J|A|C|S
COMMUNICATIONS

Published on Web 12/30/2006

Enantioselective Synthesis and Structure Revision of Solandelactone E

Jennifer E. Davoren and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

Received November 18, 2006; E-mail: sfmartin@mail.utexas.edu

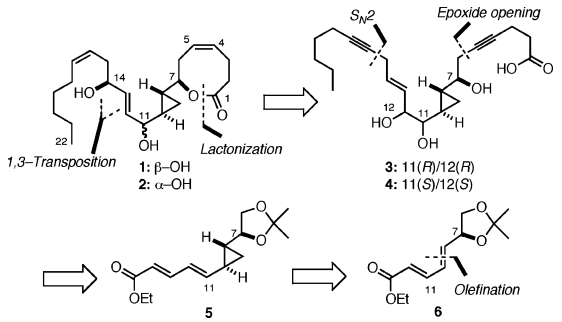
The solandelactones comprise a novel group of oxylipins that were isolated from the hydroid *Solanderia secunda* off the Korean coast in 1996.[1] The solandelactones contain cyclopropane and eight-membered lactone rings together with variable degrees of unsaturation at C(4) and C(19). Depending upon the absolute stereochemistry at C(11), they are categorized into two series, representative members of which include solandelactones F and E that were originally assigned the structures **1** and **2**, respectively. Owing to their limited availability from natural sources, these oxylipins have not been thoroughly tested, but some exhibit promising biological activity as inhibitors of farnesyl transferase.

None of the solandelactones have been synthesized, but a number of related oxylipins, including constanolactones A and B[2] and several halicholactones,[3] have succumbed to total synthesis. Arguably, tactics that were employed in these successful ventures might be applied to the solandelactones; however, none of those approaches provide adequate control of the stereochemistry at the five stereogenic centers resident in the oxylipins, especially at the cyclopropyl carbinyl stereocenters.

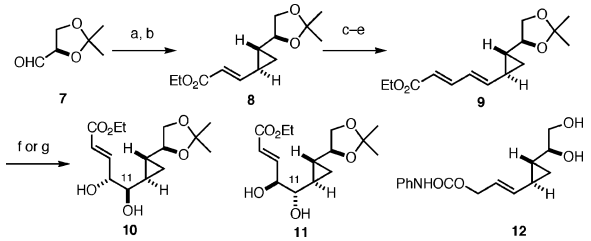
In developing a unified strategy for the synthesis of the solandelactones, we sought to address deficiencies in the prior art and thus formulated the plan outlined in retrosynthetic format in Scheme 1. The stereocenter at C(14) of **1** would be established by first inverting the stereochemistry at C(12) in diol **3** followed by a 1,3-transposition of the allylic hydroxyl group. Conversely, the synthesis of **2** would require direct 1,3-transposition of the C(12) hydroxy group in **4**. The C(1)−C(5) and C(16)−C(22) segments in **3** and **4** would be appended by epoxide openings and S_N2 reactions, whereas the absolute and relative stereochemistry of the diol arrays in **3** and **4** would be created via Sharpless asymmetric dihydroxylations of the cyclopropyl diene **5**. This diene, which would be accessed from the known ester **6**[4] by cyclopropanation and chain elongation, would serve as the pivotal intermediate for the syntheses of both series of solandelactones epimeric at C(11).

The first stage of the synthetic plan was initiated with the olefination of commercially available D-glyceraldehyde acetonide (**7**) with *trans*-triethyl phosphonocrotonate to give **6** as a mixture (10:1) of olefin isomers that was treated with $Zn(CH_2I)_2$ at 65 °C in a sealed tube to furnish cyclopropane **8** (Scheme 2).[5] The stereochemical assignment of **8** was secured by obtaining the X-ray

Scheme 1



Scheme 2 [a]



[a] Reaction conditions: (a) *trans*-$(EtO)_2P(O)CH_2CHCHCO_2Et$, LDA, THF, 0 °C, 89%, 10:1 *EE*/*EZ*; (b) Et_2Zn, CH_2I_2, CH_2Cl_2, 65 °C, 72%; (c) DIBAL, CH_2Cl_2, −78 °C, 88%; (d) TPAP, NMO, CH_2Cl_2, rt, 98%; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 89%, 10:1 *E*/*Z*; (f) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, rt, 80%, >20:1 dr; (g) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, rt, 78%, 3:1 dr.

structure of the derived carbamate **12**. Sequential hydride reduction of the ester group in **8** followed by TPAP[6] oxidation of the intermediate alcohol and olefination of the resultant aldehyde led to the diene **9** as a 10:1 mixture of *E*/*Z* olefin isomers.

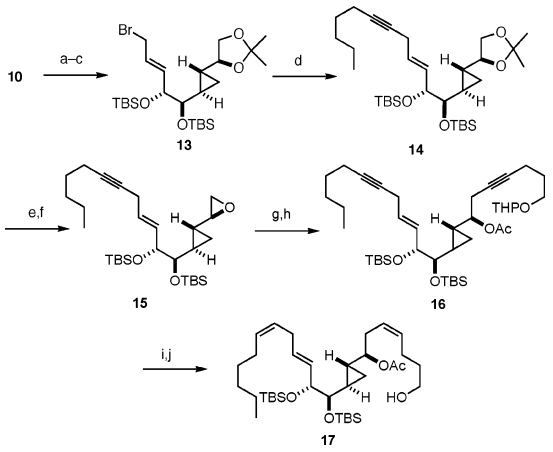
When **9** was treated with AD-mix β, diol **10** was isolated in 80% yield as a single diastereomer,[7] whereas reaction of **9** with AD-mix α provided diastereomeric diols **11** and **10** in 78% yield as an inseparable mixture (3:1). The stereochemistries of **10** and **11** were assigned to be 11(*R*)/12(*R*) and 11(*S*)/12(*S*), respectively, by applying the Sharpless model.[8] Inasmuch as **10** and **11** might be separately transformed into the corresponding diols **3** and **4**, the asymmetric dihydroxylation of **9** using either AD-mix β or AD-mix α enabled us, in principle, to prepare both C(11) epimeric series of solandelactones from a common intermediate.

Because **10** was accessible with higher efficiency than **11**, we elected to transform it into a natural solandelactone. The next phase of the synthesis thus required elaboration of **10** by introducing the remaining carbon atoms of the C(1)−C(5) and C(16)−C(22) subunits. In the event, diol **10** was protected as its bis-TBS ether, and the ester function was transformed in two steps to furnish the allylic bromide **13** (Scheme 3).[9] Treatment of **13** with lithiated 1-heptyne in the presence of a catalytic amount of Cu(I) provided the enyne **14** as the sole product. Selective removal of the acetonide moiety in the presence of the somewhat acid-labile TBS protecting groups required some experimentation, but we eventually found that hydrolysis of **14** using a two-phase solution of CH_2Cl_2 and aqueous TFA gave a diol,[10] which was converted into the corresponding epoxide **15** in a single step employing a Fraser-Reid protocol.[11] This epoxide was very acid sensitive and underwent facile rearrangement to a β-cyclopropyl aldehyde upon purification by flash silica gel chromatography.[12]

When **15** was treated with the anion of THP−pentynol according to the Yamaguchi procedure,[13] ring opening of the epoxide ensued to give an alcohol that was acetylated under standard conditions to give **16**. The tetrahydropyranyl group on **16** was selectively cleaved using *i*-PrOH as solvent, whereas use of more conventional solvents, such as H_2O, MeOH, and EtOH, led to significant loss of the TBS

10.1021/ja068270q CCC: $37.00

Scheme 3[a]



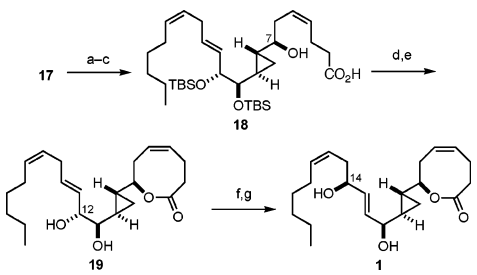
[a] Reaction conditions: (a) TBSCl, imidazole, DMF, rt, 99%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 95%; (c) CBr_4, PPh_3, CH_2Cl_2, rt, 96%; (d) *n*-BuLi, 1-heptyne, $CuBr{\cdot}SMe_2$, −78 °C to rt, 95%; (e) TFA, H_2O, CH_2Cl_2, rt, 82%; (f) NaH, 1-tosylimidazole, THF, 0 °C, ∼100%; (g) $THPO(CH_2)_3C{\equiv}CH$, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 45%; (h) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 92%; (i) *p*-TsOH, *i*-PrOH, rt, 87%; (j) H_2, Lindlar catalyst, quinoline, MeOH, rt, 94%.

protecting groups. Catalytic semihydrogenation using Lindlar's catalyst then delivered triene **17**, which incorporates the complete carbon skeleton of the solandelactones.

It then remained to form the eight-membered lactone ring and induce the 1,3-transposition of the C(12) allylic alcohol. Toward this end, a two-stage oxidation of the primary alcohol in **17**, followed by saponification of the C(7) acetate, gave the hydroxy acid **18** (Scheme 4). Cyclization of **18** to an eight-membered lactone under the conditions developed by Yamaguchi[14] and subsequent TBAF-mediated deprotection of both TBS ethers proceeded uneventfully to give diol **19**. The stage was thus set for the transposition of the allylic alcohol array at C(12)−C14). Despite the apparent simplicity of this transformation, it proved to be much more difficult to induce than we had anticipated. Ultimately, we discovered that reaction of **19** with *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine led to activation and substitution with inversion of the less-hindered alcohol at C(12) to give a selenide that was converted into **1** in modest overall yield via oxidation and [2,3]-sigmatropic rearrangement of the intermediate allylic selenoxide.[15]

On the basis of the structures assigned to the solandelactones in the literature,[1] we believed we had thus completed the total synthesis of solandelactone F. However, when we compared our spectral data with those in the literature, we realized we had not. The structural assignment of synthetic **1** seemed secure based upon the X-ray analysis of **12**, the known stereochemical preference for asymmetric

Scheme 4[a]



[a] Reaction conditions: (a) $SO_3{\cdot}$pyridine, Et_3N, DMSO, rt, CH_2Cl_2, 85%; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, rt, 90%; (c) K_2CO_3, MeOH, rt, 95%; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhMe, Δ, 81%; (e) TBAF, THF, rt, 72%; (f) *o*-NO_2PhSeCN, Bu_3P, THF, rt; (g) H_2O_2, pyridine, CH_2Cl_2, rt, 20% (2 steps).

dihydroxylations,[8] and the preferred stereoselectivity of [2,3]-sigmatropic rearrangements.[16] However, the ^1H and ^{13}C NMR data for synthetic **1** nicely matched those given for solandelactone E, which had been incorrectly depicted as the C(11) epimer **2**.[17]

In summary, we designed a novel and convergent strategy for oxylipin synthesis that culminated in the first total synthesis of solandelactone E (**1**) and a revision of the original structural assignments of the C(11) epimeric solandelactones. The synthesis, which provides the first effective solution to the numerous stereochemical challenges posed by the oxylipin class of natural products, features an acetal-directed cyclopropanation, an asymmetric dihydroxylation, and a 1,3-chirality transfer.

Acknowledgment. We thank the National Institutes of Health (GM 31077), the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for generous support of this research. We are also grateful to Dr. Christian Harcken (Boehringer Ingelheim Pharmaceuticals, Inc.) for helpful discussions, and Prof. Jongheon Shin (College of Pharmacy, Seoul National University) for providing spectral data for solandelactones E and F.

Supporting Information Available: Experimental procedures for **9**, **16**, and **1**; full characterization and copies of ^1H NMR spectra for all new compounds; and a tabular comparison of ^1H and ^{13}C NMR data for synthetic and natural **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron* **1996**, *52*, 10583.

(2) For recent examples, see: (a) Pietruszka, J.; Wilhelm, T. *Synlett* **2003**, 1698. (b) Yu, J.; Lai, J.-Y.; Ye, J.; Balu, N.; Reddy, L. M.; Duan, W.; Fogel, E. R.; Capdevila, J. H.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 3939. (c) Silva, C. B.-D.; Benkouider, A.; Pale, P. *Tetrahedron Lett.* **2000**, *41*, 3077.

(3) For recent examples, see: (a) Takahashi, T.; Watanabe, H.; Kitahara, T. *Heterocycles* **2002**, *58*, 99. (b) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81. (c) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638.

(4) Li, S.-K.; Xu, R.; Xiao, X.-S.; Bai, D.-L. *Chin. J. Chem.* **2000**, *18*, 910.

(5) For a related example, see: Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97.

(6) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(7) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.

(8) (a) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470. (b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

(9) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *87*, 801.

(10) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783.

(11) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.

(12) Meinwald, J.; Labana, S. S.; Labana, L. L.; Wahl, G. H., Jr. *Tetrahedron Lett.* **1965**, 1789.

(13) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(14) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(15) As noted by a reviewer, this transformation might also proceed via epoxide intermediates to furnish diastereoisomeric allylic selenides that would deliver solandelactone F (**2**) or the C(14) epimer of **1** upon oxidation and [2,3]-sigmatropic rearrangement. That this possibility was not the source of the discrepancy in structure assignments was established by an independent synthesis of **1** from **19** in lower overall yield by a five-step reaction sequence in which the C(11) hydroxyl group was selectively protected as a PMB ether: (a) *p*-$MeOC_6H_4(OMe)_2$, TsOH, DMF, rt, 80%; (b) $NaBH_3CN$, TFA, THF, 0 °C, 50%; (c) *o*-NO_2PhSeCN, Bu_3P, THF, rt; H_2O_2, pyridine, CH_2Cl_2, rt, 56%; (d) DDQ, H_2O, CH_2Cl_2, rt, 72%.

(16) Nishibayashi, Y.; Uemura, S. *Top. Curr. Chem.* **2000**, *208*, 2015.

(17) In corresponding with Professor Shin, it became apparent that there was a clerical error in correlating the names of the C(11) epimeric solandelactones with their respective structures in ref 1. He concurs that those assignments should be revised in accord with the present findings.

JA068270Q