ORGANIC LETTERS

2005
Vol. 7, No. 5
819−821

Stereoselective Synthesis of Cyercene A and the Placidenes

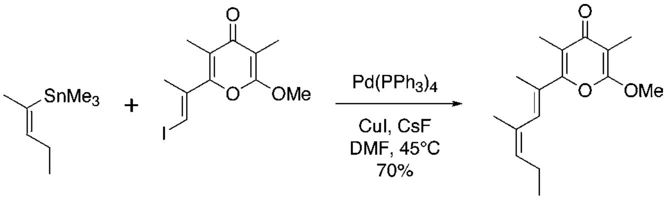
Guangxin Liang, Aubry K. Miller, and Dirk Trauner*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California—Berkeley, Berkeley, California 94720

trauner@berkeley.edu

Received November 30, 2004

ABSTRACT



placidene A

Members of a family of α-methoxy-γ-pyrone-containing polypropionate natural products have been stereoselectively synthesized. Two key iodovinyl pyrone building blocks were coupled to appropriately selected vinyl stannanes to assemble the highly substituted polyene side chains of the natural products.

Polypropionate natural products featuring pyrone moieties are commonly found among saccoglossan molluscs, a fascinating class of marine animals that sequester active chloroplasts from algae and use the organelles to live autotrophically (Figure 1).[1] Due to the fact that these molluscs live in shallow waters and are exposed to bright sunlight, it has been proposed that the highly UV-absorbant α-methoxy-γ-pyrones they produce act as sunscreens.[2] Some of their natural products, however, appear to fulfill additional biological roles. Cyercene A (**1**), for instance, has been shown to be ichthyotoxic as well as central to the remarkable regenerative properties of the mollusc from which it is obtained (*c. Cristallina*).[3]

The natural products shown in Figure 1 can be generally classified into α-methoxy-γ-pyrones with appended dienes such as cyercene A (**1**) and the placidenes (**2**−**5**)[4] and into pyrones wherein the heterocycle is linked to a more complex molecular skeleton. Photodeoxytridachione (**7**),[2] crispatene (**8**),[5] and 9,10-deoxytridachione (**9**)[5] belong to the latter class. In the case of tridachiahydropyrone (**6**), the pyrone moiety has been masked by what appears to be a 6π electrocyclization.[6]

The simple pyrones **1**−**5** have been found in almost all possible stereochemical variations. Their more complex congeners **6**−**9** also appear to stem biosynthetically from stereochemically diverse polyenes, which undergo additional cyclizations to furnish the cyclohexadiene or bicyclo[3.1.0]-hex-2-ene skeleta of the natural products.

Although some of these natural products have been known in the literature for 25 years, the synthetic community has paid little attention to them until quite recently.[7] Perhaps this is due to the difficulty associated with assembling the required trisubstituted and conjugated double bonds of specifically determined stereochemistry of the natural products or, in the case of the **6**−**9**, their presumed polyene precursors. To be synthetically useful, reactions used to this end must be highly stereoselective not only for the sake of efficiency but also because separation of isomeric polyenes

---

(1) Trench, R. K.; Greene, R. W.; Bystrom, B. G. *J. Cell Biol.* **1969**, *42*, 404.

(2) Ireland, C.; Scheuer, P. J. *Science* **1979**, *205*, 922.

(3) (a) Vardaro, R. R.; Di Marzo, V.; Crispino, A.; Cimino, G. *Tetrahedron* **1991**, *47*, 5569. (b) Di Marzo, V.; Vardaro, R. R.; Depetrocellis, L.; Villani, G.; Minei, R.; Cimino, G. *Experientia* **1991**, *47*, 1221.

(4) Vardaro, R. R.; Di Marzo, V.; Cimino, G. *Tetrahedron Lett.* **1992**, *33*, 2875.

(5) Ireland, C.; Faulkner, J. *Tetrahedron* **1981**, *37*, 233 (Supplement 1).

(6) Gavagnin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996**, *37*, 4259.

10.1021/ol047542w CCC: $30.25

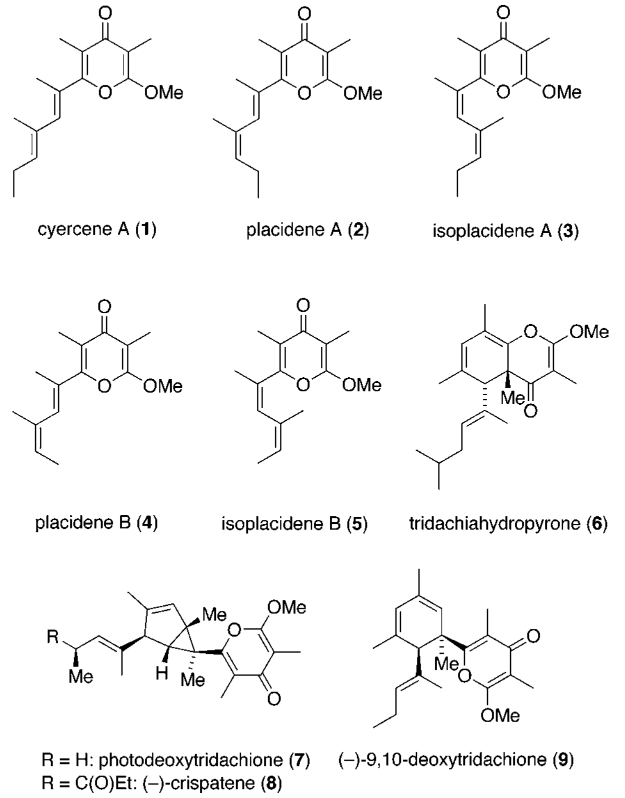


Figure 1.

can be a tedious and sometimes fruitless endeavor. Even with modern stereoselective olefination methods and transition metal-catalyzed cross-couplings at hand, these polyenes remain challenging targets.

Our group has become interested in the chemistry of these natural products and has accomplished the total synthesis of (±)-photodeoxytridachione (**7**)[7a,b] as well as (−)-crispatene (**8**).[7c] These molecules were synthesized in a linear fashion with assembly of the pyrone moiety at a late stage. Recently, we have made an effort to establish a more convergent approach to the molluscan polypropionates wherein the stereochemistry of each trisubstituted alkene can be "dialed-in" to provide the product of interest with the pyrone already in place. We envisioned two stereoisomeric iodovinyl pyrone building blocks, **10** and **11**, suited for this task (Figure 2). Stille cross-coupling of these key building blocks with appropriately chosen vinyl stannanes would provide a manifold with which all of the natural products shown in Figure 1 could be reached. We now report the synthesis of cyercene A, placidenes A and B, and isoplacidenes A and B (**1**−**5**) using this convergent strategy.

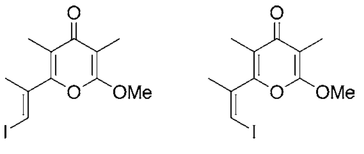
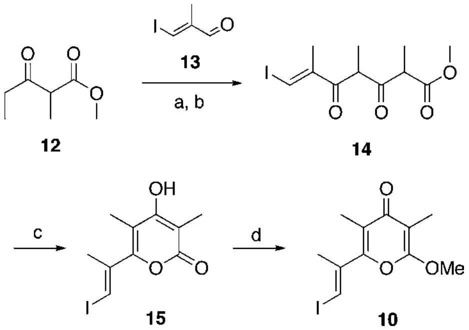

10 **11**

Figure 2.

Scheme 1. Synthesis of (*E*)-Iodovinyl Pyrone **10**[a]



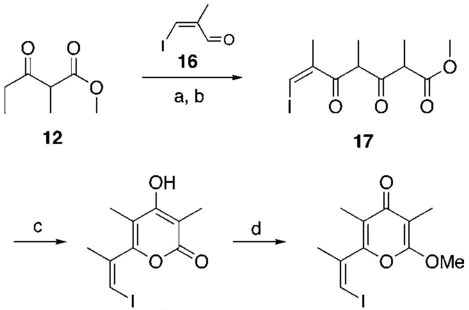
12 **14** **15** **10**

[a] Reagents and conditions: (a) NaH, THF, 0 °C, then *n*-BuLi, 0 °C, then **13**, 0 °C to room temperature. (b) Dess−Martin periodinane, wet CH$_2$Cl$_2$, rt. (c) DBU, PhH, reflux, 53% (three steps); MeOSO$_2$F, CH$_2$Cl$_2$, rt, 12 h, 95%.

(*E*)-Iodovinyl pyrone **10** was synthesized starting from readily available known (*E*)-3-iodo-2-methyl propenal (**13**)[8] (Scheme 1). Addition of the dianion of known ketoester **12** was followed by oxidation with Dess−Martin periodinane to afford diketoester **14**. Both the initial addition product and the diketoester were complex mixtures of diastereomers and were taken on without full characterization. Cyclization of the diketoester with DBU in benzene at reflux gave γ-hydroxy-α-pyrone **15** in good yield. Regioselective methylation with excess methylfluorosulfonate finally provided α-methoxy-γ-pyrone **10**. Recently, we have described an alternative approach to diketoester **14** via a one-step addition of the dianion of **12** to the Weinreb amide equivalent of **13**.[7c] However, we have found that the two-step approach starting from **13** is a more reliable and efficient sequence.

The synthesis of (*Z*)-iodovinyl pyrone **11** from readily available (*Z*)-3-iodo-2-methyl propenal (**16**)[9] proceeded analogously (Scheme 2). Addition of the dianion, followed

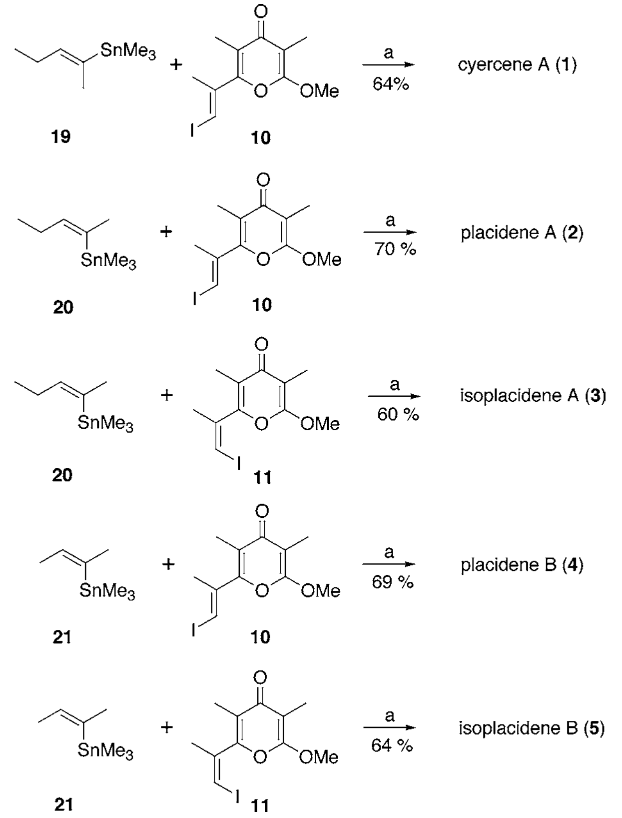
Scheme 2. Synthesis of (*Z*)-Iodovinyl Pyrone **11**[a]



12 **17** **18** **11**

[a] Reagents and conditions: (a) NaH, THF, 0 °C, then *n*-BuLi, 0 °C, then **16**, 0 °C to room temperature. (b) Dess−Martin periodinane, wet CH$_2$Cl$_2$, rt. (c) DBU, PhH, reflux., 52% (three steps); MeOSO$_2$F, CH$_2$Cl$_2$, rt, 12 h, 81%.

Scheme 3. Synthesis of Cyercene A and the Placidenes[a]



[a] Reagents and conditions: (a) 5 mol % $Pd(PPh_3)_4$, 10 mol % CuI, 2 equiv of CsF, DMF, 45 °C.

by oxidation and cyclization, afforded a γ-hydroxy-α-pyrone **18**, whose regioselective methylation gave **11**. Note that the integrity of the (*Z*)-substituted vinyl iodide moiety remained intact under the relatively harsh cyclization conditions.

To complete the synthesis of the simple molluscan polypropionates, three vinyl stannanes **19**,[10] **20**, and **21**[11] were readily prepared according to well-established procedures (Scheme 3). With both iodovinyl pyrones and vinyl stannanes in hand, we explored their cross-coupling using a variety of Stille-coupling conditions. In all cases, Baldwin's variant employing a CsF additive proved to be the fastest and most efficient procedure.[12] Whereas the yields of the cross-coupling reactions were relatively modest, all of the sensitive target compounds were formed as single stereoisomers, facilitating their purification.

In conclusion, we have achieved a convergent and concise total synthesis of five pyrone-containing polypropionate natural products, namely, cyercene A, placidenes A and B, and isoplacidenes A and B. The usefulness of two key iodovinyl pyrone building blocks was demonstrated, which we plan to explore further in the synthesis of more complex molluscan polypropionates such as tridachiahydropyrone (**6**) and 9,10-deoxytridachione (**9**).

Acknowledgment. Financial support from AstraZeneca, Eli Lilly, GlaxoSmithKline, and Merck is gratefully acknowledged. This work was supported by National Institutes of Health Grant R01 GM067636. A.K.M thanks the NSF for a predoctoral fellowship. The Center for New Directions in Organic Synthesis is sponsored by Bristol-Meyers-Squibb as a Sponsoring Member and Novartis as a Supporting Member.

Supporting Information Available: Spectroscopic and analytical data for compounds **1**−**5**, **10**, **11**, **15**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047542W

---

(7) (a) Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 549. (b) Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919. (c) Miller, A. K.; Byun, D. H.; Beaudry, C. M.; Trauner, D. *Proc. Nat. Sci. Prod.* **2004**, *101*, 12019. (d) Moses, J. E.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 6447. (e) Moses, J. E.; Baldwin, J. E.; Bruckner, S.; Eade, S.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670. (f) Bruckner, S.; Baldwin, J. E.; Moses, J.; Adlington, R. M.; Cowley, A. *Tetrahedron Lett.* **2003**, *44*, 7471. (g) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Org. Lett.* **2003**, *5*, 661.

(8) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 47.

(9) (a) Yonghong, G.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385. (b) Liu, F.; Negishi, E.-i. *J. Org. Chem.* **1997**, *62*, 8591.

(10) Cooke, M. P., Jr. *J. Org. Chem.* **1982**, *47*, 4963.

(11) Cochran, J. C.; Prindle, V.; Young, H. A.; Kumar, M. H.; Tom, S.; Petraco, N. D. K.; Mohoro, C.; Kelley, B. *Synth. React. Inorg. Met.-Org. Chem.* **2002**, *32*, 885.

(12) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.