ORGANIC LETTERS

2007
Vol. 9, No. 17
3481−3483

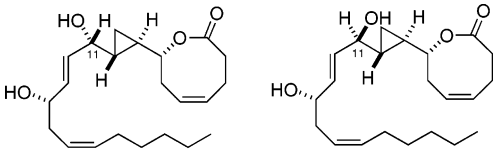
Total Synthesis of Solandelactones E and F, Homoeicosanoids from the Hydroid *Solanderia secunda*

James D. White,* William H. C. Martin, Christopher Lincoln, and Jongtae Yang

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331
james.white@oregonstate.edu

Received July 3, 2007

ABSTRACT



Asymmetric total syntheses of solandelactones E and F confirmed that hydroxyl configuration at C11 in these oxylipins had been misassigned and that the stereochemistry at this center should be reversed. Key steps in the synthesis involved a Nagao asymmetric acetate aldol reaction, a directed Simmons–Smith cyclopropanation, a Holmes–Claisen rearrangement to establish the unsaturated octalactone, and a Nozaki–Hiyama–Kishi coupling to connect two major fragments at C11–C12.

Marine invertebrates and algae are the source of at least 15 related families of metabolites with structures based on a trans disubstituted cyclopropane bearing a lactone as one substituent and an aliphatic chain as the other.[1] Included among these metabolites are the constanolactones, which contain a δ-lactone and a dodecadiendiol chain attached to a cyclopropane.[2] By contrast, the solandelactones have an eight-membered lactone, saturated or unsaturated, linked to a cyclopropane.[3] A noteworthy difference between solandelactones and constanolactones is that, whereas the latter are C_{20} eicosanoids presumably derived from arachidonic acid,[4] all of the solandelactones contain 22 carbons. There is also a curious variation in stereochemistry between solandelactones and constanolactones. Thus, cyclopropanes in the two structures have reversed absolute configuration, whereas absolute configurations at the lactone carbons, C5 and C7, and the side chain hydroxyl substituent at C12 and C14 are congruent.

The structures of constanolactones A and B, including their absolute configuration, were confirmed by synthesis.[5] However, assignments made to solandelactones rested on NMR experiments made by Shin[3] and a partial synthetic study by Datta[6] until a recent synthesis of solandelactone E by Martin[7] proved the gross structure correct but showed that hydroxyl

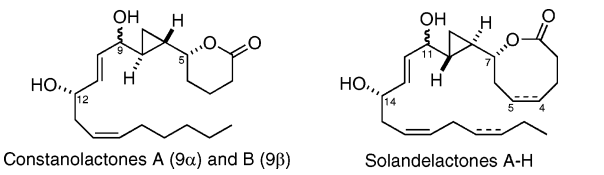


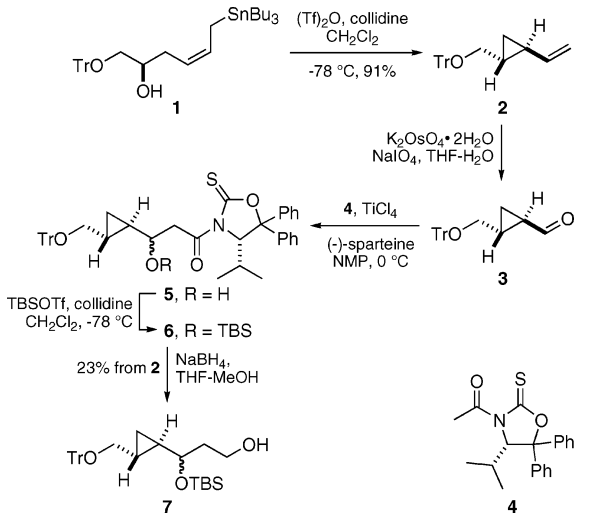
Figure 1. Constanolactone and solandelactone families of marine oxylipins

configuration at C11 should be reversed from the attribution made by Shin. Herein, we describe syntheses of solandelactones E and F which confirm that these structures are

(1) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625.
(2) Gerwick, W. H.; Nagle, D. G. *J. Org. Chem.* **1994**, *59*, 7227.
(3) Shin, J.; Seo, Y.; Cho, K. W.; Kwon, B. M.; Rho, J.-R.; Song, J.-L.; Bok, S.-H. *Tetrahedron* **1996**, *52*, 10583.
(4) (a) Brash, A. R. *J. Am. Chem. Soc.* **1989**, *111*, 1891. (b) Harris, T. M; Brash, A. R.; Baertschi, S. W. *J. Am. Chem. Soc.* **1989**, *111*, 5003.
(5) (a) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970. (b) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224.
(6) Datta, A.; Mohaptra, D. K.; Varadarajan, S. *Tetrahedron Lett.* **1998**, *39*, 1075.
(7) Davoren, J. E.; Martin, S. F. *J. Am. Chem. Soc.* **2007**, *129*, 510.

10.1021/ol701564x CCC: $37.00
Published on Web 07/21/2007

Scheme 1



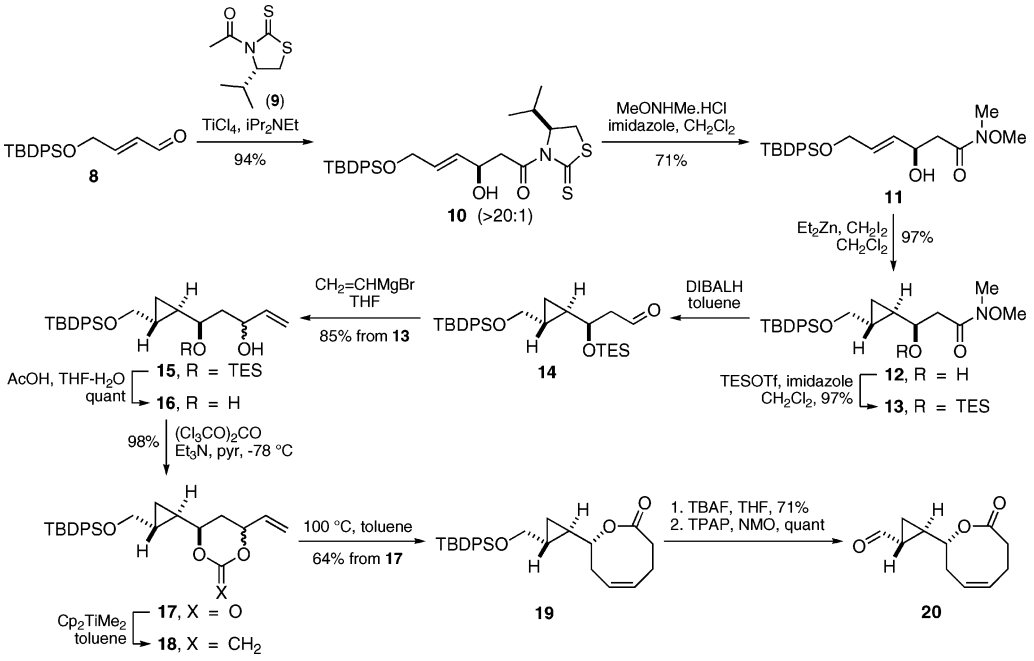
epimeric at C11 and support the assignment correction made to E by Martin.[7] An important consideration in designing a unified approach to all solandelactones is genesis of the correct configuration at C7 in a stereoselective manner. Our goal from the outset was to accomplish this via a stereocontrolled aldol reaction that would leave us with a handle for installing the $\Delta^{4,5}$ bond in the octalactone.

Previous studies from this laboratory demonstrated that alcohol **1**, obtained from (*R*)-(+)-malate, underwent rapid highly stereoselective solvolysis in the presence of triflic anhydride and a base to give (1*R*,2*S*) disubstituted cyclopropane **2** (Scheme 1).[8] Our first objective was to exploit the vinyl substituent of **2** as a site for the eight-membered lactone of the solandelactones, and to this end **2** was subjected to an osmylation−periodate oxidative cleavage[9] that led to aldehyde **3** (Scheme 2). Aldol coupling of **3** with asymmetric acetate surrogate **4**[10] gave a 2:1 mixture of stereoisomeric hydroxy amides **5** which were converted to their respective silyl ethers **6** before reductive cleavage of the chiral auxiliary to yield **7**.

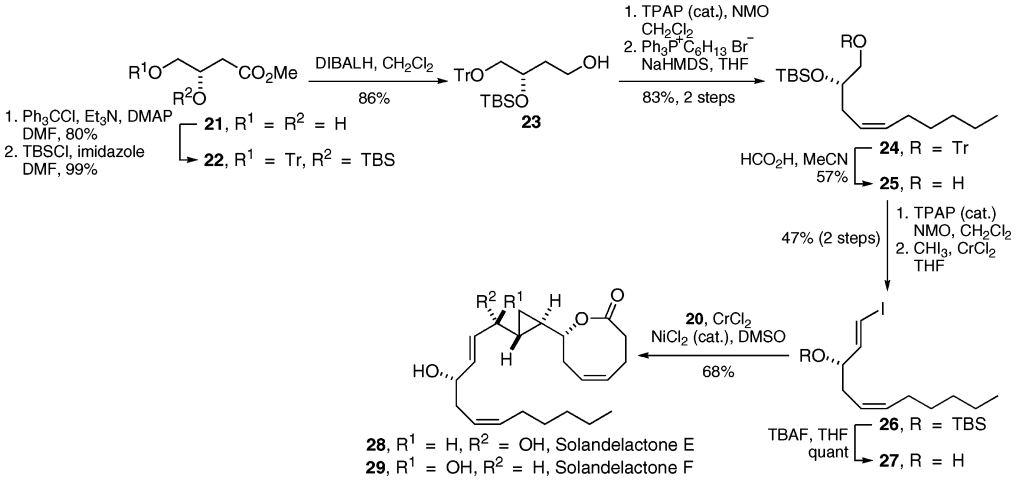
Stereoisomers of **7** were separable but the low stereoselectivity resulting from reaction of **3** with **4**, presumably the result of a configurational mismatch, together with the low overall yield from **2**, persuaded us to explore an alternate strategy for installing the C7 stereocenter of the solandelactones. Ultimately, the mismatch problem was avoided by conducting an asymmetric acetate aldol coupling with achiral aldehyde **8**, prepared from *cis*-2-butene-1,4-diol.[11] Treatment of **8** with the enolate from thionothiazolidine **9**[12] gave (*R*)-hydroxy amide **10** as the sole detectable isomer in excellent yield. Exposure of **10** to *N*,*O*-dimethylhydroxylamine cleaved the auxiliary and led to Weinreb amide **11**. When **11** was subjected to Charette's modification of the Simmons−Smith cyclopropanation,[13] **12** was produced as a single isomer.[14] After protection of alcohol **12** as its TES ether, amide **13** was reduced to aldehyde **14**, which was reacted with vinylmagnesium bromide to yield allylic alcohol **15** as an inconsequential 1:1 mixture of stereoisomers. Silyl ether **15** was then cleaved to furnish diol **16**.

Our plan with **16** was to bridge the 1,3-diol unit as a ketene acetal, then carry out a Claisen rearrangement that would lead directly to the $\Delta^{4,5}$-octenalactone moiety of the solandelactones. This lactone construction has precedent in studies by Holmes[15] and was employed successfully in a synthesis of discodermolide by Paterson.[16] However, attempts to condense diol **16** with the diethyl acetal of α-phenylsele-

Scheme 2



Scheme 3



noacetaldehyde in the presence of an acidic catalyst and effect in situ Claisen rearrangement of the ketene acetal derived from oxidative elimination of selenium as previously described[15−17] led to an inseparable mixture of products which contained <30% of lactone **19**. In an alternative move to reach this target,[18] **16** was first converted to cyclic carbonate **17** with triphosgene and **17** was then reacted with Petasis' reagent.[19] Ketene acetal **18** underwent in situ Claisen rearrangement in hot toluene to produce lactone **19** in 64% yield from **17**. Cleavage of the silyl ether from **19** followed by oxidation of the resultant alcohol gave aldehyde **20**.

Synthesis of the acyclic segment of the solandelactones for coupling with **20** commenced from dihydroxy ester **21**, prepared from dimethyl (*S*)-(+)-malate.[20] Diol **21** was advanced to its protected derivative **22** and then to alcohol **23** by reduction of the ester (Scheme 3). Subsequent oxidation yielded an unstable aldehyde[21] that underwent Wittig olefination with hexyltriphenylphosphonium bromide to furnish cis alkene **24**. Removal of the trityl residue from **24** followed by oxidation of the resultant alcohol **25** gave an aldehyde, which upon Takai−Utimoto reaction[22] with iodoform led to iodoalkene **26**.[23] The silyl ether was cleaved from **26** to yield alcohol **27** as the coupling partner for **20**.

The reaction of **27** with **20** under Nozaki−Hiyama−Hishi conditions[24] led to a mixture of two alcohols in the ratio 3.5:1. The major α alcohol **28** is the result of Felkin−Anh attack at the si face of aldehyde **20** and its NMR spectra matched precisely those of natural[3] and synthetic[7] solandelactone E. Similarly, the spectral data for the minor *β* alcohol **29** were identical with those reported for solandelactone F.[3] The proportion of **28** to **29** corresponds closely to the ratio of constanolactones A (9α OH) and B (9*β* OH) obtained from an analogous Nozaki−Hiyama−Kishi coupling of a trans iodoalkene with a cyclopropanecarboxaldehyde.[5]

In summary, we have confirmed through synthesis the revised structure of solandelactone E put forward by Martin[7] and we have firmly established the stereostructure of solandelactone F.

However, uncertainty remains regarding configurational assignments made to other solandelactones.[3] Our strategy invoking Nagao asymmetric aldol methodology for establishing configuration at C7, directed cyclopropanation, Claisen rearrangement for octalactone construction, and Nozaki−Hiyama−Kishi coupling for linking two major fragments at C11,12 offers an effective means for determining the absolute stereochemistry of other members of the solandelactone series.

Acknowledgment. We are grateful to David B. Chan, Oregon State University, for experimental assistance. Financial support for this work was provided by the National Science Foundation (0413994-CHE).

Supporting Information Available: Experimental procedures and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701564X

(8) White, J. D.; Lincoln, C. M.; Yokochi, A. F. T. *Chem. Commun.* **2004**, 2846.
(9) Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(10) Phillips, A. J.; Guz, N. R. *Org. Lett.* **2002**, *4*, 2253.
(11) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787.
(12) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.
(13) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966.
(14) Smith, A. B. III; Simov, V. *Org. Lett.* **2006**, *8*, 3315.
(15) (a) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 325. (b) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400. (c) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
(16) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.
(17) Baudat, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1406.
(18) Anderson, E. A.; Davidson, J. E. P.; Harrison, J. R.; O'Sullivan, P. T.; Burton, J. W.; Collins, I.; Holmes, A. B. *Tetrahedron* **2002**, *58*, 1943.
(19) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(20) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389.
(21) (a) Solladié, G.; Hamdouchi, C.; Ziani-Chérif, C. *Tetrahedron: Asymmetry* **1991**, *2*, 457. (b) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104.
(22) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
(23) Pietruszka, J.; Wilhelm, T. *Synlett* **2003**, 1698.
(24) Kishi, Y. *Tetrahedron* **2002**, *58*, 6239.