ORGANIC LETTERS

2006
Vol. 8, No. 22
5001−5004

^{13}C NMR-Based Empirical Rules to Determine the Configuration of Fatty Acid Butanolides. Novel γ-Dilactones from *Pterogorgia* spp

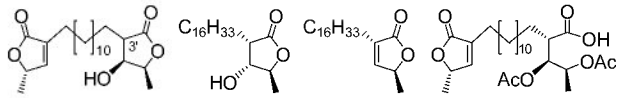
Manuel Lorenzo,[†] Inmaculada Brito, Mercedes Cueto, Luis D'Croz,[‡,§] and José Darias*

Instituto de Productos Naturales y Agrobiología del CSIC, Avenida Astrofísico F. Sánchez, 3, 38206 La Laguna, Tenerife, Spain, Universidad de Magallanes, Avenida Bulnes 01855, and Centro de Estudios del Cuaternario, Casilla 113-D, Punta Arenas, Chile, Smithsonian Tropical Research Institute (STRI), P.O. Box 2072, Balboa, Panama, and Departamento de Biología Marina y Limnología, Estafeta Universitaria, Universidad de Panamá, Panama

jdarias@ipna.csic.es

Received June 27, 2006

ABSTRACT



1: 3' β
2: 3' α
3
4
5

Diastereomeric γ-dilactones isolated from *Pterogorgia* spp allowed the establishment of ^{13}C NMR-based empirical rules to determine the relative stereochemistry of 3-alkyl-4-hydroxy-5-methyl-2(5*H*)-dihydrofuranones, γ-lactone moieties ubiquitous in many bioactive synthetic and natural products. An NMR-based method using Pirkle's reagent at low temperature allowed the absolute configuration of the naturally occurring dibutenolides to be unambiguously determined. A biogenetic pathway that involves oxidation of long-chain (C16:0 and C18:0) fatty acids is proposed.

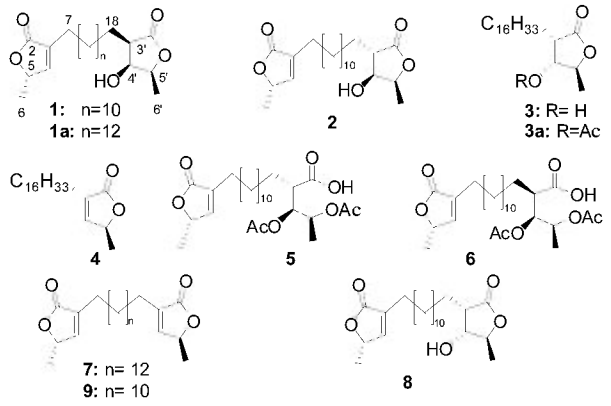
Ancepsenolide, the first bisbutenolide lipid isolated from a marine organism, the gorgonian *Pterogorgia anceps*, was described in 1966.[1] Surprisingly, after 40 years, there are very few papers related to *Pterogorgia*, despite the fact that this genus is noted for its ability to biosynthesize a unique class of interesting C_2 symmetric long-chain fatty acid dilactone derivatives, the importance of its γ-lactone unit as a generic inhibitor of enzymes,[2] and other biological[3] and biomedical properties.[2] The search for marine natural products in benthic species from both sides of the Isthmus of Panama[4] prompted us to study the Caribbean octocoral *Pterogorgia* spp. In this paper, we report on empirical rules based on ^{13}C NMR spectroscopy that allow us to determine the relative stereochemistry of the 3-alkyl-4-hydroxy-5-methyl-2(5*H*)-dihydrofuranone ring, a γ-lactone motif ubiquitous in many bioactive natural products isolated from marine organisms,[5] plant species especially of the Annonaceae family,[6] fungi,[7] and bacteria.[8] The key feature of the

[†] Universidad de Magallanes.
[‡] Smithsonian Tropical Research Institute.
[§] Universidad de Panama.

(1) Schmitz, F. J.; Kraus, K. W.; Ciereszko, L. S.; Sifford, D. H.; Weinheimer, A. J. *Tetrahedron Lett.* **1966**, 97−104.
(2) Konaklieva, M. I.; Plotkin, B. J. *Mini-Rev. Med. Chem.* **2005**, 73−95.
(3) O'Neal, W.; Pawlik, J. R. *Mar. Ecol.: Prog. Ser.* **2002**, *240*, 117−126.
(4) (a) Dorta, E.; Díaz-Marrero, A. R.; Cueto, M.; D'Croz, L.; Maté, J. L.; Darias, J. *Org. Lett.* **2004**, *6*, 2229−2232. (b) Cueto, M.; D'Croz, L.; Maté, J. L.; San-Martín, A.; Darias, J. *Org. Lett.* **2005**, *7*, 415−418.
(5) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. R.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26−78, and earlier reports in the series.
(6) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540.
(7) Pathirana, C. P.; Dwight, R.; Jensen, P. R.; Fenical, W. F.; Delgado, A.; Brinen, L. S.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 7001−7004.

10.1021/ol061572c CCC: $33.50
Published on Web 10/06/2006

method stems from the comparison of the ^{13}C NMR chemical shift average and δ values of C-4 and C-5 at the butanolide moiety of compounds isolated from *Pterogorgia* spp. These compounds include the novel **1**−**5**, isolated for the first time by us, the known **6**,[9] homoancepsenolide[10] **7**, and hydroxyancepsenolide **8**.[11]



5*S*,3 *R*,4 *S*,5 *S*-Hydroxyancepsenolide **1** was obtained as an optically active white powder $[\alpha]^{20}_D$ −24 (*c*, 0.63, $CHCl_3$) with a mass of 380.2565 corresponding to an elemental composition of $C_{22}H_{36}O_5$. The NMR spectroscopic data of **1** resemble those of the bislactone system of hydroxyancepsenolide **8**, which is in accord with the degree of unsaturation. The resonances of H-4−H-7 and C-2−C-7 in the respective ^1H NMR and ^{13}C NMR spectra of the corresponding substituted butenolide units were identical in both compounds (for ^1H and ^{13}C NMR tables, see Supporting Information). The MS spectra of **1** and **8** showed the same molecular ion and a similar fragmentation pattern. However, chemical shift differences at comparable carbons (C-2 −C-6) and protons (H-3 −H-6) of the butanolide half indicated that **8** and **1** are diastereomers.

5*S*,3 *S*,4 *S*,5 *S*-Hydroxyancepsenolide **2** was a white amorphous powder $[\alpha]^{20}_D$ −22 (*c*, 0.32, $CHCl_3$). NMR data coupled with a molecular ion at *m/z* 380 (HREIMS) suggested a molecular formula of $C_{22}H_{36}O_5$ expressing five degrees of unsaturation. The ^{13}C NMR data and a DEPT NMR experiment were consistent for a long-chain fatty acid dilactone having a butenolide and a butanolide moiety when compared with the values of **1** and **8**. That **2** is isomeric with **1** and **8** was also evidenced by their similar fragmentation patterns in the MS spectrum.

The butanolide part of **1** and **2** has three contiguous stereogenic centers embodied in the 3 -alkyl-4 -hydroxy-5 -methyl-2(5*H*)-dihydrofuranone ring, and the relative all-cis stereochemistry of the sterically congested compound **1** was inferred by the NMR and MS spectral data of **1** that are identical with those of a compound resulting from acid-catalyzed methanolysis of a known[9] metabolite **6** also isolated in this work. Furthermore, the NMR data of **1** were almost identical to those of a recently isolated homologous metabolite **1a**.[12] The observed NOEs—H_3-6 /H_2-18, H-4 /H-5 , H-3 , and H-3 /H-5 —confirmed the stereochemistry. The configuration of the butanolide fragment of **2** was deduced by comparison of its ^{13}C NMR data with those of a synthetic[13] model **d**4 (Table 1) and supported by the observed NOE between H-3 and H_3-6 .

Table 1. δ_C of C-4 and C-5 of the Butanolide Moiety

#	R	3'*R, 4'*R, 5'*S	$\delta_{C\text{-}4'}$	$\delta_{C\text{-}5'}$
a1	n-Bu[23]		79.1	79.9
a2	iso-Bu[8]		78.9	80.1
a3	$C_6H_6(CH_2)_{13}$[17,24a]		78.9	80.1
a4	$CH_3CH_2CH(CH_3)CH_2$[8]		79.8	79.9
a5	$C_{16}H_{33}$[23a]		79.1	79.8
a6	CH_2=CH$(CH_2)_2$CH=CH(C≡C)$_2(CH_2)_6$[18]		78.7	80.1
#	R	3'*R, 4'*S, 5'*S	$\delta_{C\text{-}4'}$	$\delta_{C\text{-}5'}$
b1	n-Bu[25]		71.0	79.2
b2	$C_{14}H_{29}$[24,25]		71.1	78.8
b3	$C_6H_6(CH_2)_{13}$[24a]		71.3	78.6
b4	$Me(CH_2)_7C{\equiv}C(CH_2)_{10}$[16]		71.2	79.0
1	moiety of **1**		71.2	78.7
#	R	3'*S, 4'*R, 5'*S	$\delta_{C\text{-}4'}$	$\delta_{C\text{-}5'}$
c1	$Me(CH_2)_3C{=}C(CH_2)_6$[26]		73.9	82.3
c2	$CH_2O_2C_6H_6$-$(CH_2)_9$[26]		73.7	82.5
3	moiety of **3** ($C_{16}H_{33}$)		73.8	82.5
8	moiety of **8**		73.8	82.1
#	R	3'*S, 4'*S, 5'*S	$\delta_{C\text{-}4'}$	$\delta_{C\text{-}5'}$
d1	$Me(CH_2)_3C{=}C(CH_2)_6$[26]		74.1	78.1
d2	$CH_2O_2C_6H_6$-$(CH_2)_9$[26]		74.1	78.0
d3	$CH_2O_2C_6H_6$-$(CH_2)_{11}$[26]		74.1	78.0
d4	$C_{16}H_{33}$[13]		73.8	78.8
2	moiety of **2**		74.1	78.1

Compound **3** was isolated as a white powder $[\alpha]^{20}_D$ +7 (*c*, 0.88, $CHCl_3$). NMR data coupled with a molecular ion at *m/z* 340.2983 (HREIMS) suggested a molecular formula of $C_{21}H_{40}O_3$, indicating three degrees of unsaturation. The ^{13}C NMR data and a DEPT NMR experiment were consistent for a butanolide unit having a saturated lineal C_{16} side chain when compared with the reported values for **8**. The structure **3** was corroborated by acetylation to afford a compound whose NMR data are identical to those reported for the known acetate **3a**.[14]

Compound **4** was a white powder $[\alpha]^{20}_D$ +22 (*c*, 1.1, $CHCl_3$). The molecular formula $C_{21}H_{38}O_2$, determined by HREIMS (*m/z* 322.2866), differs by 18 mass units from that of **3** suggesting that **4** is a dehydrated form of **3**. The spectroscopic data of **4** proved to be identical to those of the recently isolated enantiomer of **4**.[12]

The NMR data of **5** resemble those of the known compound **6**,[9] which is the butanolide open form of the

(8) Cho, K. W.; Lee, H.-S.; Rho, J.-R.; Kim, T. S.; Mo, S. J.; Shin, J. *J. Nat. Prod.* **2001**, *64*, 664−667.
(9) Schmitz, F. J.; Lorance, E. D. *J. Org. Chem.* **1971**, *36*, 719−721.
(10) Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod.* **1994**, *57*, 339−347.
(11) Schmitz, F. J.; Lorance, E. D.; Ciereszko, L. S. *J. Org. Chem.* **1969**, *34*, 1989−1990.
(12) Guo, Y.-W.; Gavagnin, M.; Mollo, E.; Trivellone, E.; Cimino, G. *J. Nat. Prod.* **1999**, *62*, 1194−1196.
(13) Ortuño, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1988**, *44*, 5139−5144.
(14) Ravi, B. N.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 105−112.

bislactone **1**. The structure and relative stereochemistry of **5** were secured by conversion to **2** through methanolysis.[9]

Compounds **1**, **2**, and **8** cover three of the four diastereomers resulting from hydration of one of the symmetrical butenolide units of ancepsenolide **9**. The *J* values observed in the ^{1}H NMR spectra of saturated five-membered ring compounds do not give conclusive information about the relative stereochemistry of the substituents on the ring. However, because compounds **1**, **2**, and **8**, along with **a**5 (Table 1), provide all four stereoisomers at C-4 and C-5 of the butanolide moiety, they offer an opportunity to compare their respective spectral data for stereochemical assessment. From this comparison, along with spectroscopic data available elsewhere from natural and synthetic compounds with an equivalent substitution pattern, it can be inferred that by ^{13}C NMR spectroscopy the correct relative configuration at C-3 , C-4 , and C-5 could be unambiguously established.

Table 1 shows examples of butanolide diastereomers, represented as **a**−**d**, where regular ^{13}C NMR chemical shifts for C-4 and C-5 can be observed in each of the following relative configurations: **a**, 3 **R*,4 **R*,5 **S* (entries **a**1−**a**6); **b**, 3 **R*,4 **S*,5 **S* (entries **b**1−**b**4, **1**); **c**, 3 **S*,4 **R*,5 **S* (**c**1−**c**2, **3**, **8**); and **d** 3 **S*,4 **S*,5 **S* (**d**1−**d**4, **2**). Average values around 1 ppm ($\Delta\delta_{C\text{-}5\,-C\text{-}4} \sim 1$) indicate a vicinal trans relative configuration when the lateral side chain and the methyl group are cis (typical values are $\delta_{C\text{-}4} \sim 79$ and $\delta_{C\text{-}5} \sim 80$), whereas values around 7.7 ppm ($\delta_{C\text{-}4} \sim 71.2$ and $\delta_{C\text{-}5} \sim 79$) are proper for an all-cis stereochemistry. An average of 8.6 ppm ($\delta_{C\text{-}4} \sim 73.8$ and $\delta_{C\text{-}5} \sim 82.4$) established that the alkyl side chain and the hydroxyl group are cis, and values of 4 ppm ($\delta_{C\text{-}4} \sim 74.1$ and $\delta_{C\text{-}5} \sim 78.1$) secured a relative cis configuration of the methyl and hydroxyl groups. Thus, the δ values for both C-4 and C-5 together with the ^{13}C chemical shift averages, schematized in Table 2, are differentiated and large enough to assess the whole relative configuration of an α-alkyl-β-hydroxy-γ-methyl-γ-lactone unit. The δ values for C-3 for the compounds representative of models **a**−**d** are around 48.6, 47.6, 43.7, and 49.2 ppm, respectively. These chemical shifts, except for those of models **c**, are too close to be applicable for the rule. The tabulated compounds were carefully selected for accurate comparison, looking, when possible, for diastereomers of natural and/or synthetic origin. Related work dealing with trisubstituted butanolides based on the ^{13}C chemical shift of the methyl group at C-5[15] and the α-methylene[16] of the alkyl side chain has been reported. From a survey on linear lipid butanolides, it was found that the stereochemistry of the butanolide segment of certain acetogenins does not match our criteria and should be corrected as follows: **a**3[17] (**b**→**a**). On the other hand, the unknown stereochemistry of saprathin **a**6[18] could be assigned as 3 **R*,4 **R*,5 **S*. Furthermore, structure revision[19a] based on the synthetic work of the lactone configuration of related annonaceous acetogenins, such as itrabin[19b] and jetein,[19b] supports the goodness of this rule. Therefore, this may be a useful tool for both synthetic and natural product chemists.

Table 2. ^{13}C Chemical Shift Average $\Delta\delta_C$ (ppm) of C-4 and C-5

$\Delta\delta_C$	C-3 −C-4	C-4 −C-5	C-3 −C-5	rel configuration
1	trans	trans	cis	3 **R*,4 **R*,5 **S*
4	trans	cis	trans	3 **S*,4 **S*,5 **S*
7.7	cis	cis	cis	3 **R*,4 **S*,5 **S*
8.6	cis	trans	trans	3 **S*,4 **R*,5 **S*

As far as the configuration at C-5 of the butenolide moiety is concerned, it may be epimerized upon treatment with weak base giving epimers that are undistinguishable by spectral data; in such instances, the absolute configuration of the butenolide fragment may not be known.[20] Because of the waxy nature of the linear acetogenins that do not allow direct X-ray crystallography, definite stereochemical assignments are not readily made. We therefore found it necessary to use a methodology that does not have a deleterious effect on the enantiomeric purity of the naturally occurring dilactones from *Pterogorgia* spp. Whereas intrinsic limitations make Mosher's technique inapplicable to the butanolide unit,[10] a NMR-based method using Pirkle's reagent at low temperature allowed the absolute configuration of annonaceous butenolides[21] and a γ-butenolide-containing diterpene[22] to be determined. Furthermore, this method can be successfully applied to measure the diastereomeric (or enantiomeric) excess of the same butenolide-containing compounds.[21] Thus, at first glance, it appears to be an ideal method to be applied to our compounds.

Homoancepsenolide **7** and ancepsenolide **9** are optically active compounds, implying that the methyl groups of each respective dibutenolide moiety must have the same configuration. Thus, the geometry of the chiral solvating agent (CSA)−substrate complex must produce selective shielding effects on protons of the substrate moiety as expected for an *R*,*R* or *S*,*S* configuration. It can be predicted[21] that the H-5 signal for (*S*,*S*) or (*R*,*R*) solvates appears upfield compared with the (*R*,*S*) or (*S*,*R*) solvates. Therefore, if $\Delta(\delta_{H\text{-}5R} - \delta_{H\text{-}5S})$ is positive, then the absolute configuration of the butenolide is (*S*). (*R*)- and (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (TFAE) were used to form complexes with the γ-methyl-γ-lactone units of **7**. NMR analysis of $\Delta\delta$ of H-5 of the two (CSA)−**7** complexes, tabulated in Table 3, gave clear evidence to assign the absolute stereochemistry at C-5 as 5*S*. Thus, the unknown absolute configuration of

Table 3. $\delta_{H\text{-}5}$ of Compounds **1**, **2**, **4**, and **7** with 12 equiv of *R*- and *S*-TFAE at 240 K

compound	δ_{HR}	δ_{HS}	$\Delta(\delta_{HR} - \delta_{HS})$
1	4.89331	4.85119	+0.04212
2	5.00807	4.97181	+0.03626
4	4.98596	4.95324	+0.03272
7	4.87483	4.80521	+0.06962

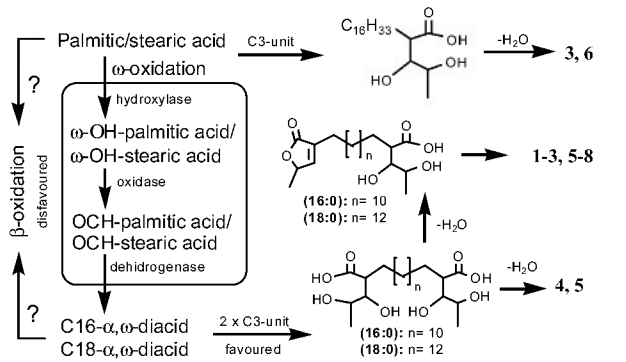
(15) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; Whitle, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846−3856.

homoancepsenolide **7** can now be assigned as 5*S*,5 *S*. The sign of the optical rotation of **7** is coincident with that of a (+)-ancepsenolide obtained from an (*S*)-lactic ester.[27] This method was also applied to resolve the absolute configuration of **1**, **2**, and **4** as 5*S*,3 *R*,4 *S*,5 *S*; 5*S*,3 *S*,4 *S*,5 *S*; and 5*S*, respectively (Table 3).

Both enantiomers of **4**[12,13] have been described. The optical rotation reported for the synthetic compound matches the optical rotation reported here for our compound (+26.7,[13] +22 in this work). Thus, the synthesis of **4** from (*S*)-lactic acid confirms the validity of Pirkle's model. Because the transformations **6**→**1** and **5**→**2** by methanolysis[9] proceeded without isomerization at either the butenolide or side-chain vicinal stereogenic centers, a 5*S*,3 *R*,4 *S*,5 *S* and a 5*S*,3 *S*,4 *S*,5 *S* absolute configuration were assigned for the naturally occurring compounds **6** and **5** due to those transformations and the coincidence of their respective optical rotations. This work provides unambiguous absolute configurations of the marine C_2 symmetric long-chain fatty acid homoancepsenolide **7**, the dilactones **1** and **2**, and their corresponding parent open forms **6** and **5**, as well as of the monobutenolide **4**. Achieving this goal seemed relevant because the absolute configuration given for some naturally occurring linear acetogenin lactones has been referenced to that of ancepsenolide[28] and related lactones obtained by synthetic methods[24b,29] involving strategies based on an aldolization, lactonization, and dehydration sequence, where no assessment of the enantiomeric purity has been reported. Thereby, the resulting absolute stereochemistry may be uncertain and could explain abnormal published $[\alpha]_D$ values for identical acetogenins.[10,20,30]

Palmitic (16:0) and stearic acid (18:0) are the most abundant lipids in coral tissue.[31] In accordance with previous[28b] models of a fatty acid oxidation pathway, we propose a biogenesis for bisbutenolides **1**−**8** that involves an enzymatic catalysis of the complete cascade of oxidation leading from a methyl group to a carboxylic acid (Scheme 1). Insertion

Scheme 1. Proposed Biogenesis for Compounds **1**−**8**



of a C3 unit, e.g., pyruvyl-CoA, into the resulting α,ω-dioic acid enolate positions would block subsequent β-oxidation, as is common in fatty acid metabolism, and lead to the dilactones.[32]

α,ω-Diacids are versatile chemical intermediates for the preparation of useful materials, and now, in an emerging industrial process, genetically engineered yeast has been developed converting fatty acids and *n*-alkanes to α,ω-dioic acids.[33] So far, naturally occurring fatty acids with a dilactone motif appear to be exclusive of the genus *Pterogorgia*—*P. anceps*,[1,11,12] *P. guadalupensis*,[9] and *P. citrina*[10]—because other marine taxa afforded related mono-γ-lactone lipids.[14,28a,34] Thus, the ability of enzymes of *Pterogorgia* to oxidize and accumulate long-chain fatty acids, emulating an engineered microbial strain where the β-oxidation was blocked by disrupting genes encoding acyl−coenzyme A oxidase, makes this octocoral an interesting organism in which to explore, at the genetic[35] and molecular level, the mechanisms by which ω-oxidation predominates over β-oxidation.

Acknowledgment. This work was supported by MEC (PPQ2002-02494, SAF2006-03004) and the DGUI Gobierno de Canarias (PI042005/003; PUB2005/030). The STRI provided facilities. Dr. M. Gupta, Lcdo. C. Vega (U de Panama), and J. del Rosario (STRI) provided technical support. The Government of Panama granted permission for the collection of the samples.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**−**5**, ^{1}H NMR of the homoancepsenolide (**7**) complex with *R*- and *S*-TFAE, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061572C

(16) Chaves, M. H.; Roque, N. F. *Phytochemistry* **1997**, *44*, 523−528.
(17) Tinto, W. F.; Jagessar, P. K.; Ketwaru, P.; Reynolds, W. F.; McLean, S. *J. Nat. Prod.* **1991**, *54*, 972−977.
(18) Etse, J. T.; Waterman, P. G. *Phytochemistry* **1986**, *25*, 1903−1905.
(19) (a) Warmerdam, E.; Tranoy, I.; Renoux, B.; Gesson, J.-P. *Tetrahedron Lett.* **1997**, *39*, 8849−8852. (b) Cortes, D.; Myint, S. H.; Leboeuf, M.; Cave, A. *Tetrahedron Lett.* **1991**, *32*, 6133−6134.
(20) Duret, P.; Figadere, B.; Hocquemiller, R.; Cave, A. *Tetrahedron Lett.* **1997**, *38*, 8077−8080.
(21) Latypov, S.; Franck, X.; Julian, J.-C.; Hocquemiller, R.; Figadere, B. *Chem.−Eur. J.* **2002**, *8*, 52−5666.
(22) Díaz-Marrero, A. R.; Dorta, E.; Cueto, M.; San-Martin, A.; Darias, J. *Tetrahedron* **2004**, *60*, 1073−1078.
(23) (a) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848−7855. (b) Ortuño, R. M.; Alonso, D.; Cardellach, J.; Font, J. *Tetrahedron* **1987**, *43*, 2191−2198.
(24) (a) Pupo, M. T.; Vieira, P. C.; Fernades, J. B.; Da Silva, M. G.-F. *Phytochemistry* **1998**, *48*, 307−310. (b) Takahashi, S.; Ogawa, N.; Sakiri, N.; Nakata, T. *Tetrahedron* **2005**, *61*, 6540−6545.
(25) Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *50*, 8337−8346.
(26) Lopes, N. P.; Silva, D. H. S.; Kato, M. S.; Yoshida, M. *Phytochemistry* **1998**, *49*, 1405−1410.
(27) Trost, B. M.; Müller, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 4985−4986.
(28) (a) Rezanka, T.; Dembistsky, V. M. *Tetrahedron* **2001**, *57*, 8743−8749. (b) Takeda, K.; Sakurawi, K.; Ishi, H. *Tetrahedron* **1972**, *28*, 3757−3776.
(29) He, Y.-T.; Yang, H.-N.; Yao, Z.-J. *Tetrahedron* **2002**, *58*, 8805−8810.
(30) Vieira, P.; Yoshida, M.; Gottlieb, O. R.; Filho, H. F. P.; Nagen, T. J.; Filhos, R. B. *Phytochemistry* **1983**, *22*, 711−713.
(31) Yamashiro, H.; Oku, H.; Higa, H.; Chinen, I.; Sakai, K. *Comp. Biochem. Physiol.* **1999**, *122*, 397−407.
(32) Scheller, U.; Zimmer, T.; Becher, D.; Schauer, F.; Schunck, W.-H. *J. Biol. Chem.* **1998**, *273*, 32528−32534.
(33) Eschenfeldt, W.; Zhang, Y.; Samaha, H.; Stols, L.; Eirich, L. D.; Wilson, C. R.; Donnelly, M. I. *App. Environ. Microbiol.* **2003**, 5992−5999.
(34) (a) Kikuchi, H.; Tsukitani, Y.; Nakanishi, H.; Shimizu, I.; Saitoh, S.; Iguchi, K.; Yamada, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1172−1176. (b) Anjaneyulu, A. S. R.; Prakash, C. V. S. *Indian J. Chem.* **1994**, *33*, 55−58.
(35) Stegeman, J. J. *Mar. Environ. Res.* **2000**, *50*, 1−81.