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Three-Component Coupling Approach to Trachyspic Acid

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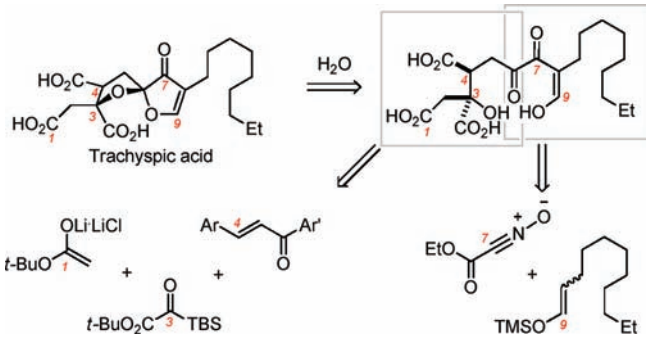
ABSTRACT



Three-component coupling of the lithium enolate of *t*-BuOAc, silyl glyoxylate, and an α,β-unsaturated ketone enables the rapid construction of the trachyspic acid carbon skeleton. A 3,4-disubstituted isoxazole is utilized to mask the C7/C9 dicarbonyl. New enolsilane/nitrile-oxide cycloadditions enable the preparation of various 3,4-disubstituted isoxazoles that are challenging to access by other means.

Trachyspic acid (**1**) was isolated from the culture broth of *Talaromyces trachyspermus* SANK 12191.[1] Trachyspic acid possesses a substituted citric acid subunit and a hydrophobic side chain, defining characteristics of the 2-alkyl citrate natural products, and as an inhibitor of tumor heparanase (IC_{50} = 36 μM), it has inspired several synthetic studies.[2−6] The contiguous C3 and C4 chiral centers and the efficient management of the unusual C6−C9 β,γ-diketoaldehyde have proven to be the principle hurdles to synthesis. For construction of the former subunit, previous syntheses of trachyspic acid have employed either aldol[2,3,6] or Ireland-Claisen rearrangement[4,5] strategies. The occurrence of the fully substituted C3 glycolic acid suggested the opportunity to develop a new silyl glyoxylate-based three-component coupling[7−13] that might permit efficient access to the core substructure. This Letter details experiments directed to this end.

The open chain form (**2**) of trachyspic acid reveals a 1,4-relationship between the C3 glycolic acid and the C6 ketone, hinting at a potential Michael addition of a silyl glyoxylate with an appropriately functionalized α,β-unsaturated ketone (Scheme 1); however, a C6/C7/C9 tricarbonyl compound would pose an intractable chemoselectivity challenge in the projected three-component

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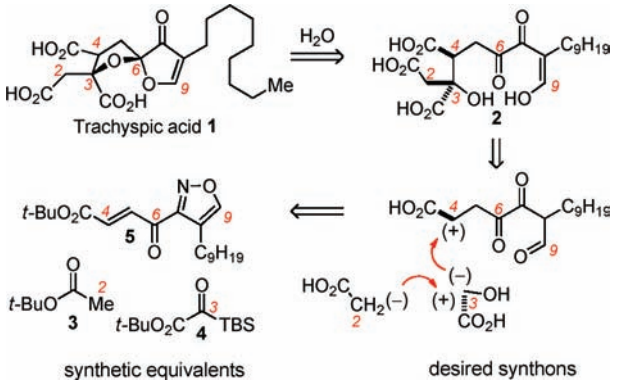
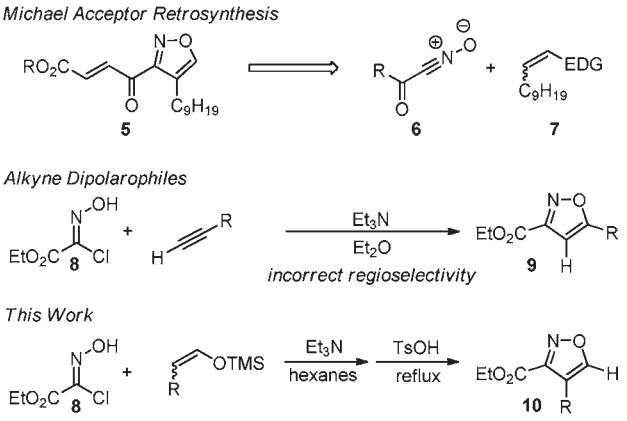
coupling. In the interest of streamlining fragment assembly and minimizing functional group and protecting group manipulations,[14] masking the C7/C9-dicarbonyl as an isoxazole emerged as an attractive possibility.[15] This particular packaging of reactive functionality was expected to present the C4 enone as the most electrophilic site on compound **5** and permit downstream unmasking of the C7/C9 keto aldehyde via N–O hydrogenolysis and hydrolysis. The ideal nucleophilic component for the proposed coupling would be an acetate enolate and the needed three-component coupling would in principle complete the full trachyspic acid carbon skeleton.

Scheme 1. Retrosynthetic Analysis of Trachyspic Acid



Preliminary studies focused on the synthesis of Michael acceptor **5**. Nitrile-oxide cycloaddition with alkynes represents a direct and reliable route to isoxazoles; however, steric effects dictate that terminal alkynes always provide 3,5-disubstituted isoxazoles **9**, the incorrect regioisomer needed for the application at hand (Scheme 2).[16] Examples of the preparation of 3,4-disubstituted isoxazoles by nitrile-oxide cycloaddition are scarce.[17] The majority of these approaches rely on a tethered nitrile-oxide[18] or a vinylogous amide or ester directing group.[19]

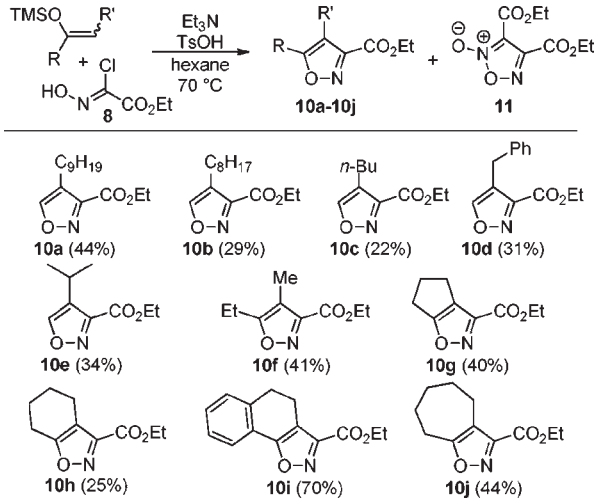
Scheme 2. Regioselectivity of Nitrile-Oxide Cycloaddition



We sought to dictate the regiochemistry of nitrile-oxide cycloaddition electronically using an electron-rich olefin dipolarophile. For the nitrile-oxide component we selected carboethoxyformonitrile oxide (CEFNO), due to its facile in situ preparation from stable ethyl chlorooximidoacetate (**8**) (Scheme 2). While nitrile-oxide precursor **8** is commercially available, it can also be prepared in one step from ethyl glycine.[20] Initial experiments utilized enol acetate and alkyl enol ether dipolarophiles, which provided the undesired furoxan dimer **11** as the major product. We hypothesized that employing a more electron-rich dipolarophile would facilitate cycloaddition with the electron-poor nitrile-oxide; thus, enolsilanes were tested. Syringe pump addition of triethylamine over 15 h to a solution of oxime **8** and an enolsilane, followed by addition of $TsOH \cdot H_2O$ and warming to reflux, resulted in the regioselective formation of a 3,4-disubstituted isoxazole.

Since the preparation of 3,4-disubstituted isoxazoles is an unsolved problem in organic synthesis, we evaluated the broader applicability this cycloaddition. Various aldehyde- and ketone-derived enolsilanes were effective dipolarophiles, including both linear and branched alkyl variants (Scheme 3). The regioselective synthesis of isoxazole **10f** (from the enolsilane of 3-pentanone) was serviceable where 2-pentyne/CEFNO cycloaddition was not (< 10% yield; ~1:1 mixture of constitutional isomers). The preparation of fused-ring isoxazoles is another challenge to organic chemists that was addressed by this method. Small and medium cycloalkynes are unstable due to ring strain, so the preparation of fused-ring isoxazoles has inspired creative methods.[21,22] Five-, six-, and seven-membered ring enolsilanes were found to be competent in the cycloaddition (**10g**–**10j**). The modest yields are believed to be due to a combination of product volatility and ester hydrolysis (during the aromatization step). The enolsilanes

Scheme 3. Enolsilane Dipolarophiles in Nitrile-Oxide Cycloaddition[a]

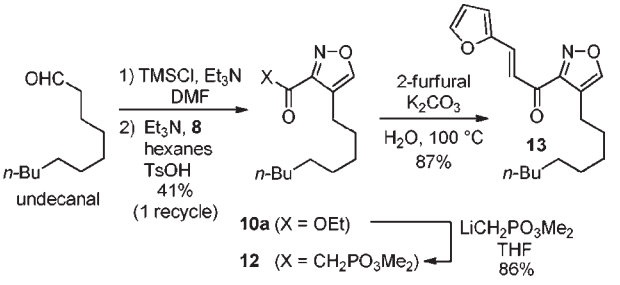


[a] Yields are of isolated material after column chromatography, average of at least two trials.

were used without prior distillation allowing for the operationally simple preparation of isoxazoles in two steps from carbonyl compounds. Prior purification of the enolsilanes did not improve the yields of isoxazole products.

Having developed a reliable, scalable (6.4 g) method for the preparation of isoxazole **10a**, we next pursued the completion of enone **5**. Claisen condensation with lithiated methyl dimethyl phosphonate provided β-ketophosphonate **12** (Scheme 4). *t*-Butyl glyoxylate underwent olefination ($LiCl/Et_3N$), but downstream operations were problematic with this substrate. Thus, the 2-furyl group was selected to mask the C4 carboxylic acid. Olefination of 2-furfural proceeded smoothly with aqueous K_2CO_3 at 100 °C to afford the desired enone **13** (> 20:1 *E*:*Z*).

Scheme 4. Synthesis of the C4–C9 Enone



Studies commenced on the heretofore unknown three-component glycolate Michael reaction. Based on prior studies in our group,[9,11] initial experiments employed Reformatsky reagents as nucleophilic triggers; however, unselective mixtures of three-component aldol and Michael addition to the enone **13** were found to be the major products. In contrast, use of lithium enolate **14** provided the Michael addition product **15** (Scheme 5), with no trace of undesired 1,2-addition. Solvent choice influenced the diastereoselectivity: THF provided 2.7:1 dr favoring the desired isomer, while the diastereoselectivity was inverted when toluene (1:1.7), hexanes (1:1.5), or diethyl ether (1:2.0) were utilized. The ability to switch the diastereoselectivity by changing solvents could be an asset for analogue synthesis. This coupling generates two C–C bonds, the critical C3 and C4 stereogenic centers, and completes the full carbon skeleton of trachyspic acid.

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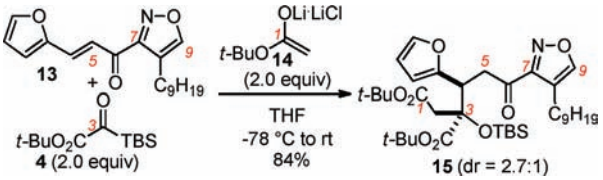
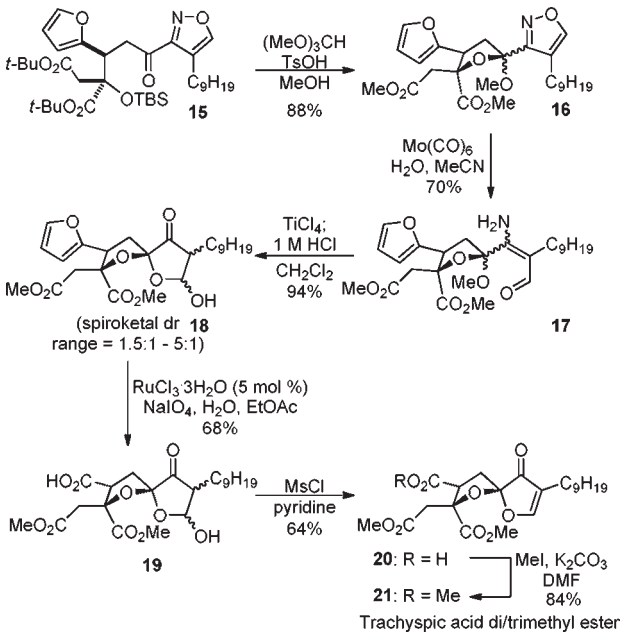
A reaction conducted with 3.7 g of enone **13** provided 4.9 g of diastereomerically pure **15**.

Scheme 5. Three-Component Coupling



With ketone **15** in hand, remaining synthetic operations included isoxazole N–O cleavage, furan oxidation, and spiroketalization. Exposing ketone **15** to either oxidative or reductive conditions was ineffective at cleaving the furan or the isoxazole, respectively. Decomposition of **15** during isoxazole reduction attempts was believed to be a consequence of the reactivity of the C6 ketone. Treating ketone **15** with acidic methanol resulted in transesterification and mixed methyl ketal formation. Ketal **16** underwent successful N–O reduction with $Mo(CO)_6$ to provide enamine **17** (Scheme 6).[23] With the C7–C9 dicarbonyl equivalent unmasked, the stage was set for formation of the 5,5-spiroketal.

Scheme 6. Progress Toward Trachyspic Acid



We expected that Brønsted acid-promoted ketalization of **17** would furnish C6 spiroketal **18**. Following the model

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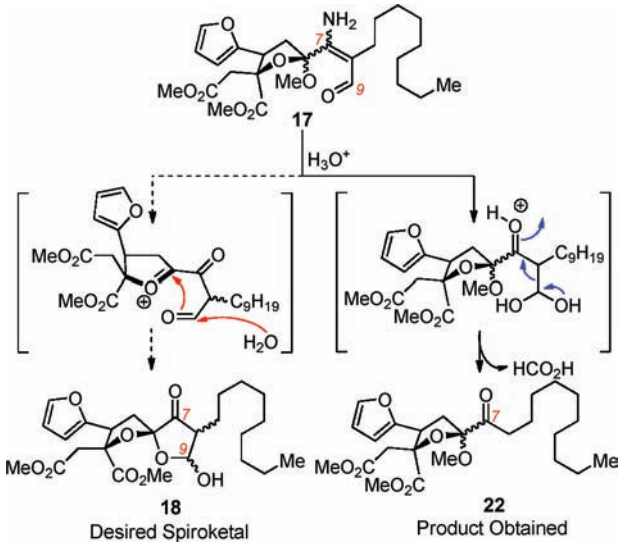
of Rizzacasa[5] and Hatakeyama,[6] enamine **17** was treated with 3 M $HClO_4$; however, rather than the expected spiroketal **18**, ketone **22** was generated as the major product (Scheme 7). Ketone **22** is presumably formed by enamine hydrolysis and retro-Claisen fragmentation of the C8−C9 bond. Other aqueous Brønsted acids were also found to trigger the same undesired fragmentation.

Scheme 7. Unexpected Retro-Claisen Fragmentation



In an effort to avoid retro-Claisen fragmentation, we tested a series of less nucleophilic ketalization conditions. A number of Lewis acids were found to induce only tautomerization or no reaction, but $TiCl_4$ demonstrated unique efficacy in promoting spiroketalization. Quenching the reaction with 1 M HCl resulted in hydrolysis of the imine intermediate and hydration of the intermediate C9 enol ether to provide spiroketal **18** as a mixture of diastereomers (Scheme 6). Multiple repetitions of the synthetic sequence revealed sporadic diastereoselectivity in the spiroketalization, which ranged from as high as 5:1 dr to as low as 1.5:1 dr The major diastereomer was found to correspond to the natural isomer in each case.

Oxidative furan deprotection furnished acid **19**, revealing the citric acid motif (Scheme 6). Subsequent hemiacetal dehydration delivered trachyspic acid dimethyl ester **20**. Methylation of the lone carboxylic acid gave the known trachyspic acid trimethyl ester **21**, as confirmed by ^1H NMR and ^{13}C NMR analysis.[1] Compounds **20** and **21** have proven to be unexpectedly recalcitrant toward numerous conventional and unconventional saponification conditions.

In summary, the trachyspic acid dimethyl ester was prepared in 10 linear steps from commercially available undecanal. Key steps include a silyl glyoxylate three-component coupling, as well as a new nitrile-oxide cycloaddition of an enolsilane dipolarophile. The latter enables the synthesis of various 3,4-disubstituted isoxazoles that are challenging to access by other means. The aim of future work is to evaluate the scope of the glycolate Michael reaction in the context of other alkyl citrate natural products.

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Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.