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A Mild Method for the Cleavage of Ketals Using IBX

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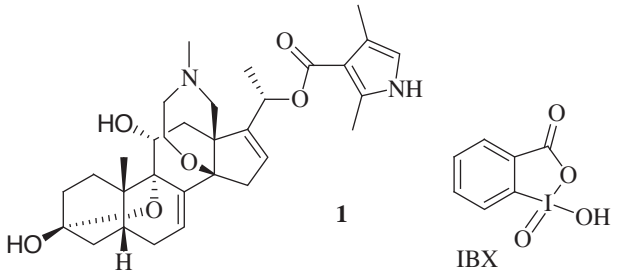
Investigation on the total synthesis of batrachotoxin **1** revealed that the cyclic ketals could be cleaved to ketone with IBX in DMSO at 70-81 °C under very mild conditions. A variety of functional groups showed no interference under these conditions except vinyl bromides, which, in fact, inhibits the single electron transfer to IBX.

Key Words: Deprotection, ketal, IBX, ketone, single electron transfer, batrachotoxin.

Introduction

The new findings directed towards the total synthesis of batrachotoxin **1** [1] has led to the discovery of several new and interesting reactions. [2] Acid catalyzed deprotection of ketals is in general practice, which has a few disadvantages in organic synthesis, for example, esterification of carboxylic acids if reaction is carried out in alcoholic solvents (MeOH, EtOH, etc.). There are a few reports that claim the deprotection of ketals and acetals under mild conditions by using stoichiometric amounts of Ph_3P / CBr_4,[3] Ce(IV) ammonium nitrate,[4] I_2 (10 mol%) in Me_2CO, etc.[5]



General Experimental

A flame dried round bottom flask was charged with (1*S*,6*R*)-8,8-ethylenedioxy-1-methyl-2-triethylsilyloxybicyclo [4.4.0]dec-2-ene **13** (0.300 g, 0.89 mmol, 1 eq), IBX (0.496 g, 1.77 mmol, 2 eq), and DMSO (20 mL). The reaction mixture was heated at 80 °C for 22 h under mild N_2 pressure. The cooled reaction mixture was then partitioned between H_2O (25 mL) and CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over *anhydrous* Na_2SO_4, filtered, and concentrated under reduced pressure to afford colorless oil (3.210 g). The chromatographic separation of the crude over flash silica (33 cm in height) in a glass column (2.0 cm external diameter) afforded the crystalline compounds **9** (79 mg) in 41^{st} to 58^{th} and **14** (62 mg) in 64^{th} to 85^{th} fraction (20 mL each) after elution with petrol (0.25 L) and 25% Et_2O/petrol (1.5 L).

(1*S*,6*R*)-1-Methylbicyclo[4.4.0]decane-2,8-dione, 9

Yield: 79 mg (49%); $\mathbf{R}_f$ 0.44 (Et_2O/petrol, 1:1), $[\alpha]_D^{31}$: +1.8 (c 1.12 in $CHCl_3$), **IR** $_{max}$/ cm^{-1}: 2939 (saturated C-H), 1699 (br. s, both C=O), δ_H (300 MHz, $CDCl_3$, in ppm): 1.14 (3H, s, Me at 1-C), 1.21 (1H, dd, J = 5.4, 3.0 Hz, 10-H$_\alpha$), 1.32 (1H, dd, J = 14.1, 4.2 Hz, 5-H$_\alpha$), 1.74 (1H, dd, J = 9.6, 1.2 Hz, 4-H$_\alpha$), 1.75 (1H, dd, J = 19.2, 9.6 Hz, 4-H$_\beta$), 1.84-1.90 (1H, m, 5-H$_\beta$), 2.05-2.16 (3H, m, 3-Hs and 6-H), 2.18 (1H, dd, J = 3.9, 0.9 Hz, 9-H$_\alpha$), 2.22 (1H, dd, J = 6.3, 1.2 Hz, 7-H$_\alpha$), 2.30 (1H, dd, J = 9.6, 1.8 Hz, 10-H$_\beta$), 2.36 (1H, dd, J = 14.7, 3.0 Hz, 9-H$_\beta$) and 2.39 (1H, d, J = 15.0 Hz, 7-H$_\beta$), δ_C (75 MHz, $CDCl_3$, in ppm): 23.3 (t, 4-C), 24.3 (q, Me at 1-C), 27.0 (t, 5-C), 34.1 (t, 10-C), 37.9, 38.8 (t, 7 & 9-C), 44.1 (t, 3-C), 46.4 (d, 6-C), 48.9 (s, 1-C), 211.8 and 214.6 (s, 2 & 8-C).

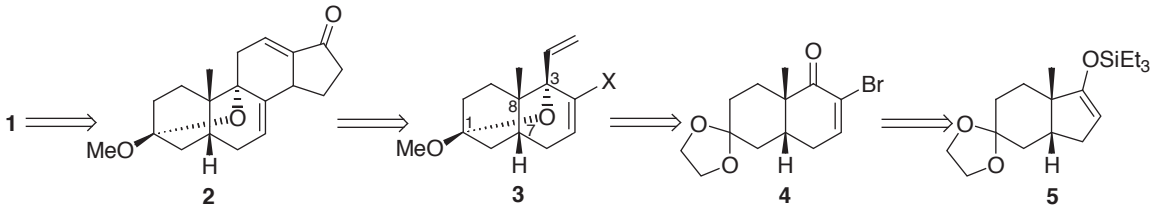
(1*S*,6*R*)-1-Methylbicyclo[4.4.0]dec-3-en-2,8-dione, 14

Yield: 62 mg (39%); $\mathbf{R}_f$: 0.42 (Et_2O/petrol, 1:1), $[\alpha]_D^{35}$: +31.6 (c 1.01 in $CHCl_3$), **ESI MS** $[M+Na]^{+\cdot}$ (amu): 201.0886 (found), 201.0655 (calc., 2.31 mmu difference), **LR EIMS** (m/z) 178 $[M^{+\cdot}]$ (48%), 150 $[M^{+\cdot}$-CO] (20%), 122 $[M^{+\cdot}$-2CO] (42%), 121 $[M^{+\cdot}$-H$\cdot$-2CO] (44%), **IR** $_{max}$/cm^{-1}: 2962 (C=C-H), 1715 (isolated C=O), 1673 (α,β-unsaturated C=O), δ_H (300 MHz, $CDCl_3$, in ppm): 1.21 (3H, s, CH_3 at C-1), 1.36 (1H, ddd, J = 12.9, 5.1, 5.1 Hz, 7-H$_\alpha$), 2.04 (1H, dd, J = 19.5, 5.1 Hz, 5-H$_\alpha$), 2.19-2.25 (2H, m, 9-Hs), 2.28 (2H, broad d, J = 6.0 Hz, 10-Hs), 2.38 (1H, broad t, J = 11.4 Hz, 6-H), 2.52 (1H, ddd, J = 13.6, 5.9, 4.1 Hz, 7-H$_\beta$), 2.73 (1H, ddd, J = 19.5, 2.4, 2.4 Hz, 5-H$_\beta$), 5.96 (1H, ddd, J = 10.2, 2.7, 1.2 Hz, 3-H) and 6.74 (1H, dddd, J = 10.2, 5.4, 2.7, 1.2 Hz, 4-H$_\beta$), δ_C (75 MHz, $CDCl_3$, in ppm): 23.6 (q, Me at 1-C), 30.0 (t, 5-C),

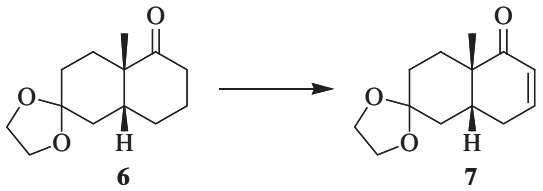
33.8 (t, 7-C), 39.0 (t, 10-C), 43.1 (d, 6-C), 44.1 (t, 9-C), 46.1 (s, 1-C), 128.2 (d, 3-C), 146.1 (d, 4-C), 202.2 (s, 2-C) and 211.1 (s, 8-C).

Results and Discussion

It has already been discovered that enones can undergo a reductive ketalisation when treated with 10% Pd[0] over charcoal and catalytic amount (0.1 mol%) of Pd[II] under the atmosphere of hydrogen in 1,2-thanediol/THF (1:1).[6] According to this synthetic approach to batrachotoxin **1**, the key intermediate **4** was required and this had been obtained by ring expansion of a 5-membered ring enol ether precursor **5** (Scheme **1**).[7] A more convenient route to **4**, which involved the conversion of the ketal 6 into the enone 7, was investigated (Scheme **2**).



Scheme 1

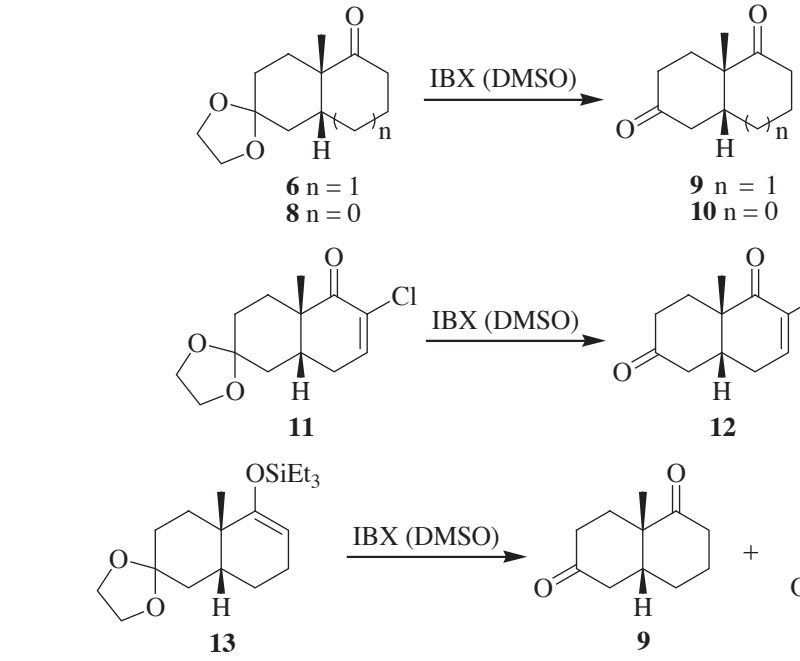


Scheme 2

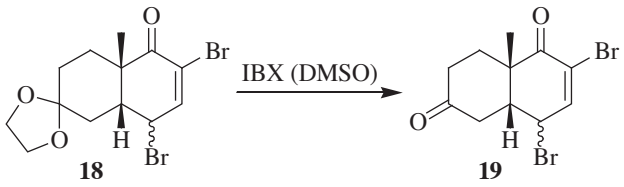
Several sequences, which include α-bromination-dehydrobromination, selenylation-selenoxide elimination, sulfenylation-sulfoxide elimination etc., were tried to achieve the α,β-unsaturated ketone **7** from **6** but very poor yields (15%-30%) were obtained. Moreover, the reaction of ketone **6** with *o*-iodylbenzoic acid (IBX) provided interesting results. The IBX is known to convert ketones into enones[8–10] through a mechanism involving single electron transfer. When the ketone **6** was reacted with IBX in dimethylsulfoxide (DMSO) no desired enone **7** was formed; instead the diketone **9** was isolated in 70% yield. Although Nicolaou has reported that thioacetals are cleaved with IBX,[11–13] we were surprised to find that ketals also react with IBX to form ketones (Table **1**). Treatment of the silyl enol ether **13** with IBX in DMSO gave a mixture of the diketone **9** and the enone **14** showing that deprotection of the ketal moiety together with oxidation of the silyl enol ether had taken place.

Of interest to note is that the bromide **18** does not react with IBX in DMSO (Scheme **3**). This would seem to suggest that the bromine atom present in **18** could inhibit single electron transfer; this antioxidant activity would hence prevent the ketal cleavage. In contrast to this, the α-chloroenone **11** deprotects to diketone **12** under same conditions with excellent yield (81%). Similarly, the vinyl chloride **15** showed deprotection to

Table 1. Cleavage of acetals with IBX in DMSO.



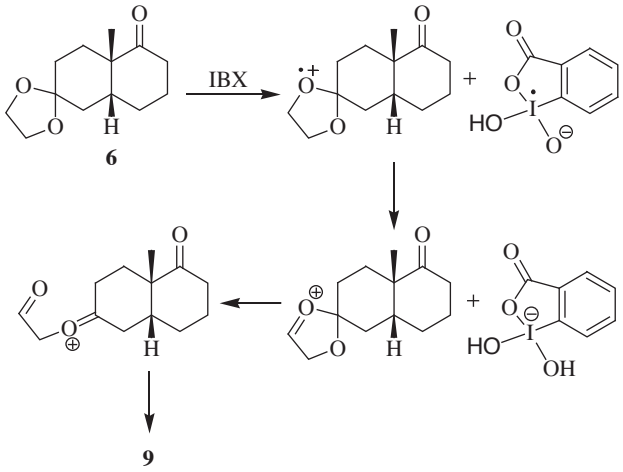
Entry	Compound	Temp. (°C)	Time (Hr)	Product(s)	% Yield
1	**6**	70	42	**9**	30
2	**8**	70	20	**10**	70
3	**11**	80	24	**12**	81
4	**13**	80	24	**9** and **14**	49, 39
5	**15**	80	22	**16** and **17**	69



Scheme 3

ketone **16** followed by intramolecular hemiacetal formation to afford **17** with acceptable yield (overall 69%). The presence of 2 singlet carbons at 220.7 (C=O in **16**) and 98.5 ppm (hemiketal C in **17**) in broadband and other nmr-assignments clearly indicated the presence of both isomers **16** and **17** in an unequal ratio. It is also interesting to note that the enol ether **13** reacts with IBX to form the diketone **9** together with the enone **14**, which results from the oxidation of the enol ether moiety present.

It is believed on the basis of observations that evidence exists for the cleavage of ketals by single electron transfer (Scheme **4**). Further support for the mechanism outlined in Scheme **4** has been obtained by experimentation. When the dibromide **18** was added to ketone **6**, followed by the addition of IBX, no ketal cleavage was observed. The dibromide **18** is thus an inhibitor of the oxidative ketal cleavage.



Scheme 4

Conclusions

We have found that IBX will cleave cyclic ketals and that further the mechanism of cleavage could involve single electron transfer. This exciting possibility will be utilized in another synthetic transformation.

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