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Synthesis of Tetrasubstituted Butenolide, Bromobeckerelide, by Regioselective Lithiation of Furan Followed by Photosensitized Oxygenation of α-Silylfuran

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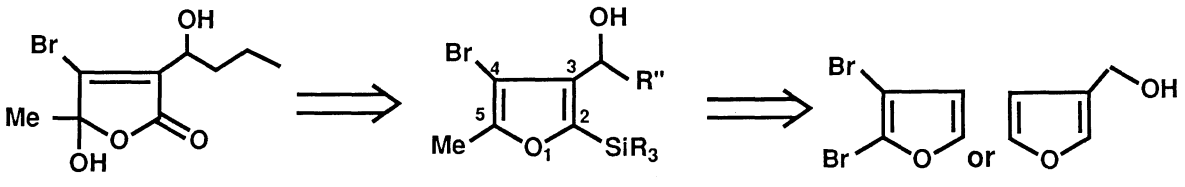
A straightforward synthesis of a tetrasubstituted halobutenolide, bromobeckerelide, was achieved by photosensitized oxygenation of a trisubstituted α-trialkylsilylfuran which was obtained by the introduction of desired substituents into a furan ring via regioselective lithiation.

In the course of our synthetic study of polysubstituted butenolides, previously we have reported that the photosensitized oxygenation of substituted α-trialkylsilylfuran affords conveniently γ-hydroxybutenolide,[1] which can be easily converted to butenolide,[2] in an excellent yield. For the synthesis of polysubstituted butenolides, therefore, we need α-trialkylsilylfurans possessing various substituents. Although substituted furans, which serve as important starting materials and intermediates in natural products syntheses, have recieved wide interest and have been studied extensively,[3] development of useful synthetic methods especially for tetrasubstituted furans have been still required. The regioselective lithiation at desired carbons of a furan ring followed by introduction of desired substituents could be the most attractive and general method for this purpose.

Now we have found the effective pathway for preparation of trisubstituted α-trialkylsilylfurans by the regioselective lithiation of a furan ring. Herein we wish to report the straightforward synthesis of a novel tetrasubstituted halobutenolide, (±)-bromobeckerelide (**1**), by photosensitized oxygenation of the trisubstituted α-trialkylsilylfuran synthesized from 2,3-dibromofuran or 3-hydroxymethylfuran by regioselective lithiation. Bromobeckerelide (**1**) was isolated from the red marine algae *Beckerella subcostatum*, and its antimicrobial activity against *Bacillus subtilis* was reported.[4,5]

Our synthetic plan is shown in Scheme 1. A key intermediate for the synthesis of **1** is the tetrasubstituted furan **2** or **3** which possesses different substituents at all carbon atoms on its furan ring. Considering the role and the nature of the four substituents of **2** or **3**, the substituent of C-2



1

2: R" = n-C_3H_7
3: R" = H

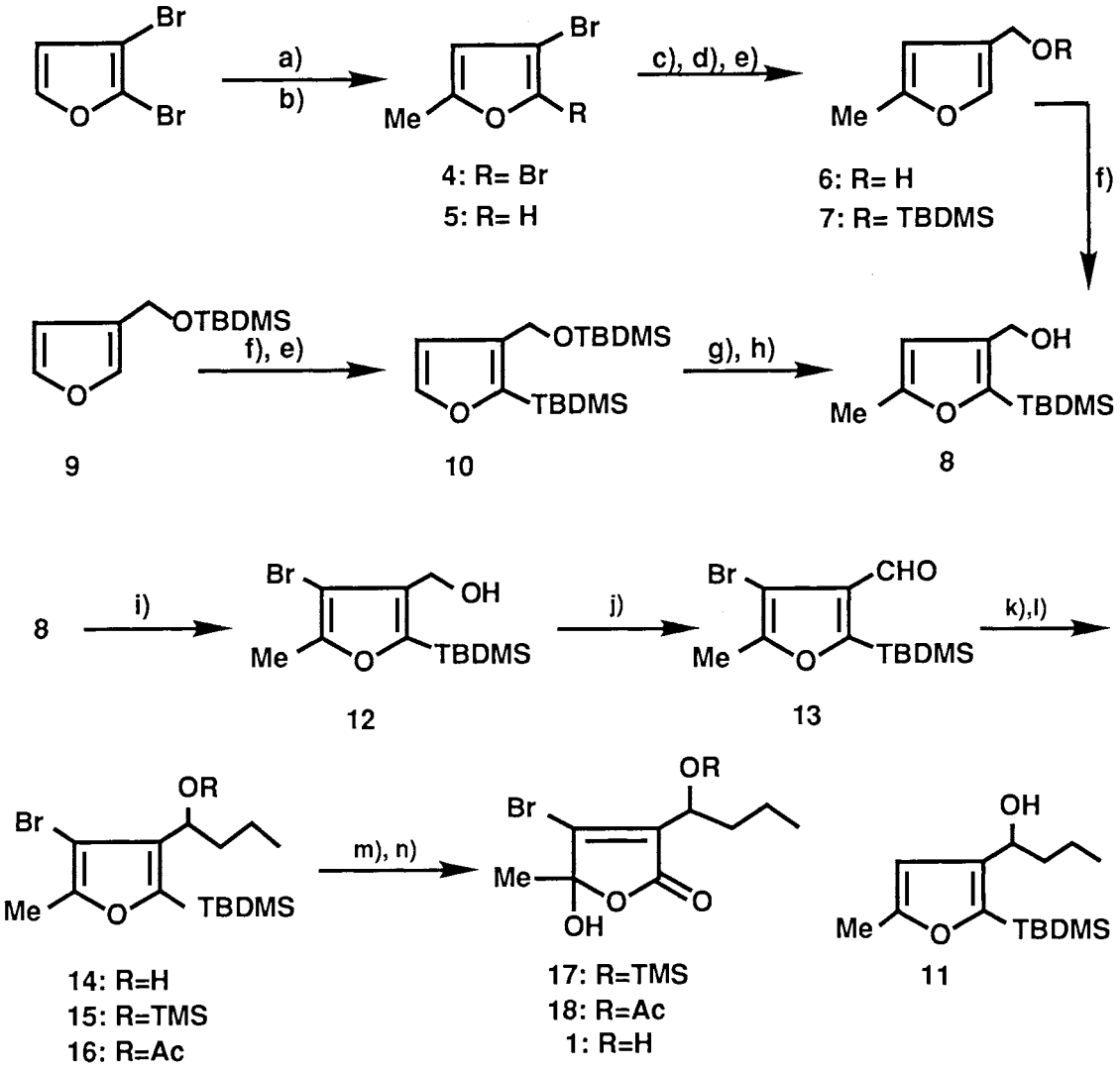
Scheme 1.

position should be a bulky trialkylsilyl group to hinder the coordination of a base to furan oxygen and to aid the regioselective lithiation at C-4 position as reported by Keay et al.[6] And bromine at C-4 position must be introduced during the final stage of the lithiation.

2,3-Dibromofuran[7] was reacted with lithium diisopropylamide followed by methyl iodide to give the methylated derivative **4** (88% yield), which was treated with n-BuLi at -78 °C for 5 min and then with wet ether to afford **5** in 80% yield.[8] The halogen-metal exchange at the C-3 position of the furan was performed by a stronger base. Thus, 3-bromo-5-methylfuran (**5**) was treated with sec-BuLi followed by a reaction with anhydrous DMF to afford 3-formyl-5-methylfuran (82% yield), which was reduced with sodium borohydride to give the alcohol **6** in 99% yield. The TBDMS (t-butyldimethylsilyl) group at C-2 position was introduced by a migration of the silyl group from the oxygen to the carbon:[6] Treatment of **7** derived from **6** (TBDMSCl, DMAP, Et_3N, 99% yield) with n-BuLi in DME-HMPA afforded **8** (81% yield).[9] Alternatively, **8** was synthesized from **9** by a similar lithiation. Thus, treatment of **9** with n-BuLi gave the rearranged product (88% yield), whose hydroxyl group was again protected with TBDMS to yield **10** quantitatively.[10] After the introduction of the methyl group at C-5 position (n-BuLi, MeI, 99% yield), the selective deprotection of the TBDMS group at the hydroxyl group was effected by treatment with 1% HCl in THF or tetrabutylammonium fluoride in THF at 0 °C to give **8** (75% yield).[11] Lithiation at the remaining unsubstituted carbon atom of the furan ring was first attempted on the secondary alcohol **11,** which was derived from **8** by oxidation ($BaMnO_4$, 90% yield) followed by alkylation (n-propyllithium, 92% yield). Unfortunately, attempts of the lithiation at C-4 position of both **11** and its THP ether were unsuccessful and the starting material was recovered unchanged. The next approach was the lithiation of the primary alcohol **8.**[6] Treatment of **8** with n-BuLi in DME (-78 °C for 1h and then 0 °C for 30min) followed by the addition of NBS in HMPA (0 °C for 30min) afforded the unstable bromide **12** (51% yield).[12] Alkylation of **13**[13] derived from **12** ($BaMnO_4$, 92% yield) was effective with the Grignard reagent to give **14** (n-PrMgBr, 94% yield).[14,15] The photoirradiation of 4-bromo-2-silylfuran **(15)**, which was obtained by the protection of the secondary alcohol in **14** with TMS (98% yield), with halogen lamp under oxygen atmosphere in the presence of catalytic amount of tetraphenylporphin at -78 °C afforded the desired γ-hydroxybutenolide **17** in 81% yield. The synthesis of (±)-bromobeckerelide (**1**) was achieved by deprotection of the alcohol in **17** with silica-gel (72% yield) (Scheme 2).

^1H- and ^{13}C-NMR (400 MHz) of the produced synthetic **1**, mp 85-87 °C (lit. 83-86 °C),[5] could not distinguish two diastereoisomers. Acetylation of the synthesized compound with acetic anhydride in pyridine gave the diacetate whose ^1H- and ^{13}C-NMR showed the presence of 1: 1 mixture of the diastereoisomers as mentioned in the literature.[4,5] The spectroscopic properties (IR, NMR, Mass) of the synthesized **1** and its diacetate were in good agreement with those of the natural specimens.[4] In addition, photosensitized oxygenation of the monoacetate **16** gave bromobeckerelide monoacetate (**18**), whose ^1H- and ^{13}C-NMR spectra were not distinguishable from those of its diastereomers either.[16]

In conclusion, the regioselective lithiation at carbon atoms of a furan ring followed by the introduction of different substituents was realized. It was worth noting that the photosensitized oxygenation of α-silylfuran proceeded smoothly even when the electron withdrawing group like bromine was present in the furan ring.



a) LDA, THF, -78 °C, MeI. b) n-BuLi, THF, -78 °C, 5 min, H_2O. c) sec-BuLi, THF, -78 °C, DMF. d) $NaBH_4$, EtOH, 0 °C, 5 min. e) TBDMSCl, DMAP, Et_3N, CH_2Cl_2. f) n-BuLi, DME, HMPA, -78 °C, 1 h. g) n-BuLi, THF, -78 °C, MeI. h) 1% HCl, THF, 0 °C, 30 min or $Bu_4NF{\cdot}3H_2O$, THF, 0 °C, 30 min. i) n-BuLi, DME, -78 °C, 1 h., 0 °C, 30 min, NBS, HMPA, 30 min. j) $BaMnO_4$, CH_2Cl_2, 35 °C, 8 h. k) n-PrMgBr, THF, -78 °C. l) TMSCl, DMAP, Et_3N, CH_2Cl_2. m) meso-TPP, O_2, hv, -78 °C. n) SiO_2, hexane-ether

Scheme 2 .

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8) Although the anion generated at C-2 position was trapped with trimethylsilyl chloride in 91% yield, the reaction of the anion with TBDMS chloride gave a complex mixture.
9) All new compounds were fully characterized by spectroscopic and analytical data.
10) Attempts of the direct introduction of the TBDMS group at C-2 position of 3-hydroxymethylfuran via the dianion was unsuccessful and gave TBDMS ether **9** in 95% yield. The one pot preparation of **10** from **9** was done in 65% yield.
11)While **8** was more conveniently synthesized from **9** than from 2,3-dibromofuran, the latter might be a more versatile compound to introduce various substituents into a furan ring.
12)The purity of NBS was remarkably important in this bromination. 2-(t-Butyldimetylsilyl)-3-formyl-5-metylfuran was the major by-product when NBS was used without recrystallization. In this bromination, NBS was a better reagent than bromine with regard to the yield of the conversion.
13)**13**: HRMS, Found: 302.0332, 304.0289. Calcd for $C_{12}H_{19}O_2SiBr$: 302.0332, 304.0312; ^{1}H-NMR($CDCl_3$) δ= 0.35 (6H, s), 0.93 (9H, s), 2.33(3H, s), 9.97(1H, s); ^{13}C-NMR ($CDCl_3$) δ= -5.8, 11.9, 17.2, 26.3, 95.6, 135.0, 155.3, 168.7, 185.8; IR($CHCl_3$): 2960, 1680 cm^{-1}.
14)**14**: HRMS, Found: 289.0235, 291.0223 (M - t-Bu). Calcd for $C_{11}H_{18}O_2Si_2Br$ (M - t-Bu): 289.0254, 291.0234; ^{1}H-NMR($CDCl_3$) δ= 0.25(3H, s), 0.27(3H, s), 0.92(9H, s), 0.96(3H, t, J=8.0 Hz), 1.2 - 2.15(5H, m), 2.28(3H, s), 4.70(1H, t, 7.3 Hz); ^{13}C-NMR($CDCl_3$) δ= -5.3, 11.8, 13.9, 17.1, 19.3, 26.4, 40.0, 66.6, 98.9, 139.2, 152.6, 157.3; IR($CHCl_3$): 3675, 2960 cm^{-1}.
15)Reaction of **13** with n-propyllithium gave **11** as a major product along with a small amount of the desired **14** and the starting aldehyde. It is noteworthy that the exchange of the bromine with lithium was faster than the addtion of propyllithium to the aldehyde.
16)**18**: ^{1}H NMR($CDCl_3$) δ= 0.95(t, J=8 Hz), 1.25 - 1.50(2H, m), 1.70(3H, s), 1.74 - 1.83(1H, m), 1.88 - 1.96(1H, m), 2.10(3H, s), 5.40(1H, t, J=8.0 Hz); ^{13}C-NMR($CDCl_3$) δ= 13.6, 18.5, 20.7, 23.8, 33.8, 69.0, 105.6, 131.1, 146.2, 166.1, 171.0.

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