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The influence of distal substitution on the base-induced isomerization of long-chain terminal alkynes

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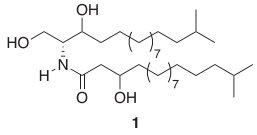
ABSTRACT

When compared to a long-straight chain terminal alkyne, a long chain terminal alkyne with a distal isopropyl unit (isobranched) isomerizes about two times faster when treated with strong base under identical conditions, and appears to follow pseudo first order kinetics. In both cases, equilibration to a 95–97:5–3 mixture of terminal:internal alkyne accompanies isomerization. The difference in rate may be due to an unusual folding of both long-chain alkynes, bringing the distal substituent close to the carbon-carbon-triple bond moiety. The distal isopropyl moiety may provide unanticipated steric hindrance that disrupts such folding, making the propargylic proton more available for reaction with base.

Introduction

Inflammatory periodontal disease in adults is initiated with the accumulation of specific bacteria in the sulcus around the teeth, followed by a chronic inflammatory reaction by the host against the colonizing microorganisms. The anaerobic Gram-negative organism, *Porphyromonas gingivalis*, is thought to be a major periodontal pathogen[1] associated with destructive periodontal disease in adults. *P. gingivalis* and other phylogenetically related organisms produce a variety of novel lipids,[2] including phosphorylated dihydroceramide lipids (see **1**).[3] More recent work in our laboratories identified serine dipeptide lipid classes in *P. gingivalis* that comprise a new class of ligands (see **2** and **3**) for Toll-like receptor 2 (TLR2).[4] These agonists are also produced by common oral and intestinal *Bacteroidetes*,[5] and they are recovered in chronically inflamed human tissues including destructive periodontal disease and atherosclerosis tissues.[2]



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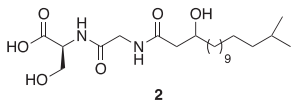

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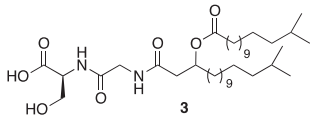

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The base-induced isomerization of the triple bond of terminal alkynes is well known,[6] proceeding through an allene intermediate.[7] This isomerization typically requires a strong base and KOH in alcohol, but sodium amide in DMSO has been used.[8] Small amounts of the allene were sometimes isolated during the isomerization reaction[9] although the allene was prone to polymerization and was not always detected. In another study,[10] a mechanism for the isomerization of pent-1-yne was proposed, using KOH in ethanol, in a sealed tube at 175 °C, deprotonation led to allene formation, which led to the thermodynamically more stable internal

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alkyne, pent-2-yne.[6a] Analysis of the products for this latter study showed the presence of 1–4% of pent-1-yne, with some penta-1-2,diene.

In previous work, we synthesized the putative C17 and C19 dihydroceramides (**1**) to prove their structure and showed that the long aliphatic chain terminated in an isopropyl unit,[4,2] and that this terminal isopropyl unit is critical for expression of the biological activity.[11] Two TLS2 ligand are serine dipeptide lipid classes that were labeled lipid 430 and lipid 654, 2 and 3 respectively. Recently we observed that the lipid 654 can be hydrolyzed by specific lipases to lipid 430. A terminal isopropyl unit in a long aliphatic chain is hereafter referred to as an isobranch. We recently reported the convergent synthesis of **2** and **3**.[12,13]

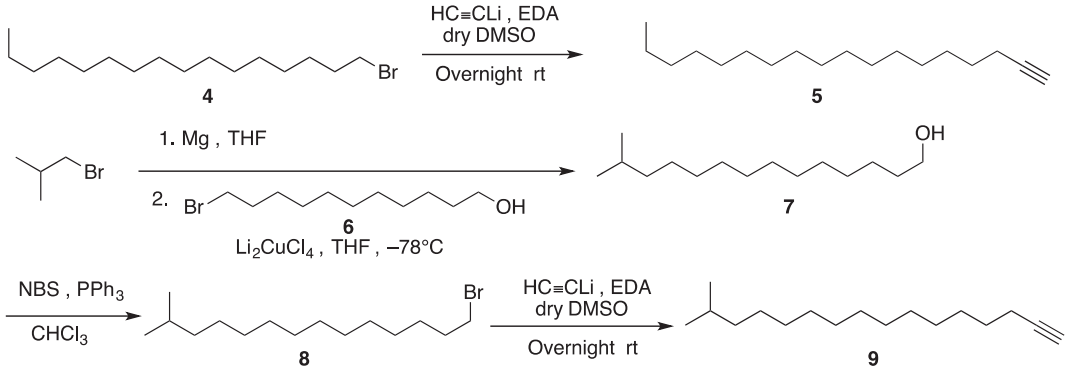
Results and discussion

To determine the kinetics of base-induced isomerization, we required an unambiguous synthesis of both the straight-chain alkyne (**5**) and the distal isobranched terminal alkyne (**9**). The synthesis of the straight-chain alkyne proceeded without problem, via coupling of lithium acetylide with commercially available 1-bromohexadecane (**4**), in dry DMSO, to give octadec-1-yne (**1**) in 73% yield (see Scheme 1). We prepared the isobranched intermediate, 13-methyl-1-bromotetradecan-1-ol (**7**), using, in part, methodology reported by Singh[14] and by Mori.[15] This synthesis began with a lithium tetrachlorocuprate-mediated coupling reaction of the Grignard reagent prepared *in situ* by reaction of 1-bromo-2-methylpropane with commercially available 11-bromoundecan-1-ol (**6**), which gave 13-methyltetradecan-1-ol (**7**) in 79% yield. Conversion to the bromide (**8**) with NBS and PPh_3 (81% yield) was followed by reaction with lithium acetylide to give 15-methylhexadec-1-yne (**9**) in 77% yield.

The kinetics for both **5** and **9** were obtained in DMSO at 55 °C and also at 75 °C, temperatures at which reasonable data could be collected.[16] Samples were prepared that were 0.042 M alkyne in DMSO. Potassium *tert*-butoxide was added to each sample and aliquots were removed at the time intervals shown in Figs. 1 and 2, quenched with water, the products extracted with hexane, and ^{1}H NMR was used to monitor the reaction.

We plotted [alkyne] vs. time, ln [alkyne] vs. time and 1/[alkyne] vs. time, but the linear plots were obtained only for ln [alkyne] vs. time. Our results point to a pseudo first order reaction for all rate constants reported herein. This observation is reasonable if one of the reactants, possibly the base, is in excess relative to the deprotonation reaction with the alkyne. Fig. 1 shows a comparison of the reactions of **5** and **9** at 55 °C and 75 °C. Fig. 2 shows the changes in rate at 55 °C and at 75 °C for **5** and for **9**.

Based on the results in Figs. 1 and 2, it is clear that isomerization of the isobranched alkyne is faster than that of the straight-



Scheme 1. Synthesis of alkynes **5** and **9**.

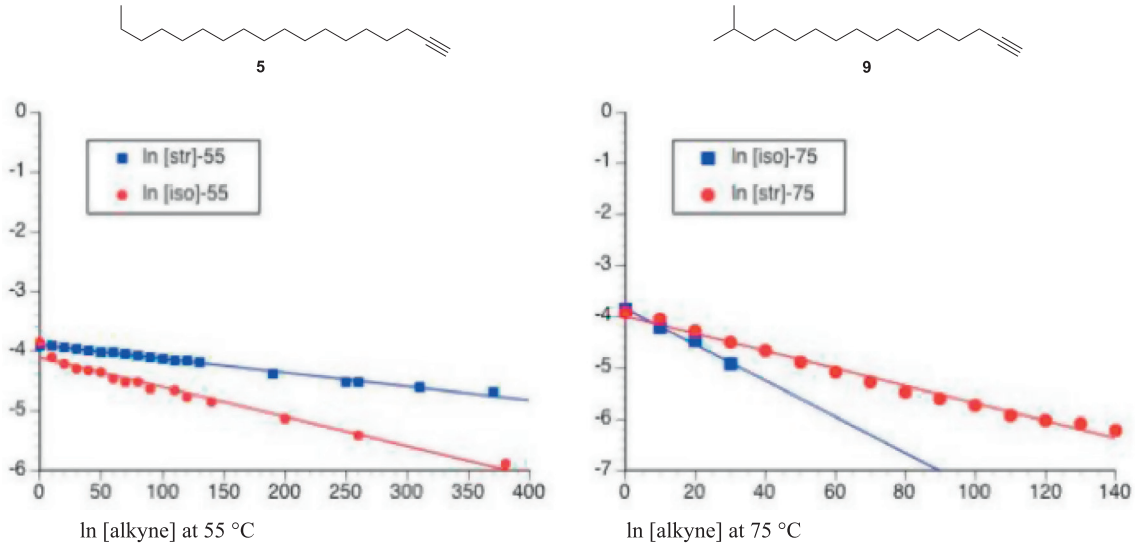


Fig. 1. Plot of ln [**5**] and ln [**9**] vs. time (min.) at both 55 °C and 75 °C.