ORGANIC LETTERS

2011
Vol. 13, No. 5
908–911

Asymmetric Total Synthesis of (+)-Danicalipin A

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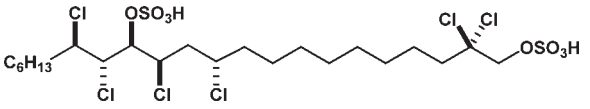
Received December 6, 2010

ABSTRACT



(+)-Danicalipin A

A convergent asymmetric total synthesis of (+)-danicalipin A is accomplished, in which two chlorinated fragments are stereoselectively joined by 1,3-dipolar coupling, leading to the confirmation of the absolute configuration of the natural product.

Certain types of algae produce unique molecules that are necessary for survival in the natural environment. Polychlorosulfolipids have been shown to exist in some algae and feature heavily chlorinated linear hydrocarbon motifs that are rarely seen in other natural products. The dawn of polychlorosulfolipid research was first recorded in the literature that described the discovery of unusual sulfolipids from the freshwater alga *Ochromonas danica* in the late 1960s by the groups of Haines, Elovson, and Vagelos.[1a−j] Shortly after that discovery, various chlorosulfolipids from other species were identified by several research groups, including those of Mercer and Davies.[1k−n] More recently, Gerwick and co-workers discovered malhamensilipin A, a biologically active chlorosulfolipid metabolite from the cultured freshwater alga chrysophyte *Poterioochromonas malhamensis*.[2] However, details of the stereochemical structures of chlorosulfolipids had long been unclear until quite recently due to the lack of means to elucidate their complex stereochemistry, and this had led to the delay in understanding their properties at the molecular level.

In 2001, Fattorusso, Ciminiello, and co-workers established the stereochemistry of a cytotoxic hexachlorosulfolipid (Mytilipin A) isolated from Adriatic mussels[3a] by conducting extensive NMR studies using Murata's

(1) (a) Haines, T. H.; Pousada, M.; Stern, B.; Mayers, G. L. *Biochem. J.* **1969**, *113*, 565–566. (b) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957–963. (c) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110–3126. (d) Mooney, C. L.; Mahoney, E. M.; Pousada, M.; Haines, T. H. *Biochemistry* **1972**, *11*, 4839–4844. (e) Mooney, C. L.; Haines, T. H. *Biochemistry* **1973**, *12*, 4469–4472. (f) Haines, T. H. In *Lipids and Biomembranes of Eukaryotic Microorganisms*; Erwin, J. A., Ed.; Academic Press: New York, 1973; pp 197−232. (g) Haines, T. H. *Annu. Rev. Microbiol.* **1973**, *27*, 403–412. (h) Elovson, J. *Biochemistry* **1974**, *13*, 3483–3487. (i) Elovson, J. *Biochemistry* **1974**, *13*, 2105–2109. (j) Chen, L. L.; Pousada, M.; Haines, T. H. *J. Biol. Chem.* **1976**, *251*, 1835–1842. (k) Thomas, G.; Mercer, E. I. *Phytochemistry* **1974**, *13*, 797–805. (l) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1974**, *13*, 1607–1610. (m) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1975**, *14*, 1545–1548. (n) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1979**, *18*, 457–462.

(2) (a) Chen, J. L.; Proteau, P. J.; Roberts, M. A.; Gerwick, W. H.; Slate, D. L.; Lee, R. H. *J. Nat. Prod.* **1994**, *57*, 524–527. (b) Gerwick, W. H. *Biochim. Biophys. Acta* **1994**, *1211*, 243–255. (c) Gerwick, W. H.; Roberts, M. A.; Proteau, P. J.; Chen, J. L. *J. Appl. Phycol.* **1994**, *6*, 143–149. Recently, the revised structure of this natural compound was reported:(d) Pereira, A. R.; Byrum, T.; Shibuya, G. M.; Vanderwal, C. D.; Gerwick, W. H. *J. Nat. Prod.* **2010**, *73*, 279–283.

(3) (a) Ciminiello, P.; Fattorusso, E.; Forino, M.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Org. Chem.* **2001**, *66*, 578–582. The name 'mytilipin' was associated with the mussel from which it was extracted (communicated with Prof. Fattorusso and Prof. Ciminiello). (b) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, F.; Magno, S.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Am. Chem. Soc.* **2002**, *124*, 13114–13120. (c) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; Di Meglio, P.; Ianaro, A.; Poletti, R. *Tetrahedron* **2004**, *60*, 7093–7098. For reviews, see: (d) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S. *Pure Appl. Chem.* **2003**, *75*, 325–336. (e) Ciminiello, P.; Fattorusso, E. *Eur. J. Org. Chem.* **2004**, 2533–2551. (f) Chao, C.-H.; Huang, H.-C.; Wang, G.-H.; Wen, Z.-H.; Wang, W.-H.; Chen, I.-M.; Sheu, J.-H. *Chem. Pharm. Bull.* **2010**, *58*, 944–946.

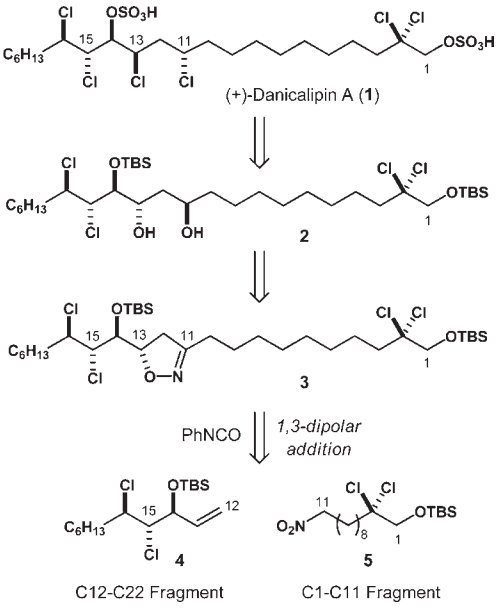
10.1021/ol1029518
Published on Web 02/02/2011

J-based configuration analysis (JBCA),[4] which was later utilized in the stereochemical assignment of undecachlorosulfolipid (Mytilipin B),[3b] a cytotoxin that is structurally far more complex than hexachlorosulfolipid. Okino and co-workers also applied the Murata method to the elucidation of the stereochemistry of danicalipin A (**1**).[5] Besides such progress in structural analysis, the recent development of a synthetic means to install chlorine functionalities has allowed synthetic chemists to gain access to this class of natural compounds.[6] In this context, avid research aimed at the establishment of stereoselective routes to chlorosulfolipids has culminated in the total synthesis of (±)-hexachlorosulfolipid by Carreira and co-workers[7] and in the syntheses of (±)-danicalipin A (**1**)[8] and (+)-malhamensilipin A by Vanderwal's group,[9] all of which have revealed the unique reactivity of the chlorinated molecular architecture toward chemical reactions.

Our group has also been engaged in the synthesis of natural chlorosulfolipid toxins and has developed a method for the asymmetric construction of chlorinated hydrocarbon motifs relevant to the polychlorosulfolipids.[10] Application of the method has allowed us to accomplish the asymmetric total synthesis of (+)-hexachlorosulfolipid.[11] As part of our continuing efforts to establish a chlorosulfolipid library that would enable us to pursue structure−activity relationship studies of this new class of natural toxins, we have initiated a research program to devise an enantioselective access to the algal toxin (+)-danicalipin A (**1**). In the present study, we disclose a convergent asymmetric total synthesis of (+)-danicalipin A (**1**), in which two chlorinated fragments are stereoselectively joined by a 1,3-dipolar coupling reaction, establishing a successful route to the polychlorinated molecular architecture.

(+)-Danicalipin A (**1**), isolated from the cellular and flagellar membranes of the freshwater alga *Ochromonas danica*, contains six chlorine atoms in its linear hydrocarbon motif bearing two sulfates. The chemical synthesis of this molecule in the racemic form was recently accomplished by Vanderwal and co-workers, which features the sequential use of stereoselective chlorination of an unsaturated hydrocarbon motif.[8] Okino's group also succeeded in the isolation of natural (+)-danicalipin A (**1**) from the cultured chrysophyte *O. danica* (IAM CS-2) and confirmed its absolute stereochemistry and toxicological properties.[5]

Scheme 1. Retrosynthesis of (+)-Danicalipin A



Our convergent synthesis of danicalipin A is retrosynthetically outlined in Scheme 1. In our approach, target compound **1** was dissected into two parts, i.e., C12−C22 fragment **4** and C1−C11 fragment **5**. C12−C22 unit **4** was prepared in an enantiomerically pure form from a dichloride readily obtainable from a chiral epoxide. C1−C11 fragment **5**, a 1,3-dipolar precursor, would be connected to fragment **4**, giving rise to the whole hydrocarbon motif bearing oxygen functionalities suitable for the stereoselective installation of two more chlorine atoms at a later stage.

C12−C22 fragment **4** was synthesized from known chiral epoxy alcohol **6** with 80% ee, which was prepared by the asymmetric epoxidation of commercially available *cis*-2-nonene-1-ol (Scheme 2).[12] Epoxy alcohol **6** was initially protected as pivalate **7** (95%), which, by dichlorination with the chlorophosphonium reagent generated *in situ* from NCS and triphenylphosphine, furnished dichloride **8** in 86% yield. DIBAL reduction of resultant dichloride **8** allowed the removal of the ester group, providing alcohol **9** in 94% yield. This compound **9** was then oxidized with Dess−Martin periodinane to furnish unstable aldehyde **i**, which was immediately reacted with vinylmagnesium bromide at −78 to 0 °C in Et_2O to deliver alcohol **10** stereoselectively. The facial selectivity observed for the vinylation (ds = 1.7: 1 determined by ^1H NMR analysis of the crude mixture; for details, see Supporting Information) can be rationalized by considering the Cornforth transition

(4) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.

(5) Kawahara, T.; Kumaki, Y.; Kamada, T.; Ishii, T.; Okino, T. *J. Org. Chem.* **2009**, *74*, 6016–6024.

(6) (a) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514–12518. (b) Kanady, J. S.; Nguyen, J. D.; Ziller, J. W.; Vanderwal, C. D. *J. Org. Chem.* **2009**, *74*, 2175–2178. For a review, see: Bedke, D. K.; Vanderwal, C. D. *Nat. Prod. Rep.* **2011**, *28*, 15–25.

(7) (a) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573–576. For the related study, see:(b) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 15866–15876.

(8) (a) Bedke, D. K.; Shibuya, G, M.; Pereira, A. R.; Gerwick, W. H.; Haines, T. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7570–7572. (b) While this manuscript was under review, asymmetric total synthesis of (+)-danicalipin A was reported;Umezawa, T.; Shibata, M.; Kaneko, K.; Okino, T.; Matsuda, F. *Org. Lett.* **2011**, ASAP (DOI: 10.1021/ol102882a).

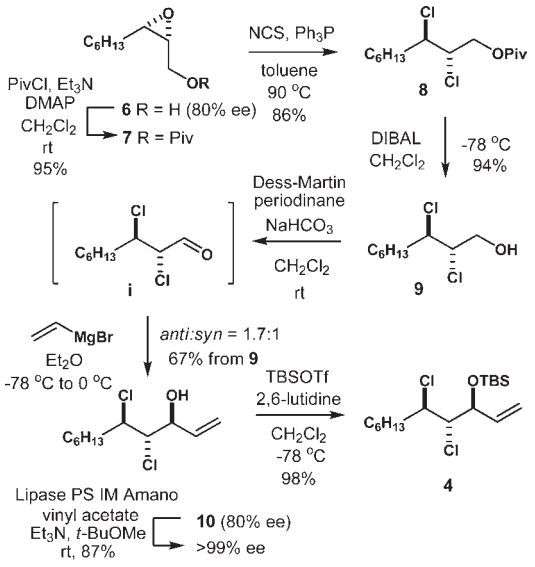
(9) Bedke, D. K.; Shibuya, G, M.; Pereira, A. R.; Gerwick, W. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 2542–2543.

(10) (a) Yoshimitsu, T.; Fukumoto, N.; Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696–702. For the recent development of this method in catalysis, see: (b) Denton, R. M.; Tang, X.; Przeslak, A. *Org. Lett.* **2010**, *12*, 4678–4681.

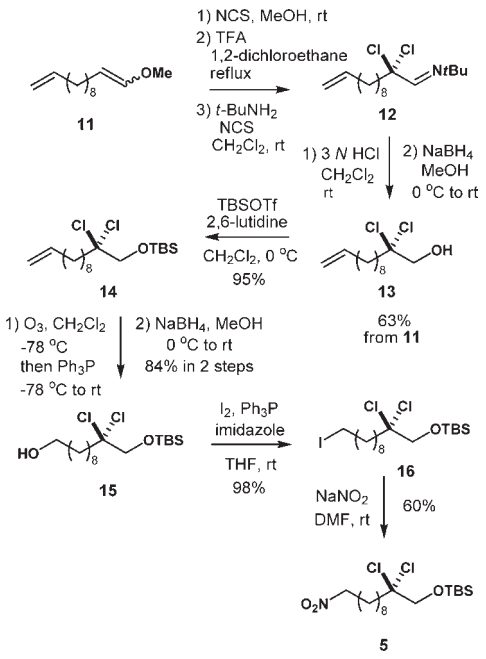
(11) Yoshimitsu, T.; Fukumoto, N.; Nakatani, R.; Kojima, N.; Tanaka, T. *J. Org. Chem.* **2010**, *75*, 5425–5437.

(12) (a) Burke, C. P.; Shi, Y. *Org. Lett.* **2009**, *11*, 5150–5153. (b) Kanerva, L. T.; Vänttinen, E. *Tetrahedron: Asymmetry* **1993**, *4*, 85–90. (c) Yu, L.; Wang, Z. *J. Chem. Soc., Chem. Commun.* **1993**, 232–234. The enantiomeric purity of this epoxide was determined by the Mosher method. For details, see the Supporting Information.

Scheme 2. Synthesis of C12−C22 Fragment **4**



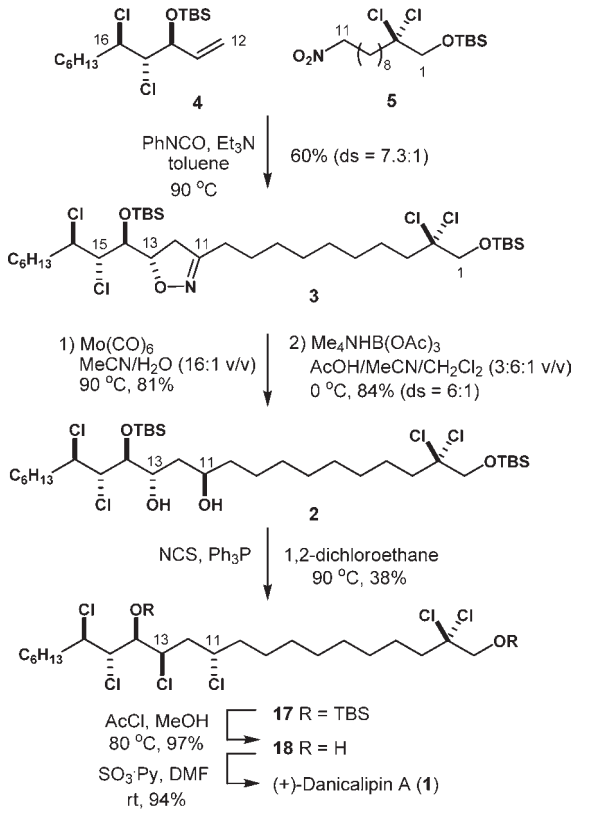
Scheme 3. Synthesis of C1−C11 Fragment **5**



state model.[13] Fortunately, numerous efforts at this stage to increase the ee of enantiomerically enriched intermediate **10** eventually led to the discovery that an enzymatic separation using Lipase PS IM Amano was best suited for obtaining the optically pure material. Enantiomerically pure alcohol **10** was then transformed into C12−C22 fragment **4** (>99% ee) by protecting the hydroxyl group as TBS ether.

(13) For instances, see: (a) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920–2930. (b) Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083–5086.

Scheme 4. Completion of Total Synthesis of (+)-Danicalipin A via 1,3-Dipolar Coupling between C1−C11 Fragment **5** and C12−C22 Fragment **4**



The preparation of C1−C11 fragment **5** was initiated by the sequential chlorination of diene **11** (*E*/*Z* = 3:2), which was prepared by the Wittig methoxy alkenylation of 10-undecenal (Scheme 3). The chlorination of diene **11** with NCS, followed by treatment of the resultant crude mixture with TFA, gave an α-chloroaldehyde that, by enamine formation with *t*-BuNH$_2$ followed by further chlorination with NCS in one pot, furnished α,α-dichloroimine **12**.[14] Hydrolysis of imine **12** with 3 *N* HCl, followed by reduction of the resultant aldehyde (structure not shown) with NaBH$_4$ in MeOH, afforded *β*,*β*-dichloroalcohol **13** in 63% overall yield from diene **11**. Then, the hydroxyl group of compound **13** was silylated with TBSOTf in the presence of 2,6-lutidine to provide TBS ether **14** in 95% yield. Alcohol **15** was prepared in 84% yield in two steps by cleaving the terminal double bond of **14** by ozonolysis, followed by the reduction of the resultant aldehyde with NaBH$_4$. Iodination of the hydroxyl group and subsequent substitution of the resultant iodide with sodium nitrite in DMF furnished C1−C11 fragment **5** in 60% yield.[15] With these two fragments **4** and **5**, the intermolecular nitrile oxide 1,3-dipolar assembly was examined (Scheme 4).

(14) Vanderwal's group reported the dichlorination of a *tert*-butyl aldimine derived from 11-bromoundecanal with NCS. See ref 8a; also, see: Verhé, R.; De Kimpe, N.; De Buyck, L.; Schamp, N. *Synthesis* **1975**, 455–456.

(15) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **2000**, *11*, 3063–3068.

After numerous attempts were made to optimize the reaction conditions, we found that desired isoxazoline **3** could be successfully produced in a ratio of C13/C14 *anti*/*syn* = 7.3: 1 (determined by ^{1}H NMR analysis) by the slow and stepwise addition of phenyl isocyanate into the mixture of compound **4** and nitro compound **5** in heating toluene.[16] The preferential formation of desired C13/C14 *anti*-isoxazoline **3** can be rationalized by considering a stereoelectronically favored transition state of substrate **4**, as proposed by Houk and co-workers.[17] The *anti*-stereochemistry of the C13/C14 positions of isoxazoline **3** was confirmed by its derivatization into an epoxide by the Payne-type rearrangement.[18] Isoxazoline **3** was then reduced with molybdenum hexacarbonyl in aqueous MeCN to afford an aldol (structure not shown) in 81% yield.[19,20] The *anti*-diol motif necessary for the installation of chlorine atoms at the C11 and C13 positions was successfully furnished by the *anti*-selective reduction of the aldol under Evans conditions to afford diol **2** (*anti*/*syn* = 6:1 by ^{1}H NMR analysis).[21,22] The next task was to chlorinate both hydroxyl groups at C11 and C13 positions of compound **2**. This transformation was carried out using Ph_3P/NCS to provide desired chlorinated motif **17** albeit in moderate yield (38%) along with some byproducts, including an olefin.[23] Then, removal of the two TBS groups of compound **17** under acidic conditions (97%), followed by sulfation of the resultant diol **18** with $SO_3\cdot$Py in DMF,[24] smoothly delivered natural (+)-sulfolipid **1** in 94% yield. The identity of synthetic diol **18** and danicalipin A (**1**) was unambiguously confirmed by comparison with reported spectroscopic data; the ^{1}H and ^{13}C NMR data of diol **18** and synthetic (+)-danicalipin A (**1**) were in good agreement with those reported by Okino's group and Vanderwal's group.[25]

In conclusion, the asymmetric total synthesis of natural (+)-danicalipin A (**1**) was accomplished. Our synthesis features 1,3-dipolar addition that unifies chlorinated fragments **4** and **5** to effect the stereoselective construction of the requisite molecular framework of (+)-danicalipin A, leading to the confirmation of the reported absolute configuration of the natural product. The present route, simply by switching the starting materials, would provide a flexible route to all of the stereoisomeric members of danicalipin. We plan to utilize synthetic danicalipin A in toxicological research to understand how it exerts its toxicity. The next task will include the preparation of the stereoisomers of (+)-danicalipin A by adopting the present route, which would enable us to pursue structure−activity relationship studies that would provide vital clues to understand the properties of chlorosulfolipids. Studies along this line will be disclosed in due course.

Acknowledgment. We express our sincere appreciation to Professor Toshikatsu Takanami and Ms. Tamami Koseki of Meiji Pharmaceutical University (MPU) for conducting mass spectroscopic analysis. This work was partialy supported by a Grant-in-Aid for Scientific Research on Innovative Areas [No. 22136006] from the Ministry of Education, Culture, Sports, Science and Technology of Japan (T.Y.).

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H/^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.

(17) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754–2755.

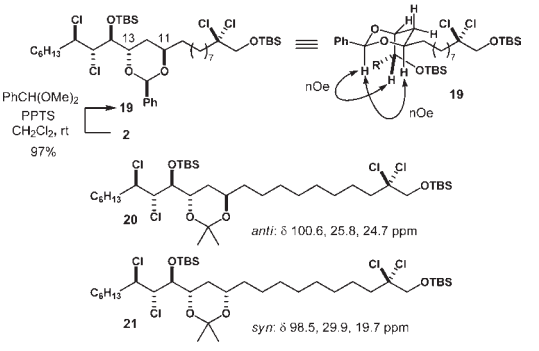
(18) For details, see Supporting Information.

(19) (a) Zhang, D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 755–759. (b) Zhang, D.; Suling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885–888. (c) Zhang, D.; Ghosh, A.; Suling, C.; Miller, M. J. *Tetrahedron Lett.* **1996**, *37*, 3799–3802.

(20) (a) For pioneering studies on the use of isoxazolines as latent aldol motifs, see: Curran, D. P. *Adv. Cycloaddit.* **1988**, *1*, 129. (b) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026. (c) Torssell, K.; Zeuthen, O. *Acta Chem. Scand. Ser. B* **1978**, *32*, 118. Excellent developments of this concept in polyketide synthesis; for a recent instance, see:Lohse-Fraefel, N.; Carreira, E. M. *Chem.—Eur. J.* **2009**, *15*, 12065–12081 and references cited therein.

(21) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(22) The *anti*-stereochemistry of major diol **2** was unambiguously established by NOE analysis of benzylidene acetal **19** derived from diol **2** (for details, see Supporting Information.). NOE analysis of acetal **19** revealed the proximity of the benzylic proton to the C11 and C14 protons, suggesting the *anti*-relationship between C11 and C13 configurations. Further ^{13}C NMR analysis of corresponding acetonides **20** and **21** that were prepared from *anti*-diol **2** and its *syn*-isomer with 2,2-dimethoxypropane in the presence of PPTS, respectively, allowed us to confirm that the stereochemical assignments of both isomers perfectly matched those predicted by Rychnovsky's empirical rule. *anti*-Acetonide **20** showed carbon resonances for the acetonide methyl groups in the range 25.8−24.7 ppm, while *syn*-isomer **21** has methyl resonances at 29.9 and 19.7 ppm.(a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100.



(23) The major byproduct was an olefin (40% yield) that possessed a double bond at C12. A small amount of diastereomeric chloride, tentatively assigned as an (11*S*,13*S*)-*syn*-isomer, was also produced (5% yield), suggesting that anchimeric assistance of the neighboring chlorine atom may take place. The details will be reported in due course.

(24) It has been reported that $SO_3\cdot$Py was not suitable for the installation of the sulfate functionality to diol **18** due to the occurrence of desulfation during workup and purification (ref 8a). We found that direct filtration of the reaction mixture to ensure the removal of the residual reagents prior to the chromatographic purification of the crude residue was essential for the successful isolation of danicalipin A (for details, see Supporting Information).

(25) Optical rotation of diol **18** $[\alpha]^{25}_D$ +33.1 (*c* 0.71, MeOH); lit.[5] $[\alpha]^{22}_D$ +35.9 (*c* 0.005, MeOH). Optical rotation of synthetic (+)-danicalipin A (**1**) $[\alpha]^{26}_D$ +33.0 (*c* 0.40, MeOH); lit.[5] $[\alpha]^{25}_D$ +12.8 (*c* 0.2, MeOH); lit.[8] $[\alpha]^{24}_D$ +38 (*c* 0.78, solvent not indicated).