjustment of the A-ring in **D** to set the stage for another oxidative dearomatization to yield epoxide **E**. Finally, Diels–Alder reaction followed by ozonolysis of the more electron-rich double bond in diene **H** gave **I**, which was transformed into 4-hydroxyzinowol in eleven additional steps.

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

General Strategy for Synthesis of C-19 Methyl-Substituted *Sarpagine/Macroline/Ajmaline* Indole Alkaloids Including Total Synthesis of 19(*S*),20(*R*)-Dihydroperaksine, 19(*S*),20(*R*)-Dihydroperaksine-17-al, and Peraksine *J. Org. Chem.* **2014**, *79*, 10030–10048.

Total Synthesis of (+)-Dihydroperaksine-17-al, (+)-Dihydroperaksine, and (+)-Peraksine

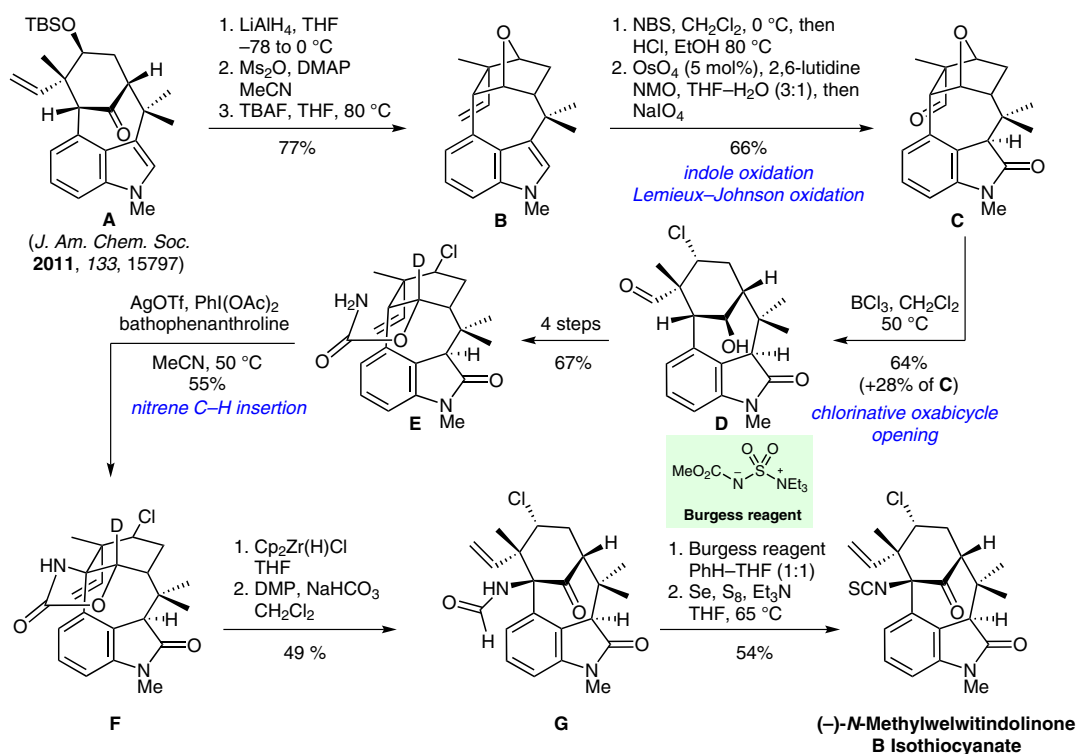


Significance: The sarpagine alkaloids (+)-19(*S*),20(*R*)-dihydroperaksine-17-al, (+)-19(*S*),20(*R*)-dihydroperaksine (both isolated from *Rauwolfia serpentina*) and (+)-peraksine (isolated from *Rauwolfia perakensis*) have in common the structural feature of a β -methyl group at C-19. Cook and co-workers report the first enantio- and stereospecific synthesis of all three alkaloids.

Comment: After introduction of the chiral methyl group by N-alkylation, the pentacyclic core was formed by haloboration followed by a palladium-catalyzed intramolecular α -vinylation of the ketone. Common intermediate **F** was then converted into (+)-peraksine, (+)-dihydroperaksine-17-al, and (+)-dihydroperaksine by a specific acetal protection and hydroboration–oxidation sequence.

SYNFACTS Contributors: Erick M. Carreira, Adrien Joliton
Synfacts 2015, 11(1), 0010 Published online: 15.12.2014
DOI: 10.1055/s-0034-1379677; **Reg-No.:** C07514SF

Synthesis of (–)-*N*-Methylwelwitindolinone B Isothiocyanate



Significance: The family of the welwitindolinone natural products represents a formidable challenge for synthetic chemists. Structurally, the majority of these molecules consist of an indolinone imbedded into a [4.3.1]bicycle. While several efforts towards the synthesis of congeners have been reported to date, the challenge of (–)-*N*-methylwelwitindolinone B isothiocyanate has not been met. This compound is unique due to the alkyl chloride, which has been found to undergo various side reactions. The approach presented by Garg and co-workers relies on a chlorinative oxabicyclic ring opening culminating in the first total synthesis of the target molecule.

Comment: The synthesis commenced with ketone **A**, which was generated using an elegant indoline cyclization (*J. Am. Chem. Soc.* **2011**, *133*, 15797; *Synfacts* **2011**, *7*, 1281). Diastereoselective reduction, followed by ring closure, generated oxabicycle **B**. The subsequent BCl_3 -mediated chlorinative ring opening proved to be efficient only when the vinyl group was first converted into an aldehyde. Carbamate **E**, obtained in a few steps, underwent nitrene C–H insertion under conditions previously reported. Finally, carbamate cleavage, oxidation, dehydration, and sulfurization delivered (–)-*N*-methylwelwitindolinone B isothiocyanate.