Short and Efficient Synthesis of Cadiolide B

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Received 4 October 2004

Abstract: The first synthesis of cadiolide B has been achieved in 6 steps and 42% overall yield from 4-bromo-2(5*H*)-furanone. The pathway involves sequential, regiocontrolled introduction of the three furanone substituents by means of aldol reactions and Suzuki cross coupling.

Key words: cross coupling, aldol reaction, 2-furanolates, lactones, total synthesis

Reported by Ireland in 1998,[1] cadiolides A and B (**1**, **2**) are a pair of densely functionalized 3,4,5-trisubstituted furanones obtained from an Indonesian ascidian of the genus *Botryllus* (Figure 1). Structurally, the cadiolides belong to a family of biogenetically related non-nitrogenous marine metabolites derived from phenylalanine or tyrosine that includes the antibiotic rubrolides,[2–4] exemplified by rubrolide A (**3**), which was also isolated from *Botryllus* sp.[1]

Although both cadiolides and rubrolides share the same 4-aryl-5-arylmethylenefuranone unit, the former are distinguished by an additional 3-ketoaryl substituent and a novel carbon skeleton. These unusual structural features along with the useful biological activities of related lactones, such as Merck's selective COX-2 inhibitor rofecoxib (VIOXX®, **4**),[5] make cadiolides worthwhile targets for synthesis.

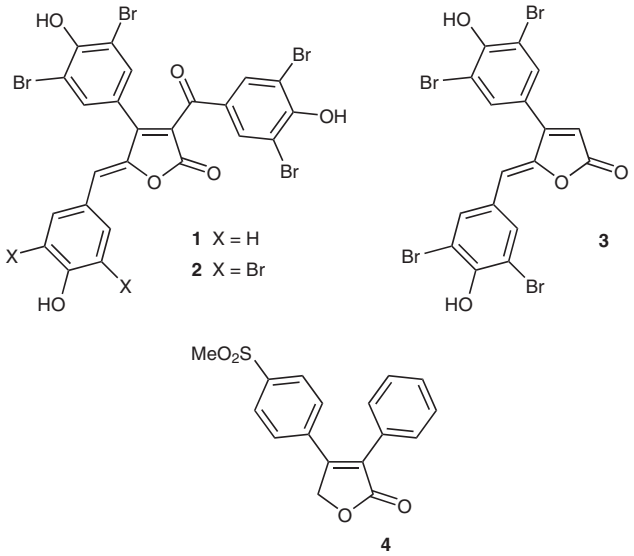


Figure 1

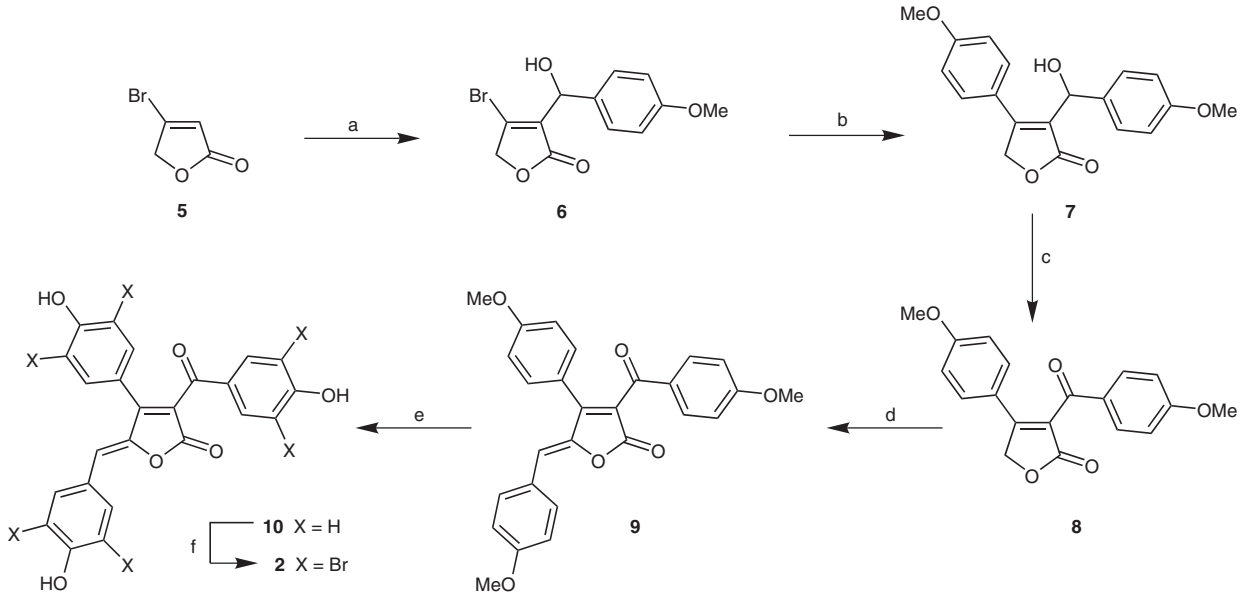
In keeping with our interest in the expedient construction of arylfuranones,[3] we now report the first synthesis of cadiolide B which demonstrates a new pathway for regiocontrolled assemblage of 3-ketoaryl-4-aryl-5-arylmethylenefuranones.

The starting point of our synthesis is the readily available 4-bromo-2(5*H*)-furanone[6] (**5**, Scheme 1). Attachment of the requisite C3-substituent was accomplished by conversion of **5** to the corresponding dibutylboron 2-furanolate using *n*-Bu_2BOTf in the presence of di-isopropylethylamine,[7] followed by in situ aldolization with *p*-anisaldehyde. In contrast to previous experience with aliphatic aldehydes which provided excellent yields of 3-(1-hydroxyalkyl)furanones under the same conditions,[7] the desired alcohol **6** was obtained only in modest yield (43%). We reasoned that **6** may be prone to base-induced decomposition by a retroaldol reaction which could conceivably be suppressed by the use of a weaker base. Indeed, when diisopropylethylamine was replaced by 2,6-lutidine the yield of **6** was improved to 64%.[8]

With a supply of **6** in hand, we initially explored its conversion to **8** by oxidation to the corresponding ketone (not shown) followed by Pd(0)-catalyzed cross coupling with 4-methoxyphenylboronic acid.[3] This sequence, however, proved to be problematic due to the low yield and/or instability of the intermediate ketone. Accordingly, we decided to perform cross coupling before oxidation, as depicted in Scheme 1. Although we had previously found the original Suzuki regimen [$Pd(PPh_3)_4$, aq Na_2CO_3, PhH, EtOH, 80 °C] to work well for arylating simple 4-bromo-2(5*H*)-furanones,[3] the propensity of **6** to undergo base-catalyzed retroaldol reaction (vide supra) entailed the use of a milder procedure. Gratifyingly, adaptation of Johnson's protocol[9,10] [$PdCl_2(PhCN)_2$, Ag_2O, $AsPh_3$, aq THF, 23 °C] delivered the desired alcohol **7** in 86% yield after purification by flash chromatography. Subsequent oxidation with Dess–Martin periodinane provided ketone **8** in high yield (89%).[11]

Appendage of the C5-substituent was achieved by application of our one-pot arylmethylenation procedure.[3] Thus, aldol reaction of **8** with *p*-anisaldehyde in the presence of TBSOTf and *i*-Pr_2NEt, followed by in situ β-elimination with DBU afforded the corresponding (*Z*)-arylmethylenefuranone **9** as sole stereoisomer in 94% yield.[12]

SYNLETT 2005, No. 2, pp 0343–0345
Advanced online publication: 22.12.2004
DOI: 10.1055/s-2004-837220; Art ID: S09604ST



Scheme 1 *Reagents and conditions*: (a) 2,6-lutidine, *n*-Bu_2BOTf, *p*-anisaldehyde, THF, –78 °C to –20 °C, 45 min, 64%; (b) *p*-methoxyphenyl-boronic acid, $AsPh_3$, Ag_2O, $PdCl_2(PhCN)_2$, THF, H_2O, 23 °C, 20 h, 86%; (c) Dess–Martin periodinane, CH_2Cl_2, 23 °C, 15 h, 89%; (d) TBSOTf, *p*-anisaldehyde, *i*-Pr_2NEt, CH_2Cl_2, 23 °C, 1 h; DBU, 23 °C, 2 h, 94%; (e) BBr_3, CH_2Cl_2, –78 °C to 23 °C, 20 h, 93%; (f) Br_2, KBr, dioxane, H_2O, 23 °C, 1 h, 98%.

Next, exposure of **9** to boron tribromide accomplished removal of all three methyl groups to furnish lactone **10** with high efficiency.[13] Bromination of **10** with Br_2/KBr[14] delivered cadiolide B as an amorphous orange solid whose ^1H NMR and ^{13}C NMR properties were in full agreement with those reported for the natural product.[1]

In conclusion, the first synthesis of cadiolide B has been accomplished in concise and efficient fashion (6 steps, 42% overall yield) by a new, inherently flexible pathway that is especially attractive for generating libraries of analogues for biological evaluation.

Acknowledgment

We thank NSERC (Canada), Merck Frosst Canada and Eisai Research Institute (MA, USA) for financial support. We also thank NSERC for a postgraduate scholarship to M. Pouliot.

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(8) Compound **6**: yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.66 (br s, 1 H), 3.79 (s, 3 H), 4.82 (s, 2 H), 5.62 (s, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 69.0, 73.4, 114.1, 127.1, 132.1, 132.4, 139.3, 159.6, 170.2. Anal. Calcd for $C_{12}H_{11}BrO_4$: C, 48.19; H, 3.71. Found: C, 48.13; H, 3.57.
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(11) Compound **7**: white solid; mp 90–92 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.82 (s, 3 H), 4.15 (d, *J* = 9.8 Hz, 1 H), 5.03 (d, *J* = 16.9 Hz, 1 H), 5.22 (d, *J* = 16.9 Hz, 1 H), 5.79 (d, *J* = 9.8 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 55.3, 68.4, 70.8, 114.1, 114.6, 122.4, 124.8, 127.7, 129.2, 133.4, 156.8, 159.3, 161.6, 174.6. HRMS: *m/z* calcd for $C_{19}H_{18}O_5$: 326.1154; found: 326.1158.
Compound **8**: yellow solid; mp 166–167 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.85 (s, 3 H), 5.30 (s, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.91 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 55.5, 70.3, 114.1, 114.6, 121.4, 123.4, 128.7, 129.6, 132.0, 159.7, 162.4, 164.6, 171.1, 190.1. Anal. Calcd for $C_{19}H_{16}BrO_5$: C, 70.36; H, 4.97. Found: C, 70.12; H, 5.02.
(12) Compound **9**: yellow solid; 189–190 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 6.23 (s, 1 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 7.36 (d, *J* = 8.6 Hz, 2 H), 7.80 (d, *J* = 8.6 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2,

55.3, 55.4, 113.7, 114.2, 114.4, 116.8, 121.3, 122.7, 125.7, 129.2, 130.7, 132.0, 132.9, 145.7, 156.8, 160.9, 161.2, 164.1, 166.6, 188.1. HRMS: *m/z* calcd for $C_{27}H_{22}O_6$: 442.1416; found: 442.1424.

(13) Compound **10**: yellow solid; 262–263 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.33 (s, 1 H), 6.77 (d, *J* = 8.7 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.6 Hz, 2 H), 7.70 (d, *J* = 8.7 Hz, 2 H), 7.75 (d, *J* = 8.7 Hz, 2 H), 10.06 (br s, 1 H), 10.18 (br s, 1 H), 10.55 (br s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 115.5, 115.8, 116.1, 116.4, 119.5, 121.5, 124.1, 127.5, 130.9, 132.2, 133.1, 144.7, 156.0, 159.4, 159.6, 163.1, 166.1, 188.1. HRMS: *m/z* calcd for $C_{24}H_{16}O_6$: 400.0947; found: 400.0956.

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