Universidad de Panamá

Facultad de Medicina

NAPROC-13. Una Herramienta para la Elucidación y la Revisión Estructural de Productos Naturales

En Reconocimiento al Dr. Mahabir Gupta

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Dpto. Farmacología
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NAPROC-13

- Disponible en la URL: https://c13.usal.es
- Libre acceso
- Información estructural, espectroscópica y bibliográfica de 25 000 productos naturales (PNs)
  - Más de 350 de estas estructuras proceden de fuentes panameñas

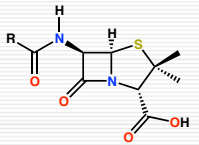
2

Importancia de la elucidación correcta de PNs

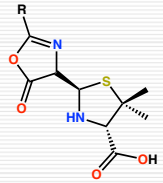
- Establecimiento de REA
- Aspectos Legales
- Conocer la estructura correcta para poder sintetizarlo
  - Desarrollo del fármacos

3

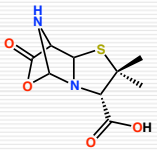
Penicilina



Crawfoot-Hodgkin[2]
difracción de rayos X



oxazolo-tiazolidina
propuesta Robinson[1]

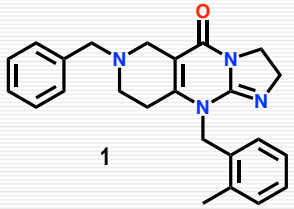


estructura tricíclica
propuesta Woodward[2]

1. The Chemistry of Penicillin (Eds.: H. T. Clarke, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, 1949, p. 1094.
2. J. C. Sheehan, The Enchanted Ring: The Untold Story of Penicillin, MIT Press, Cambridge, 1984, p. 224.

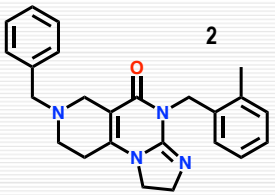
4

Reasignación de la estructura de TIC-10 (imidazopirimidina)



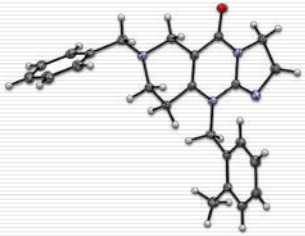
1

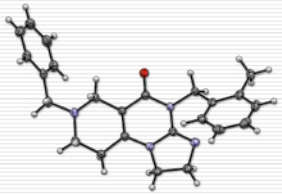
estructura publicada



2

estructura revisada





inductor de apoptosis originada por el factor de necrosis tumoral (TNF)

Jacob, N. T., Lockner, J. W., Kravchenko, V. V., and Janda, K. D. (**2014**). Pharmacophore reassignment for induction of the immunosurveillance cytokine TRAIL. *Angew Chem Int Ed Engl* ***53***, 6628-6631.

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Surgimiento de NAPROC-13 como herramienta para la elucidación y corrección estructural

NAPROC-13

6

- Desarrollada por el Dr. José Luis López Pérez
- 2003
- URL "http://c13.usal.es"
- Inicialmente 6000 PNs
- Se desarrolló íntegramente en JAVA
- Publicada en la primera revista del mundo de la especialidad, Bioinformatics
  - *(López-Pérez, J. L., R. Theron, E. del Olmo, and D. Diaz. "Naproc-13: A Database for the Dereplication of Natural Product Mixtures in Bioassay-Guided Protocols."Bioinformatics 23, 2007, 3256-7).*

NAPROC-13

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PERGAMON

PHYTOCHEMISTRY

Phytochemistry 51 (1999) 793–801

Terpenes and lignans from leaves of *Chamaecyparis formosensis*

Tung-Chieh Lin, Jim-Min Fang*, Yu-Shia Cheng

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan

Received 27 May 1998; accepted 30 November 1998

Abstract

84 chemical constituents were isolated from the leaves of *Chamaecyparis formosensis*. These components include 18 sesquiterpenes, 40 diterpenes, 8 flavones, 7 lignans and 11 miscellaneous compounds. Among them 3 sesquiterpenes, 7 diterpenes and one lignan are new compounds, the structures of which were determined by chemical and spectral methods.

Keywords: *Chamaecyparis formosensis*; Cupressaceae; Leaves; Sesquiterpenes; Diterpenes; Flavones; Lignans; Sterols

1. Introduction

Chamaecyparis formosensis Matsumura, known as Taiwan red cypress (Li & Keng, 1994) is indigenous to the high mountain area of Taiwan. It is called red cypress since the bark appears to be slightly reddish

2. Results and discussion

The acetone extract of the leaves of *C. formosensis* was subjected to chromatography to give 84 components, including 18 sesquiterpenes, 40 diterpenes, 8 flavones, 7 lignans and 11 miscellaneous compounds

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Accesos a NAPROC-13

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JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

REVIEW

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Databases on Food Phytochemicals and Their Health-Promoting Effects

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[§]Nutrition and Food Science Department, XaRTA INSA, INGENIO−CONSOLIDER Program, Fun-C-Food CSD2007-063/AGL200913906-C02-01, Pharmacy School, University of Barcelona, Avinguda Joan XXIII s/n, 08028 Barcelona, Spain

[#]RIKEN Plant Science Center and Department of Biophysics and Biochemistry, Graduate School of Science, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, 113-0033 Tokyo, Japan

[⊥]Institute of Food Research, Colney Lane, NR4 7UA Norwich, United Kingdom

[⊗]INRA, Centre de Recherche de Clermont-Ferrand/Theix, and Université Clermont 1, UFR Médecine, UMR1019, Unité de Nutrition Humaine, 63122 Saint-Genès-Champanelle, France

[△]Department of Computing Science, University of Alberta, Edmonton, Alberta, Canada T6G 2E8

ABSTRACT: Considerable information on the chemistry and biological properties of dietary phytochemicals has accumulated over the past three decades. The scattering of the data in tens of thousands publications and the diversity of experimental approaches and reporting formats all make the exploitation of this information very difficult. Some of the data have been collected and stored in electronic databases so that they can be automatically updated and retrieved. These databases will be particularly important in the evaluation of the effects on health of phytochemicals and in facilitating the exploitation of nutrigenomic data. The content of over 50 databases on chemical structures, spectra, metabolic pathways in plants, occurrence and concentrations in foods, metabolism in humans and animals, biological properties, and effects on health or surrogate markers of health is reviewed. Limits of these databases are emphasized, and needs and recommendations for future developments are underscored. More investments in the construction of databases on phytochemicals and their effects on health are clearly needed. They should greatly contribute to the success of future research in this field.

KEYWORDS: phytochemicals, foods, metabolism, health, databases, bioinformatics, nutrigenomics

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databases that may be particularly useful for phytochemical analysis and identification. In many cases, the spectra contained in these open access spectral databases can be easily imported into existing phytochemical or nutrient databases. Unfortunately, despite their ready availability, this has not yet happened.

With regard to NMR spectral resources for phytochemicals and other natural products, there are at least seven freely available resources and at least three commercial databases (see Table 4). The two largest are NAPROC-13[32] and NMRShiftDB.[31] Both of these databases appear to have a fairly substantial collection of natural product and phytochemical spectra under a variety of solvent conditions. Because of the large spectral dispersion, the relative chemical shift invariance, and the simplicity of ^{13}C NMR spectra, most analytical chemists prefer to use ^{13}C NMR for the identification of phytochemicals, phytochemical metabolites, and other natural products. In this regard, NAPROC-13, which is a ^{13}C NMR database of natural products, probably represents the richest NMR resource for phytochemists and phytochemical databases.

With regard to GC-MS spectral resources for phytochemicals and other natural products, the most widely used database is the NIST database. The latest release contains EI-MS spectra for 192,100 compounds and retention index (RI) values for 121,800 compounds. Unfortunately, many of the NIST compounds are not natural products or phytochemicals. Four other databases, albeit somewhat smaller in size, also provide some GC-MS data for phytochemical identification. These are the Golm Metabolome Database,[33] the Manchester Metabolome Database,[34] the

DATABASES ON PHYTOCH PATHWAYS IN PLANTS

Pathway databases are expect degradation routes of metabolite functional roles. Because descrip requires detailed knowledge on rel extensive expertise is necessary for pathway databases. Each databas compile pathway knowledge and depending on its expected usage here categorize them into three t databases, specialized pathway dat approaches to accumulate pathwa

Comprehensive Databases. online counterparts of the cl (Roche's and Sigma's versions are online information), covering all single map. The KEGG database hensiveness and provides the pa loadable format for over 1200 fully genomes are bacterial, and for pl included (thale cress, black cotton Japanese rice, sorghum, and ma pathway reconstruction is semiau designed pathway charts are prep tion, on which precomputed resu search can be projected for a specif

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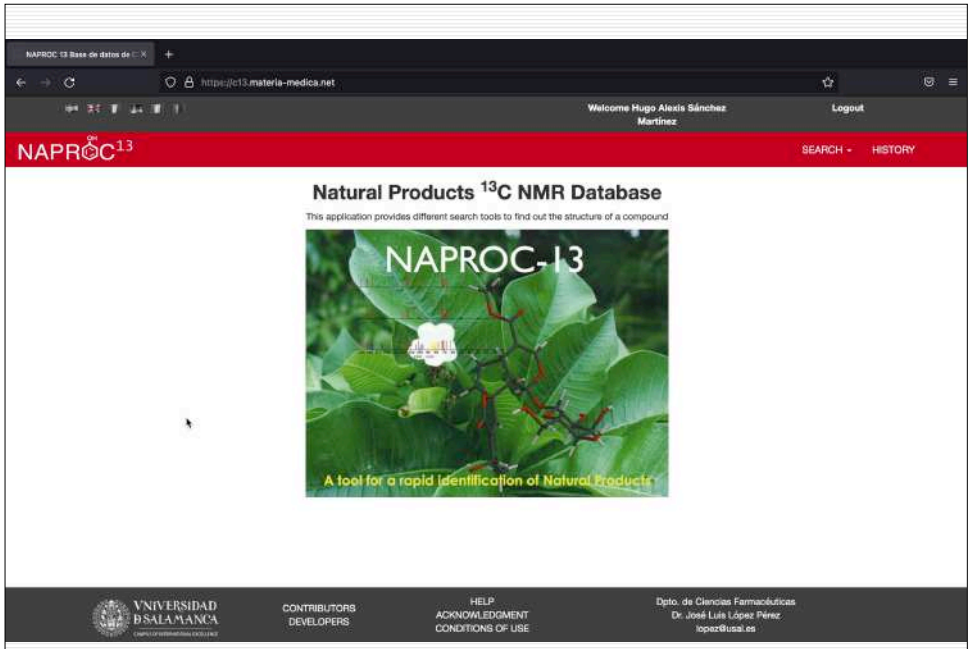
NAPROC-13 base de datos para la consulta de las estructuras y datos espectrocópicos

12



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NAPROC-13 base de datos para la revisión estructural de Productos Naturales (PNs)

- Contiene un número muy significativo de sustancias cuya estructura ha sido revisada
  - Aparecidos en artículos de revisión
  - Detectados en NAPROC-13
  - Aplicación de la red neuronal desarrollada por Vawefunction
  - Cálculo computacional

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JOURNAL OF NATURAL PRODUCTS

Article

pubs.acs.org/jnp

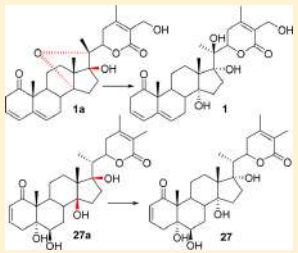
Withanolide Structural Revisions by ^{13}C NMR Spectroscopic Analysis Inclusive of the γ-Gauche Effect

Huaping Zhang and Barbara N. Timmermann*

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045, United States

Supporting Information

ABSTRACT: A classic withanolide is defined as a highly oxygenated C_{28} ergostane-type steroid that is characterized by a C_{22}-hydroxy-C_{26}-oic acid δ-lactone in the nine-carbon side chain. Analysis of the reported ^{13}C NMR data of classic withanolides with hydroxy groups (C-14, C-17, and C-20) revealed that (1) a hydroxy (C-14 or C-17) substituent significantly alters the chemical shifts (C-7, C-9, C-12, and C-21) via the γ-gauche effect; (2) the chemical shift values (C-9, C-12, and C-21) reflect the orientation (α or β) of the hydroxy moiety (C-14 or C-17); (3) a double-bond positional change in ring A (Δ^2 to Δ^3), or hydroxylation (C-27), results in a minuscule effect on the chemical shifts of carbons in rings C and D (from C-12 to C-18); and (4) the ^{13}C NMR γ-gauche effect method is more convenient and reliable than the traditional approach (^{1}H NMR shift comparisons in C_5D_5N versus $CDCl_3$) to probe the orientation of the hydroxy substituent (C-14 and C-17). Utilization of these rules demonstrated that the reported ^{13}C NMR data of withanolides **1a**−**29a** were inconsistent with their published structures, which were subsequently revised as **1**−**16** and **12** and **18**−**29**, respectively. When combined, this strongly supports the application of these methods to determine the relative configuration of steroidal substituents.



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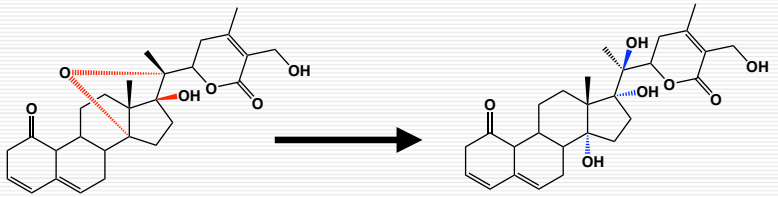
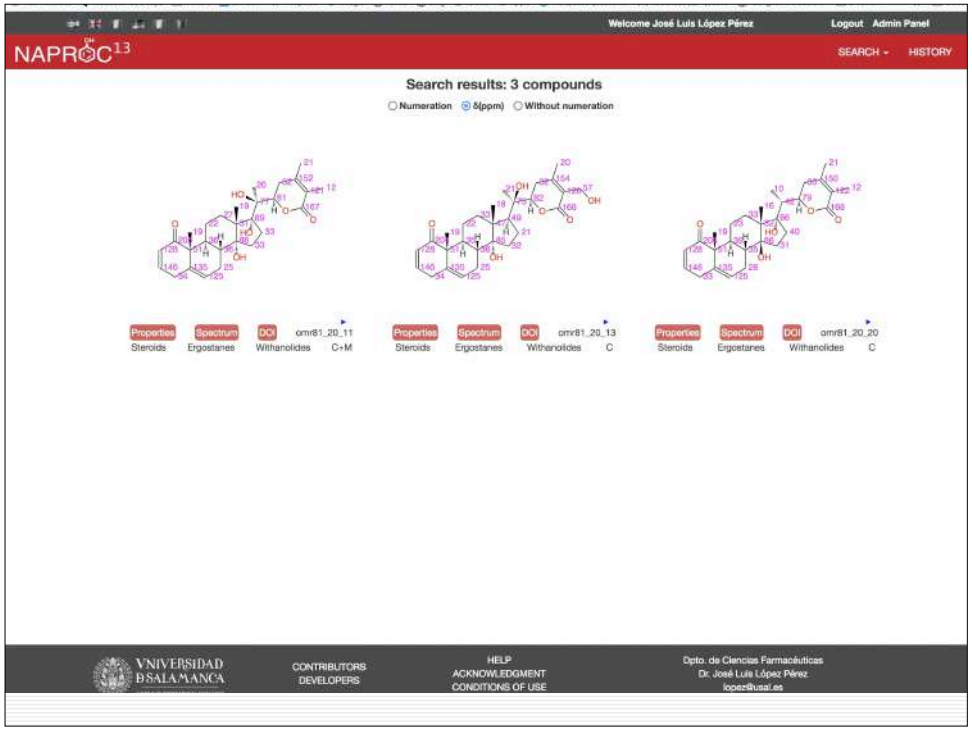
Corrección de la estructura de Withanolidas



Atta-ur-Rahman, Abbas, S., Dur-e-Shahwar, Jamal, S.A., Choudhary, M.I.; *J Nat Prod* (1993) **56**: 1000-6.

Zhang, H., Timmermann, B.N.; *J Nat Prod* (2016) **79**: 732-42.

16



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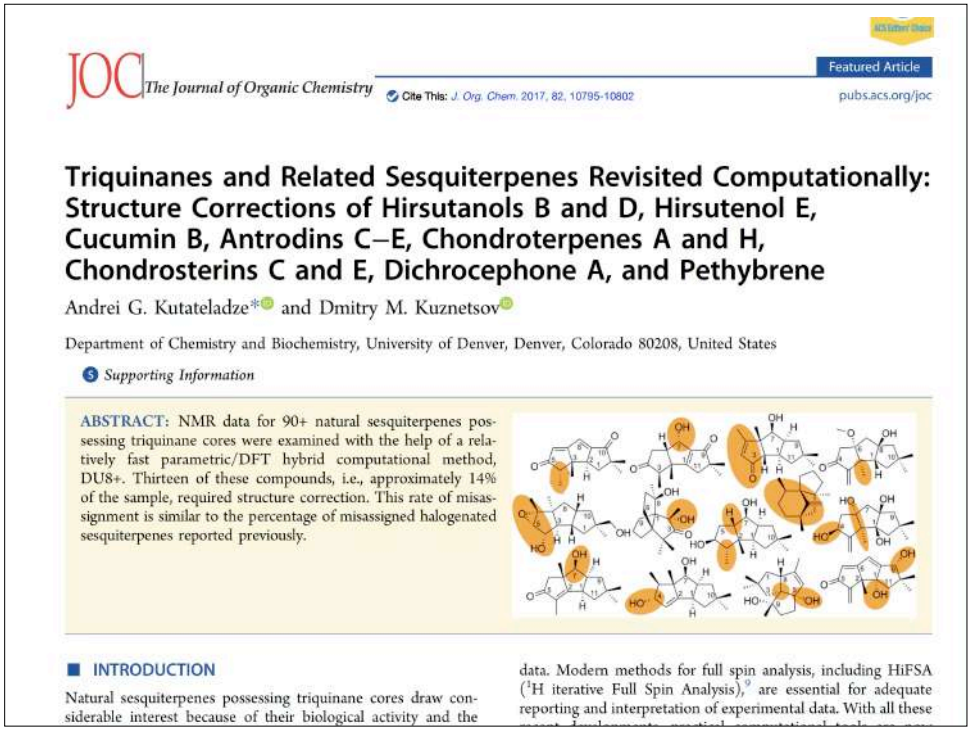

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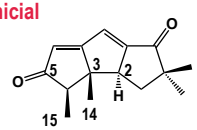
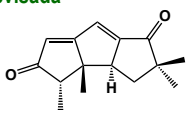
Cucumin B: Cálculo de δ ^{13}C RMN mediante DU8+

Propuesta inicial



C-nom	iGau	Exp	Calc	diff
C1	9	35.98	36.05	0.07
C2*	1	46.97	54.07	7.10
C3	5	62.81	62.79	-0.02
C4*	8	52.87	55.57	2.70
C5	7	212.91	207.79	-5.12
C6~	6	121.84	121.13	-0.71
C7	4	191.78	191.70	-0.08
C8~	3	123.66	124.32	0.66
C9	2	158.54	157.05	-1.49
C10	11	206.93	208.70	1.77
C11	10	51.84	52.18	0.34
C12=*	15	24.18	24.49	0.31
C13=*	14	25.31	24.68	-0.63
C14=	12	26.90	22.94	-3.96
C15	13	17.91	10.42	-7.49

Estructura revisada



C-nom	iGau	Exp	Calc	diff
C1	9	35.98	35.95	-0.03
C2*	1	46.97	48.84	1.87
C3	5	62.81	62.67	-0.14
C4*	8	52.87	53.86	0.99
C5	7	212.91	210.24	-2.67
C6~	6	121.84	120.64	-1.20
C7	4	191.78	191.98	0.20
C8~	3	123.66	123.75	0.09
C9	2	158.54	158.36	-0.18
C10	11	206.93	208.78	1.85
C11	10	51.84	52.21	0.37
C12=*	15	24.18	24.56	0.38
C13=*	14	25.31	24.79	-0.52
C14=	12	26.90	27.59	0.69
C15	13	17.91	18.41	0.50

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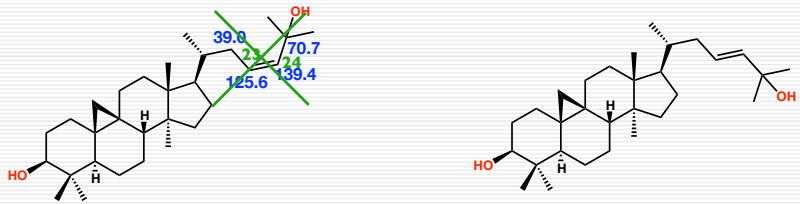
Propagación de errores en la identificación de PN

Cicloartanos



Kitajima, J., Kimizuka, K., Tanaka, Y.; *Chem Pharm Bull* (**1998**) 46: 1408-11.

Dellagreca, M., Fiorentino, A., Monaco, P., Previtera, L.; *Phytochemistry* (**1994**) 35: 1017-22.

de Pascual Teresa, J., Urones, J.G., Marcos, I.S., Basabe, P., Sexmero Cuadrado, M.J., Fernandez Moro, R.; *Phytochemistry* (**1987**) 26: 1767-76.

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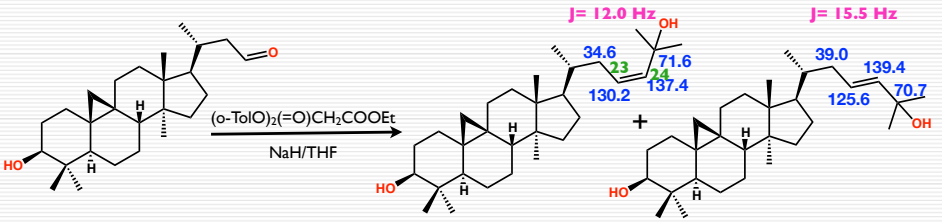
Ambigüedad en la isomería *Z/E* cadena de triterpenos

- Dificultad de determinación de la cte. de acoplamiento del H-24 (solapamiento de señales cuando el espectro se registra en $CDCl_3$)
  - Solución: obtener el espectro con otros disolventes deuterados
- Ambos isómeros han sido obtenidos mediante síntesis: Takahashi, *et al*.
- Resuelta la ambigüedad, la comparación de los desplazamientos de RMN ^{13}C será decisiva.
- La resolución de esta ambigüedad podrá ser aplicada a todos los triterpenos con la misma cadena: cicloartanos, euphanes, tirucallanes... con hidroxilo en C-25



Takahashi, S., Satoh, H., Hongo, Y., Koshino, H.; *J Org Chem* (**2007**) 72: 4578-81.

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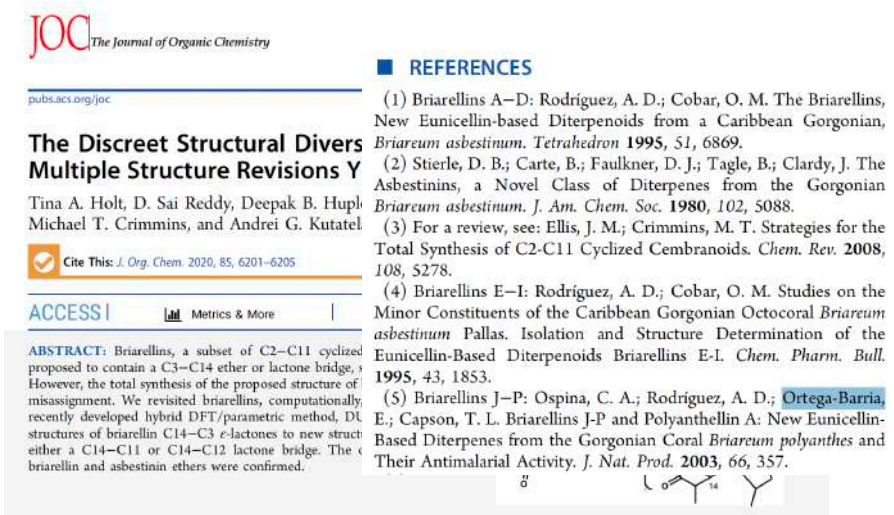
Corrección de la estructura de Briarellins



JOC The Journal of Organic Chemistry

pubs.acs.org/joc

The Discreet Structural Divers Multiple Structure Revisions Y

Tina A. Holt, D. Sai Reddy, Deepak B. Hupl Michael T. Crimmins, and Andrei G. Kutatel

Cite This: *J. Org. Chem.* 2020, 85, 6201−6205

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ABSTRACT: Briarellins, a subset of C2−C11 cyclized proposed to contain a C3−C14 ether or lactone bridge, However, the total synthesis of the proposed structure of misassignment. We revisited briarellins, computationally, recently developed hybrid DFT/parametric method, DU structures of briarellin C14−C3 *ε*-lactones to new struct either a C14−C11 or C14−C12 lactone bridge. The briarellin and asbestinin ethers were confirmed.

REFERENCES

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(2) Stierle, D. B.; Carte, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. The Asbestinins, a Novel Class of Diterpenes from the Gorgonian *Briareum asbestinum*. *J. Am. Chem. Soc.* **1980**, *102*, 5088.

(3) For a review, see: Ellis, J. M.; Crimmins, M. T. Strategies for the Total Synthesis of C2-C11 Cyclized Cembranoids. *Chem. Rev.* **2008**, *108*, 5278.

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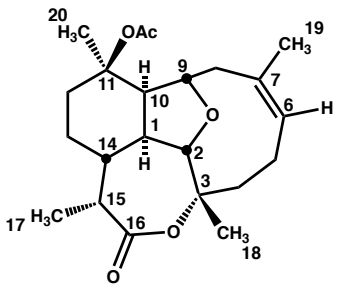
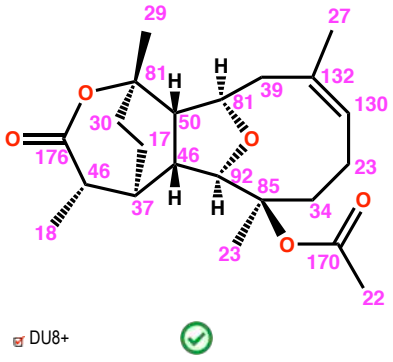
Corrección de la estructura de Briarellins



Briarelina J

Ospina, C.A., Rodríguez, A.D., Ortega-Barria, E., Capson, T.L.; *Journal of Natural Products* (2003) **66**: 357-63. 10.1021/np0204500



DU8+

Holt, T.A., Reddy, D.S., Huple, D.B., West, L.M., Rodríguez, A.D., Crimmins, M.T., Kutateladze, A.G.; *The Journal of Organic Chemistry* (2020) **85**: 6201-5. 10.1021/acs.joc.0c00555

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JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Structure Revision of Four Classes of Prenylated Aromatic Natural Products Based on a Rule for Diagnostic ^{13}C NMR Chemical Shifts

Fu-Cai Ren,‖ Li-Xia Wang,‖ Yong-Feng Lv, Jiang-Miao Hu,* and Jun Zhou*

Cite This: *J. Org. Chem.* 2021, 86, 10982−10990 Read Online

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ABSTRACT: Errors in elucidating the structures of four natural classes of prenylated aromatic compounds with 2,3-epoxy, 2,3-dihydroxy, and cyclization with an *ortho*-phenolic hydroxyl to give a pyran or furan ring moiety are frequent and inevitable. Based on rigorous literature research and a series of chemical transformation experiments, a rule for the rapid determination of these four classes of prenylated derivates based on ^{13}C NMR data was formulated, and 57 corrections featuring these fragments were accordingly reported.

Ren, F.-C., Wang, L.-X., Lv, Y.-F., Hu, J.-M., Zhou, J.; *The Journal of Organic Chemistry* (2021) **86**: 10982-90. 10.1021/acs.joc.0c02409

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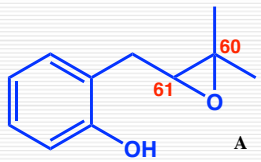
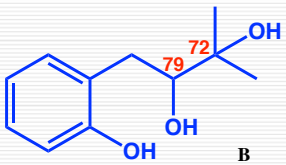


A



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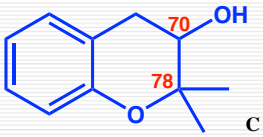
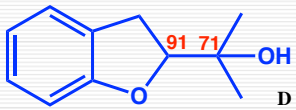


C



D

Presentes:

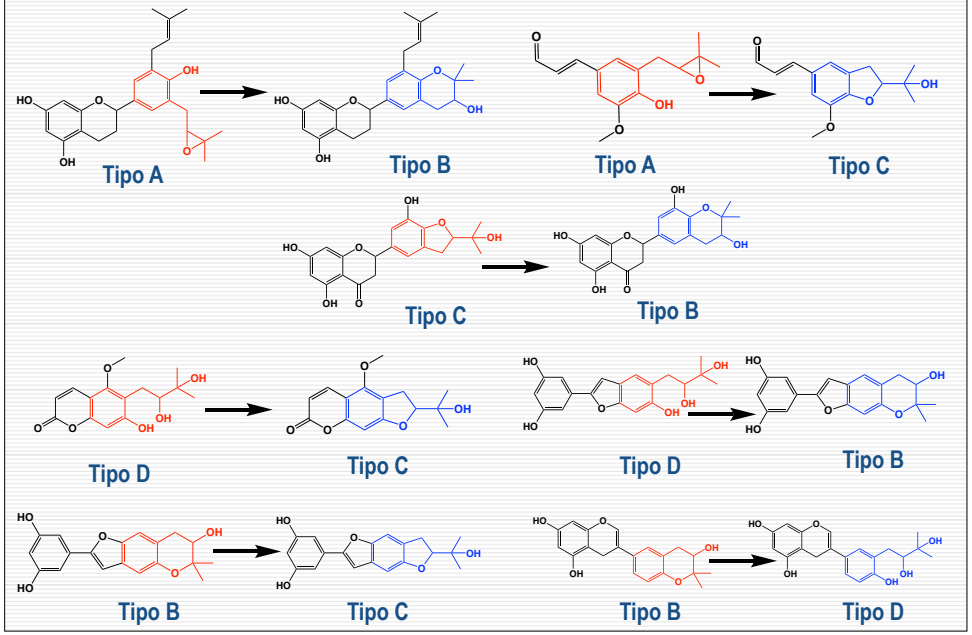
- Flavonoides
- Cumarinas
- Pterocarpanos
- Benzofenonas
- Xantonas
- Antraquinonas
- Neolignanos
- Cromanos

Valores numéricos expresados en ppm (partes por millón)

Ren, F.-C., Wang, L.-X., Lv, Y.-F., Hu, J.-M., Zhou, J.; *The Journal of Organic Chemistry* (2021) **86**: 10982-90. 10.1021/acs.joc.0c02409

25

Revision de prenilos oxidados en Productos Naturales

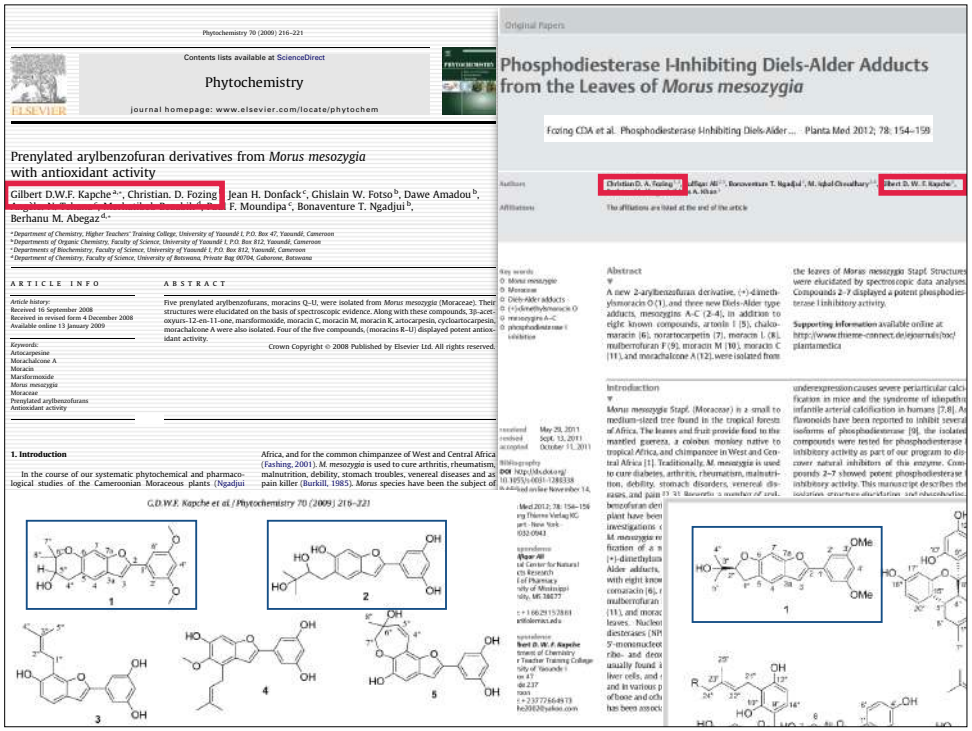


26

NAPROC-13 base de datos para la revisión estructural de Productos Naturales (PNs)

- Contiene un número muy significativo de sustancias cuya estructura ha sido revisada
  - Aparecidos en artículos de revisión
  - Detectados en NAPROC-13
  - Aplicación de la red neuronal desarrollada por Vawefunction
  - Cálculo computacional

27



Phytochemistry 70 (2009) 216–221

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem

Prenylated arylbenzofuran derivatives from *Morus mesozygia* with antioxidant activity

Gilbert D.W.F. Kapche [a,*], Christian. D. Fozing [a], Jean H. Donfack [c], Ghislain W. Fotso [b], Dawe Amadou [b], F. Moundipa [c], Bonaventure T. Ngadjui [b], Berhanu M. Abegaz [d,*]

ARTICLE INFO

ABSTRACT

Five prenylated arylbenzofurans, moracins Q–U, were isolated from *Morus mesozygia* (Moraceae). Their structures were elucidated on the basis of spectroscopic evidence. Along with these compounds, 39-acetoxyeurycomanone, oxyurs-12-en-11-one, mansfornoxide, moracin C, moracin M, moracin K, artocarpesin, cycloartocarpesin, and morachalcone A were also isolated. Four of the five compounds, (moracins R–U) displayed potent antioxidant activity.

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1. Introduction

In the course of our systematic phytochemical and pharmacological studies of the Cameroonian Moraceous plants (Ngadjui

Africa, and for the common chimpanzee of West and Central Africa (Fashing, 2001). *M. mesozygia* is used to cure arthritis, rheumatism, malnutrition, debility, stomach troubles, venereal diseases and as pain killer (Burkill, 1985). *Morus* species have been the subject of

G.D.W.F. Kapche et al. / Phytochemistry 70 (2009) 216–221

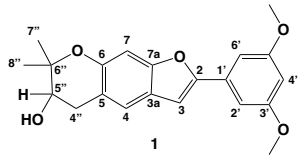
Original Papers

Phosphodiesterase I-Inhibiting Diels-Alder Adducts from the Leaves of *Morus mesozygia*

Fozing CDA et al. Phosphodiesterase I-Inhibiting Diels-Alder ... Planta Med 2012; 78: 154–159

28

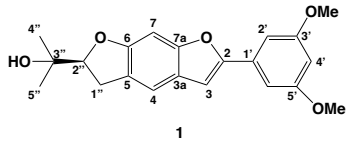
Phytochemistry



1

Position	^{13}C
1	–
2	155.6
3	103.6
3a	123.7
4	117.5
5	125.9
6	160.3
7	93.5
7a	156.4
1′	133.9
2′	103.4
3′	162.7
4′	101.4
5′	162.7
6′	103.4
4″a	31.1
4″b	
5″	91.7
6″	71.9
7″a	26.5
7″b	
8″	26.0
3′-OCH$_3$	56.2
5′-OCH$_3$	56.2

Phosphodiesterase I-Inhibiting Diels-Alder Adducts from the Leaves of *Morus mesozygia*



1

Table 1 $^{1}H^{a}$ and $^{13}C^{b}$ NMR spectroscopic data for (+)-dimethylsmoracin O (**1**).

Position	δ_H, mult.	δ_C, mult.
2	–	154.6, C
3	6.88, s	101.8, CH
3a	–	123.5, C
4	7.26, s	116.0, CH
5	–	123.6, C
6	–	157.9, C
7	6.91, s	92.9, CH
7a	–	155.1, C
1′	–	132.5, C
2′	6.93, d, 2.1	102.4, CH
3′	–	161.1, C
4′	6.41, t, 2.1	100.5, CH
5′	–	161.1, C
6′	6.93, d, 2.1	102.4, CH
1″	3.23, dd (15.6, 8.4)	30.4, CH_2
	3.39, dd (15.6, 9.0)	
2″	4.67, dd (9.0, 8.4)	90.3, CH
3″	–	71.8, C
4″	1.35, s	26.2, CH_3
5″	1.22, s	24.0, CH_3
3′-OCH_3	3.85, s	55.5, CH_3
5′-OCH_3	3.85, s	55.5, CH_3
3″-OH	1.92, s	–

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Drimane Sesquiterpenoids from the Fungus *Aspergillus ustus* Isolated from the Marine Sponge *Suberites domuncula*

Hongbing Liu,[†,▽] RuAngelie Edrada-Ebel,[‡] Rainer Ebel,[§] Yao Wang,[†] Barbara Schulz,[⊥] Siegfried Draeger,[⊥] Werner E. G. Müller,[#] Victor Wray,[∧] Wenhan Lin,*[,○] and Peter Proksch*[,†]

Institut für Pharmazeutische Biologie und Biotechnologie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, Geb. 26.23, 40225 Düsseldorf, Germany, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, The John Arbuthnott Building, 27 Taylor Street, Glasgow G4 0NR, U.K., Department of Chemistry, University of Aberdeen, Meston Building, Meston Walk, AB24 3UE, Aberdeen, U.K., Institut für Mikrobiologie, Technische Universität Carolo-Wilhelmina zu Braunschweig, Spielmannstrasse 7, 38106 Braunschweig, Germany, Institut für Physiologische Chemie und Pathobiochemie, Johannes-Gutenberg-Universität, Duesbergweg 6, 55128 Mainz, Germany, Helmholtz Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany, State Key Laboratory of Natural and Biomimetic Drugs, Peking University, 100083 Beijing, People's Republic of China, and Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, 266003 Qingdao, People's Republic of China

Received April 15, 2009

Seven new drimane sesquiterpenoids (**1**–**3**, **6**–**9**), along with the known compounds deoxyuvidin B (**4**), strobilactone B (**5**), and RES-1149-2 (**10**), were obtained from cultures of the fungus *Aspergillus ustus*, which was isolated from the marine sponge *Suberites domuncula*. Their structures were established by means of spectroscopic analyses including one- and two-dimensional NMR spectroscopy and high-resolution MS. Compounds **6**, **7**, and **10** showed cytotoxic activity against a panel of tumor cell lines, including L5178Y, HeLa, and PC12 cells, with **7** being the most active (EC_{50} against L5178Y cell line: 0.6 μg/mL).

Drimane sesquiterpenoids are widely recognized as bioactive metabolites of terrestrial plants, marine animals such as sponges and mollusks, and fungi[1] and have attracted wide attention due to their biological activities, which include antibacterial, antifungal, antifeedant, plant-growth regulatory, cytotoxic, phytotoxic, piscicidal, and molluscicidal effects.[1−3] Fungal drimanes have a broad occurrence and have been reported from various members of the genus *Aspergillus*[4,5] including strains isolated from marine sponges.[6] In our continued search for new biologically active metabolites from marine-derived fungi,[6] the sponge-derived fungus *Aspergillus ustus* attracted our attention due to the cytotoxic activity of its crude EtOAc extract against the murine lymphoma cell line L5178Y. Chromatographic separation of the extract resulted in the isolation and structural identification of 10 drimane sesquiterpenoids including the new natural products **1**–**3** and **6**–**9**. Structure elucidation of the new compounds by one- and two-dimensional NMR spectroscopy and mass spectrometry and evaluation of their cytotoxic activity are reported.

Results and Discussion

The cytotoxic EtOAc extract of an *Aspergillus ustus* (Trichocomaceae) culture was subjected to repeated column chromatography over silica gel and Sephadex LH-20 and to semipreparative HPLC to afford seven new drimane sesquiterpenoids (**1**–**3** and **6**–**9**), together with three known compounds: deoxyuvidin B (**4**), isolated previously from the plant pathogen *Alternaria brassicae*;[7] strobilactone B (**5**), obtained from the edible mushroom *Strobilurus ohshimae*;[8] and RES-1149-2 (**10**), from an *Aspergillus* sp.[4,5]

Compound **1** was isolated after purification by HPLC as a white powder. The molecular formula $C_{15}H_{24}O_4$ was assigned to **1** on the basis of HRESIMS (found *m/z* 269.1750 [M + H]$^+$, calcd 269.1753). The ^{1}H NMR spectrum (Table 1) exhibited resonances for four tertiary methyl groups [δ_H 0.98 (H_3-15), 1.00 (H_3-14), 1.11 (H_3-13), and 1.95 (d, J = 1.3 Hz, H_3-12)], an oxymethylene [δ_H 3.62 and 3.50 (both d, J = 11.3 Hz, H_2-11)], an olefinic proton [δ_H 5.59 (d, J = 1.3 Hz, H-7)], and three exchangeable protons [δ_H 4.37 (OH-3), 4.95 (OH-9), and 4.83 (OH-11)]. The ^{13}C NMR spectrum (Table 2) displayed 15 carbon signals, including those assigned to a ketone carbonyl group (δ_C 200.5, C-6), two olefinic carbons, three oxygenated carbons, four methyls, and five sp^3 carbons. With four degrees of unsaturation accounted for by the molecular formula, the structure of **1** was suggested to contain two rings, in association with a double bond and a carbonyl group. The NMR data of **1** (Tables 1 and 2) were closely related to those of 9,11-dihydroxy-6-oxodrim-7-ene,[3] indicating the presence of a drimane sesquiterpenoid skeleton. The key difference was that **1** possesses an additional hydroxyl group, which resides at C-3 of ring A on the basis of correlations in the COSY experiments, between OH-3/H-3, H-3/H_2-2, and H_2-2/H_2-1, and based on HMBC correlations from H_3-13 and H_3-14 to C-3. The relative configuration of **1** was

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⊥ Technische Universität Carolo-Wilhelmina zu Braunschweig.
Johannes-Gutenberg-Universität.
∧ Helmholtz Centre for Infection Research.
○ Peking University.
▽ Ocean University of China.

10.1021/np900220r CCC: $40.75
Published on Web 08/14/2009

Sesquiterpenoids and Benzofuranoids from the Marine-Derived Fungus *Aspergillus ustus* 094102

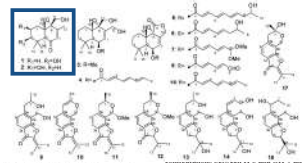
Zhenyu Lu,[†] Yi Wang,[†] Chengdu Miao,[‡] Peipei Liu,[†] Kui Hong,*[,†,§] and Weiming Zhu*[,†]

Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, People's Republic of China, and Institute of Tropical Biological Sciences and Biotechnology, Chinese Academy of Tropical Agricultural Science, Haikou 571101, People's Republic of China

Received May 1, 2009

Eight drimane sesquiterpenes (**1**–**8**), six isochromane derivatives (**9**–**14**), and three known compounds, daldinin B (**15**), 9α-hydroxy-6β-[(2*E*,4*E*,6*E*)-octa-2,4,6-trienoyloxy]-5α-drim-7-en-11,12-olide (**16**), and pergillin (**17**), were isolated from the EtOAc extract of the marine-derived fungus *Aspergillus ustus* 094102. The structures of the new compounds were elucidated on the basis of spectroscopic analysis. The cytotoxic effects on A549 and HL-60 cell lines were evaluated by SRB and MTT methods. Ustusorane E (**13**) showed significant cytotoxicity against HL-60 cells with an IC_{50} value of 0.13 μM. Ustusolates C (**6**) and E (**8**) exhibited moderate cytotoxicity against A549 and HL-60 cells with IC_{50} values of 10.5 and 9.0 μM, respectively, and ustusolate A (**4**) showed weak cytotoxicity against HL-60 and A549 cells with IC_{50} values of 20.6 and 30.0 μM, respectively.

As a part of our ongoing search for active compounds from microorganisms isolated from unusual or specialized ecological niches,[1−3] we recently have focused on the microorganisms from mangrove plants. Due to the special living environment of low-



tification of 14 new compounds including three drimane sesquiterpenes [ustusols A−C (**1**−**3**), five drimane sesquiterpene esters [ustusolates A−E (**4**−**8**)], six benzofuran derivatives [ustusoranes A−F (**9**−**14**)], and three known compounds [daldinin B (**15**),[12] 9α-hydroxy-6β-[(2*E*,4*E*,6*E*)-octa-2,4,6-trienoyloxy]-5α-drim-7-en-11,12-olide (**16**),[13] and pergillin (**17**)[14]] from the fermentation broth of *A. ustus* 094102. Among them, compounds **7**, **11**, and **12** are all methyl acetals and might be isolation artifacts formed by the reaction of the corresponding aldehyde (**8**) or hemiacetals with MeOH. Only seven drimane sesquiterpene esters esterified at C-6 have been reported previously.[10,14]

Results and Discussion

Ustusol A (**1**), obtained as a white solid, was assigned the molecular formula $C_{15}H_{24}O_4$ from HRESIMS (*m/z* 269.1762 [M + H]$^+$), which was consistent with four degrees of unsaturation. The IR spectrum showed the presence of hydroxy groups (3520, 3440, 3380 cm^{-1}) and a conjugated carbonyl group (1660 cm^{-1}). The ^{1}H

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‡ Institute of Tropical Biological Sciences and Biotechnology.

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Published on Web 09/21/2009

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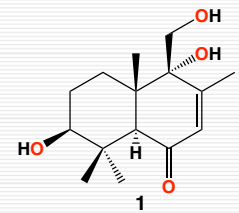
Sesquiterpenoides aislados del hongo *Aspergillus ustus*



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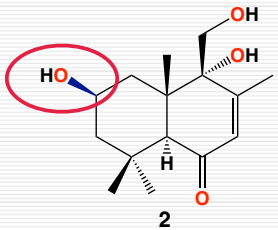
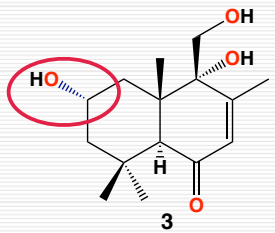


2

Ustusol A



3

Epímero C-2

Liu, H., Edrada-Ebel, R., Ebel, R., Wang, Y., Schulz, B., Draeger, S., Müller, W.E.G., Wray, V., Lin, W., Proksch, P.; *Journal of Natural Products* (2009) **72**: 1585-8.

Lu, Z., Wang, Y., Miao, C., Liu, P., Hong, K., Zhu, W.; *Journal of Natural Products* (2009) **72**: 1761-7.

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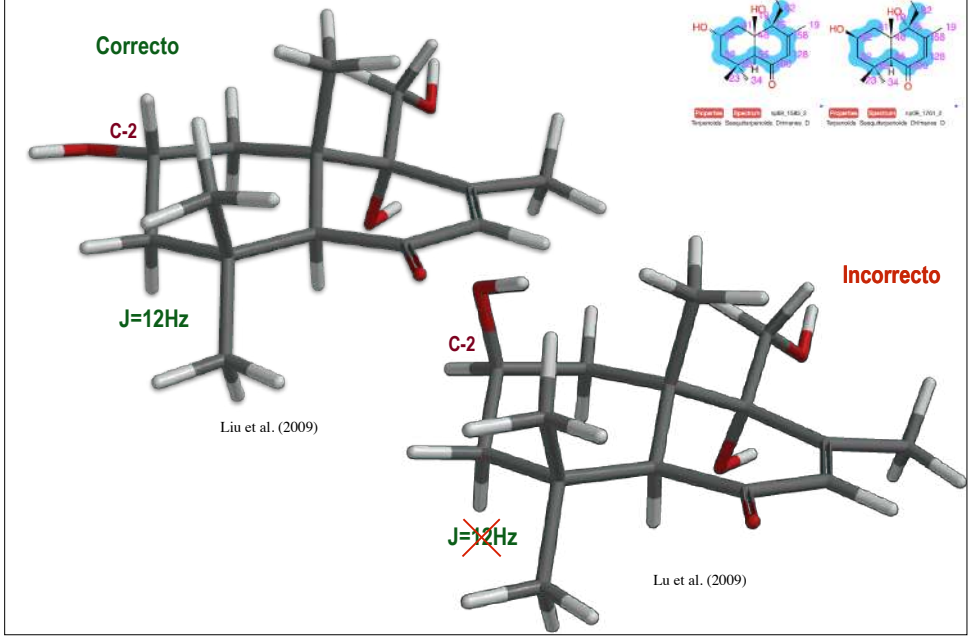

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Propagación de errores - Caso Rubesanolide D

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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5039

www.rsc.org/obc

PAPER

Rubesanolides C–E: abietane diterpenoids isolated from *Isodon rubescens* and evaluation of their anti-biofilm activity†

Juan Zou,[a,b] Lutai Pan,*[a] Qiji Li,[a] Jianxin Pu,[b] Ping Yao,[c] Min Zhu,[d] Jeffrey A. Banas,[d] Hongjie Zhang*[c] and Handong Sun[b]

Received 26th January 2012, Accepted 13th April 2012
DOI: 10.1039/c2ob25192b

Phytochemical study of the leaves of the medicinal plant *Isodon rubescens* led to the isolation of three novel abietane diterpenoids, rubesanolides C–E (**1–3**). These diterpenes contain a unique *γ*-lactone subgroup formed between C-8 and C-20. Their structures were determined from analysis of spectroscopic data, and were further confirmed by X-ray crystallographic data. The compounds were evaluated for their antibacterial activity, and rubesanolide D (**2**) demonstrated inhibition activity against biofilm formation of the dental bacterium *Streptococcus mutans*.

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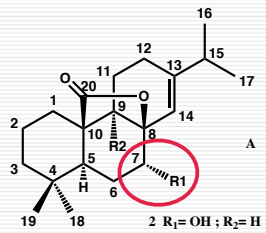
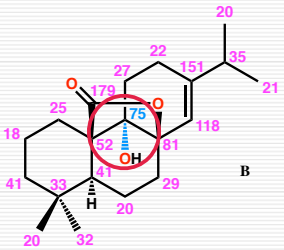
Propagación de errores - Caso Rubesanolide D





Número de carbono	Desplazamiento; multiplicidad obc12_5039_2		
1	24.7; CH_2	11	26.6; CH_2
2	18.1; CH_2	12	22.2; CH_2
3	41.2; CH_2	13	150.7; C
4	33.4; C	14	117.7; CH
5	41.4; CH	15	34.7; CH
6	19.8; CH_2	16	20.2; CH_3
7	28.8; CH_2	17	20.7; CH_3
8	81.1; C	18	32.1; CH_3
9	75.1; C	19	20.0; CH_3
10	51.8; C	20	178.8; CH_3

Zou, J., Pan, L., Li, Q., Pu, J., Yao, P., Zhu, M., Banas, J.A., Zhang, H., Sun, H.; *Organic & Biomolecular Chemistry* (2012) **10**: 5039-44. 10.1039/C2OB25192B

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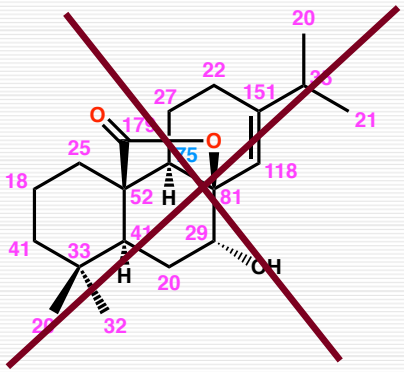
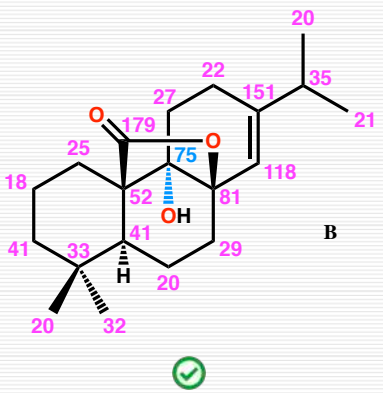
Propagación de errores - Caso Rubesanolide D





Zou, J., Pan, L., Li, Q., Pu, J., Yao, P., Zhu, M., Banas, J.A., Zhang, H., Sun, H.; *Organic & Biomolecular Chemistry* (2012) **10**: 5039-44. 10.1039/C2OB25192B

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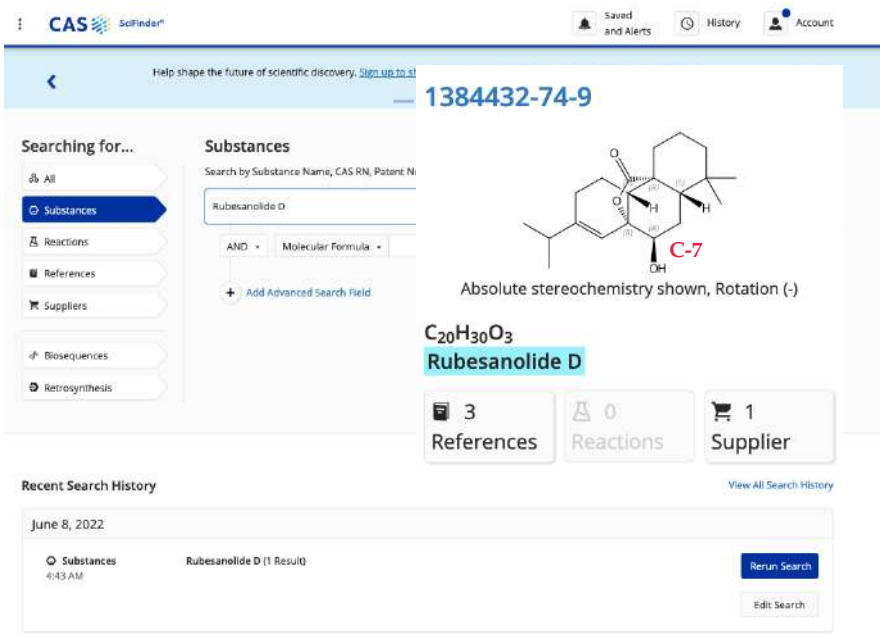
Búsqueda del CAS con SciFinder - Caso Rubesanolide D



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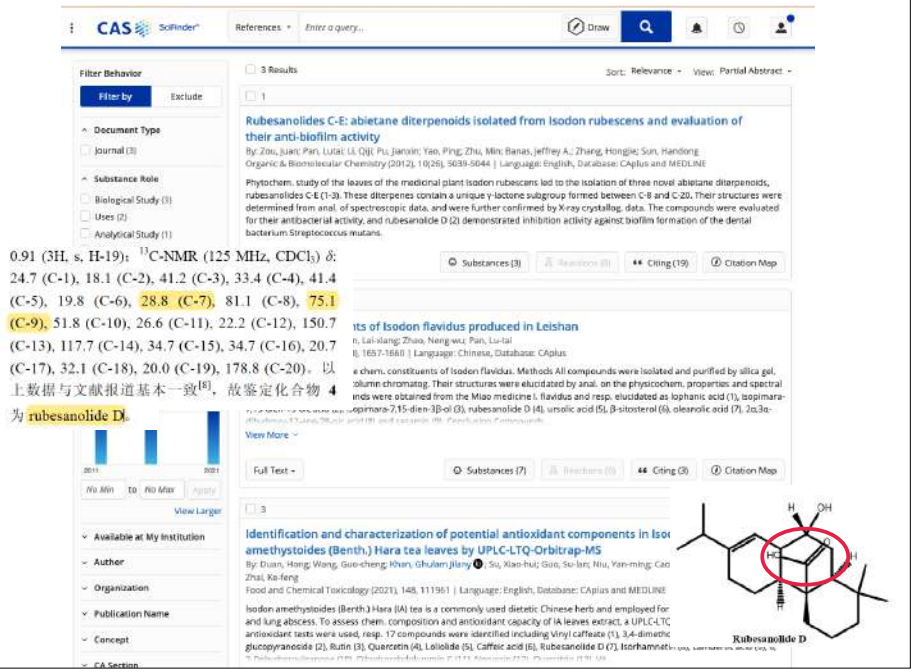
Búsqueda CAS con SciFinder- Caso Rubesanolide D



0.91 (3H, s, H-19); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.7 (C-1), 18.1 (C-2), 41.2 (C-3), 33.4 (C-4), 41.4 (C-5), 19.8 (C-6), 28.8 (C-7), 81.1 (C-8), 75.1 (C-9), 51.8 (C-10), 26.6 (C-11), 22.2 (C-12), 150.7 (C-13), 117.7 (C-14), 34.7 (C-15), 34.7 (C-16), 20.7 (C-17), 32.1 (C-18), 20.0 (C-19), 178.8 (C-20)。以上数据与文献报道基本一致[8]，故鉴定化合物 **4** 为 rubesanolide D。

NAPROC-13 base de datos para la revisión estructural de Productos Naturales (PNs)

- Contiene un número muy significativo de sustancias cuya estructura ha sido revisada
  - Aparecidos en artículos de revisión
  - Detectados en NAPROC-13
  - Aplicación de la red neuronal desarrollada por Vawefunction
  - Cálculo computacional

Protocolo para realizar cálculos computacionales para 13C

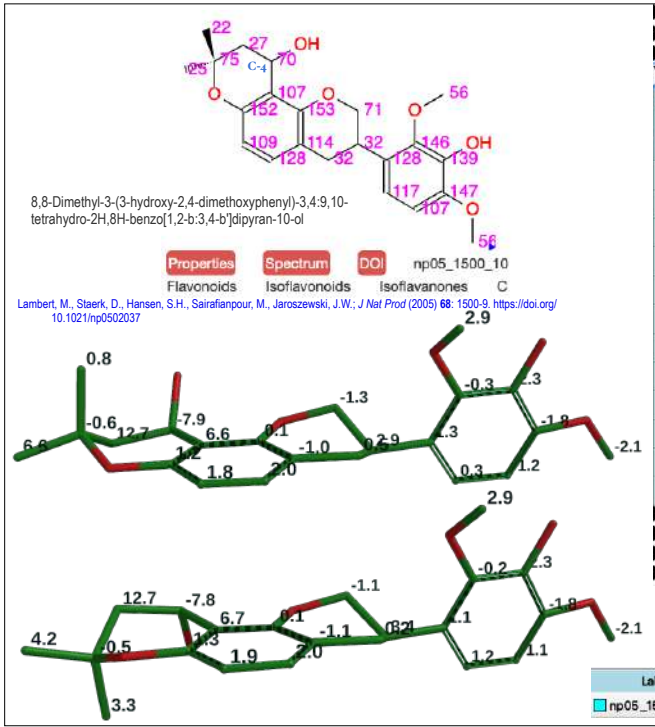
1) Búsqueda conformacional sistemática mediante mecánica molecular MMFF; se eliminan confómeros duplicados y con energía superior a 40kJ/mol por encima del mínimo global

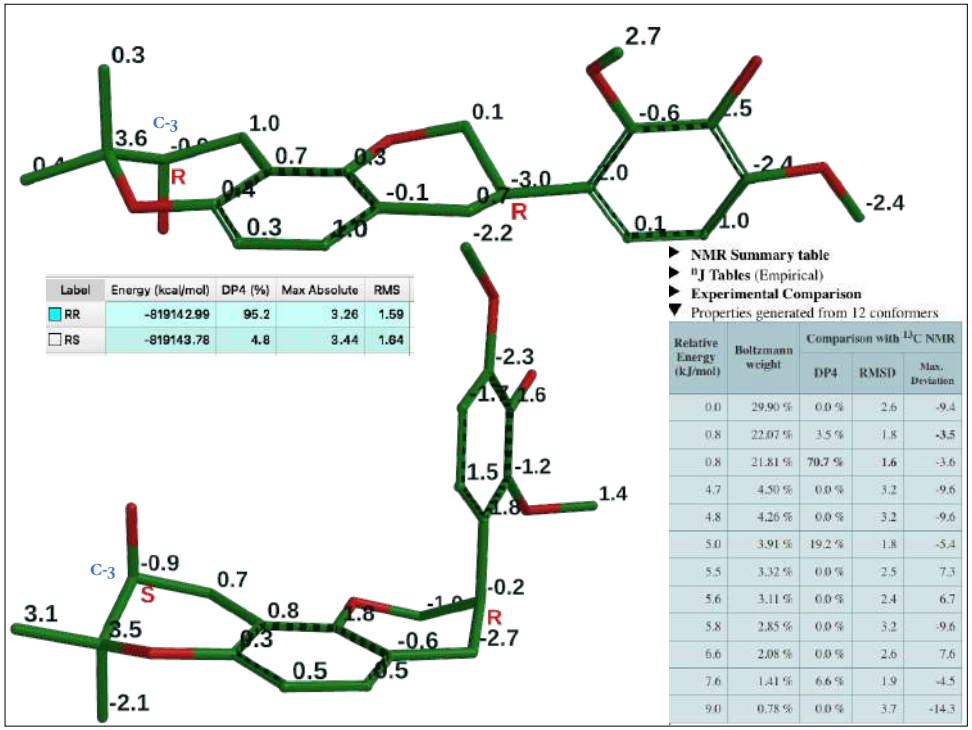
2) Cálculo geométrico con HF/3-21G, eliminando confómeros duplicados y aquellos con energía superior a 40kJ/mol por encima del mínimo global

3) Cálculo energético con el modelo ωB97X-D/6-31G* y eliminación de confómeros superiores a 15kJ/mol respecto al mínimo global

4) Cálculo de la geometría con el modelo ωB97X-D/6-31G* y eliminación de los conformadores con energías superiores a 10 kJ/mol respecto a la del mínimo global

5) Cálculo energético con el modelo ωB97X-V/6-311+G(2df,2p) [6-311G*].





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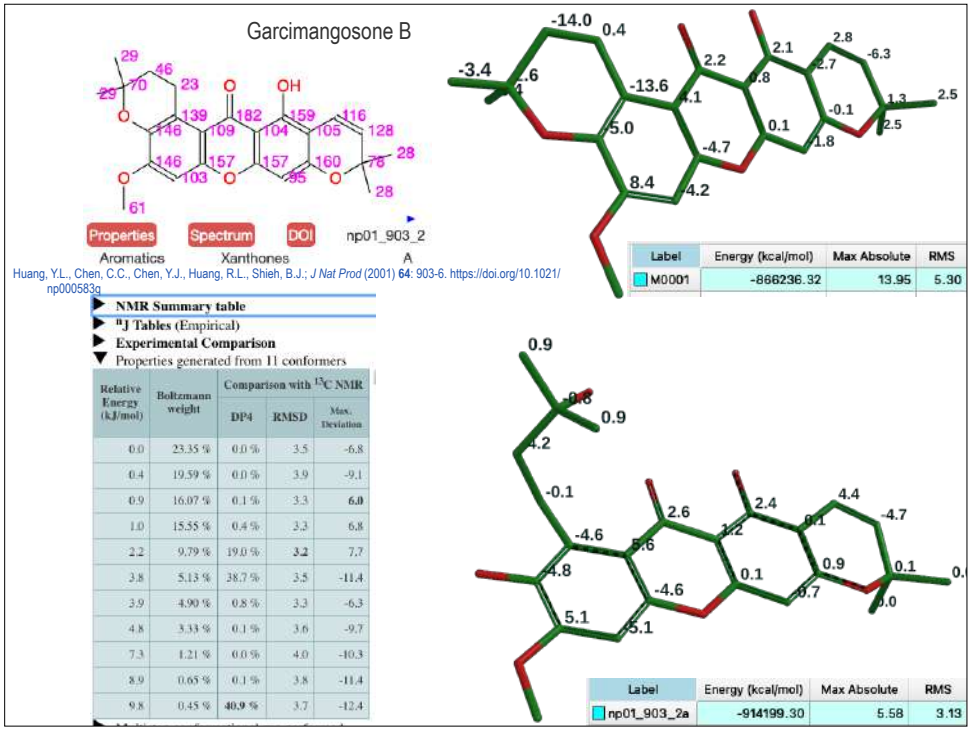

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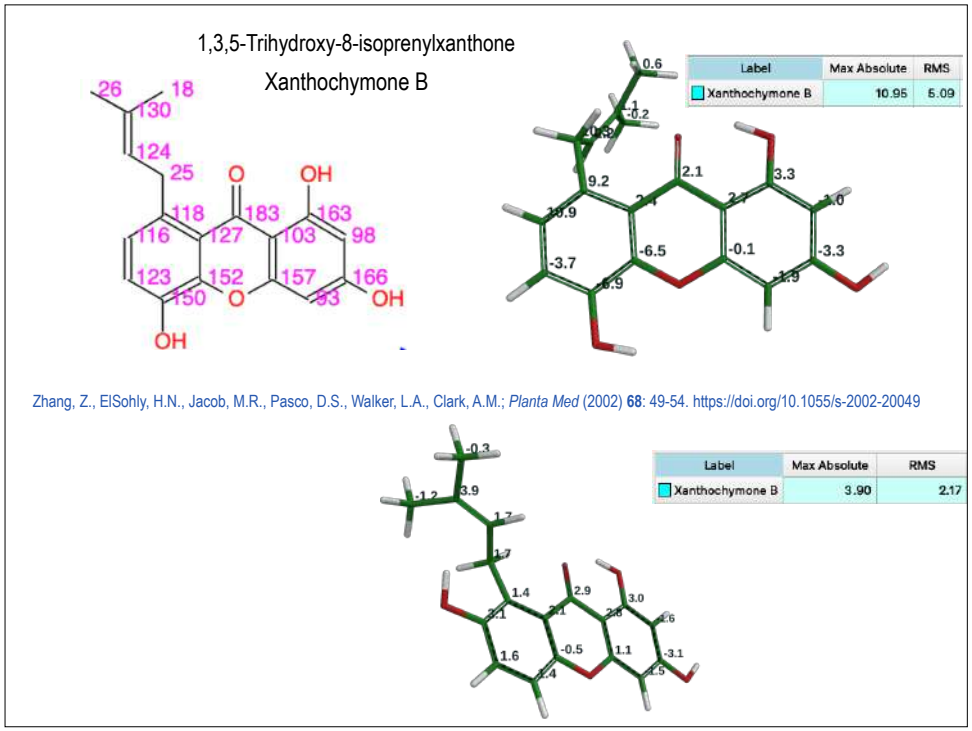

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Consideración final

- **Actualmente se ha priorizado la revisión estructural para mejorar la calidad de NAPROC-13**

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Conclusiones

- NAPROC-13 representa una poderosa herramienta en lo que sigue siendo un gran desafio como lo es el descubrimiento de PNs
- NAPROC-13 es una herramienta confiable en la investigación química ya que de forma constante se realizan revisiones y correcciones de errores estructurales.
- NAPROC-13 propicia el desarrollo de una nueva línea de investigación, donde la aplicación de la química computacional sobre estructuras dudosas permite validar y proponer una estructura correcta.
- NAPROC-13 al ser una base de datos de de-replicación optimiza el tiempo y la obtención de resultados de las investigaciones que tienen como objeto los PNs.

- La comunidad científica estamos llamados a ser parte de este proyecto, para su implementación, uso y contínuo desarrollo.
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