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TOTAL SYNTHESIS OF BROMOBECKERELIDE[1]

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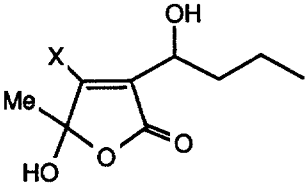
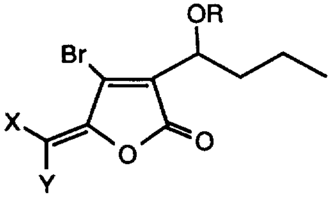
Summary. The first synthesis of (±)-bromobeckerelide has been accomplished in five steps from 5-methylfurfural by exploiting the regiospecific aldolization of a dialkylboron 2-furanolate.

The red marine algae *Beckerella subcostatum* and *Delisea fimbriata* contain a variety of halogenated butenolides as secondary metabolites.[2,3] Representative examples are the chloro- and bromobeckerelides (**1** and **2**)[2] and the hydroxy- and acetoxyfimbrolides (**3** and **4**).[3] These novel, highly substituted structures, in view of their potent antifungal and antimicrobial properties, have prompted considerable synthetic activity.[4-9] Nevertheless, little success has been achieved so far apart from the synthesis of a less functionalized fimbrolide congener[5,6] and some analogues.[7] Typically, obstacles have been encountered in constructing from acyclic precursors butenolides which have the right substituents[4] or in selectively brominating 2-(1′-hydroxybutyl)-2-buten-4-olide despite its availability from γ-butyrolactone.[9] We have recently demonstrated that 2-furanol derivatives offer an economical means for the direct assembly of butenolides of pre-determined substitution.[10,11] Boron and tin(II) 2-furanolates, on account of their pronounced C3 regioselectivity on aldolization,[11] provide a convenient solution to the aforementioned difficulties. We now describe the application of this technology to the first synthesis of bromobeckerelide (**2**).



1 X = Cl

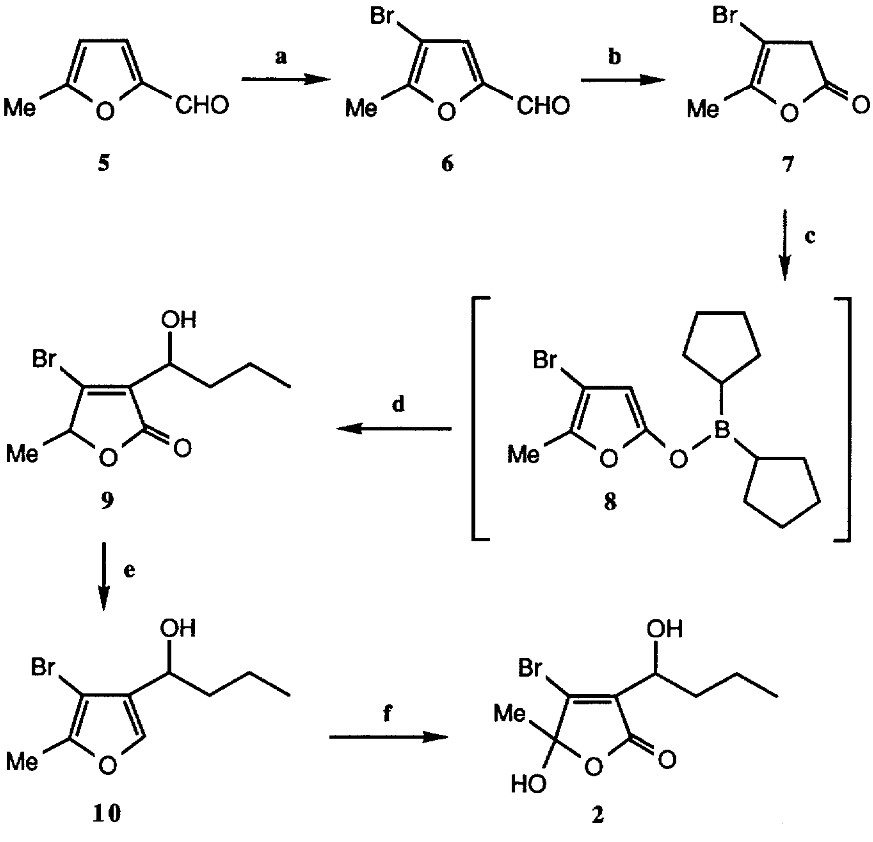
2 X = Br



3 R = H; { X = H, Y = Cl, Br, I
and
Y = H, X = Cl, Br, I
4 R = Ac; or X = Y = Br }

The plan required the prior installation of the bromine and methyl substituents, thereby enabling the final functionality to be developed by a sequence of alternating furan-lactone transformations (Scheme). Consequently, a logical starting point was commercial 5-methylfurfural (**5**), which on Lewis acid-catalyzed bromination afforded the known 4-bromo derivative **6**.[12] Baeyer-Villiger oxidation of **6** was modelled on that used for furfural.[13] The action of formic acid (2 equiv.), sodium sulfate (0.7 equiv.) and hydrogen peroxide (aq. 30%, 8.1 equiv.) in CH_2Cl_2 at 24°C for 24 h furnished the lactone **7** in 69% yield.[14,15] With **7** in hand, the crucial aldolization was undertaken. Exposure of **7** to dicyclopentylboron trifluoromethanesulfonate (1.1 equiv.) and N,N-diisopropylethylamine (1.1 equiv.) in CH_2Cl_2 at -78°C for 30 min generated the furanolate **8**. Its treatment *in situ* at the same

Scheme



Reagents and Conditions: **a.** Br_2, $AlCl_3$, 24^0 C, 17 h. **b.** HCOOH, aq. 30% H_2O_2, Na_2SO_4, CH_2Cl_2, 24^0 C, 24 h. **c.** $(c\text{-}C_5H_9)_2BOTf$, $i\text{-}Pr_2EtN$, CH_2Cl_2, -78^0 C, 30 min. **d.** $n\text{-}C_3H_7CHO$, -78^0 C, 6 h. **e.** DIBAL, THF, -20^0 C, 3.5 h ***or*** LAH, Et_2O / i-PrOH, -50^0 C, 3 h. **f.** MMPP, i-PrOH / H_2O, 24^0 C, 6 h.

temperature with butyraldehyde (1 equiv.) for 6 h delivered a sole product, the trisubstituted lactone **9** in 85% yield.[15] In keeping with our previous findings on α-angelica lactone,[11] aldolization proceeded regiospecifically. Reaction had occurred exclusively at the C3 position. Reduction of **9** with either diisobutylaluminium hydride (DIBAL) (4.5 equiv.) in THF at -20°C for 3.5 h[16] or lithium aluminium hydride (LAH) (4 equiv.) in ether and isopropanol at -50°C for 3 h[17] furnished the furan **10** in a consistent yield of 71%.[15] An attractive, appropriate method for effecting the conversion of **10** to **2**, namely dye-sensitized photo-oxygenation in the presence of base,[18] was tried, but only some 40% of product **2** could be obtained. Finally, smooth oxidation of **10** to **2** was achieved in 72% yield by using magnesium monoperoxyphthalate (MMPP) (1.6 equiv.) in isopropanol and water (3:7) at 24°C for 6 h.[7,19] The synthetic, racemic product **2** was obtained as colorless crystals, m.p. 83-86°C, and consisted of a pair of diastereomers just like the natural material.[20] Synthetic **2** also exhibited spectral properties in full agreement with those reported for a natural sample contaminated with ~9% of **1**.[2,15]

The present synthesis is simple to perform, requires no protection-deprotection steps, and provides a unique source of chemically pure **2**. Access to other members of this class, namely **3** and **4**, should be possible by extension of the same methodology. Moreover, enantioselective aldolization[21] or resolution of the racemic intermediate alcohol **10**, both of which should be feasible, would lead to chiral bromobeckerelide. These possibilities are under study and the results will be reported in due course.

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14. Butenolide **7** has been detected in an estimated yield of 2% in the complex mixture obtained by bromination of α-angelica lactone (ref. 8).

15. Yields refer to chromatographically purified products. All were characterized spectroscopically (^{1}H and ^{13}C NMR, IR) and by elemental analyses (C, H, Br). New compounds have the following ^{1}H NMR data (360 MHz, $CDCl_3$): **9** (mixture of 2 diastereomers); both isomers: δ 4.98 (q, J=6.5 Hz, 1H), 4.54 (m, 1H), 2.53 (br s, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.26-1.51 (m, 2H); major isomer: 1.52 (d, J=7 Hz, 3H), 0.95 (t, J=7 Hz, 3H); minor isomer: 1.54 (d, J=6.5 Hz, 3H), 0.92 (t, J=7 Hz, 3H). **10**: δ 7.23 (s, 1H), 4.60 (t, J=6.5 Hz, 1H), 2.26 (s, 3H), 2.21 (br s, 1H), 1.77 (m, 2H), 1.42 (m, 2H), 0.93 (t, J=7 Hz); and ^{13}C NMR data (50 MHz, $CDCl_3$): **9**, major diastereomer: δ 13.72 (q), 18.59 (t), 18.62 (q), 37.96 (t), 67.40 (d), 80.50 (d), 132.45 (s), 145.19 (s); **10**, δ 11.85 (q), 13.81 (q), 18.85 (t), 38.53 (t), 66.66 (d), 96.50 (s), 128.80 (s), 137.43 (d), 149.97 (s).

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20. Beckerelides **1** and **2** are isolated from the alga as an inseparable 1:10 mixture in the form of an oil. Moreover, both exist as two diastereomers in a 1:1 ratio. There is evidence, which we will discuss elsewhere, that **1** and **2** undergo rapid epimerization at the anomeric carbon atom through open chain tautomers.

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