Palladium Catalyzed Polyene Cyclizations: An Approach to the Pentacyclic Carbon Framework of Halenaquinone and Xestoquinone

W.A. Cristofoli and B.A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

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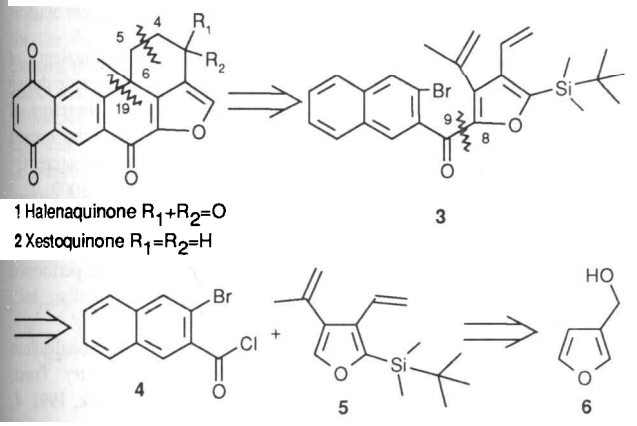
Abstract: A seven step synthesis of the pentacyclic framework of xestoquinone and halenaquinone is described beginning with 3-(hydroxymethyl)furan and 3-bromo-2-naphthoyl chloride utilizing, as the key step, a palladium catalyzed polyene cyclization.

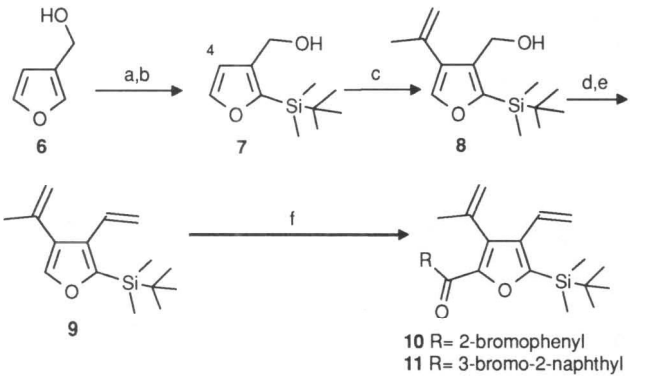
The pentacyclic polyketides halenaquinone (**1**) and xestoquinone (**2**) have been isolated from a variety of sea sponges[1,2] and shown to possess antibiotic[1a] and cardiotonic[1c] activity, and to inhibit protein tyrosine kinases.[3] To date, only one synthesis of halenaquinone[4a] and xestoquinone[4b] have been reported; both starting from the optically pure Wieland-Miescher ketone. In addition, a formal total synthesis of xestoquinone using a furan ring transfer reaction as the key step,[4c] and an approach to both halenaquinone and xestoquinone requiring the synthesis of a 5a-methyl-2*H*-naphthol[1,8-*bc*]furan have been reported.[4d] As part of our efforts to develop new strategies for the use of furan rings in synthesis,[5] we describe herein a new approach towards the preparation of the pentacyclic framework of halenaquinone and xestoquinone, which involves only seven steps from the readily available 3-(hydroxymethyl)furan.

Since the palladium catalyzed polyene cyclization has been shown to be a useful synthetic reaction for the construction of two or more rings in one step,[6] we examined the possibility of employing this reaction to build the pentacyclic carbon skeleton of halenaquinone and xestoquinone. Our retrosynthetic analysis using this reaction is illustrated in Scheme 1. Thus, functional group interconversions and concomitant cleavage of the C_4-C_5 and C_6-C_{19} bonds lead to the ketofuran **3**, which, when cleaved at the C_8-C_9 bond, provided 3-bromo-2-naphthoyl chloride (**4**) and furan (**5**). Furan **5** could be prepared from 3-(hydroxymethyl)furan by employing our recently reported variation of the Susuki reaction in which a furyl-boronic acid is generated and used *in situ*.[7]



Scheme 1

To test the feasibility of using a palladium catalyzed polyene cyclization in the presence of a furan ring, the two precursors **10** and **11** were prepared as illustrated in Scheme 2. The *t*-butyldimethylsilyl ether of 3-(hydroxymethyl)furan (**6**) underwent a [1,4] O→C silyl migration[5d] when treated with a mixture of *n*-BuLi/HMPA in THF at 0°C to provide furan **7** in 87% yield. Furan **7** was then subjected to our modified Susuki reaction conditions.[7] Thus, treatment of furan **7** with 2.2 equivalents of *n*-BuLi (DME, 0°C) for 1 hour formed the C-4 anion of **7** exclusively. Trimethylborate (2 equiv.) was then added and after the solution was stirred for 1 hour at 0°C, 2-bromopropene (1 equiv.), H_2O (2 mL), and 3 mol% $Pd(PPh_3)_4$ were added and the reaction mixture heated to reflux for 4 hours. Normal workup provided furan **8** in 84% yield. Swern oxidation[8] (oxalyl chloride, DMSO, Et_3N) of furan **8** followed by a Wittig reaction provided dienyl furan **9** in 65% yield over 2 steps. The C-5 lithiation of furan **9** proceeded smoothly by the addition of 1.5 equivalents of *n*-BuLi and 1.2 equivalents of HMPA to a solution of **9** at -78°C in THF. Treatment of the C-5 anion of furan **9** with either 2-bromobenzoyl chloride or 3-bromo-2-naphthoyl chloride[9] provided ketones **10** (68%) and **11** (77%), respectively.[10] With furans **10** and **11** in hand, palladium catalyzed polyene cyclization reactions were investigated.



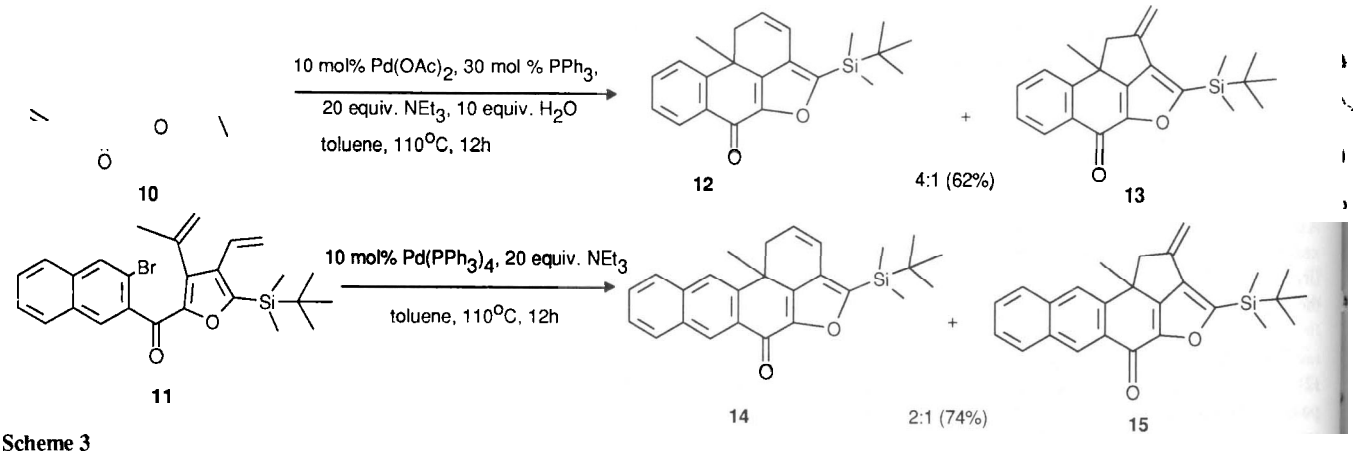
Conditions: a) TBDMSCl, imidazole, DMF (96%); b) n-BuLi, THF, HMPA, 0°C (87%); c) 2.2 equiv. n-BuLi, DME, 0°C, 1h; then add $(MeO)_3B$, 0°C, 1h; then add 10 mol % $Pd(PPh_3)_4$, H_2O, 2-bromopropene, 80°C, 4h (85%); d) Swern [O] (75%); e) $Ph_3P{=}CH_2$, THF (87%); f) 1.5 equiv. n-BuLi, HMPA, THF, -78°C, 1h; then add 2-bromobenzoyl chloride (68%) or 3-bromo-2-naphthoyl chloride (77%).

Scheme 2

Treatment of bromide **10** with palladium acetate (10 mol%), triphenylphosphine (30 mol%),[11] triethylamine (20 equiv.), and water (10 equiv.) in toluene at 100°C for 12 hours afforded a 4:1 (by ^1H NMR) mixture of tetracyclic compounds **12** and **13** (Scheme 3). Compounds **12** and **13** were easily separated through a silica gel column (hexane:EtOAc, 20:1) and assigned their structures based on spectral data.[12] The formation of the extremely strained tetracyclic furan **13** was surprising based on geometry optimized AM1 level calculations,[13] which indicated the ΔH_f of furan **12** was 25.1 kcal/mole lower in energy than the ΔH_f of furan **13**. Since the final step involved in the formation of furans **12** and **13** is a *syn*-elimination of H-Pd-Br, which has been reported to be fast process,[14] we conclude that the 4:1 ratio of **12**:**13** is a kinetic ratio.

Finally, furan **11**, when treated with 10 mol% $Pd(PPh_3)_4$ in the presence of Et_3N in toluene (100°C) for 12 hours, provided a 2:1 ratio (by ^1H NMR) of pentacyclic furans **14**[15] and **15**[16] in 74% yield (Scheme 3). We are currently attempting to optimize the yield of compound **14** by varing the reaction conditions or by changing the structure of precursor **11**.[17]

We have shown that the pentacyclic framework of halenaquinone and xestoquinone can be built in seven steps from 3-(hydroxymethyl)furan using a palladium catalyzed polyene cyclization as the key step. Application of this methodology to the synthesis of halenaquinone and xestoquinone will be the subject of future reports.



Scheme 3

Acknowledgements

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References and Notes

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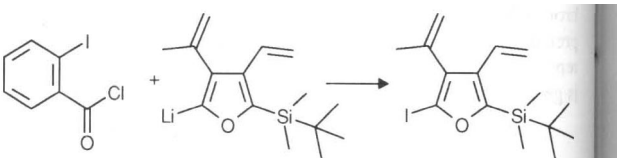
(9) 3-Bromo-2-naphthoyl chloride was prepared in two steps from 3-bromo-2-naphthaldehyde. The latter was oxidized to 3-bromo-2-naphthoic acid ($NaClO_2$-H_2O_2, $NaHPO_4$, MeOH, 10°C, 6h) in 90% yield and treated with oxalyl chloride (benzene, 80°C, 92%). 3-Bromo-2-naphthaldehyde was prepared according to the procedure reported by Smith *et al*: Smith, J.G.; Dibble, P.W.; Sandborn, R.P. *J. Org. Chem.* **1986**, *51*, 3762.

(10) Treatment of the C-5 anion of furan **9** with 2-iodobenzoyl chloride (**16**) resulted in a halogen-metal exchange to provide furan **17**.



16 **17**

(11) Amatore *et al* have shown that one equivalent of triphenylphosphine is oxidized to triphenylphosphine oxide during the reduction of palladium acetate to Pd(0). Therefore, 3 equivalents of triphenylphosphine was used relative to the amount of palladium acetate employed in the reaction; see: Amatore, C.; Jutand, A.; M'Barki, M.A. *Organometallics* **1992**, *11*, 3009.

(12) All compounds provided analytical and/or spectroscopic data consistent with their structures.

(13) The geometry optimized AM1 level calculations were performed using the *SPARTAN* software package (Wavefunction, Inc., Irvine, CA, USA) on an IBM Risc 6000 workstation.

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(15) Compound **14**: bp 136-140°C (0.07 torr); IR (neat) 1672 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.40 (s, 6H), 0.98 (s, 9H), 1.52 (s, 3H), 2.68 (ddd, 1H, J=17, 1.2 and 1.2 Hz), 3.06 (dd, 1H, J=17 and 6.1 Hz), 6.09 (ddd, 1H, J=1.2, 6.1 and 9.1 Hz), 6.69 (dd, 1H, J=9.1 and 1.2 Hz), 7.56 (m, 2H), 7.88 (m, 1H), 7.90 (s, 1H), 8.04 (m, 1H), 8.95 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -6.0 (x2), 17.3, 26.3 (x3), 32.3, 35.2, 119.3, 123.6, 123.7, 123.9, 126.3, 127.2, 127.9, 128.3, 129.5, 130.9, 131.9, 134.6, 143.9, 145.7, 147.3, 160.8, 172.5; HRMS calcd. for $C_{26}H_{28}O_2Si$: 400.1859. Found: 400.1851. Anal. calcd. for $C_{26}H_{28}O_2Si$: C, 77.95; H, 7.04. Found: C, 77.38; H, 6.87.

(16) Compound **15**: bp 130-138°C (0.07 torr); IR (neat) 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.38 (s, 3H), 0.41 (s, 3H), 0.99

(s, 9H), 1.52 (s, 3H), 3.41 (m, 2H), 5.36 (bd, 1H, J=1.7 Hz), 5.48 (bd, 1H, J=1.7 Hz), 7.55 (m, 2H), 7.79 (s, 1H), 7.85 (m, 1H), 7.99 (m, 1H), 8.90 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -6.7, -6.0, 15.2, 26.4, 32.2, 41.5, 55.6, 110.5, 125.5, 126.4, 127.1, 128.4, 129.7, 130.8, 131.6, 134.3, 134.5, 139.7, 141.5, 145.8, 145.6, 162.4, 163.4, 172.8; Mass Spectrum, m/z 400 (M^+), 343 (M^+-*t*-Bu); Anal. calcd. for $C_{26}H_{28}O_2Si$: C, 77.95; H, 7.04. Found: C, 77.72; H, 7.09.

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Synthesis of α-Alkinylenamines by Trimethylsilanolate-Induced α-Deprotonation of Propyne Iminium Salts

Martina Brunner, Robert Reinhard, Rainer Rahm, Gerhard Maas*

Fachbereich Chemie, Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

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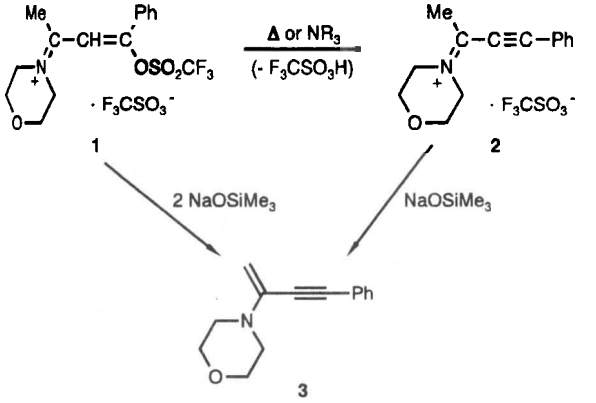
Abstract: Iminium salts bearing an α-CH group are efficiently deprotonated with sodium trimethylsilanolate in a non-aqueous reaction medium. In this manner, little known α-alkinylenamines can be obtained from propyne iminium triflates.

Alkali trimethylsilanolates have been recognized as hydroxide ion equivalents that are appreciably soluble even in some non-hydroxylic organic media.[1] In organic synthesis, they have been used so far mainly for the formation of anhydrous carboxylate salts from the corresponding esters,[1,2] and to initiate certain polymerization reactions. The use of sodium trimethylsilanolate ($NaOSiMe_3$) to promote elimination of MeOH from a ß-methoxyketone[3] suggests that this salt may also find wider use as a non-aqueous base. We report here that $NaOSiMe_3$ is indeed an excellent reagent for the efficient α-deprotonation of certain iminium salts to give the related enamines.



A base that converts propyne iminium triflate **2** by α-deprotonation into α-alkinylenamine **3** must fulfill two major requirements: (a) The deprotonation must be fast, since otherwise, already formed enamine **3** undergoes nucleophilic addition to the precursor salt **2** with subsequent oligomerization. This postulate excludes tertiary amines as bases, which on the other hand can be applied to synthesize **2** from 3-trifloxypropene iminium salt **1**.[4] (b) The nucleophilic properties of the base must not be competitive; for example, alkylation of the iminium group of **2** occurs with *n*-BuLi and *t*-BuLi,[5] and morpholine undergoes conjugate addition to **2** to form a vinamidinium salt.[6]

We have now found that deprotonation of **2** by $NaOSiMe_3$ is fast at room temperature, and that reaction of enamine **3** with precursor salt **2** can be suppressed by slow addition of **2** to a solution of the base in acetonitrile. In an analogous manner, enamine **3** is obtained in 65 % yield when salt **1** is exposed to two equivalents of $NaOSiMe_3$. Nevertheless, the two-step sequence **1**→**2**→**3** is preferable with respect to the overall yield, since **2** can be obtained *quantitatively* from **1** by solvent-free vacuum thermolysis.[7] Although the nucleophilic properties of trialkylsilanolates are well documented, e.g. towards CS_2,[8] metal-Cl,[9] Si-X,[10] and P-X[11] (X = Cl, F) bonds, no addition product of Me_3SiO^- to either **1** or **2** could be detected.

Deprotonation of the semicyclic propyne iminium salts **4a-e**[12,13] in the same manner furnishes 2-alkinyl-4,5-dihydro-1-methylpyrroles **5a-d** and 2-alkinyl-1-methyl-4,5,6,7-tetrahydroazepine **5e**, respectively (see Table). It should be pointed out that α-alkinylenamines represent a barely known class of functionalized enamines. We are currently studying the utility of these compounds as synthetic building blocks, especially by addition and cycloaddition reactions to the electron-rich double bond, and will report our results in due course.

The last entry of the Table illustrates another advantageous aspect of iminium ion deprotonation with $NaOSiMe_3$. We have previously reported that morpholinoindene **7** is obtained in 26 % yield, when iminium salt **6** is exposed to aqueous $NaHCO_3$.[7] In contrast, treatment of **6** with $NaOSiMe_3$ in CH_3CN yields **7** in 85 % yield. Certainly, the low yield in the former case is due to partial hydrolysis of the enamine, whereas the use of $NaOSiMe_3$ avoids the aqueous reaction medium and does not require aqueous workup of the reaction mixture.

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