Organic & Supramolecular Chemistry

Diastereoselective Synthesis of Spirodihydrobenzofuran Analogues of the Natural Product Filifolinol

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Filifolinol is a natural occurring spirodihydrobenzofuran isolated from the resinous exudates of Heliotropium filifolium, a Chilean endemic shrub. Filifolinol and some of its derivatives have shown interesting biological activities against pathogens that attack salmonid species. Whereas the synthesis of spirodihydrobenzofurans has been limited to the use of an ortho allylphenol unit herein we report a different approach based on a C–H activation/C–O cyclization reaction for the synthesis of analogues of Filifolinol. Moreover, a diastereoselective approach was developed using the different facial preference of hydride species and organolithium compounds towards cyclic ketones.

Introduction

The development of the Aquaculture has become essential to the economies of many countries around the world and nowadays is considered a global industry.[1] It is the fastest-growing sector among the industries producing food of animal origin, associated to the continuously growing of human population.[2] However, the intensive farming of aquatic animal species, has resulted in an increased susceptibility of fish to bacterial and viral diseases, affecting the aquaculture and causing high mortality in salmonid cultures.[1] The unmeasured use of chemicals, mainly antibiotics, which are commonly used for prevention and treatment of bacterial disease in salmon farming,[3] have resulted in antibiotic resistance with the consequence impacts on human health.[4] Therefore a suitable alternative therapy instead of the abusive use of antibiotics is more than necessary. In this sense, vaccines and immunostimulants for prophylaxis,[5] have become focus of research. However, fish vaccines provide incomplete protection and the lack of good and safe immunostimulants and/or adjuvants to generate an appropriate and protective response remains as one of the major limitations.[6] Based on this, since several years the group of Modak have investigated the use of Filifolinol (Figure 1) and some of its derivatives against pathogens that attack salmonid species.[7] Filifolinol is a rearranged geranyl compound isolated for the first time from the resinous exudates of Heliotropium filifolium, a Chilean endemic shrub that grows in the Atacama region.[8] This natural compound have also showed antiviral activity against Hanta-virus, Sabin poliovirus, Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), Junin virus and syncytial respiratory virus (RSV).[9] Moreover, other studies have shown that Filifolinol and some of its derivatives act as inhibitors of the classical complement pathway.[10] These results are very attractive since the growing understanding of the role of the complement system in several diseases. Beside the interesting properties of Filifolinol and its derivatives, further biological investigations, such as structure-activity relationships, are limited to the use of Filifolinol as starting compound. For example, Filifolinone (Figure 1), one of the most promising compounds with immunostimulant activity, it is commonly obtained by oxidation of Filifolinol,[9b] even though it can be isolated from the resinous of Heliotropium huascoense,[11] nevertheless, in very low quantities. Thus, design of a synthetic route to obtain analogues of Filifolinol is highly desirable. Herein we present a convenient synthesis and preliminary biological evaluation of analogues of Filifolinol and their immunomodulatory activity.

Results and Discussion

Our retrosynthetic plan considered a simplified Filifolinol structure by removing the methyl ester group from the aromatic moiety (Scheme 1).

Our initial point was the synthesis of the cyclic β-hydroxyketone **3** by selective reduction of 2,2,4-trimethylcyclohexane-1,3-dione **5** which in turn was synthesized by a

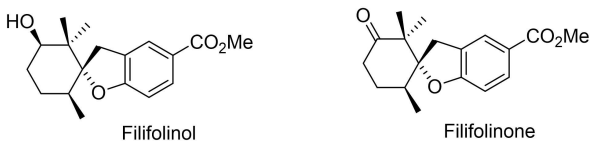

Figure 1. Geranyl compounds Filifolinol and Filifolinone.

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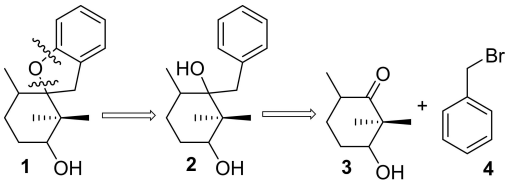
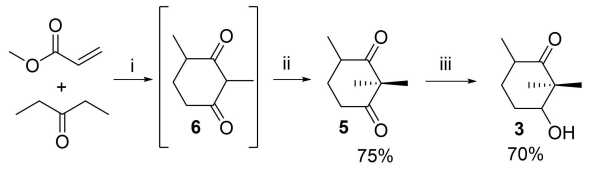


Scheme 1. Retrosynthetic plan for the synthesis of Filifolinol analogous.

combination of a Michael addition and a Claisen condensation reaction in a one pot reaction using 3-pentanone and methyl acrylate as starting materials and methyl iodide as the source of the methyl group in a formal [3 + 3] process (MC-[3 + 3]).[12] In this way, compound **5** was obtained as a colorless oil in 75% of yield (Scheme 2). We also attempted a stepwise synthesis according to literature reports.[13] However, synthesis and isolation of 1,3-cyclohexanedione **6** was only partially achieved, due to its high hygroscopicity and difficulty to handle. Our attempts to use it immediately after work up using sodium hydride as base (NaH) and methyl iodide in dry DMF failed.

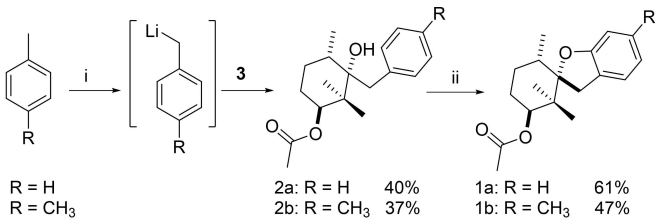
For the regioselective reduction of **5**, we considered the different steric hindrance of both carbonyl groups to the nucleophilic attack of a hydride species. Since the ketone at C-3 position is more precluded than the ketone at C-1 position, we expected that the latter would be more easily reduced. On the other hand, the stereoselective reduction of cyclic ketones has normally been achieved using metal hydrides or complex reducing agents.[14] In this sense, the nucleophilic addition can potentially result in a diastereomeric pair of enantiomers because of the preference of some reagents for the axial or equatorial approach. This facial selectivity is influenced by the size of the reductant agent. Bulky reducing agents favor the approach to the carbonyl group via an equatorial trajectory since the axial face is more hindered, giving the thermodynamically less stable axial alcohol,[15] although valuable methodologies have been devised in order to obtain the more stable equatorial alcohols.[16] Moreover, the stereoelectronic basis of these facial preferences has been extensively studied through computational methods.[17] Thus, the so called steric approach control, a term coined by Dauben,[18] and further developed in the torsional strain model proposed by Fehlkin and Ahn,[19] would allow us to obtain the stereoisomer with the hydroxyl group in axial position as observed in the X-ray structure of Filifolinol Acetate.[20] Recently however, it has been shown that although the use of small nucleophiles tends to add to the axial face, some six-membered cyclic ketones suffered the



Scheme 2. [3 + 3] process for the synthesis of 3. i) *t*-BuOK (1.2 eq.), THF, 0 °C; ii) CH_3I (3.0 eq.); iii) $NaBH_4$ (0.25 eq.), CH_3OH.

hydride addition from the equatorial face even when a small hydride reagent such as sodium borohydride ($NaBH_4$) is used.[21] With this in mind, three bulky hydride reagents, -H, $LiAlH(t\text{-}BuO)_3$ and $NaBH(OCOCH_3)_3$ in order to favor the equatorial approach of the hydride to the carbonyl compound were used. Unfortunately, all of them failed since no reduction was observed. Additionally, $NaBH_4$ was subjected to our reaction. After a small screening of reaction conditions, we found out that the use of 0.25 equivalent of $NaBH_4$ at 0 °C afforded exclusively to **3** in 70% of yield along with unreacted material. This structure was confirmed by 2D NMR spectroscopy. The HMBC experiment showed the correlation between the C-1 carbon atom and the methyl groups at C-2 and C-6 respectively. Interesting, besides the steric hindrance of the ketone at C-1, the use of 1 equivalent of $NaBH_4$ afforded almost exclusively to the undesired diol product. The stereoselective monoreduction of the dione **5**, had already been observed with similar substrates.[22]

Next step was to afford the carbon-carbon bond formation between **3** and benzyl bromide **4**. The most common method to produce an alcohol from an alkyl halide and a ketone is the Grignard reaction. However, despite its great utility, this method needs to bypass several challenges such as strict exclusion of moisture and air and protection–deprotection of the acidic hydrogens in the substrates as in our case. Several years ago, a Barbier reaction was reported in the synthesis of the ring-A of Taxoids,[23] a family of compounds derivatives from Taxol with antineoplastic properties.[24] In that work, using Lithium in tetrahydrofuran (THF) under ultrasonic irradiation a single diastereomer was formed from the coupling reaction between benzyl bromide and a carvone derivative. Encouraged by this stereochemical outcome, we performed the reaction under identical reaction conditions, the desired product **2** was formed but only in 10% of yield, being the unwanted Wurtz coupling product, 1,2-diphenylethane, the main product, because of the rapid lithium-halogen exchange process.[25] **2** was completely characterized by 1D and 2D NMR. We reasoned that the low yield of the reaction was due the low concentration of the Li^+ species in the reaction media. To overcome this problem, the use of chelating agents, such as tetramethylethylenediamine (TMEDA) has been reported to increase the reactivity of organolithium reagents.[26] Thus, we modified our original proposal and benzyllithium, prepared in situ from toluene and n-buthyllithiium (n-BuLi) in presence of TMEDA, was used instead of benzyl bromide **4** and allowed to react with compound **3** (Scheme 3). Based on this methodology a white solid compound was obtained from a complex mixture in a moderate 40% of yield. Unexpectedly, 1D and 2D RMN spectra analysis showed that the new compound corresponded to the O-acetyl derivative of **2**. The O-acetylation occurs during the work up of the reaction. Interesting, this compound is structurally closer to Filifolinyl acetate, another unusual spiro compound isolated from the cuticle of *Heliotropium filifolium*.[8] This reaction is ruled by the same principle concerning the stereoselective reduction of cyclic ketones discussed above. Thus, it was expected that the bulky organolithium reagent



Scheme 3. Coupling reaction and Hydroxyl-directed C–H activation/C–O bond formation for the synthesis of **1a** and **1b**. i) n-BuLi (2 eq), 50 °C, 1.5 h, n-heptane; ii) $Pd(OAc)_2$ (10 mol %), Li_2CO_3 (1.5 eq.), $PhI((OAc)_2$ (2 eq.), C_6F_6, 100 °C, 36 h.

would approach to the carbonyl compound of **3** by the less hindered equatorial face.

Indeed, from the X-ray structure of **2a** (Figure 2), it is observed the hydroxyl group at C-2 in the axial position. Moreover, the methyl group at C-4 and the acetoxy group at C-1 in equatorial positions. Worthy to mention is that Filifolinol acetate shows the acetyloxy group at C9 in the axial orientation and the secondary methyl group at C12 in an equatorial disposition. This structure was assigned using NMR and single crystal X-ray analysis, and its absolute configuration was determined as 2S,9S,12R using VCD and DFT (B3LYP/DGDZVP) calculations.[20]

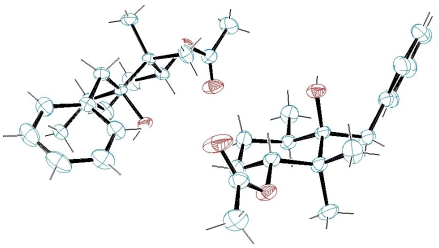


Figure 2. X ray structure of **2a**.

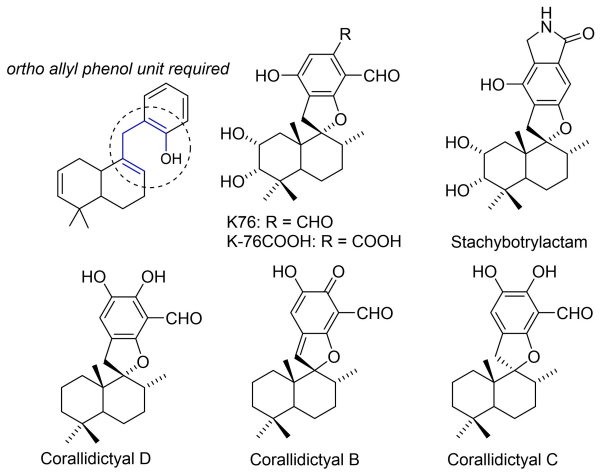


Figure 3. Natural occurring compounds containing the spirodihydrobenzofuran moiety.

At late stage of the synthesis, examination of literature reports involving synthesis of spirodihydrobenzofurans, showed that only a few methodologies to carry out the key spiroannulation reaction have been reported. For example, in the total synthesis of K-76 (Figure 3), a fungal metabolite isolated from Stachybotrys complementi nov. sp,[27] and one of the most widely used complement inhibitors,[10] the spirocyclization reaction was achieved using a THF-ethylene glycol- 2.0 N hydrochloric acid mixture.[28] Only a few years later, the cyclization reaction was performed using an excess of Amberlyst ion-exchange resin in CH_2Cl_2.[29a] Analogues of K-76 have also been synthesized using this strategy.[29b] Stachybotrylactam, an spirodihydrobenzofuranlactam active as antagonist of endothelin and as inhibitor of HIV-1 protease,[30] isolated from the cultures of two different Stachybotrys species,[31] and various other analogous have also been synthesized using the cationic resin as the cyclizing agent.[32] An interesting N-iodosuccinimide-triphenylphosphine (NIS-PPh_3) system, as a selective reagent for the spiroannulation reaction was introduced for the total synthesis of Corallidictyal D,[33] a spirosesquiterpene aldehyde isolated from the marine sponge Aka coralliphaga with protein kinase inhibitory activity.[34] Using the same system (⁻)-F1839-I and Corallidictyal B and C were also successfully synthesized[35,36] (Figure 3).

Despite the above mentioned methodologies have proven to be very efficient to construct the spiro-skeleton, most of them were limited to the use of *ortho*-allylphenol (Figure 3) either, for the intramolecular cyclization, or to obtain the corresponding substrate prior to the annulation, such as epoxydes.[37] Moreover, depending of the substitution pattern several steps are required to form the corresponding alkyl halide, necessary for the Friedel-Crafts alkylation reaction, although interesting variations have been reported. A palladium-catalyzed direct cross-coupling reaction of tosylhydrazone and a substituted iodobenzaldehyde,[38] or Friedel-Craft variation using alcohols as alkylating agents instead of alkyl halides.[35] In 2010, the palladium-catalyzed C–H activation/C–O cyclization reaction for the construction of dihydrobenzofuran compounds was reported by the group of Yu.[39] C–H activation has evolved as an environmentally-benign and step-economical synthetic approach with interesting application to the synthesis of complex natural products.[40] Indeed, in this work, the developed methodology was indicated to be relevant to the synthesis of natural products containing spirocyclic dihydrobenzofurans and two representative compounds were prepared. However, the corresponding alcohols, cyclohexanol and decahydronaphthalenol were used without any substituent in their structures. Unlike those examples, natural products show normally high substitution pattern. To the best of our knowledge this approach has not been reported nor in the total synthesis of natural products containing a spiro moiety neither in the synthesis of their analogous. To our delight, under identical reaction conditions developed by the group of Yu, the intramolecular cyclization to generate the spirocyclic skeleton furnished compound **1a** in 61 % of yield. By using *para*-xylene instead of toluene and under identical optimized reaction conditions developed for **1a**, a second derivative **1b** was

obtained. Moreover, considering the reduction reaction of **5** and the coupling reaction yielding to **2** as stereoselective reactions, our synthetic strategy can be regarded as a diasteroselective synthesis of Filifolinol analogous.

Since none of these compounds have been previously investigated, we performed a preliminary biological evaluation of **2a**, **1a**–**b** and their immunomodulatory effects in vitro on the SHK-1 cell line, derived from salmon head kidney quantifying the expression levels of IFNα and IL-12 cytokines. Previously biological investigations showed that Filifolinone increased IFNα, in the kidney of trout, important in the early activation of antiviral response, and IFNγ and IL-12, important for the control of intracellular pathogens as IPNV and P.salmonis.[41] It was also showed that Filifolinone induced IL-17D in rainbow trout, which may have a role in early inflammatory response and in innate responses. Filifolinol have also shown to increase the transcripts of IFNγ and IL-12, although to a lesser extent than Filifolinone.[42] The increase of the mRNAs related to teleost adaptive responses by effect of Filifolinol and mainly for Filifolinone suggested that these two compounds could induce those Th-type responses in the kidneys of trout. Based on these results, Filifolinone, instead of Filifolinol, was used in our experiments.

To evaluate the immunostimulatory effect in vitro, SHK-1 cells grown to confluence were incubated with 5 μg/mL of compounds **2a**, **1a**–**b** and Filifolinone. Compound concentration was chosen based on previous assays that we conducted with dendritic cells. The effect on the transcription level of the IFN-α and IL-12 cytokines, both keys in the Th1-type immune cellular response, was measured. Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular pathogen, such as viruses and some bacteria that affect salmon farming, and for perpetuating autoimmune responses (Figure 4). It is possible to observe that compounds **1a**–**b** did not show an immunostimulatory effect expressed through modulation of IFN-α and IL-12 cytokines levels. However, the levels of transcription caused by compound **2a** increased significantly in relation to the negative control (cells without treatment) and are also higher than those obtained with Filifolinone. It is still not clear whether compounds **1a**–**b** were inactive due the stereochemical outcome, lack of the ester group or because of the hydroxy protected group but is matter of further investigations. However, the most interesting result is that pre-cyclized compounds such as **2a** which has never been evaluated is an excellent candidate to be tested in vivo as an activator of the immune system that controls the response against intracellular pathogens that attack fish.

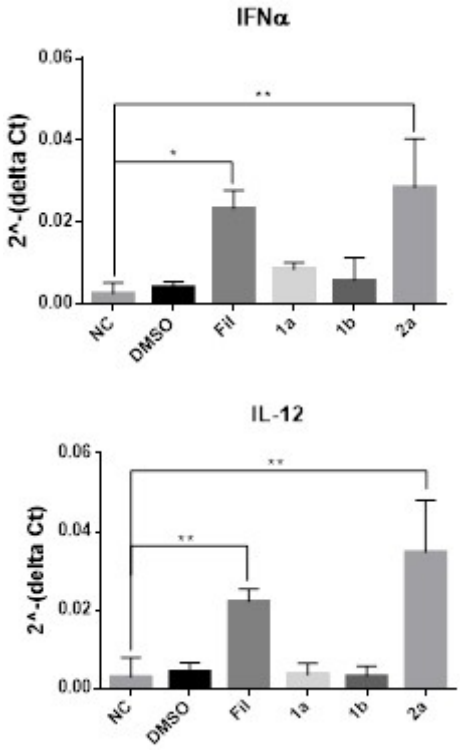


Figure 4. Analysis of the transcript levels of innate immune system in SHK-1 cells. Cells were incubated with 5 μg/mL of the compounds for 24 hours. Total RNA extraction was per-formed from the cell cultures and IFN-α and IL-12 gene expression was determined by qRT-PCR with three technical replicates. The control corresponded to negative control (NC) and DMSO. Statistical differences were determined by one-way ANOVA Mann Whitney test (*$P < 0.05$; **$P < 0.01$)

Conclusion

In conclusion, we have developed a rapid and convenient diastereoselective synthesis of analogous of natural product Filifolinol without the use of chiral reagents. Moreover, we have identified a new candidate to be evaluated as immunostimulant to treat fish diseases.

Deposition number 2044067 for **2a**, contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information Summary

Details of synthetic procedures, characterization of products, copies of ^{1}H and ^{13}C spectra are included in Supporting Information.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: diastereoselective synthesis · C–H activation · fish · immunostimulant · spiro compounds

[1] P. J. Walker, J. R. Winton, *Vet. Res.* **2010**, 41–51.
[2] F. Kibenge, *Curr. Opin. Virol.* **2019**, *34*, 97–103.

[3] C. Miranda, *Antimicrobial Resistance in the Environment*, eds P. L. Keen, M. H. H. M. Montforts (Hoboken, NJ:Wiley-Blackwell), **2012**, 423–451.
[4] a) F. C. Cabello, *Environ. Microbiol.* **2006**, *8*, 1137–1144; b) L. Burridge, J. S. Weis, F. Cabello, J. Pizarro, K. Bostick, *Aquaculture*, **2010**, *306*, 7–23; c) J. Romero, C. G. Feijoó, P. Navarrete, *Antibiotics in Aquaculture-use, Abuse and Alternatives*, **2012**, Rijeka: INTECH Open Access Publisher. doi: 10.5772/28157.
[5] B. Magnadottir, *Mar. Biotechnol.* **2010**, *12*, 361–379.
[6] C. Tafalla, J. Bøgwald, R. A. Dalmo, *Fish Shellfish Immunol.* **2013**, *35*, 1740–1750.
[7] A. Urzúa, J. Echeverría, M. C. Rezende, M. Wilkens, *Molecules*, **2008**, *13*, 2385–2393.
[8] R. Torres, L. Villarroel, A. Urzúa, F. Delle Monache, G. Delle Monache, E. Cacs-Baitz, *Phytochemistry*, **1994**, *36*, 249–250.
[9] a) B. Modak, H. Galeno, R. Torres, *J. Chil. Chem. Soc.* **2004**, *49*, 143–145; b) R. Torres, B. Modak, A. Urzúa, F. Delle Monache, E. Damonte, C. Pujol, *Bol. Soc. Chil. Quim.* **2002**, *47*, 259–263; c) R. Torres, H. Galeno, B. Modak, *Nat. Prod. Commun.* **2008**, *3*, 527.
[10] a) M. Useglio, P. M. Castellano, M. A. Operto, R. Torres, T. Kaufman, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5097–5101; b) E. Larghi, M. A. Operto, R. Torres, T. Kaufman, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6172–6175; c) E. Larghi, M. A. Operto, R. Torres, T. Kaufman *Eur. J. Med. Chem.* **2012**, *55*, 74–84.
[11] M. Parra, B. Valenzuela, M. Imarai, B. Modak, *J. Fish Dis.* **2018**, *41*, 157–159.
[12] T. Ishikawa, R. Kadoya, M. Arai, H. Takahashi, Y. Kaisi, T. Mizuta, K. Yoshikai, S. Saito, *J. Org. Chem.* **2001**, *66*, 8000–8009.
[13] M. E. Jung, J. Cordova, M. Murakami, *Org. Lett.* **2009**, *17*, 3882–3885.
[14] T. Hayashi, S. Kikuchi, Y. Asano, Y. Endo, Y. T. Yamada, *Org. Process Res. Dev.* **2012**, *16*, 1235–1240.
[15] a) N. M. Yoon, K. E. Kim, J. Kang, *J. Org. Chem.* **1986**, *51*, 226–229; b) H. C. Brown, B. Nazer, J. S. Cha, J. A. Sikorski, *J. Org. Chem.* **1986**, *51*, 5264–5270.
[16] N. Kennedy, T. Cohen, *J. Org. Chem.* **2015**, *16*, 8134–8141.
[17] a) Y. D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **1987**, *109*, 908–910; b) Y. D. Wu, K. N. Houk, M. N. Paddon-Row, *Angew. Chem. Int. Ed.* **1992**, *31*, 1019–1021; *Angew. Chem.* **1992**, *104*, 1087–1089; c) R. T. Luibrand, I. R. Taigounov, A. A. Taigounov, *J. Org. Chem.* **2001**, *66*, 7254–7262.
[18] W. C. Dauben, G. J. Fonken, D. S. Noyce, *J. Am. Chem. Soc.* **1956**, *78*, 2579–2582.
[19] a) M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *9*, 2199–2204; b) M. Cherest, H. Felkin, *Tetrahedron Lett.* **1971**, 383–386; c) N. T. Anh, O. Eisenstein, J.-M. Lefour, M.-E. Tran Huu Dau, *J. Am. Chem. Soc.* **1973**, *95*, 6146–6147.
[20] M. Muñoz, A. Urzúa, J. Echeverría, B. Modak, P. Joseph-Nathan, *Nat. Prod. Commun.* **2011**, *6*, 759–762.
[21] F. Guo, R. C. Dhakal, R. K. Dieter, *J. Org. Chem.* **2013**, *78*, 8451–8464.
[22] D. W. Brooks, H. Mazdiyasni, P. G. Grothaus, *J. Org. Chem.* **1987**, *52*, 3223–3232.
[23] G. Mehta, Sh K. Chattopadhyay, J. D. Umarye, *Tetrahedron Lett.* **1999**, *40*, 4881–4884.
[24] M. Marty, J. M. Extra, S. Giacchetti, C. Cuvier, M. Espie, *Nouv. Rev. Fr. Hematol.* **1994**, *36*, 25–28.
[25] R. E. Merrill, E. Negishi, *J. Org. Chem.* **1974**, *39*, 23, 3452–3453.
[26] L. Chen, B. W. Rawe, K. Adachi, D. P. Gates, *Chem. Eur. J.* **2018**, *24*, 18012–18019.
[27] a) E. L. Larghi, T. S. Kaufman, *Arkivoc* **2011**, 49–102; b) W. Miyazaki, H. Tomaoka, M. Shinohara, H. Kaise, T. Izawa, Y. Nakano, T. Kinoshita, K. Hong, K. Inoue, *Microbiol. Immunol.* **1980**, *24*, 1091–1108.
[28] E. J. Corey, J. Das, *J. Am. Chem. Soc.* **1982**, *104*, 5551–5553.
[29] a) J. E. McMurry, M. D. Erion, *J. Am. Chem. Soc.* **1985**, *107*, 2712–2720; b) B. J. Bradbury, P. Bartyzel, T. S. Kaufman, M. J. Nieto, R. D. Sindelar, S. M. Scesney, B. R. Gaumond, H. C. Marsh, *J. Med. Chem.* **2003**, *46*, 13, 2697–2705.
[30] A. Wang, Y. Xu, Y. Gao, Q. Huang, X. Luo, H. An, J. Dong, *Phytochem. Rev.*, **2015**, 14, 623–655.
[31] B. E. Roggo, F. Petersen, M. Sills, J. L. Roeselll, T. Moerker, H. H. Peter, *J. Antibiot.* **1996**, 13–19.
[32] A. S. Kende, W.-P. Deng, M. Zhong, X.-Ch. Guo, *Org. Lett.* **2003**, *5*, 1785–1788.
[33] M. J. Cano, H. Bouanou, R. Tapia, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun, E. Alvarez-Manzaneda, *J. Org. Chem.* **2013**, *78*, 9196–9204.
[34] A. Grube, M. Assmann, E. Lichte, F. Sasse, J. R. Pawlik, M. Köck, *J. Nat. Prod.* **2007**, *70*, 504–509.
[35] D. H. Dethe, B. D. Dherange, S. Ali, M. M. Parsutkar, *Org. Biomol. Chem.* **2017**, *15*, 65–68.
[36] J.-L. Wang, H.-J. Li, Y.-Ch. Wu, *J. Org. Chem.* **2018**, *83*, 8716–8723.
[37] P. V. Fish, G. Pattenden, *Tetrahedron Lett.* **1988**, 3857–3860.
[38] H.-Sh. Wang, H.-J. Li, X. Nan, Y.-Y. Luo, Y.-Ch. Wu, *J. Org. Chem.* **2017**, *82*, 12914–12919.
[39] X. Wang, Y. Lu, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12203–12205.
[40] D. J. Abrams, Ph. A. Provenchert, E. J. Sorensen, *Chem. Soc. Rev.* **2018**, *47*, 8925–8967.
[41] B. Valenzuela, M. Imarai, R. Torres, B. Modak, *Dev. Comp. Immunol.* **2013** *41*, 675–682.
[42] B. Valenzuela, J. Obreque, S. Soto-Aguilera, K. Maisey, M. Imarai, B. Modak, *Fish Shellfish Immunol.* **2016**, *49*, 45–53.

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