Total Synthesis of Marine Oxylipins Constanolactone A and B

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Received 5 June 2003

Abstract: A short, high-yielding synthesis of the marine oxylipins constanolactone A and B was reported. Starting from cinnamyl alcohol (**3**), the cylopropyl lactone moiety **2** was obtained in 28% yield (11 steps). The second coupling partner, vinyl iodide **1**, was isolated in 7 steps and 32% yield. Chromium mediated addition yielded the natural products as a 2:1 mixture (74%).

Key words: natural products, total synthesis, asymmetric synthesis, cyclopropane, ozonolysis

Marine oxylipins bearing a cyclopropyl lactone moiety have attracted considerable interest in recent years. The isolation of hybridalactone,[1] solandelactones,[2] halicholactone,[3] neohalicholactone,[3] and constanolactones[4] provoked a synthetic response.[5] In this communication, we present a route to constanolactones A and B. Constanolactones A-G were isolated by Nagle and Gerwick from the red alga *Constantinea simplex* – harvested off the Oregon coast – in 1990.[4] The structures were determined through degradation and spectroscopic methods; a biosynthetic pathway was proposed.[6] Syntheses of constanolactone A and B[5f–h] as well as constanolactone E[5i,j] were reported, partly driven by the fact that despite the known biological activity of cyclopropyl lactones, physiological data are still scarce. Our own synthetic efforts first focussed on the synthesis of constanolactones A and B with an attempt to efficiently provide the key intermediates **1** and **2** (Figure 1) that should readily give the natural products by a known chromium mediated addition.[5f] It is important to note that the iodide **1** is also the common precursor for several solandelactones.

First, we thought to investigate the formation of the cyclopropyl lactone moiety by means of a model sequence (Scheme 1). Starting from cinnamyl alcohol (**3**), we obtained essentially enantiomerically pure cyclopropane **4** by a combination of enantioselective catalytic cyclopropanation according to a Denmark protocol[7] and a kinetic enzymatic resolution.[8] Oxidation under Ley's conditions[9] (90%) followed by an allyl addition with the Roush reagent **5**,[10] yielded the homoallyl alcohols **6** and **7** in 81% as an easily seperable 19:81 diastereomeric mixture. The minor diastereoisomer could be converted directly to the desired acrylic ester **8** with acrylic acid under Mitsunobu conditions,[11] however, the yield was unsatisfactory (40%). A two step procedure proved superior: Oxidation

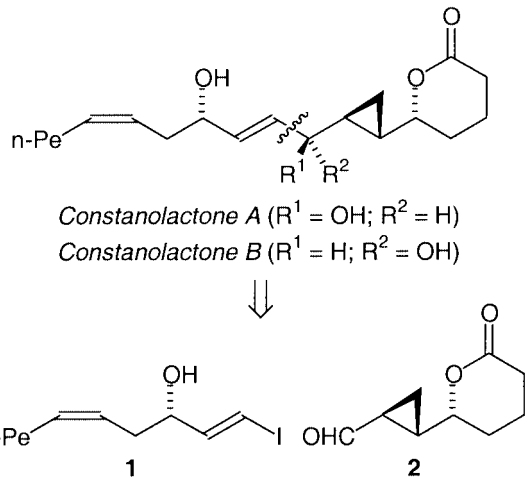


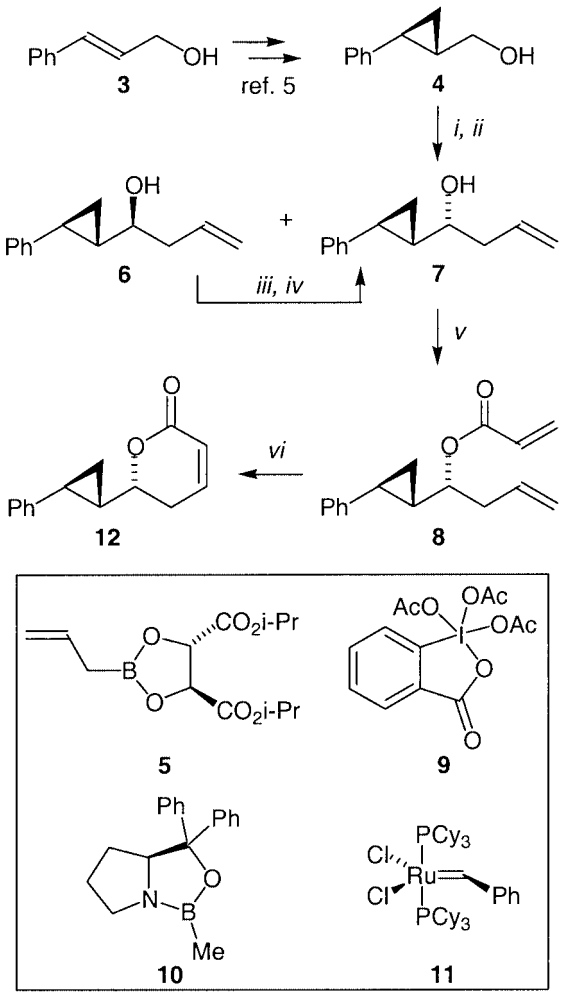
Figure 1 Retrosynthesis of constanolactone A and B.

of alcohol **6** using Dess–Martin periodinane **9**[12] and a typical CBS-reduction[13] with catalytic amounts of reagent **10** furnished exclusively diastereomer **7** in 81% yield. Direct acylation to diene **8** was conveniently performed with acryloyl chloride (96% yield). Next, a ring-closing metathesis followed, using the modified protocol by Fürstner and Langemann:[14] In the presence of a Lewis acid and the Grubbs catalyst **11**,[15] the envisaged model lactone **12** was obtained in high yield (97%, Scheme 2).

A closer examination of the model compound **12** revealed that only 4 steps were missing to finish the synthesis of the key intermediate **2** for all constanolactones: Obviously, the crucial step would be the hydrogenolysis of the double bond, since ring-opening of the cyclopropane ring to compound **13** would be expected. Indeed, when performing the reaction at room temperature, this transformation is the only one we found. Nevertheless, it was observed that the addition to the double bond is considerable faster and consequently lowering the reaction temperature should disfavor the formation of the benzyl derivative **13**. It proved ideal to reduce the olefin at a temperature between –20 to –10 °C thus minimizing the amount of **13** formed and maximizing the yield of cyclopropyl lactone **14** (89% yield). All that remained to be done was to oxidatively degrade the phenyl group in order to obtain a carbonyl group. It was found that ozonolysis[16] with a reductive work-up conveniently furnished the carboxylic acid **15** (70%)[17] along with some dicarboxylic acid **16** (20%; formed during work-up). Strict absence of water was essential in order to minimize the amount of **16**. As a matter of course, both derivatives could be converted to the acid

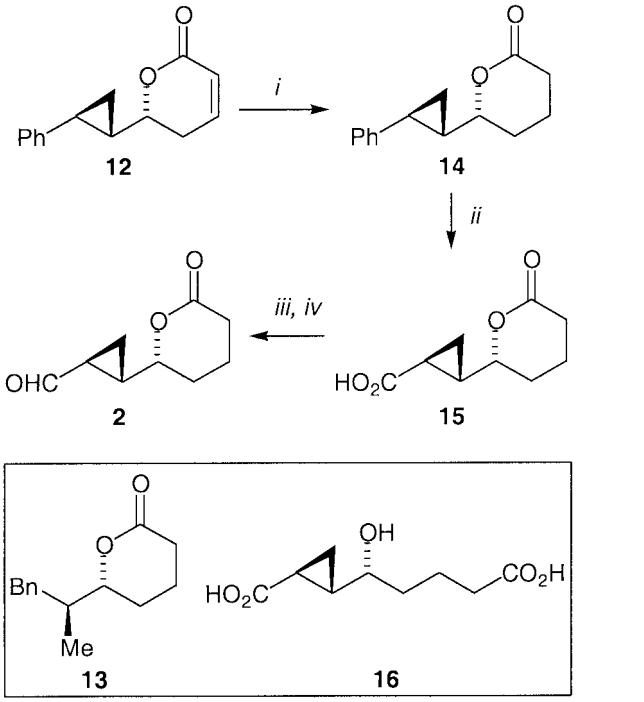
Synlett 2003, No. 11, Print: 02 09 2003. Web: 05 08 2003.
Art Id.1437-2096,E;2003,0,11,1698,1700,ftx,en;D12903st.pdf.
DOI: 10.1055/s-2003-40986

chloride in near quantitative yield, followed by a Rosenmund reduction[18] to furnish aldehyde **2** [(65% yield over two steps; 28% starting from cinnamyl alcohol (**3**)]. Alternative coupling strategies failed: no suitable precursors for the natural products were formed via the acid chloride or even the carboxylic acid.

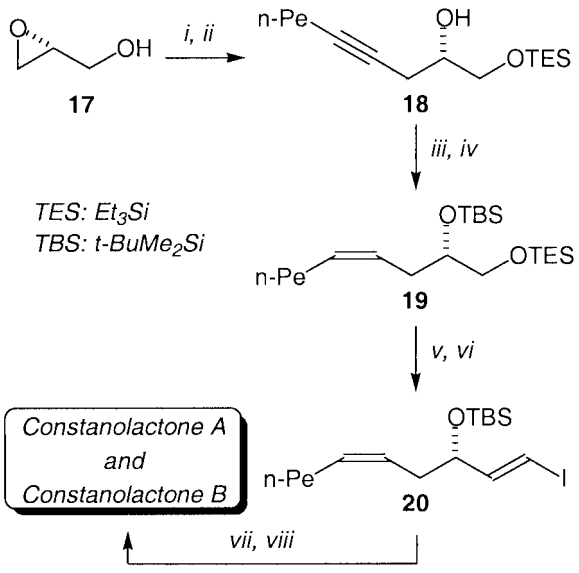


Scheme 1 *i* n-Pr_4NRuO_4, *N*-methylmorpholine *N*-oxide, 4 Å molecular sieves, CH_2Cl_2, 0 °C to r.t. (90%); *ii* **5**, toluene, –78 °C. (94%, dr **6**:**7** 19:81); *iii* **9**, 4 Å molecular sieves, CH_2Cl_2, r.t. (81%); *iv* cat. **10**, 2 equiv catecholborane, toluene, –78 °C (quant., dr **7**:**6**>98:2); *v* CH_2=CHCOCl, *i*-Pr_2NEt, 4-(dimethylamino)pyridine, CH_2Cl_2, –78 °C (96%); *vi* 0.1 equiv **11**, 0.3 equiv Ti(O-*i*-Pr)$_4$, CH_2Cl_2, 40 °C (97%).

The vinyl iodide **1** contains only one stereogenic center that we introduced via the epoxide **17** (Scheme 3). After the introduction of a silyl protecting group (94%), ring-opening with lithiated heptyne in the presence of $BF_3{\cdot}OEt_2$ (91%) yielded pure secondary alcohol **18**.[19] Formation of a *tert*-butyldimethylsilyl ether under standard conditions (86%) and *syn*-selective reduction of the triple bond led to *Z*-olefin **19** (90%). Under Swern conditions the primary silyl protecting group was cleaved; consecutive oxidation to the aldehyde occurred in the same step (72%).[19] The Takai–Utimoto[20] reaction led to vinyl iodide **20**[21] (77%; 37% in 6 steps starting from epoxide **17**).



Scheme 2 *i* Pd/C, H_2, EtOAc, –20 to –10 °C (89% + 6% **13**); *ii* a) O_3, CH_2Cl_2, 4 Å molecular sieves, 0 °C, b) Me_2S, CH_2Cl_2, 4 Å molecular sieves, –78 °C to r.t. (70% + 20% **16**); *iii* $SOCl_2$, –78 °C to r.t.; *iv* a) *i*-Pr_2NEt, Pd/$BaSO_4$, 4 Å molecular sieves, H_2, toluene, 0 °C, b) reflux (65% over 2 steps).



Scheme 3 *i* Imidazole, TES-Cl, CH_2Cl_2, r.t. (94%); *ii* 1-heptyne, $BF_3{\cdot}OEt_2$, BuLi, THF, –78 °C to r.t. (91%); *iii* imidazole, TBS-Cl, CH_2Cl_2, r.t. (86%); *iv* Lindlar-cat., H_2, toluene, r.t. (90%); *v* a) 4 equiv $(COCl)_2$, 8 equiv DMSO, CH_2Cl_2, –78 °C, b) **19**, CH_2Cl_2, –78 °C to –20 °C, c) Et_3N, –78 °C to r.t. (72%); *vi* 8 equiv $CrCl_3$, 4 equiv $LiAlH_4$, 2 equiv CHI_3, THF/dioxane (1:6) (77%); *vii* n-$Bu_4NF{\cdot}3H_2O$, THF, r.t. (88%); *viii* 6 equiv $CrCl_2$, 4 Å molecular sieves, DMSO (74%, dr 67:33).

For the high *E*-selectivity it was of vital importance to use not less than 2 equivalents of iodoform: Under the same conditions, but with 1.75 equivalents we obtained an also highly reproducable 88% yield, however, the reaction furnished an inseparable 80:20 mixture of *E*- and *Z*-olefin. Deprotection with *n*-Bu_4NF afforded the second essential coupling partner. The final step of the constanolactone A and B synthesis was the well established $CrCl_2$-mediated addition to aldehyde **2**;[5f] in 74% yield the natural products were obtained as a 67:33 mixture of diastereoisomers. The spectroscopic data were in full agreement with those published.[5f]

In conclusion, we succeeded to synthesize the two natural products, constanolactone A and B via a convergent route (longest linear chain: 12 steps, 21% yield). The building blocks used, were synthesized in just a few, high yielding steps.

Acknowledgment

The generous support of this project by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Otto-Röhm-Gedächtnisstiftung is gratefully acknowledged. Donations from the Boehringer Ingelheim KG, the Degussa AG, the Bayer AG, the BASF AG, the Roche Diagnostics GmbH, the Wacker AG, and the Novartis AG were greatly appreciated. We are also grateful to the Institut für Organische Chemie der Universität Stuttgart for their ongoing support.

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