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# Vitamin D side chain triazole analogs via cycloaddition 'click' chemistry

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**Abstract**—Cycloaddition of a vitamin D side chain terminal acetylene with phenyl azide and separately with a vitamin D side chain terminal azide produced the corresponding 1,2,3-triazole monomeric and dimeric analogs of 1α-hydroxyvitamin $D_3$ in good yields.


Many azasteroids are biologically active.[1] For example, some 1- and 6-azasteroids are 5α-reductase inhibitors[2,3] as well as antifungal agents,[4,5] and 8,13-diazasteroids have analgesic activity.[6] Also, 8,16-diazasteroids have cardiotonic and hypotensive activities,[7] and 11-azasteroids have glucocorticoid activity.[8] Some 17-azasteroids are $GABA_A$ receptor modulators.[9] Very few aza-analogs of vitamin D, however, have been reported despite vitamin D's broad spectrum of biological activities.[10] A 24-amino vitamin $D_3$ has been reported,[11] as well as heterocyclic diazirine[12] and pyrazole[13] side chain vitamin D analogs in which the pyrazole unit was assembled via a cycloaddition reaction.[13–15] Only one side chain triazole vitamin D analog, however, has been described,[16,17] prepared via triazole displacement of a 22-tosylate.[16] We report here synthesis of a vitamin $D_3$ side chain 1,2,3-triazole analog via cycloaddition[18] of a terminal acetylene with phenyl azide (Scheme 1).

In Scheme 1, after acetylide displacement of the C-22 primary tosylate, the first key step involved successful cycloaddition of the C-23 acetylene with phenyl azide, an example of 'click' chemistry.[18–20] The second key step involved successful Lythgoe-type[21] coupling of the racemic A-ring allylic phosphine oxide with the C-8 keto side chain triazole; vitamin $D_3$ triazole analog **1a** was isolated pure in 65% yield from this final coupling and desilylation protocol,[22] and its A-ring stereochemistry was assigned based on NMR spectroscopic analogy with previous analogs[23] ($^1$H NMR $C_6$–H $\delta$ 6.37 for **1a**, $\delta$ 6.38 for **1b**).

'Click' chemistry[18–20] allowed cycloaddition also of a vitamin D C-23 terminal acetylene with a vitamin D side chain azide to form dimer **2** in which two of the same vitamin D units are linked through their side chains via a 1,2,3-triazole unit (Scheme 2).

Each of the chemical transformations in Scheme 2 proceeded in at least 69% yield, and the key cycloaddition step to form vitamin D dimer triazole **13** proceeded in 73%.

Evaluation of the in vitro antiproliferative activity of monomer phenyl triazole **1a** was done in murine keratinocytes using our standard protocol.[24] No significant antiproliferative activity, however, was found even at 1 μM concentration of monomer phenyl triazole **1a**. For comparison, a somewhat similar 1-α-hydroxyvitamin D C-25 oxime methyl ether analog, even though lacking the traditional C-25 hydroxyl group, showed high in vitro antiproliferative activity,[24] and various side chain aromatic vitamin D analogs (arocalciferols) have significant biological activities.[25] Dimer triazole **2** did not show any interesting in vitro antiproliferative activity.

In summary, cycloaddition of a vitamin D side chain terminal acetylene with phenyl azide and separately with a vitamin D side chain azide successfully produced the corresponding 1,2,3-triazole analogs of 1-α-hydroxyvitamin $D_3$ in good yields. This is the first report of 'click' chemistry in the vitamin D field and the first

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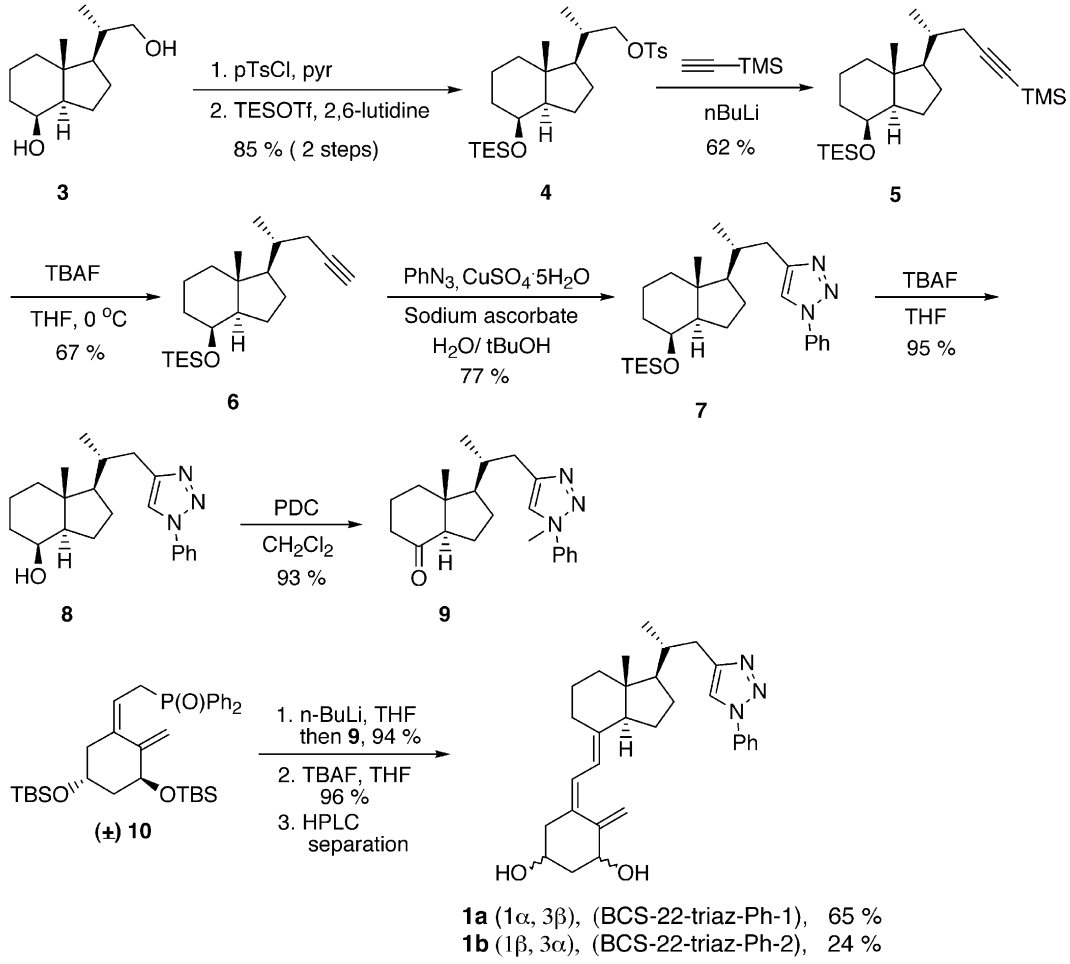
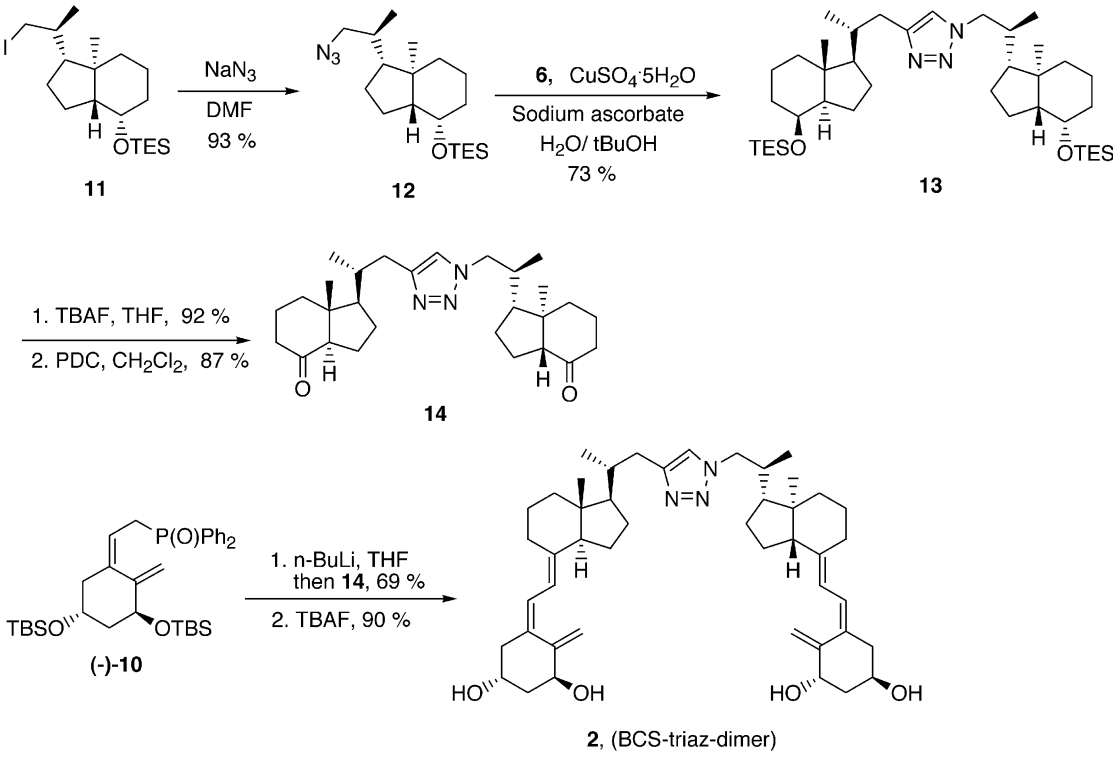



**Scheme 1.**




**Scheme 2.**

synthesis of a vitamin D dimeric analog in which the monomeric vitamin D units are linked via a side chain heteroaromatic ring.[26]

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