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Synthetic Studies Towards Batrachotoxin 2. Formation Of The Oxazepane Ring System Via A Michael Reaction

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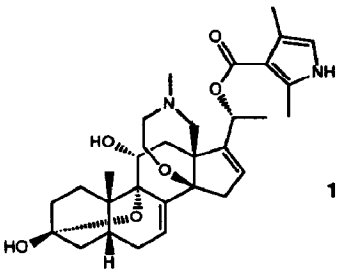
Abstract: The oxazepane ring system present in batrachotoxin has been synthesized within the framework of an advanced intermediate via a novel Michael reaction.

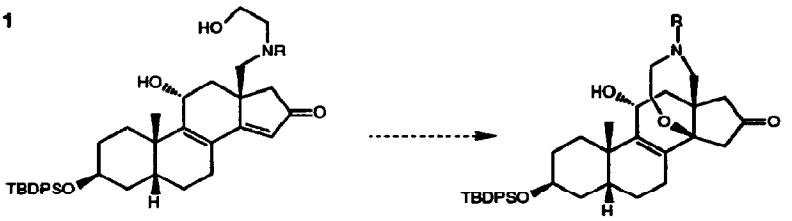
Batrachotoxin (**1**), an extremely potent steroidal neurotoxin,[1] contains a uniquely disposed heterocycle spanning the C-D ring junction,[2] which is known to be essential to its biological activity.[1] In our synthetic planning, we hoped to construct this heterocyclic system via a Michael



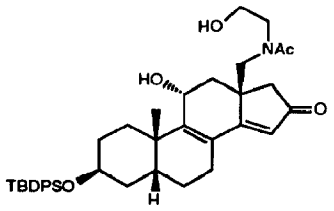
1 : Batrachotoxin

reaction of the type depicted in Scheme 1. Our chief concerns were that this process entails seven-membered ring-formation and is accompanied by a significant increase in steric congestion. In this paper, we report a solution to these obstacles and the realization of the proposed cyclization.

Scheme 1



The dienone **2** was prepared in good overall yield from one of the intramolecular Diels-Alder products reported in the preceding paper.[3] In spite of extensive efforts, we could not detect any sign of the desired cyclization under typical Michael conditions.[4] We were concerned that the $\Delta^{8,9}$ olefin of **2** might deactivate the C.14 position towards the Michael addition. Therefore, the epoxide **3**[5] was also subjected to a variety of the Michael conditions, but without success.



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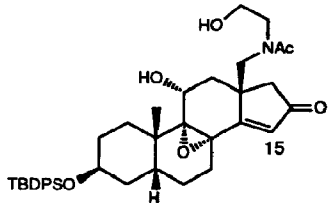

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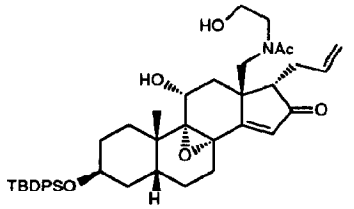
At this point, deuterium-exchange experiments were conducted to determine whether any reversible, undetected Michael addition was occurring.[6] Thus, **2** and **3** were exposed to a CD_3OD solution containing CD_3ONa (catalytic or excess) at room temperature, and the reaction was monitored by ^1H NMR. The dienone **2** incorporated deuterium only at the normally expected positions. However, when the epoxy enone **3** was exposed to these conditions, the signal arising from the C.15 vinyl proton disappeared within a few hours. This result unambiguously showed that some sort of reversible but thermodynamically disfavored Michael addition was occurring. Two additional experiments suggested that the reaction was intramolecular in nature: (1) when the primary hydroxyl group of **3** was protected, no vinyl proton exchange with a deuterium was observed and (2) no epoxide was detected when **3** was treated with a basic H_2O_2 solution. These experiments demonstrated that the proposed ring-closure was attained but the desired cyclization product was thermodynamically disfavored. Thus, we were faced with the challenge of making this process synthetically useful. The epoxy enones **4** and **5** were tested with the hope that the extra substituents might induce a favorable equilibrium for steric reasons. These substrates once again showed a facile deuterium exchange at C.15, but no cyclized product was detected.



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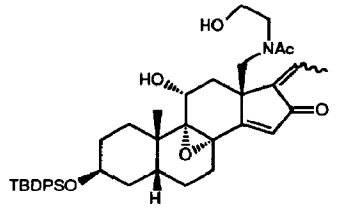
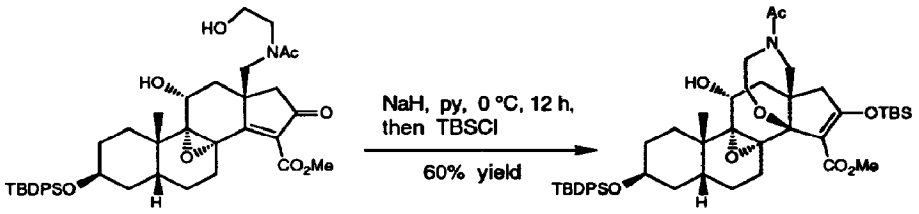


5

We then shifted our attention to the possibility of overcoming this problem via further activation of the Michael acceptor. The doubly activated substrate **6** was prepared from **2**[7]and subjected to the deuterium exchange experiment. Exposure of **6** to a CD_3OD solution containing CD_3ONa (excess) at room temperature led to completion of the desired Michael reaction (^1H NMR) within 5 min. However, all the attempts to isolate the Michael adduct were unsuccessful; upon neutralization, starting material was recovered. Apparently, this process was driven to completion by the formation of the stabilized enolate, but, upon protonation, this stabilization was lost and a

retro-Michael reaction took place.[8] This difficulty was finally overcome by trapping the cyclized enolate; on treatment of **6** with NaH in THF, followed by the addition of TBS-Cl, the silyl enol ether **7** was isolated in good yield (Scheme 2).

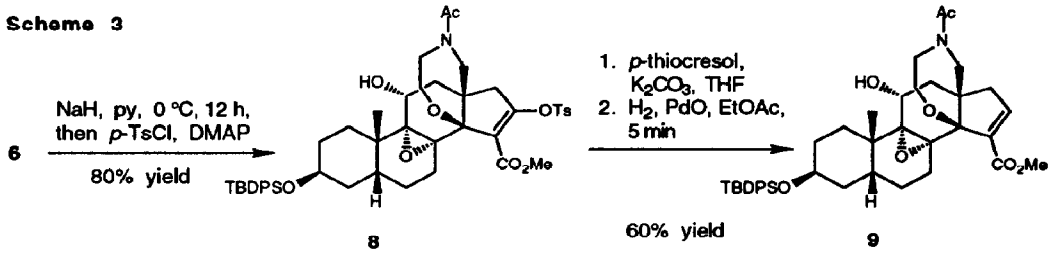
Scheme 2



6 **7**

Subsequently, we found NaH in pyridine at 0 °C for 12 hours to be a more reliable, higher-yielding procedure. In addition, we discovered that the enolate was cleanly tosylated (*p*-TsCl, DMAP, py) to give the stable, crystalline enoltosylate **8**[9] in 80% overall yield. It is worth noting that this adduct was further converted in a good overall yield to the unsaturated ester **9**[10], a substrate sufficiently elaborate[11] to introduce the functionalities required to complete a total synthesis of batrachotoxin.

Scheme 3



8 **9**

In summary, we have developed a noteworthy Michael cyclization in connection with a batrachotoxin synthesis. Among its distinguishing features are its reliance on a stoichiometric quantity of base to drive this process to completion, and the degree of steric density it generates.

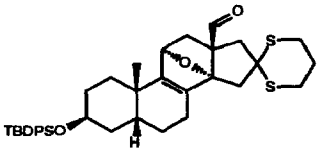
Acknowledgments. Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged. T.J.G. thanks Eli Lilly Company for a predoctoral fellowship.

References and Footnotes

1. Batrachotoxin is a powerful Na^+-channel potentiator; see: (a) Brown, G. B.; Tieszen, S. C.; Daly, J. W.; Warnick, J. E.; Albuquerque, E. X. *Cell. Mol. Neurobiol.*, **1981**, *1*, 19. (b) Daly, J. W.; Herz, E. H.; Grisebach, H.; Kirby, G. W. *Progress in the Chemistry of Natural Products*, **1982**, *41*, 206-235.

2. The standard steroid numbering and ring lettering system will be used throughout this paper.

3. The aldehyde **10** was generated as previously (Grinsteiner, T. J.; Kishi, Y. the preceding paper). The BF_3-etherate was quenched with 1 eq. of NEt_3, and the product subjected to reductive amination (ethanolamine-AcOH, $MgSO_4$, $NaCNBH_3$, THF, MeOH). The crude ethanolamine was then acetylated (Ac_2O, DMAP, py) and purified. Transketalization ($PhI(OTFA)_2$, MeOH, $CaCO_3$) and ketal solvolysis ($CHCl_3$ satd. with conc. HCl) was followed by cleavage of the C.14 ether (NaOMe, MeOH) to give the dienone **2**.



10

4. This included a variety of acids (PPTS, AcOH, oxalic acid, *p*-TsOH, CSA, PPTS with $(MeO)_3CH$) and bases (NaOH, LiOMe, NaOMe, Cs_2CO_3, *t*-BuONa, NaH) in protic (aq. MeOH, MeOH, EtOH, *t*-BuOH) and aprotic (THF, DME, Et_2O, benzene, py) media.

5. Treatment of **2** with *p*-nitroperbenzoic acid in CH_2Cl_2/pH 7 buffer afforded a single product in high yield.

6. For similar deuteration experiments, see: Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L.; *J. Org. Chem.*, **1977**, *42*, 3846.

7. The following sequence was employed: (1) TES-Cl, imidazole, CH_2Cl_2. (2) ICl, py, MeCN. (3) $Pd_2(dba)_3$-$CHCl_3$, PPh_3, CO (1 atm), DMF, MeOH, NEt_3, RT, 12 h. (4) TBAF, THF. The corresponding enal was also prepared from the α-iodoenone intermediate: (1) $(CH_2{=}CH\text{-})_4Sn$, $Pd_2(dba)_3$-$CHCl_3$, PPh_3, DMF. (2) O_3, CH_2Cl_2, -78 °C; DMS. (3) TBAF, THF. The deprotected α-formyl-α,β-unsaturated ketone was highly reactive, but did not provide any isolable Michael adduct.

8. Exposure of the silylenolether **7** to TBAF or HF-py led to immediate conversion back to **6**.

9. Spectroscopic data for **8**: HRMS cald. for $C_{48}H_{59}NO_{10}SSi$ 892.3526 ($M+Na^+$), found 892.3566; ^1H NMR (500 MHz, C_6D_6) δ 7.8 ppm (4H, m), 7.2 (8H, m), 6.69 (2H, d, J = 8.2 Hz), 4.0 (1H, m), 3.9 (1H, m), 3.53 (1H, d, J = 14 Hz), 3.46 (1H, t, J = 14 Hz), 3.37 (3H, s), 2.9 (1H, m), 2.65 (3H, m), 2.4-1.8 (6H, m), 1.78 (3H, s), 1.62 (3H, s), 1.75-1.1 (9H, m), 1.26 (3H, s), 1.20 (9H, s); IR 3400 cm^{-1}, 2940, 1730, 1630, 1180, 1105, 1095.

10. Spectroscopic data for **9**: HRMS cald. for $C_{41}H_{53}NO_7Si$ 722.3489 ($M+Na^+$), found 722.3487; ^1H NMR (500 MHz, C_6D_6) δ 7.8 ppm (4H, m), 7.2 (6H, m), 6.68 (1H, t, J = 1 Hz), 4.0, (1H, m), 3.9 (1H, m), 3.49 (3H, s), 3.0-2.5 (6H, m), 2.4-0.9 (15H, m), 1.62 (3H, s), 1.24 (3H, s), 1.20 (9H, s); IR 3400 cm^{-1}, 2940, 1735.

11. The intramolecular Diels-Alder product with an ethyl side-chain at C.17 is also available (Grinsteiner, T. J.; Kishi, Y. the preceding paper).

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