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Substituted azabicyclo[3.1.0]hexan-1-ols from aspartic and glutamic acid derivatives via titanium-mediated cyclopropanation

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ABSTRACT

The Kulinkovich cyclopropanation reaction has been used to synthesize azabicyclo[3.1.0]hexanols from amino acid derivatives containing two ester moieties.

Small heterocycles have great potential for biological activity. Constrained derivatives of naturally occurring heterocycles can have important pharmaceutical applications and their syntheses are desirable. For these reasons, our research group has studied the synthesis of azabicycles from amino acid derivatives via the Kulinkovich reaction.[1,2] Prior to our work, it was shown that bicyclic cyclopropanols could be made from esters in good yields with an intramolecular variant of this reaction.[3] This reaction was extended to *N*-alkylated amino acid esters, allowing incorporation of nitrogen into the ring.[4] Although many variations of the Kulinkovich reaction have been well-investigated, cyclizations of substrates with two esters are less explored.

We attempted to apply the Kulinkovich reaction to the synthesis of a novel cyclopropane-substituted indolizidine (**2**). The double cyclopropanation of *N*,*N*-diallyl aspartic acid dimethyl ester (**1**) would give a compound similar to a synthetic analog of the anticancer agent, Swainsonine.[5] Diester **1** was exposed to a stoichiometric amount of $ClTi(Oi\text{-}Pr)_3$ and to an excess of $c\text{-}C_5H_7MgBr$, which is a slight modification to the original Kulinkovich conditions and is more often applied to the cyclization of amides.[6] Rather than the desired indolizidine, almost exclusive formation of [3.1.0]cyclopropanol **3** was observed (Fig. 1).[7] Other variations of the Kulinkovich reaction conditions were tried and it was found that when $Ti(Oi\text{-}Pr)_4$ was used, mixtures of piperidinols and pyrrolidinones were produced. It was also noted that transesterification of the methyl ester with an isopropoxide ligand from titanium occurred, which is a common Kulinkovich side reaction.[8]

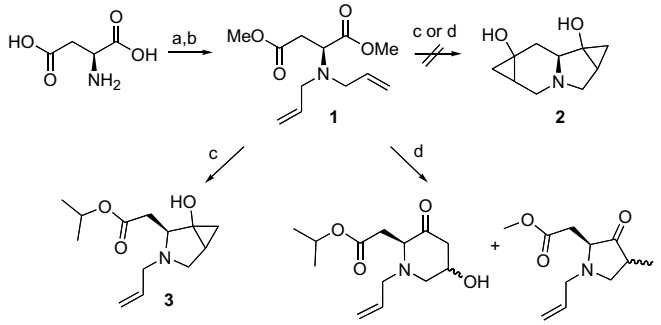

Figure 1. Cyclization of diallylated aspartic acid methyl ester. Reagents and conditions: (a) $SOCl_2$, MeOH, quant.; (b) allyl bromide, K_2CO_3, Bu_4NI, MeCN, 90%; (c) $ClTi(Oi\text{-}Pr)_3$, $c\text{-}C_5H_7MgBr$, THF, 35%; (d) $Ti(Oi\text{-}Pr)_4$, *i*-PrMgCl, THF.

To improve the yield and applicability of our aspartic acid-derived cyclopropanol, *N*-benzyl-*N*-allyl aspartic acid methyl ester was made and cyclized. This substrate showed similar selectivity for the [3.1.0] system, and transesterification was observed (Fig. 2).

Additionally, an azabicyclic propionic acid ester was obtained via cyclization of a glutamate derivative (Fig. 3). Not surprisingly, only [3.1.0]cyclopropanol was formed.

Independently, Ollivier and co-workers performed competitive cyclizations of succinate derivatives, and found a clear preference for bicyclo[3.1.0]hexanol formation over bicyclo[2.1.0]hexanol.[9] In addition, they exposed a monoallylated isopropyl aspartate derivative to the Kulinkovich cyclopropanation (Fig. 4). This reaction, however, did not result in isolation of the cyclopropanol, but rather a pyrrolidinone. The researchers hypothesized that

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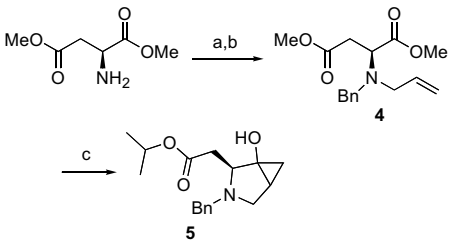

Figure 2. Synthesis of azabicyclo[3.1.0]hexanol. Reagents and conditions: (a) benzaldehyde, $Na(OAc)_3BH$, CH_2Cl_2, 95%; (b) allyl bromide, K_2CO_3, Bu_4NI, MeCN, 86%; (c) $ClTi(Oi\text{-}Pr)_3$, $c\text{-}C_5H_7MgBr$, THF, 64%.

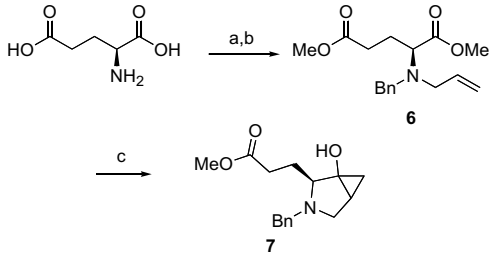

Figure 3. Bicyclo[3.1.0]hexanol from glutamic acid. Reagents and conditions: (a) $SOCl_2$, MeOH, quant.; (b) benzaldehyde, $Na(OAc)_3BH$, CH_2Cl_2, 90%; (c) allyl bromide, K_2CO_3, Bu_4NI, MeCN, 85%; (c) $ClTi(Oi\text{-}Pr)_3$, $c\text{-}C_5H_7MgBr$, THF, 65%.

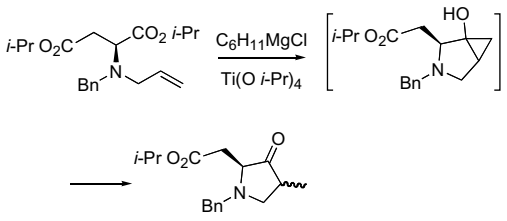

Figure 4. Ollivier's cyclization of *N*-allyl-*N*-benzylaspartate.

the observed pyrrolidinone resulted from a rearrangement of cyclopropanol.

The preferential formation of five-membered rings observed by Ollivier is in accord with our results. However, all of our attempts to convert the cyclopropanol into a pyrrolidinone resulted in decomposition or recovery of starting material (Fig. 5). Only a few oxidative reagents would react with the cyclopropanol, and those experiments led to a ring-expanded product, which is consistent with the literature precedent.[10]

As a pyrrolidinone was isolated from the cyclopropanation reaction, but not directly from the cyclopropanol, we believe that another intermediate, possibly a titanacycle from the accepted

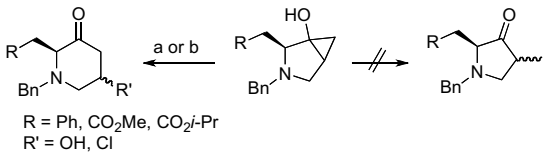

Figure 5. Cyclopropanol ring-opening. Reaction conditions: (a) silica gel, O_2; R′ = OH; (b) $FeCl_3$, pyridine, DMF; R′ = Cl.

Kulinkovich mechanism, must have given rise to the unexpected pyrrolidinone.

In conclusion, we have synthesized three azabicyclo[3.1.0]hexanols (**3**, **5**, and **7**). The [3.1.0] system is formed preferentially over other cyclic systems, and slight changes in cyclization conditions give much lower yields and monocyclic side products.

Acknowledgments

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Supplementary data

Experimental procedures, characterization, and spectra for compounds **1**, **3**, **4**, and **5** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.114.

References and notes

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