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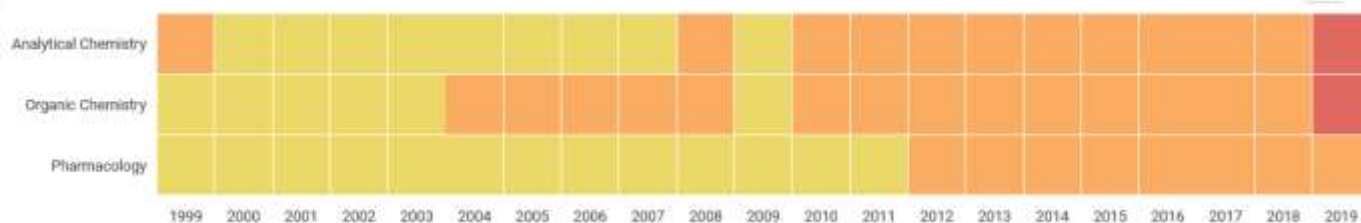
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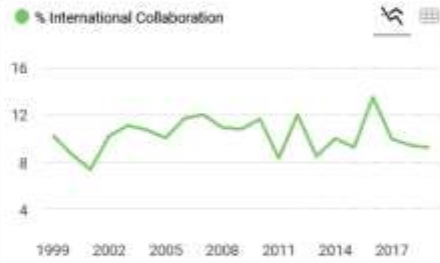
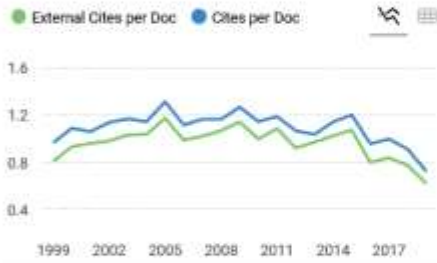
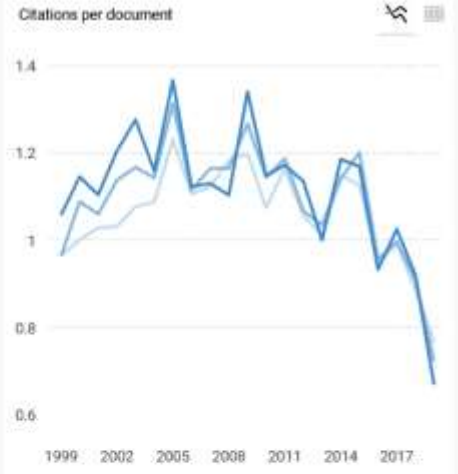
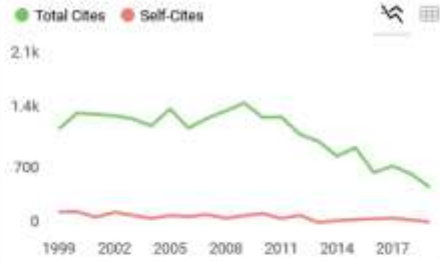
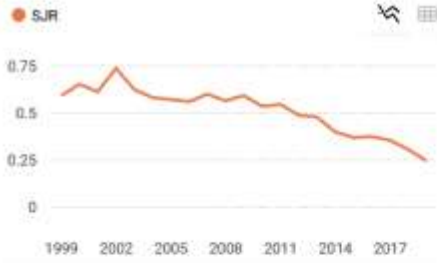
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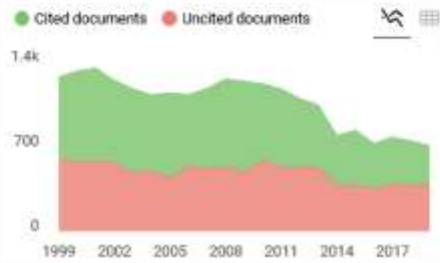
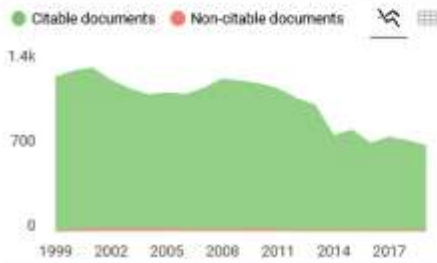
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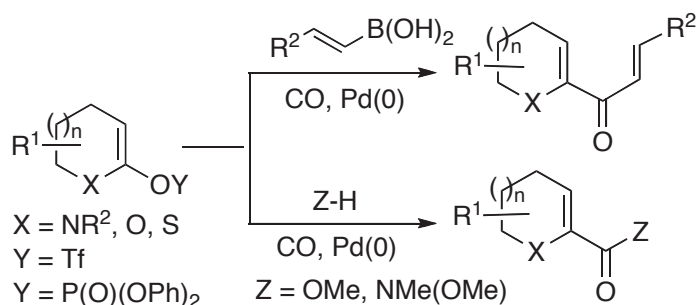
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## ■ REVIEWS

- 697 **Carbonylative Palladium-Catalyzed Reactions of Lactam-, Lactone-, and Thiolactone-Derived Vinyl Triflates and Phosphates for the Synthesis of *N*-, *O*-, and *S*-Heterocycles**

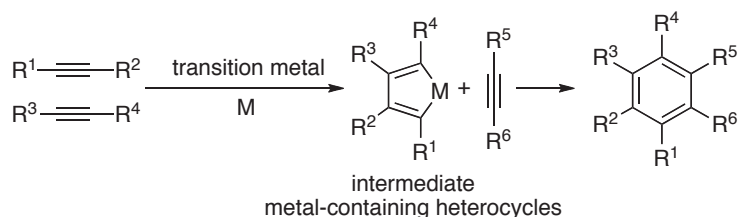
Ernesto G. Occhiato,\* Dina Scarpi, and Cristina Prandi\*



Palladium Carbonylation Coupling Reaction Boronic Acid Nazarov Reaction

- 725 **Recent Development for Formation of Aromatic Compounds *via* Metallacyclopentadienes as Metal-Containing Heterocycles**

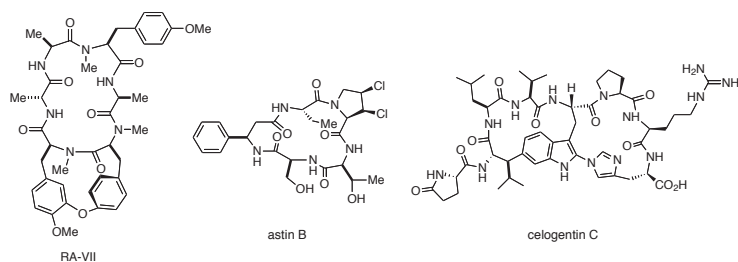
Lishan Zhou, Shi Li, Ken-ichiro Kanno, and Tamotsu Takahashi\*



Aromatic Compound Intermolecular Coupling Reaction Alkyne Metallacyclopentadiene Selectivity

- 739 **Bioactive Cyclic Peptides from Higher Plants**

Hiroshi Morita\* and Koichi Takeya

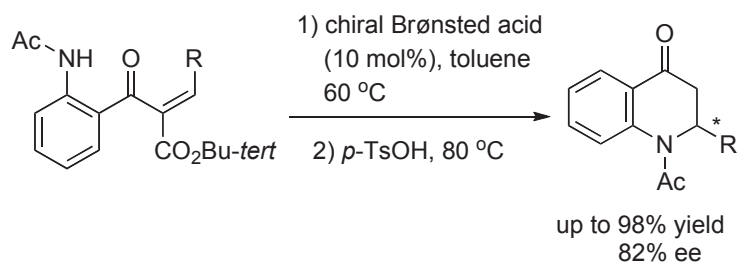


Cyclic Peptide Cyclopeptide Higher Plant

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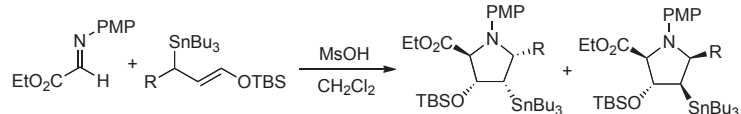
Zhen Feng, Qing-Long Xu, Li-Xin Dai, and Shu-Li You\*



Asymmetric Catalysis *N*-Triflylphosphoramidate Enantioselectivity Michael Addition Organocatalysis

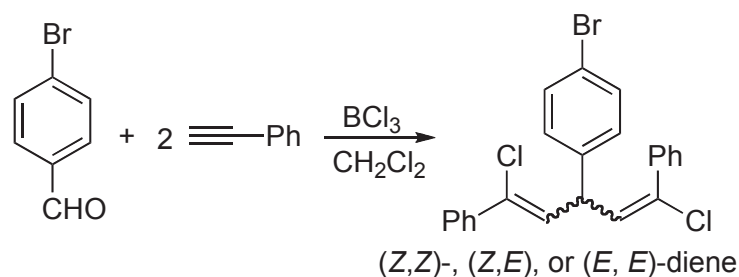
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Makoto Shimizu,\* Hiromi Ando, Hitoshi Shibuya, and Iwao Hachiya


 Pyrrolidine-2-carboxylate    Cyclization    Allylstannane     $\alpha$ -Iminoacetate    Methanesulfonic Acid

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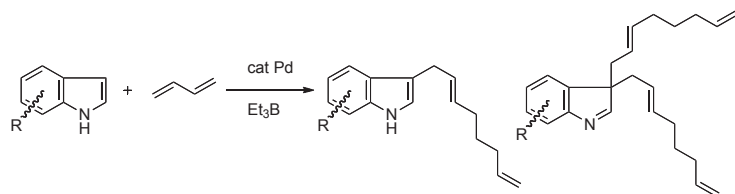
Min-Liang Yao, Michael P. Quinn, and George W. Kabalka\*



Boron Halide    Diene    Aldehyde Reaction    Synthesis

**787 Allylic Alkylation of Indoles with Butadiene Promoted by Palladium Catalyst and Triethylborane**

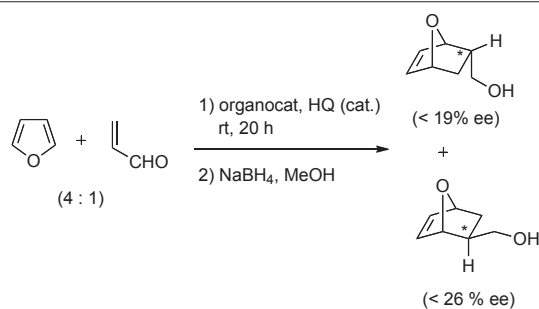
Masanari Kimura,\* Katsumi Tohyama, Yumi Yamaguchi, and Tomohiko Kohno



Indole    Butadiene    Palladium    Triethylborane    Allylation

**799 Organocatalytic Asymmetric Diels-Alder Reaction of Furan under High Pressure**

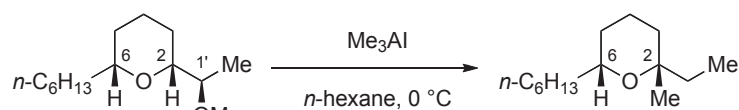
Akiko Mimoto, Keiji Nakano, Yoshiyasu Ichikawa, and Hiyoshizo Kotsuki\*



Organocatalyst    Asymmetric Diels-Alder Reaction    Furan    Acrolein    High Pressure Reaction

**805 Methyl Insertion Reactions of Tetrahydropyrans Having a C1'-Mesyloxy Group on the C2-Side Chain with Trimethylaluminum**

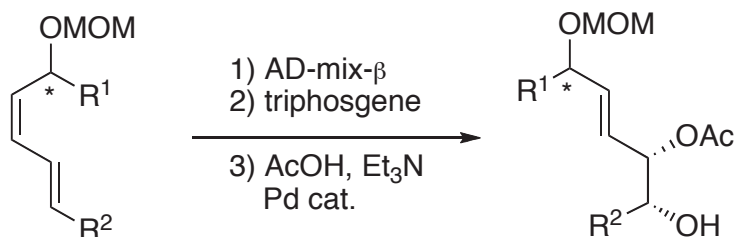
Keigo Nakamura, Atsushi Kimishima, and Tadashi Nakata\*



Trimethylaluminum    Tetrahydropyran    Methyl Insertion    Antiperiplanar    1,2-Hydride Shift

**811 Synthesis of the 1,2-Anti Type of 3*E*-Alkene-1,2,5-triol Derivatives**

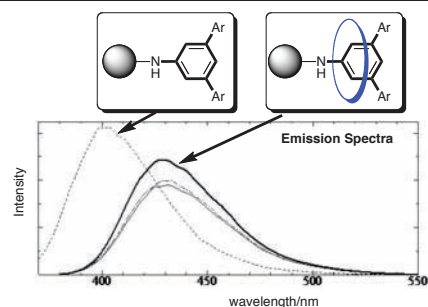
Yuichi Kobayashi,\* Akira Takeuchi, and Hatsuhiko Hattori



Borate    Boronate Ester    Nickel    Palladium Catalyzed Reaction    Trioxilin A3

**819 Preparation and Photochemical Properties of [2]Rotaxanes Containing an Aniline Moiety Encapsulated by Crown Ethers**

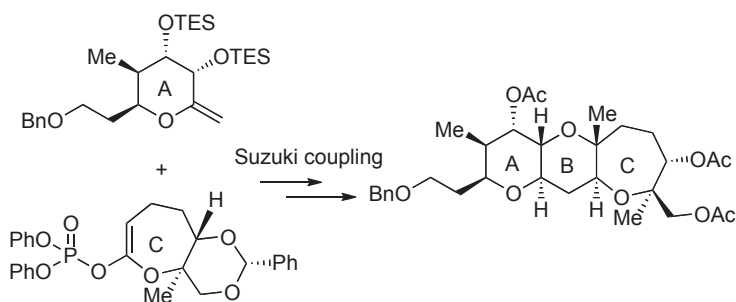
Yuji Tokunaga,\* Satoshi Nakashima, Takuya Iwamoto, Kei Gambayashi, Kenji Hisada, and Tomonori Hoshi



Rotaxane    Aniline    Crown Ether    UV-VIS and Emission Spectra

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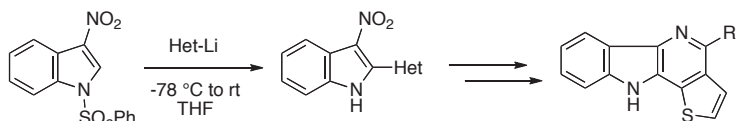
Naohito Ohtani, Ryosuke Tsutsumi, Takefumi Kuranaga, Tomohiro Shirai, Jeffrey L. C. Wright, Daniel G. Baden, Masayuki Satake,\* and Kazuo Tachibana\*



Suzuki-Miyaura Cross Coupling Reaction    Ketene Acetal Phosphate    Polycyclic Ether

**831 Nucleophilic Addition of Hetarylithium Compounds to 3-Nitro-1-(phenylsulfonyl)indole: Synthesis of Tetracyclic Thieno[3,2-*c*]-5-carbolines**

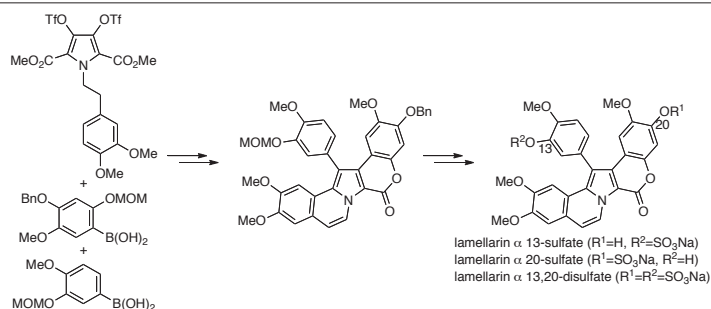
Philip E. Alford, Tara L. S. Kishbaugh, and Gordon W. Gribble\*



3-Nitroindole    Michael Addition    Arylation    Electron-Deficient Indole

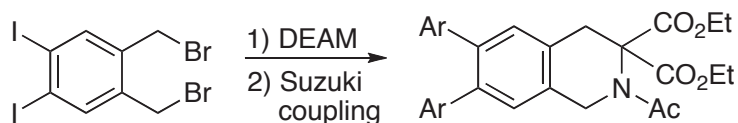
**841 Divergent Synthesis of Lamellarin  $\alpha$  13-Sulfate, 20-Sulfate, and 13,20-Disulfate**

Tsutomu Fukuda, Takeshi Ohta, Sho Saeki, and Masatomo Iwao\*


 Lamellarin  $\alpha$  13-Sulfate    Lamellarin  $\alpha$  20-Sulfate    Lamellarin  $\alpha$  13,20-Disulfate

**847 Diversity-Oriented Approach to 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (Tic) Derivatives Using Diethyl Acetamidomalonate as a Glycine Equivalent: Further Expansion by Suzuki–Miyaura Cross-Coupling Reaction**

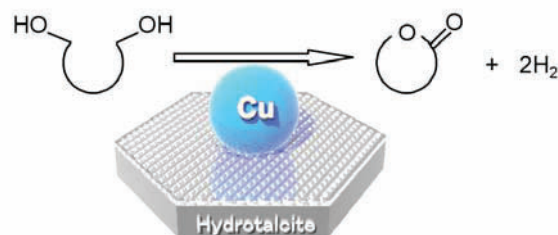
Sambasivarao Kotha,\* Shilpi Misra, Nimita Gopal Krishna, Nagaraju Devunuri, Henning Hopf, and Abhilash Keecherikunnel



Unusual Amino Acid    Building Block Approach    Suzuki Coupling Reaction    Boronic Acid

**855 Oxidant-Free Lactonization of Diols Using a Hydrotalcite-Supported Copper Catalyst**

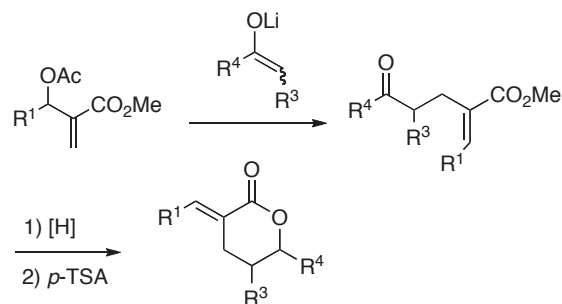
Yusuke Mikami, Kaori Ebata, Takato Mitsudome, Tomoo Mizugaki, Koichiro Jitsukawa, and Kiyotomi Kaneda\*



Copper Nanoparticle    Heterogeneous Catalyst    Dehydrogenation    Lactone

**863 Synthesis of  $\alpha$ -Alkylidene- $\delta$ -valerolactones *via* the Conjugate Addition of Ketone Enolates to Functionalized Allyl Acetates**

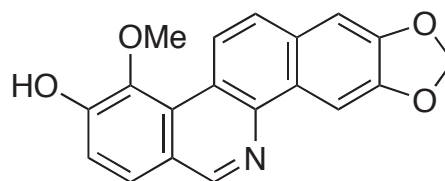
P. Veeraraghavan Ramachandran\* and Annyt Bhattacharyya



Alkylidenevalerolactone    Conjugate Addition    Cyclization    Keto Ester

**873 Synthesis of Zanthoxyline and Its Related Compounds: Revision of the Reported Structure**

Hitoshi Abe,\* Naoko Kobayashi, Yasuo Takeuchi, and Takashi Harayama\*

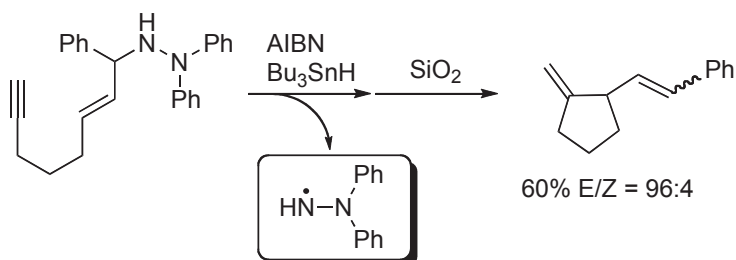


zanthoxyline (reported structure)

Benzo[*d*]phenanthridine    Palladium Catalyzed Reaction    Coupling Reaction

**879 Novel Radical Cyclization Method Accompanied by Elimination of Hydrazyl Radical**

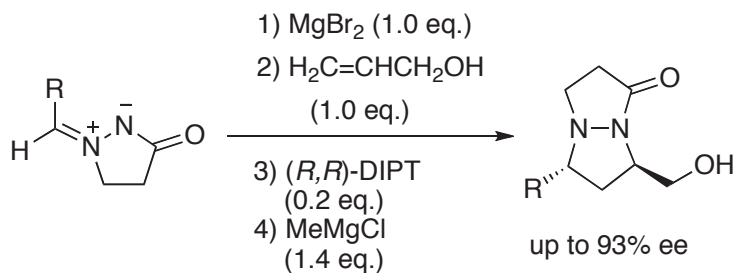
Shoji Kobayashi, Hidefumi Hirao, Tatsuro Kawauchi, and Ilhyong Ryu\*



Hydrazine    Hydrazyl Radical    Vinyl Radical    5-Exo Cyclization    1,4-Diene

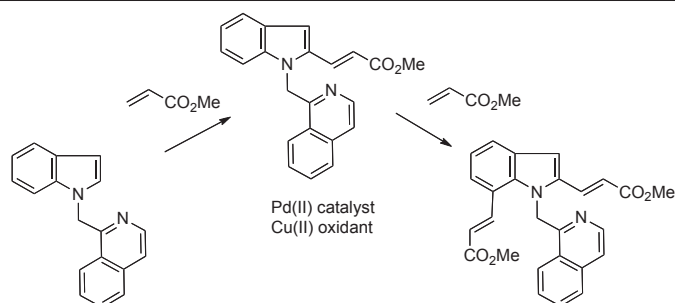
**887 Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines to Allyl Alcohol Utilizing Tartaric Acid Ester as a Chiral Auxiliary**

Katsuyoshi Tanaka, Tomomitsu Kato, Yutaka Ukaji,\* and Katsuhiko Inomata\*


 Enantioselective 1,3-Dipolar Cycloaddition    Azomethine Imine    Optically Active Pyrazolidine    Magnesium Bromide    Diisopropyl  $(R,R)$ -Tartrate

**895 Observation of 2,7-Disubstitution in Palladium Catalyzed Directed C-H Activation of Indoles**

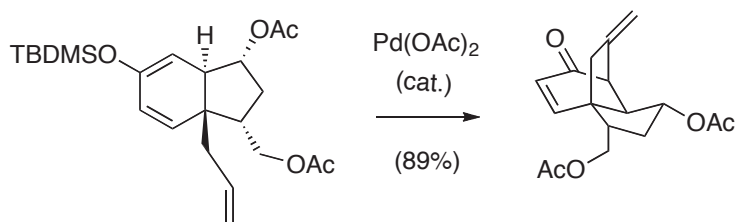
Guilia Fanton, Nicola M. Coles, Andrew R. Cowley, Jonathan P. Flemming, and John M. Brown\*



Palladium (II)    Alkenylation    Indole    Directing Group    X-Ray

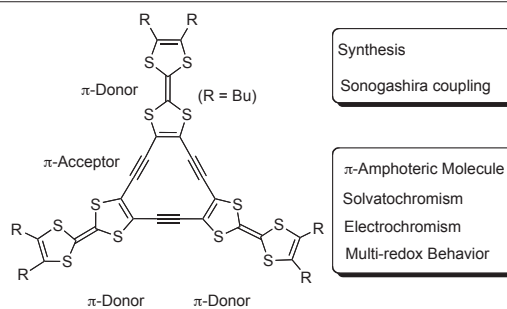
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Akihiro Ishihata, Megumi Saeki, Masaru Watanabe, Masataka Ihara, and Masahiro Toyota\*


 Quadrone    *Aspergillus terreus*    Cycloalkenylation    Palladium Acetate    Intramolecular Michael Addition

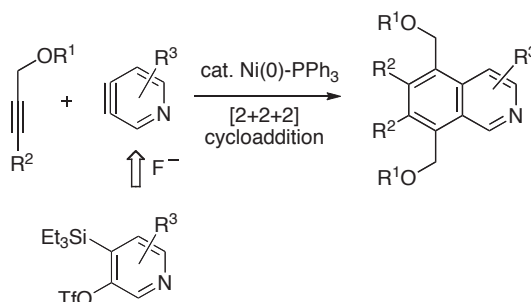
**909 Synthesis and  $\pi$ -Amphoteric Properties of Tris(tetrathiafulvaleno)hexadehydro[12]annulene**

Kenji Hara, Masashi Hasegawa, Yoshiyuki Kuwatani, Hideo Enozawa, and Masahiko Iyoda\*


 Annulene    Cation Radical     $\pi$ - $\pi$  Interaction    Redox Behavior    Tetrathiafulvalene

**917 Synthesis of Substituted Isoquinolines via Nickel-Catalyzed [2+2+2] Cycloaddition of Alkynes and 3,4-Pyridynes**

Toshihiko Iwayama and Yoshihiro Sato\*

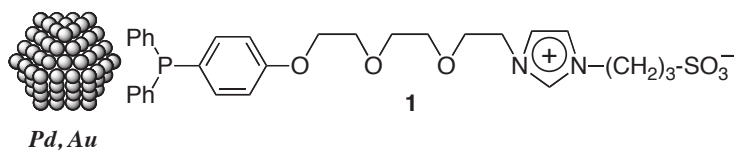


[2+2+2] Cycloaddition    Nickel    3,4-Pyridyne    1,3-Diyne    Isoquinoline



925 **Water-Soluble Palladium and Gold Nanoparticles Functionalized by a New Phosphine with Zwitterionic Liquid Based on Imidazolium Sulfonate Linked Ethylene Glycol Moiety**

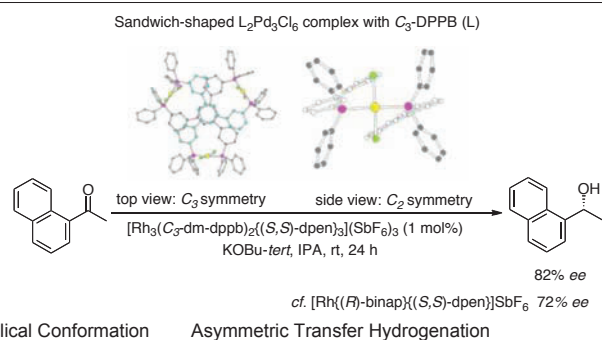
Taichi Akiyama, Chiharu Iбата, and Hisashi Fujihara\*



Imidazolium Ion    Palladium Nanoparticle    Ionic Liquid    Suzuki Coupling Reaction

933 **Helical Chirality Control of *Tropos* Sandwich-Shaped  $L_2M_3$  Complexes with  $C_3$ -Symmetric Tris(diphenylphosphinophenyl)benzene Ligand**

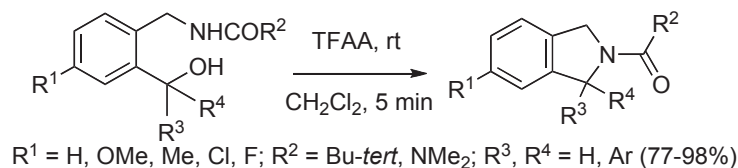
Kazuki Wakabayashi and Koichi Mikami\*



■ PAPERS

941 **A Simple and Convenient High Yielding Synthesis of Substituted Isoindolines**

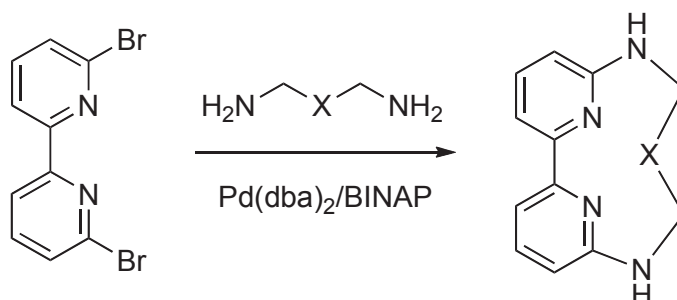
Keith Smith,\* Gamal A. El-Hiti, Amany S. Hegazy, and Ahmed Fekri



Cyclization    Dehydration    Heterocycle    Substituted Benzyl-*N,N*-dimethylurea    Synthesis

957 **Synthesis of Polyazamacrocycles Comprising 6,6'-Diamino-2,2'-bipyridine Moieties *via* Pd-Catalyzed Amination**

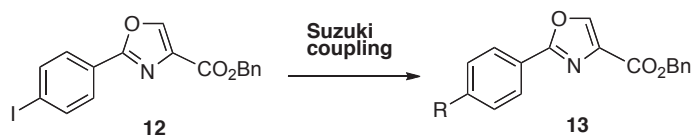
Alexei D. Averin,\* Alexei N. Uglov, Alexei K. Buryak, Alla G. Bessmertnykh, Roger Guillard, and Irina P. Beletskaya\*



2,2'-Bipyridine    Amination    Polyamine    Pd Catalysis    Macrocycle

**977 Utilization of the Suzuki Coupling to Enhance the Antituberculosis Activity of Aryloxazoles**

Garrett C. Moraski, Scott G. Franzblau, and Marvin J. Miller\*

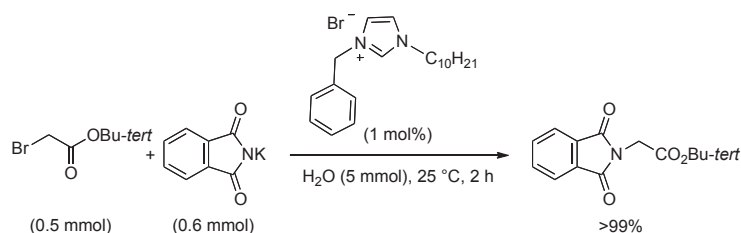


R = 2-chlorophenyl (**14**), 3-chlorophenyl (**15**), 4-chlorophenyl (**16**),  
 2-methoxyphenyl (**17**), 3-methoxyphenyl (**18**), 4-methoxyphenyl (**19**),  
 4-trifluoromethoxyphenyl (**20**), 4-cyanophenyl (**21**), 3-benzyloxyphenyl (**22**)

Antituberculosis Agent    Suzuki Coupling Reaction    Aryloxazole    Palladium Catalyzed Cross Coupling Reaction

**989 Design of Reaction Media for Nucleophilic Substitution Reactions by Using a Catalytic Amount of an Amphiphilic Imidazolium Salt in Water**

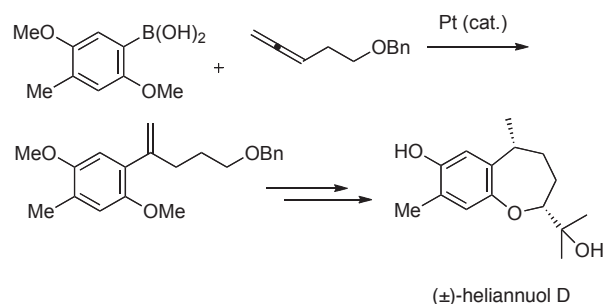
Keisuke Asano and Seiji Matsubara\*



Imidazolium Salt    Amphiphilicity    Water    Self-Assembly    Hydrophobic Effect

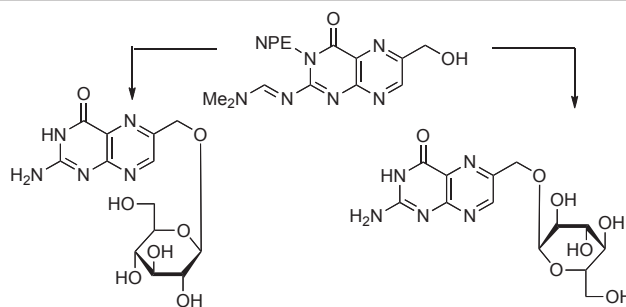
**1003 Synthesis of (±)-Heliannuol D Based on Platinum Catalyzed Regioselective Addition of Arylboronic Acids to Allenes**

Mayu Osaka, Makoto Kanematsu, Masahiro Yoshida, and Kozo Shishido\*

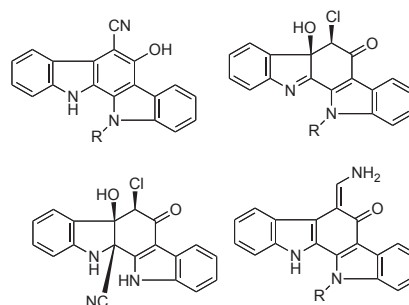

 (±)-Heliannuol D    (±)-10-*epi*-Heliannuol D    Total Synthesis    Platinum Catalyzed Addition    Allene

**1013 Synthesis of 6-Hydroxymethylpterin α- and β-D-Glucosides**

Tadashi Hanaya,\* Hiroki Baba, Kazumasa Ejiri, and Hiroshi Yamamoto

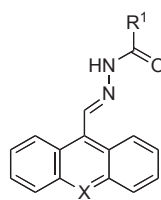
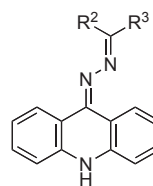

**1027 Synthetic Study Directed toward Derivatives of Biologically Active Indolo[2,3-*a*]carbazole**

Masako Sato, Yoshiaki Suzuki, Fumio Yamada, and Masanori Somei\*



**1047 Novel Carbohydrazone and Hydrazone Biomarkers Based on 9-Substituted Acridine and Anthracene Fluorogens**

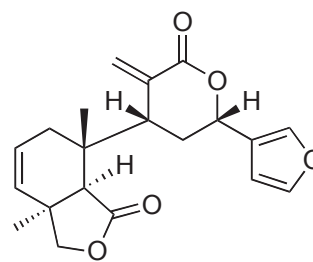
Zdenka Bedlovičová, Ján Imrich,\* Pavol Kristian, Ivan Danihel, Stanislav Böhm, Danica Sabolová, Mária Kožurková, Helena Paulíková, and Karel D. Klika


 $X = \text{N, CH}$   
 $R^1 = \text{Me, C}_6\text{H}_2, 3\text{-Py, 4-Py, 9-oxoacridin-4-yl}$ 

 $R^2 = \text{H, Me}$   
 $R^3 = \text{Me, Ph, 4-BrC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 2,4,6\text{-triMeC}_6\text{H}_2, 2,4,6\text{-triMeOC}_6\text{H}_2$ 

Acridine    Carbohydrazone    Hydrazone    Fluorescence    DFT

**1067 Synthetic Study on Clutiolide Based on a Remote Chelation Controlled Ireland-Claisen Rearrangement**

Jun Ishihara,\* Okihisa Tokuda, Kazunori Shiraishi, Yukihiro Nishino, Keisuke Takahashi, and Susumi Hatakeyama\*

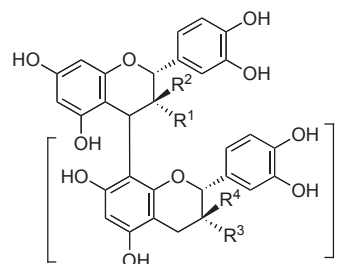


clutiolide

Clutiolide    Diterpene    Ireland-Claisen Rearrangement    Chelation Control    Diels-Alder Reaction

**1081 Structure-Activity Relationships of Synthesized Procyanidin Oligomers: DPPH Radical Scavenging Activity and Maillard Reaction Inhibitory Activity**

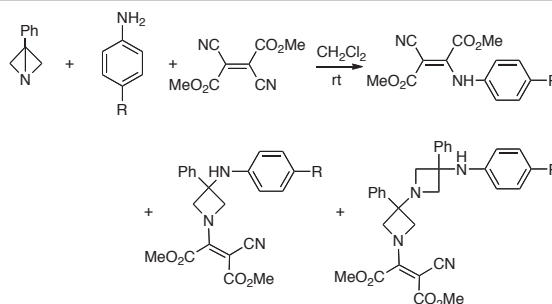
Akiko Saito and Noriyuki Nakajima\*


 $R^1 = R^2 = R^3 = R^4: \text{H, OH or O-Galloyl, } n = 0 - 4$ 

Condensed Tannin    Antioxidant    Tea Catechin    Polyphenol    Artificial Procyanidin Oligomer

**1091 Three-Component Reactions with 3-Phenyl-1-azabicyclo-[1.1.0]butane, Dimethyl Dicyanofumarate, and Primary Aromatic Amines**

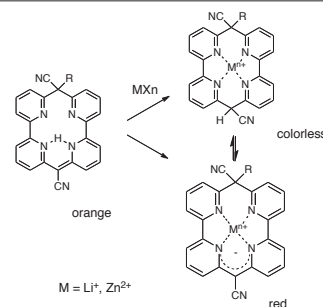
Grzegorz Mlostoń\* and Heinz Heimgartner\*



1-Azabicyclo[1.1.0]butane    2,3-Dicyanofumarate    Zwitterionic Intermediate    Three-Component Reaction    Addition Reaction

**1103 Unusual Reactions of the Highly Strained Macrocycles with Lithium Salts: Anion Control for the Reaction Rates and Elucidation of the Properties of Their Lithium Complexes**

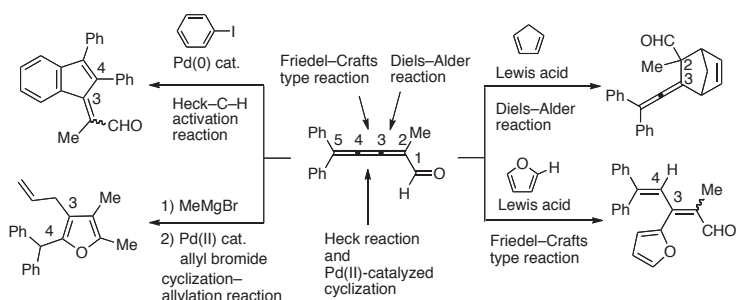
Junko Morita, Shinji Tsuchiya, Nao Yoshida, Nirei Nakayama, and Shojiro Ogawa\*


 $M = \text{Li}^+, \text{Zn}^{2+}$ 

Tetraazamacrocyclic    Lithium Complex    Unsymmetrical Structure    Strained Molecule    Anion Control

**1125 Reaction Behavior of Cumulene: Diels–Alder, Friedel–Crafts, and Pd-Catalyzed Domino Reactions**

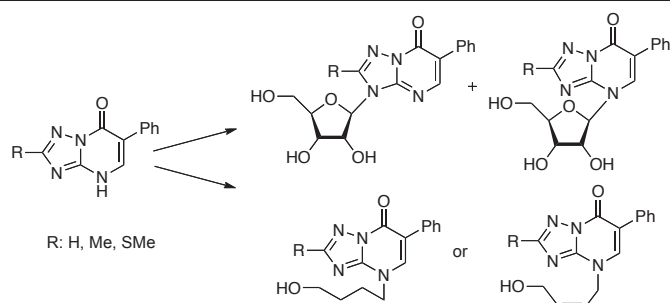
Tomohiro Asakawa, Mie Inuma, Yuko Wakasugi, Mayumi Kuno, Takumi Furuta,\* Satoshi Fujii, Kiyoshi Tanaka, and Toshiyuki Kan\*



Cumulene    Diels–Alder Reaction    Friedel–Crafts Reaction    Heck Reaction    Domino Reaction

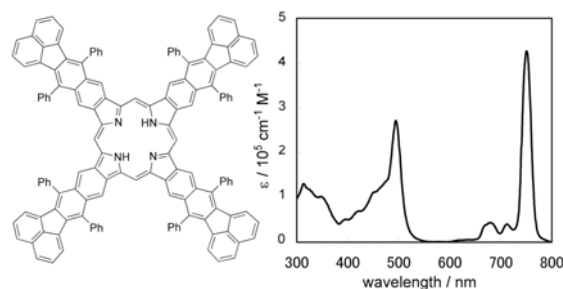
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Oleg N. Chupakhin,\* Tatiana S. Shestakova, Sergey L. Deev, Oleg S. Eltsov, and Vladimir L. Rusinov


 Non-Natural Nucleoside    Nucleoside Analog    1,2,4-Triazolo[1,5-*a*]pyrimidin-7-one    Glycosylation    Alkyl Fragment

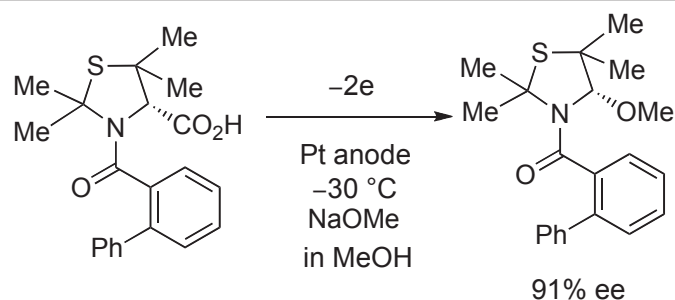
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Jun Nakamura, Tetsuo Okujima,\* Yuya Tomimori, Naoki Komobuchi, Hiroko Yamada, Hidemitsu Uno, and Noboru Ono


 [2,3]Fluoranthobenzoporphyrin    Retro Diels–Alder Reaction     $\pi$ -Expanded Porphyrin    Strong Absorption in Near-IR Region

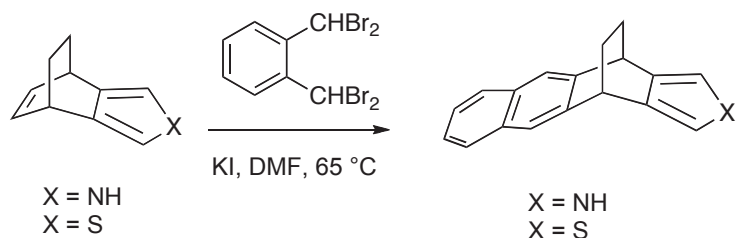
**1177 Memory of Chirality in the Electrochemical Oxidation of Thiazolidine-4-carboxylic Acid Derivatives**

George Ng'anNg'a Wanyoike, Yoshihiro Matsumura, Masami Kuriyama, and Osamu Onomura\*


 Electrochemical Oxidation    Memory of Chirality    Carbon–Carbon Bond Cleavage    Chiral *N,O*-Acetal    Thiazolidine-4-carboxylic Acid

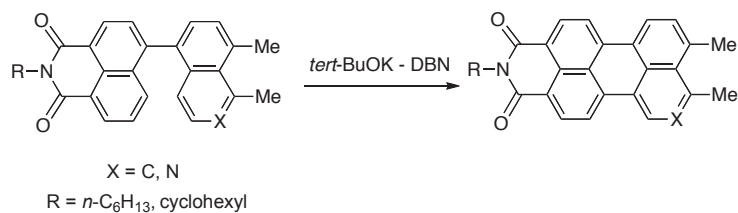
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Hiroki Uoyama, Cai Chenxin, Hiroyuki Tahara, Yusuke Shimizu, Hideki Hagiwara, Yasuaki Hanasaki, Hiroko Yamada, Tetsuo Okujima, and Hidemitsu Uno\*


 Anthra[2,3-*c*]pyrrole    Anthra[2,3-*c*]thiophene    Diels–Alder Reaction    X-Ray Structure     $\sigma$ -Quinodimethane

**1197 Synthesis and Properties of Dicarboximide Derivatives of Perylene and Azaperylene**

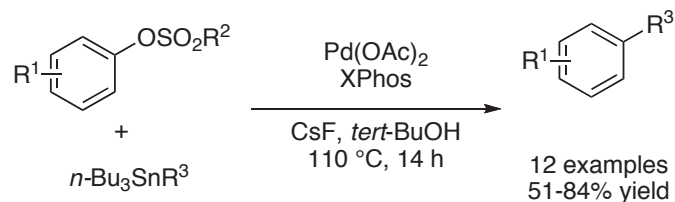
Yukinori Nagao,\* Tatsuro Yoshida, Koji Arimitsu, and Kozo Kozawa



Coupling Reaction    Ring Closure Reaction    Absorption Spectrum    Fluorescence Spectrum

**1215 Stille Cross-Coupling Reactions of Aryl Mesylates and Tosylates Using a Biarylphosphine Based Catalyst System**

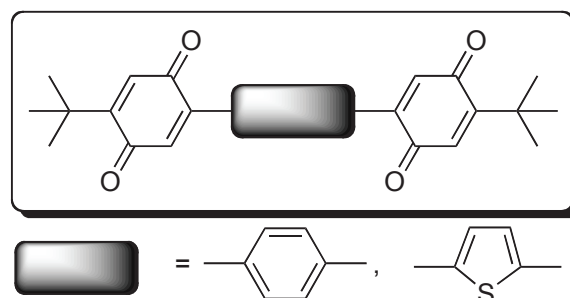
John R. Naber, Brett P. Fors, Xiaoxing Wu, Jonathon T. Gunn, and Stephen L. Buchwald\*



Aryl Mesylate    Palladium Catalysis    C-C Bond Formation    Stille Reaction    Aryl Tosylate

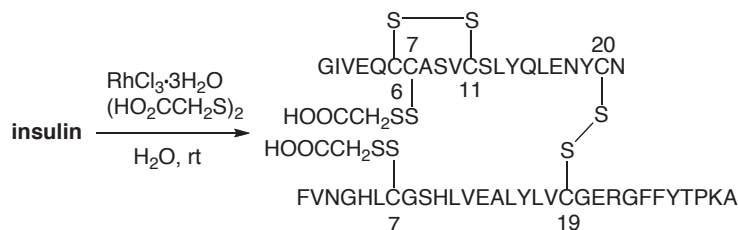
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Naoto Hayashi,\* Teru Sakakibara, Takahiro Ohnuma, Junro Yoshino, and Hiroyuki Higuchi


 $\pi$  Linker    Quinone    Electronic Absorption Spectra     $\pi$ -Conjugation System    Cyclic Voltammetry

**1239 RhCl<sub>3</sub>-Catalyzed Disulfide Exchange Reaction of Insulin and Dithiodiglycolic Acid**

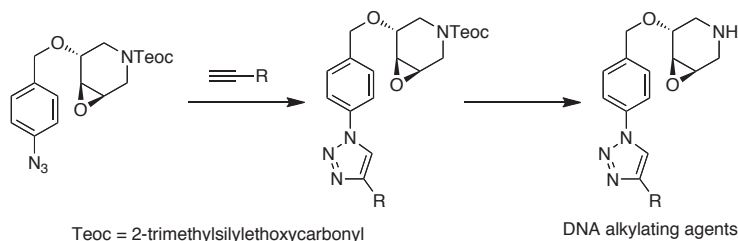
Mieko Arisawa, Manabu Kuwajima, Atsushi Suwa, and Masahiko Yamaguchi\*



Rhodium Chloride    Disulfide Exchange Reaction    Catalysis    A7/B7 Disulfide    Insulin

**1249 Synthesis and Evaluation of Novel 3,4-Epoxy piperidines as Efficient DNA Alkylating Agents**

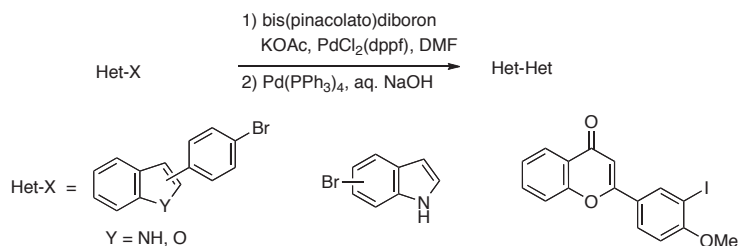
Yuji Kawada, Tetsuya Kodama, Kazuyuki Miyashita, Takeshi Imanishi, and Satoshi Obika\*



DNA Alkylating Agent    Epoxypiperidine    Huisgen Reaction    Anticancer    Azinomycin

**1267 Synthesis of Some New Biheterocycles by a One-Pot Suzuki-Miyaura Coupling Reaction**

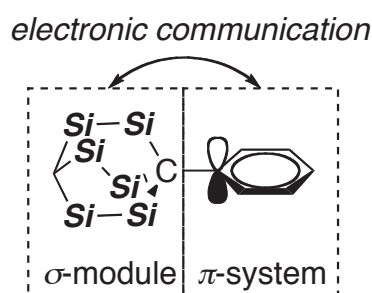
Mandar Deodhar, David StC. Black,\* Daniel Shiu-Hin Chan, and Naresh Kumar\*



Suzuki-Miyaura Coupling Reaction    Biheterocycle    Synthetic Methodology    Biindole    Bibenzofuran

**1275 Synthesis and Photophysical Properties of 2,3,5,6,7,8-Hexasilabicyclo[2.2.2]octan-1-yl-substituted Arenes**

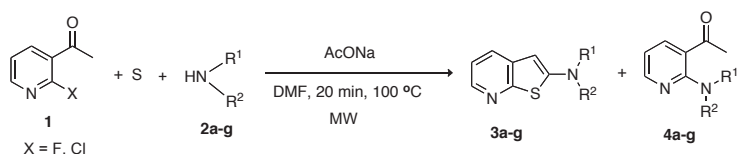
Masaki Shimizu,\* Tomoaki Kawaguchi, Hisashi Nakagawa, Katsunari Oda, and Tamejiro Hiyama\*



Silaheterocycle    Bicyclo[2.2.2]octane    Fluorescence    Conjugation    UV Absorption

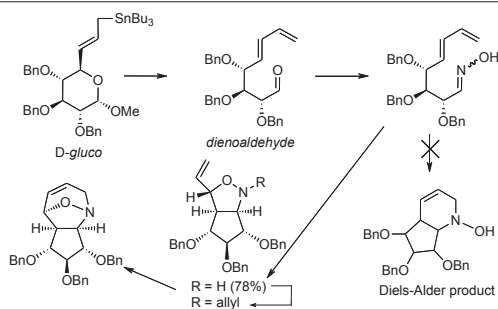
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Haribabu Ankati and Edward R. Biehl\*


 Microwave Heating    1-(2-Aminopyridin-3-yl)ethanone    2-Amino Derivatives of 3-Methylisothiazolo[5,4-*b*]pyridine and Thieno[2,3-*b*]pyridine

**1303 Application of Sugar Allyltin Derivatives for the Preparation of Heterocyclic Compounds**

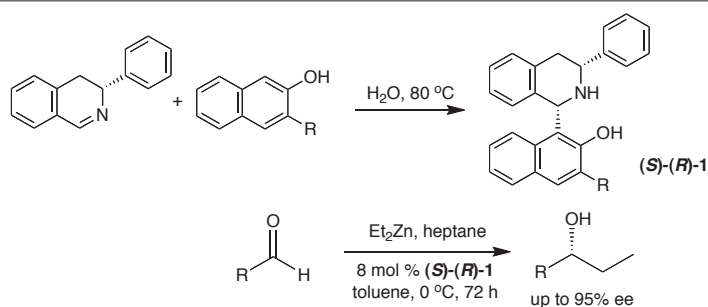
Marta Magdycz, Piotr Cmoch, and Sławomir Jarosz\*



Oxime-Olefin Cyclization    Nitron    Sugar Allyltin    Ring Closing Metathesis

**1319 Synthesis of Chiral 1,3-Disubstituted Tetrahydroisoquinolines and Their Use in the Asymmetric Addition of Diethylzinc to Aldehydes**

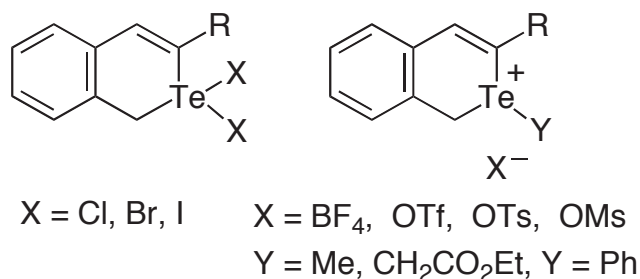
Patricia D. MacLeod, Amy M. Reckling, and Chao-Jun Li\*



Chiral Tetrahydroisoquinoline    Asymmetric Addition    Diethylzinc    Chiral Ligand    Aza Friedel-Crafts Reaction

**1339 2-Substituted Isotellurochromenium Salt Derivatives: Preparations, Structures, Spectroscopic Properties**

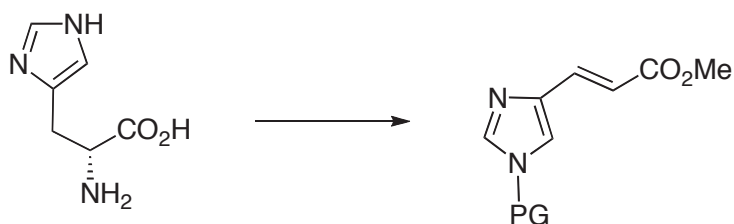
Haruki Sashida,\* Shoko Nakabayashi, Mamoru Kaname, and Mao Minoura



Isotellurochromene    Telluride    Tellurium Salt    Tellurane

**1353 Efficient Preparation of Urocanic Acid Derivatives from Histidine**

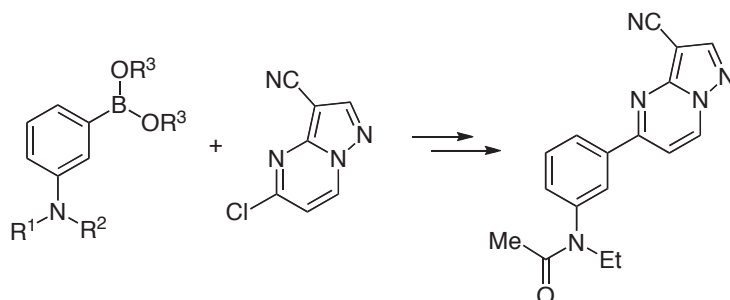
Carl J. Lovely,\* Rasapalli Sivappa, Sabuj Mukherjee, Thomas Doundoulakis, Heather M. Lima, and Muhammed Yousuffudin



Imidazole    Elimination    X-Ray Structure    Regioselective    Diazotization

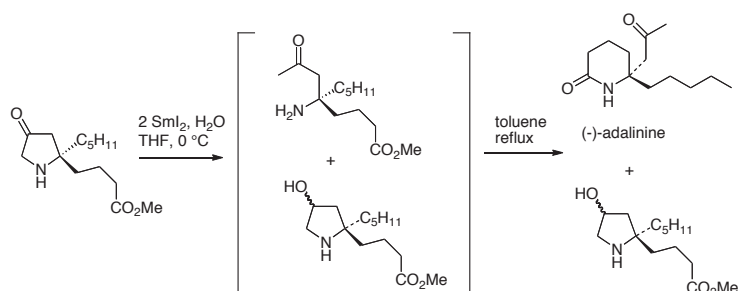
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Stanislav Rádľ,\* Michaela Blahovcová, Marcela Tkadlecová, and Jaroslav Havlíček


 Zaleplon Regioisomer    Synthesis    Spectral Property    5-Arylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile    Suzuki-Miyaura Cross Coupling Reaction

**1381 Application of Samarium Diiodide-Promoted Reductive Carbon-Nitrogen Bond Cleavage Reaction to 3-Oxopyrrolidine Derivatives: Alternative Synthesis of a Coccinellid Alkaloid, (-)-Adalinine**

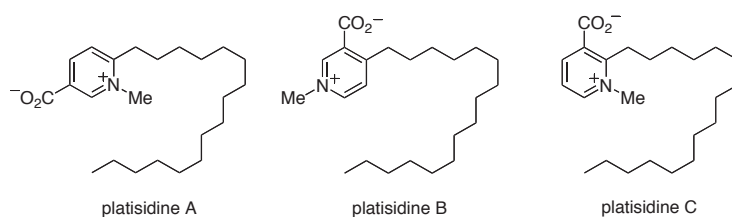
Toshio Honda\* and Chihiro Hisa



Samarium Diiodide    Adalinine    Carbon-Nitrogen Bond Cleavage Reaction    4-Hydroxyproline    Chiral Synthesis

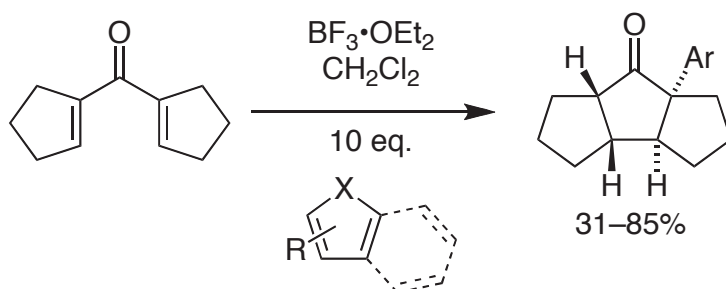
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Takaaki Kubota, Yuichiro Ishiguro, Sunao Yamamoto, Jane Fromont, and Jun'ichi Kobayashi\*


 Sponge    *Plakortis* species    Pyridinium Alkaloid    Platisidines A-C    Acetylcholinesterase Inhibitor

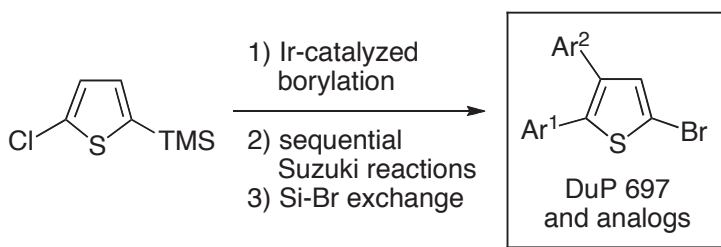
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Curtis J. Rieder, Ryan J. Fradette, and Frederick G. West\*



Nazarov Reaction    Domino Process    Heteroaromatic    Electrophilic Aromatic Substitution    Triquinane

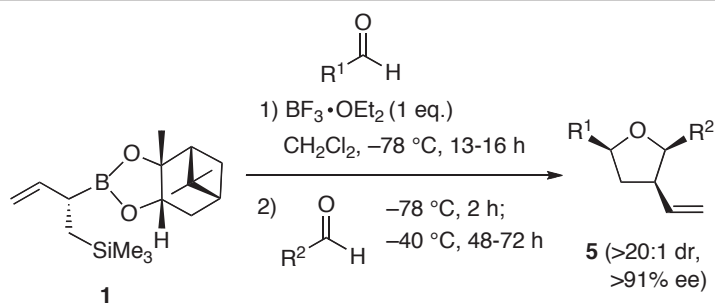
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 Venkata A. Kallepalli, Luis Sánchez, Hao Li,  
 Nathan J. Gesmundo, Clarissa L. Turton,  
 Robert E. Maleczka, Jr.,\* and Milton R. Smith, III\*


Thiophene    C-H Activation    Boronic Ester    Suzuki Coupling Reaction    COX-2

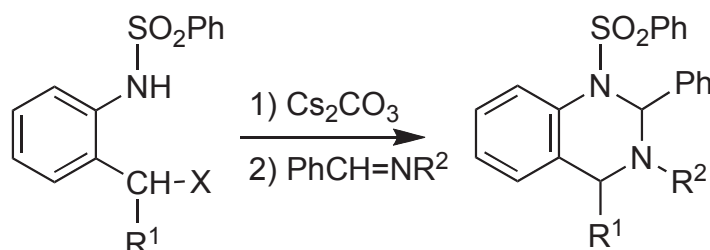
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Umakanthan Sivasubramaniam and Dennis G. Hall\*



Tetrahydrofuran    Carbonyl Allylation    Allylboration    Multicomponent Reaction    Stereocontrol

**1457 Tetrahydroquinazoline Derivatives by Aza Diels-Alder Reaction**

 Giuseppe Cremonesi, Piero Dalla Croce,\* Maddalena Gallanti,  
 and Concetta La Rosa

 Tetrahydroquinazoline    *o*-Azaxylylene    Aza Diels-Alder Reaction    Imine





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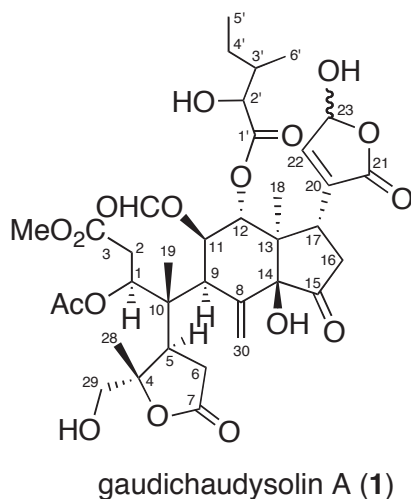
## GAUDICHAUDYSOLIN A, A NEW LIMONOID FROM THE BARK OF *DYSOXYLUM GAUDICHAUDIANUM*

Yuta Nagakura,<sup>a</sup> Reiko Yamanaka,<sup>a</sup> Yusuke Hirasawa,<sup>a</sup> Takahiro Hosoya,<sup>a</sup>  
Abdul Rahman,<sup>b</sup> Idha Kusumawati,<sup>b</sup> Noor Cholies Zaini,<sup>b</sup> and Hiroshi  
Morita<sup>a,\*</sup>

<sup>a</sup>Faculty of Pharmaceutical Sciences, Hoshi University, Shinagawa-ku, Tokyo  
142-8501, Japan; <sup>b</sup>Faculty of Pharmacy, Airlangga University, Jalan  
Dharmawangsa Dalam, Surabaya 60286, Indonesia

**Abstract** – A new limonoid, gaudichaudysolin A (**1**) was isolated from the bark  
of *Dysoxylum gaudichaudianum* (Meliaceae) and the structure was elucidated by  
spectroscopic analysis.

Limonoids, highly oxidative unique secondary metabolites obtained from Meliaceae are produced by a unique biosynthetic route through tetranortriterpenoid nucleus,<sup>1,2</sup> and are known to show various biological activities such as insecticidal, insect antifeedant, antibacterial, antifungal, antimalarial, anticancer, and antiviral activities.<sup>3</sup> Recently, we have isolated new limonoids, ceramicines A – D<sup>4</sup> with an unique tetranortriterpenoid skeleton from *Chisocheton ceramicus* and walsogyne A<sup>5</sup> with a ring C–*seco* limonoid from *Walsura chrysogyne*. They showed an antiplasmodial and cytotoxic activities.<sup>4,5</sup>



<sup>†</sup>Dedicated to Professor Emeritus Akira Suzuki, Hokkaido University, on the occasion of his 80<sup>th</sup> birthday.

In continuation of our research on limonoids containing in the plants belonging to Meliaceae family, we have isolated a new limonoid, gaudichaudysolin A (**1**) from the bark of *Dysoxylum gaudichaudianum*. Herein we report the structure elucidation of gaudichaudysolin A (**1**) by spectroscopic methods.

The bark of *D. gaudichaudianum* was extracted with MeOH, and the MeOH extract was in turn partitioned between EtOAc and H<sub>2</sub>O. EtOAc-soluble materials were subjected to a silica gel column (hexane/EtOAc, 1:0→1:1; CHCl<sub>3</sub>/MeOH, 1:0→0:1) and the fractions eluted by hexane/EtOAc (1:1) were subjected to a silica gel column (Toluene/EtOAc, 1:0→5:5; CHCl<sub>3</sub>/MeOH, 1:0→5:5; CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O, 5:5:1) followed by C<sub>18</sub> HPLC (40% CH<sub>3</sub>CN/0.1%TFA) to afford gaudichaudysolin A (**1**, 0.00002 %).

Gaudichaudysolin A {**1**, [ $\alpha$ ]<sub>D</sub><sup>23</sup> -126 (c 0.2, MeOH)} was obtained as a colorless solid and was revealed to have the molecular formula C<sub>36</sub>H<sub>48</sub>O<sub>17</sub>, by HRESITOFMS [*m/z* 775.2780 (M+Na)<sup>+</sup>,  $\Delta$  -0.9 mmu]. IR absorptions implied the presence of hydroxyl (3425 cm<sup>-1</sup>) and carbonyl (1755 and 1680 cm<sup>-1</sup>) groups. UV spectrum (230 nm) indicated the presence of an unsaturated carbonyl group. <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1) revealed thirty six carbon resonances due to seven carbonyls, two sp<sup>2</sup> quaternary carbons, three sp<sup>3</sup> quaternary carbons, one sp<sup>2</sup> methine, ten sp<sup>3</sup> methines, one sp<sup>2</sup> methylene, five sp<sup>3</sup> methylenes, and seven methyl groups. Among them, eight sp<sup>3</sup> carbons ( $\delta_C$  67.3, 70.0, 72.0, 75.2, 76.3, 81.4, 93.1, and 98.8) and seven sp<sup>2</sup> carbons ( $\delta_C$  163.5, 172.1, 172.9, 173.2, 173.3, 177.8, and 208.0) were ascribed to those bearing an oxygen atom.

Six partial structures **a** (C-1 to C-2), **b** (C-5 to C-6), **c** (C-9 and C-11 to C-12), **d** (C-16 to C-17), **e** (C-22 to C-23), and **f** (C-2' to C-6') were deduced from <sup>1</sup>H-<sup>1</sup>H COSY analysis of **1** in CD<sub>3</sub>OD (Figure 1). Unit **A** composed of the partial structures **a** and **b** was assigned as shown in Figure 1 with a  $\gamma$ -lactone ring by using HMBC and NOESY correlations as follows. HMBC correlations of H<sub>3</sub>-28 ( $\delta_H$  1.58) to C-4 ( $\delta_C$  93.1), C-5 ( $\delta_C$  43.8), and C-29 ( $\delta_C$  67.3), H<sub>2</sub>-6 ( $\delta_H$  2.80) to C-4 and C-7 ( $\delta_C$  177.8), and H<sub>2</sub>-29 ( $\delta_H$  3.72 and 3.78) to C-4 revealed the presence of a  $\gamma$ -lactone ring<sup>6</sup> with a hydroxymethyl and a methyl groups at C-4. Acetoxy group at C-1 and a methyl carboxylate at C-2 were assigned by the HMBC correlations as shown in Figure 1. Connection between the partial structures **a** and **b** through C-10 ( $\delta_C$  49.6), was deduced by an HMBC correlation of H<sub>2</sub>-6 to C-10 and the NOESY correlations as shown in Figure 2. Unit **B** composed of the partial structures **c** and **d** was assigned as an octahydroinden-1-one ring system with a methyl, an exo-methylene, a hydroxyl, and two ester functions as follows. These functions can be connected by the HMBC correlations of H<sub>3</sub>-18 ( $\delta_H$  1.02) to C-12 ( $\delta_C$  75.2), C-13 ( $\delta_C$  51.5), C-14 ( $\delta_C$  81.4), and C-17 ( $\delta_C$  36.8), H-9 ( $\delta_H$  3.29) to C-8 ( $\delta_C$  142.0) and C-14, and H<sub>2</sub>-30 ( $\delta_H$  5.75 and 5.84) to C-9 and C-14. This ring system and functions were also supported by the comparison of the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts [C-14 ( $\delta_C$  81.4), C-15 ( $\delta_C$  208.0), and C-16 ( $\delta_C$  40.8)] with those [C-14 ( $\delta_C$  79.5), C-15 ( $\delta_C$  209.3), and C-16 ( $\delta_C$  42.0)] of rohituka 14<sup>7</sup> isolated from the seeds of *Aphanamixis polystacha*. The presence of a formate at C-11 was indicated by an HMBC correlation of an aldehyde proton to C-11 ( $\delta_C$

72.0). Connection between the units **A** and **B** was indicated by HMBC correlations of H-9 to C-5 and C-10. Unit **C** composed of the partial structure **e**, which was attached at C-17 in the unit **B**, was assigned as an  $\alpha$ -substituted  $\gamma$ -lactone ring system with a hydroxyl at  $\gamma$  position by HMBC correlations of H-17 ( $\delta_{\text{H}}$  3.86) and H-22 ( $\delta_{\text{H}}$  7.19) to C-20 ( $\delta_{\text{C}}$  136.5), H-23 ( $\delta_{\text{H}}$  6.10) to C-21 ( $\delta_{\text{C}}$  172.9), and IR absorption at  $1755\text{ cm}^{-1}$ . Unit **D** composed of the partial structure **f** was assigned as a 2-hydroxy-3-methylpentanoic acid by the  $^1\text{H}$ - $^1\text{H}$  COSY correlation in Figure 1 and the comparison of NMR data in turrapubesin D,<sup>8</sup> which might be attached at the hydroxy group at C-12 ( $\delta_{\text{C}}$  75.2). Thus, the gross structure of **1** was assigned as A,B-*seco*-tetranorlimonoid skeletal system with a  $\gamma$ -butanolide at C-17.

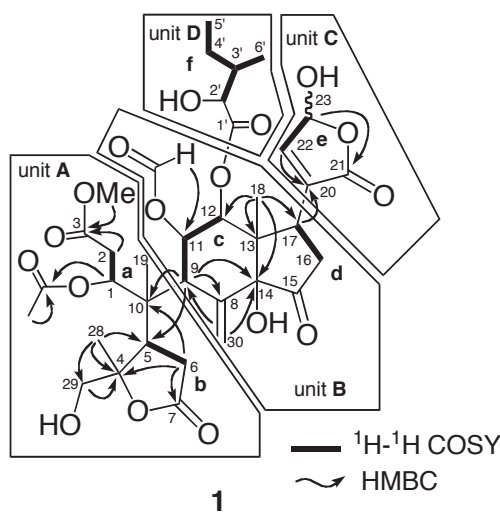


Figure 1. Selected 2D NMR correlations for **1**

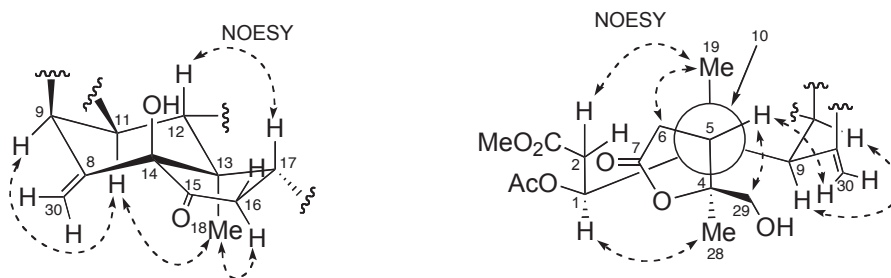


Figure 2. Selected NOESY correlations in unit **B** and rotation model of C-5/C-10 bond in unit **A** for **1**

The relative stereochemistry with selected NOESY correlations in unit **B** and rotation model of C-5/C-10 bond in unit **A** for **1** were elucidated by NOESY correlations as shown in Figure 2. Configurations of C-9, C-11, C-12, C-13, and C-17 in the unit **B** were elucidated by NOESY correlations of H<sub>3</sub>-18/H-11 and H-16a, H-12/H-17, and H-9/H-11. As you can see the rotation model of C-5/C-10 bond, NOESY correlations of H<sub>3</sub>-19/H-2 and H<sub>2</sub>-6, H<sub>3</sub>-28/H-1, and H-5/H<sub>2</sub>-29 and H-30 indicated connectivity of C-5/C-10 bond and the relative stereochemistry in the unit **A** as shown in Figure 2. Thus, the relative configuration of **1** was assigned to be shown in computer-generated 3D drawing in Figure 3 except for



C-2' and C-3' in the 2-hydroxy-3-methylpentanoic acid.

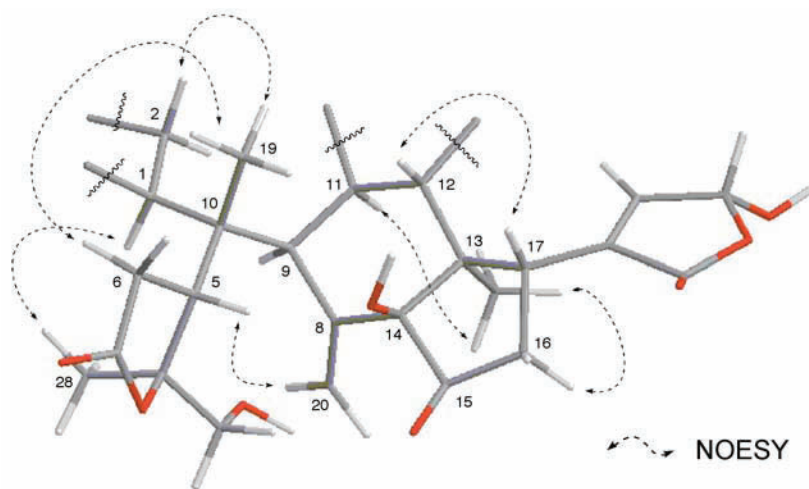


Figure 3. Selected NOESY correlations and relative configurations for **1**

From the bark of *Dysoxylum gaudichaudianum*, a series of dysoxylins A – D with a tetranortriterpenoid nucleus have already been isolated.<sup>9</sup> Biogenetically, gaudichaudysolin A (**1**) may be derived by a unique oxidative route through this tetranortriterpenoid nucleus. Gaudichaudysolin A (**1**) was evaluated *in vitro* for cytotoxicity against five human cancer cell lines, HL60 (human blood premyelocytic leukemia), RPMI8226 (multiple myeloma), NCI-H226 (non-small cell lung carcinoma), HCT116 (human colon cancer), and MCF7 (human breast adenocarcinoma) cells, using MTT assay, but showed no inhibitory activity against five tested cell lines ( $IC_{50} > 50 \mu M$ ).

## EXPERIMENTAL

**General Experimental Procedures.**  $^1H$  and 2D NMR spectra were recorded on a Bruker AV600 spectrometer and chemical shifts were reported using residual  $CD_3OD$  ( $\delta_H$  3.31 and  $\delta_C$  49.0) as internal standards. HSQC experiments were optimized for  $^1J_{CH}=145$  Hz and HMBC experiments for  $^nJ_{CH}=8$  Hz. Mass spectra were recorded on a Micromass LCT spectrometer.

**Plant Material.** The bark of *D. gaudichaudianum* was collected at Alas Purwo, Indonesia in 2007. A voucher specimen is deposited at the Purwodadi Botanical Garden, Indonesia.

**Extraction and Isolation.** The bark of *D. gaudichaudianum* (1370 g) was extracted with MeOH, and the MeOH extract was partitioned between EtOAc and  $H_2O$ . Water-soluble materials were extracted with BuOH. EtOAc-soluble materials were subjected to a silica gel column (hexane/EtOAc, 1:0→1:1;  $CHCl_3$ /MeOH, 1:0→0:1) and the fractions eluted by hexane/EtOAc (1:1) were subjected to a silica gel column (toluene/EtOAc, 1:0→5:5;  $CHCl_3$ /MeOH, 1:0→5:5,  $CHCl_3$ /MeOH/ $H_2O$  5:5:1) followed by  $C_{18}$  HPLC (40%  $CH_3CN$ /0.1% TFA) to afford gaudichaudysolin A (**1**, 1.3 mg, 0.00002 %).

Table 1.  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data [ $\delta_{\text{H}}$  ( $J$ , Hz) and  $\delta_{\text{C}}$ ] of Gaudichaudysolin A (**1**) in  $\text{CD}_3\text{OD}$  at 300K

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
1	5.70 (1H, m)	70.0
2a	2.70(1H, dd,15.0,11.4)	36.0
2b	3.05 (1H, d, 14.4)	
3		173.2
4		93.1
5	3.16 (1H, m)	43.8
6	2.80 (2H, d, 10.2)	35.7
7		177.8
8		142.0
9	3.29 (1H, m)	55.4
10		49.6
11	5.38 (1H, t, 10.2)	72.0
12	5.97 (1H, d, 10.8)	75.2
13		51.5
14		81.4
15		208.0
16a	2.51 (1H, m)	40.8
16b	2.86 (1H, m)	
17	3.86 (1H, m)	36.8
18	1.02 (3H, s)	13.0
19	1.44 (3H, s)	20.0
20		136.5
21		172.9
22	7.19 (1H, br s)	148.6
23	6.10 (1H, br s)	98.8
28	1.58 (3H, s)	20.0
29a	3.72 (1H, d, 13.2)	67.3
29b	3.78 (1H, d, 13.2)	
30a	5.52 (1H, br s)	123.3
30b	5.84 (1H, br s)	
1-OAc	2.04 (3H, s)	21.1
		172.1
3-OMe	3.65 (3H, s)	52.4
11-OCHO	8.15	163.5
1'		173.3
2'	3.86 (1H, m)	76.3
3'	1.62 (1H, m)	39.3
4'a	1.28 (1H, m)	24.4
4'b	1.20 (1H, m)	
5'	0.86 (3H, s)	11.9
6'	0.93 (3H, s)	15.9

**Gaudichaudysolin A (1):** a colorless amorphous solid;  $[\alpha]_D^{23}$  -126 (*c* 0.2, MeOH); IR (KBr)  $\nu_{\max}$  3425, 1755, 1680, 1630, 1585, 1440, 1390, 1200, 1135, 1075, 840, and 801  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\max}$  230 ( $\epsilon$  9000);  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Table 1); ESIMS  $m/z$  775 ( $\text{M}+\text{Na}$ ) $^+$ ; HRESITOFMS  $m/z$  775.2780 [ $\text{M}+\text{Na}$ ] $^+$ , calcd for  $\text{C}_{36}\text{H}_{48}\text{O}_{17}$ , 775.2789].

**Cytotoxic Activity.** Each cell line [HL60 (human blood premyelocytic leukemia), RPMI8226 (multiple myeloma), NCI-H226 (non-small cell lung carcinoma), HCT116 (human colon cancer), and MCF7 (human breast adenocarcinoma) cells] was seeded onto 96-well microtiter plates at  $1 \times 10^4$  cells per well for HL60 and RPMI8226 and  $5 \times 10^3$  cells per well for NCI-H226, HCT116, and MCF7, respectively. Cells were preincubated for 24 h at 37°C in humidified atmosphere of 5%  $\text{CO}_2$ . Different concentrations of each compound (10  $\mu\text{L}$ ) were added to the cultures, and then the cells were incubated at 37°C for 48 h. On the third day, 15  $\mu\text{L}$  MTT solution (5 mg/mL) was added into each well of the cultured medium. After further 2 h of incubation, 100  $\mu\text{L}$  of 10% SDS-0.01N HCl solution was added to each well and the formazan crystals in each well were dissolved by stirring with a pipette. The optical density measurements were made using a micropipette reader (Benchmark Plus microplate spectrometer, BIO-RAD) equipped with a two wavelengths system (550 and 700 nm). In each experiment, three replicate of wells were prepared for each sample. The ratio of the living cells was determined based on the difference of the absorbance between those of samples and controls. These differences are expressed in percentage and cytotoxic activity was indicated as an  $\text{IC}_{50}$  value.

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