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A New Route to Highly Functionalized Heterocyclic Rings

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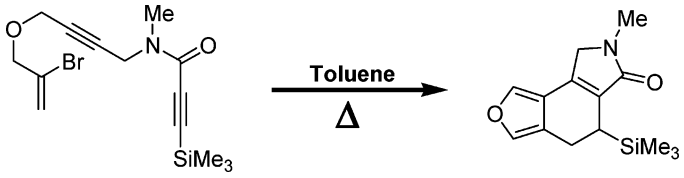
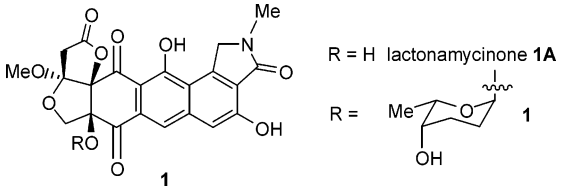


A novel cascade reaction has been developed for the rapid construction of heterocyclic rings. The cyclization is thermally induced and does not involve the use of metal ions. This highly efficient construction of furans has been developed during studies directed toward the synthesis of the antibiotic lactonamycin **1**.

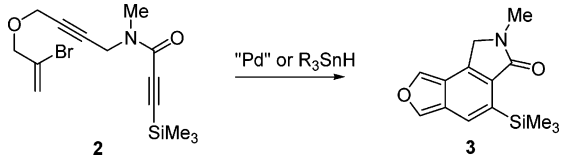
Introduction

Furan and its analogues are very useful diene partners in the Diels−Alder reaction.[1] Recently, Kelly et al. have elegantly demonstrated the use of a furan/quinone Diels−Alder reaction in the synthesis of a model for the construction of lactonamycin **1**.[2]



The furan required for the key Diels−Alder reaction was prepared in eight synthetic steps, demonstrating that 3,4-disubstituted furans are often nontrivial to make. In a recent review,[3] de Meijere has described the use of palladium complexes in mediating ring-forming reactions, which include the formation of a range of heterocyclic compounds. Radical cyclization reactions have also been used for the construction of heterocyclic rings.[4] Carbon-centered radicals can cyclize onto double bonds to form rings which contain heteroatoms;[5] nitrogen- or oxygen-centered radicals can be generated and then added to double or triple bonds in the intramolecular sense to form rings.[6] A large volume of work has been published on metal-catalyzed [2 + 2 + 2] cycloadditions. Cobalt-mediated [2 + 2 + 2] cycloadditions of alkynes represent a very powerful technique for the construction of fused rings.[7] Vollhardt[8] has published extensively in the area of cobalt-mediated cycloadditions, and recently Tanaka[9] et al. have published a rhodium-mediated cycloaddition of dienes using isothiocyanates or carbon

SCHEME 1. Strategy for the Formation of Substituted Furans



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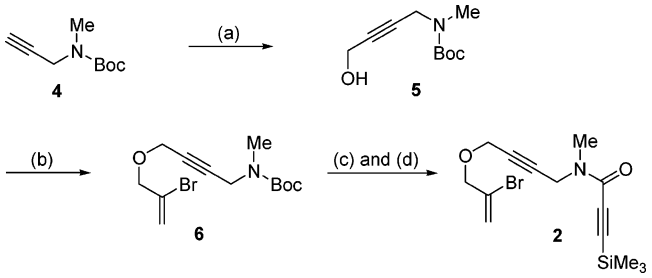
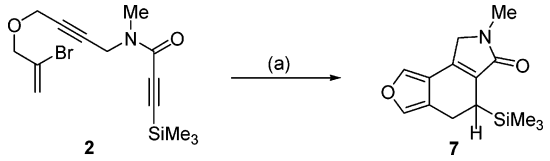
SCHEME 2. Synthesis of the Cyclization Precursor 2[a]



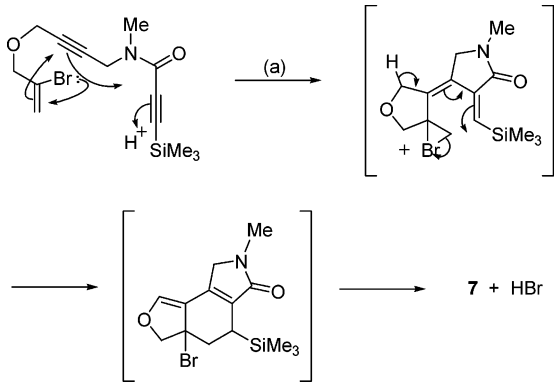
[a] Conditions: (a) *n*-BuLi then $(CH_2O)_n$ (85%); (b) NaH, 2,3-dibromopropene (81%); (c) TFA, CH_2Cl_2; (d) trimethylsilylpropynoyl chloride, NEt_3, CH_2Cl_2 (85%).

SCHEME 3. Thermal Cyclization of Amide 4[a]



[a] Conditions: (a) Toluene, reflux, epoxyhexene, 1 h (90%).

SCHEME 4. Acid-Catalyzed Mechanism for the Conversion of 2 into 7[a]

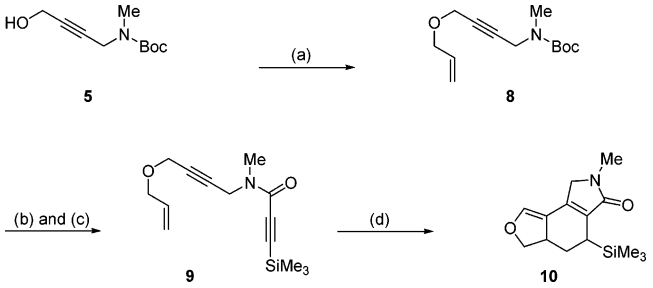


[a] Conditions: (a) Toluene, reflux, 1 h.

disulfide, which furnished thiopyrans, as a cycloaddition partner.[10] A double [2 + 2 + 2] cycloaddition has recently been reported for the synthesis of tetra-ortho-substituted axially chiral biaryls.[11]

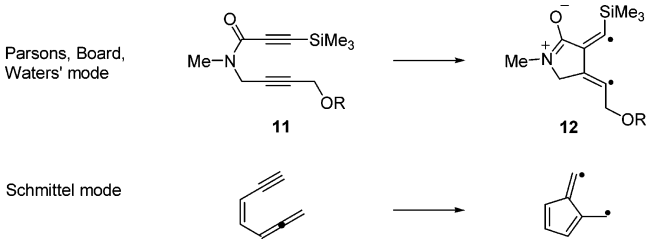
We envisaged that a tin- or palladium-mediated[12] cascade reaction could be used for the construction of a range of furans, which could subsequently be used for [4 + 2] cycloaddition reactions. The furan **3** would also be a useful precursor for anion

SCHEME 5. Formation and Thermolysis of the Amide 9[a]

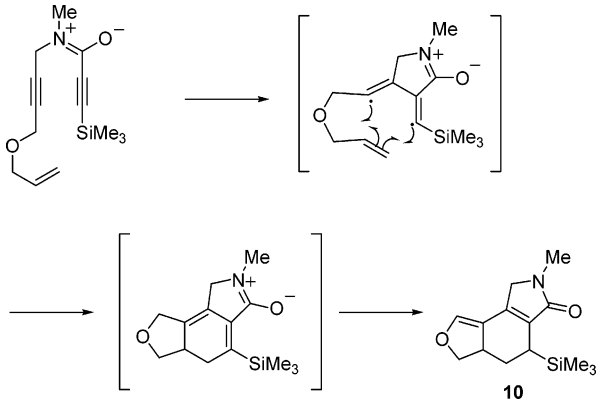


[a] Conditions: (a) NaH, allylbromide, THF (100%); (b) TFA, CH_2Cl_2; (c) trimethylsilylpropynoyl chloride, NEt_3, CH_2Cl_2 (89%); (d) toluene, reflux, 1 h (92%).

SCHEME 6. The Close Proximity of the Alkyne Functionality in 5 and its Analogues Compared to the Schmittel Mode of Cyclization



SCHEME 7. Formation of a Biradical for the Cyclization of 2 and its Analogues



chemistry, which would allow intramolecular cycloaddition reactions to be investigated (Scheme 1).[13]

Results and Discussion

The desired cyclization precursor **2** was synthesized as shown in Scheme 2. Treatment of *N*-Boc-*N*-methylpropargylamine with *n*-butyllithium followed by *para*-formaldehyde gave the alcohol **5** (85%). Treatment of **5** with sodium hydride, followed by the addition of 2,3-dibromopropene, afforded ether **6**, which was isolated in 81% yield. Removal of the Boc protecting group with trifluoroacetic acid followed by N-acylation with trimethylsilylpropynoyl chloride gave the desired cyclization precursor **2**.[14,15]

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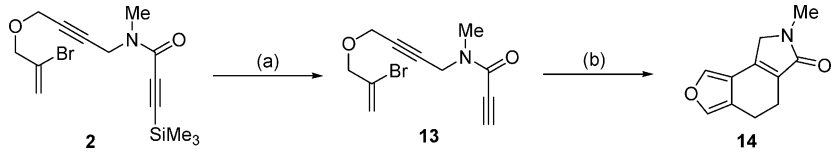
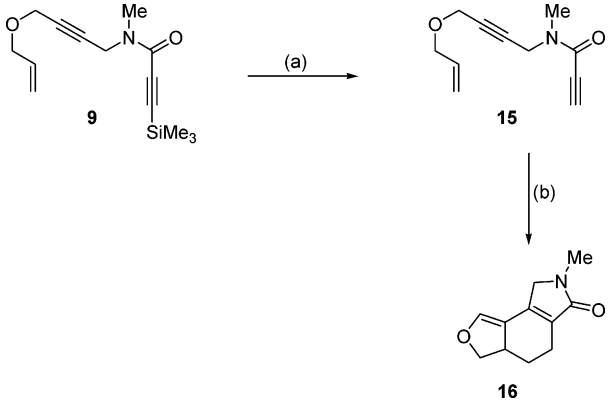
SCHEME 8. Removal of the Trimethylsilyl Group from 2 and the Thermal Cyclization of 13[a]



[a] Conditions: (a) NaOMe, MeOH, CH_2Cl_2 (95%); (b) toluene, reflux, epoxyhexene, 13 h (97%).

SCHEME 9. Formation and Thermolysis of the Amide 15[a]



[a] Conditions: (a) NaOMe, MeOH, CH_2Cl_2 (88%); (b) toluene, reflux, 13 h (89%).

When the amide **2** was heated in boiling toluene without the addition of tri-*n*-butyltin hydride or a palladium salt, a smooth cyclization occurred to give the furan **7** in 38% yield. Addition of 10 equiv of epoxyhexene as an acid trap further improved the yield of the cyclization product **7** to 90% (Scheme 3).

Corey used epoxypropene[16] as an acid trap in his synthesis of gibberellic acid. The use of the higher boiling epoxyhexene, in our case, was highly effective and, in each example, gave higher yields of cyclized product.

The mechanism of the novel cyclization is intriguing. An acid-catalyzed mechanism was proposed (Scheme 4) but was discounted in favor of a radical process because the cyclization still proceeds in the absence of an alkenyl bromide (see Scheme 5). We have also found that tri-*n*-butyltin hydride inhibits the cyclization reaction.

Synthesis of the cyclization precursor **9** was carried out in order to test the validity of the acid-catalyzed mechanism proposed in Scheme 4. Treatment of the alcohol **5** with allyl bromide in the presence of sodium hydride led to the formation of the allyl ether **8** in quantitative yield; the *N*-Boc group was then removed with trifluoroacetic acid, and this was followed by reaction of the free amine under basic conditions with trimethylsilylpropynoyl chloride, which yielded the cyclization precursor **7** (89%) that cyclized in refluxing toluene to the dihydrofuran **10** (92%) (Scheme 5).

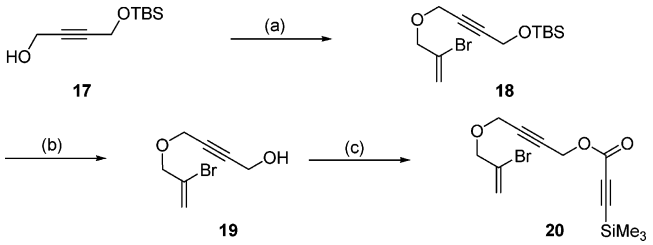
The use of base-washed glassware and the fact that **9** cyclized smoothly to **10** indicate that the mechanism of cyclization is unlikely to be acid catalyzed. Given that tri-*n*-butyltin hydride inhibits the formation of the furan **7**, we propose that the cyclization could be analogous to the Bergman[17] and Schmittel[18] cyclizations. Examination of molecular models shows that the alkyne groups in **11** and its analogues can be very close in space (Scheme 6). The proposed biradical intermediate **12** bears a close similarity to the Schmittel mode of cyclization for enyne−allene cyclization (Scheme 6).[19]

Cyclization of the biradical intermediates followed by a double bond shift to minimize ring strain would lead to tricyclic products (Scheme 7).

We wished to investigate the effect of the trimethylsilyl group on the rate of cyclization; removal of this group from **2** using sodium methoxide in methanol and dichloromethane gave the alkyne **13** (Scheme 8). Removal of the trimethylsilyl group in **2** resulted in a dramatic reduction in the rate of cyclization from **13** into **14**. This adds further credence to the idea of the facile formation of a radical α to silicon.[15] Reduction in the rate of cyclization was also observed in the cyclization of **15** to form **16** (Scheme 9).

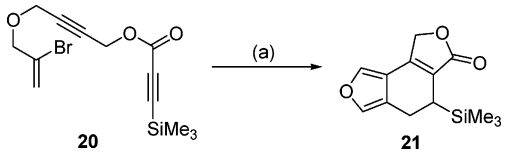
In order to investigate the importance of amide functionality in the cyclization cascade, we elected to change the amide to an ester linkage. In Scheme 10, the synthesis of the ester cyclization precursor **20** is outlined. Treatment of the mono-

SCHEME 10. Synthesis of the Acetylenic Ester 20[a]



[a] Conditions: (a) 2,3-dibromopropene, NaH (80%); (b) TBAF, THF (86%); (c) trimethylsilylpropionic acid, CH_2Cl_2, EDCI (84%).

SCHEME 11. Thermal Cyclization of the Ester 20[a]



[a] Conditions: (a) toluene, epoxyhexene, reflux, 52 h (76%).

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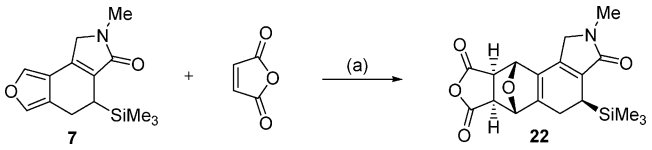
SCHEME 12. Diels−Alder Reaction of 7 with Maleic Anhydride[a]



[a] Conditions: (a) Et_2O, rt, 24 h (53%).

tert-butyldimethylsilyl ether of butyne-1,4-diol[20] with sodium hydride and 2,3-dibromopropene gave the ether **18** in 80% yield. Removal of the silyl protecting group in **18** with tetrabutylammonium fluoride in THF gave the alcohol **19** in 86% yield.[21] The alcohol **19** was reacted with trimethylsilanylpropionic acid in the presence of EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) to give the ester **20** in 84% yield.

When a solution of **20** in toluene was heated under reflux for 52 h, the cyclization product was formed but in 76% yield as compared to a 90% yield for **7** (Scheme 11). Parker et al.[22] have shown that facile cyclizations occur in the intramolecular Diels−Alder reactions of amides; the corresponding esters, however, failed to cyclize.

In order to evaluate the use of the furan **7** in synthesis, the reaction of **7** with maleic anhydride was investigated (Scheme 12). The Diels−Alder adduct **22** was smoothly formed using diethyl ether as the solvent. X-ray crystallography demonstrated that the exo adduct was the exclusive product.[23]

Conclusions

We have uncovered a new cyclization cascade sequence which allows the formation of heterocyclic ring systems in one synthetic operation. Although numerous publications have appeared on metal-catalyzed [2 + 2 + 2] cyclizations,[24] namely, mediated by cobalt[7,8] and rhodium[9−11,25] compounds, to our knowledge, this is the first example of a metal-free cascade involving an amide spacer group. We are confident that this new environmentally friendly sequence will be of wide and general applicability in synthesis.

Acknowledgment. We thank GlaxoSmithKline and the EPSRC for generous financial support to A.J.W., Dr. Richard Jackson for useful mechanistic discussions, Richard Bouglas for the generous donation of starting materials, and Peter Hitchcock for his crystal structure assignments.

Supporting Information Available: Full experimental procedures, ^1H and ^{13}C NMR spectra for compounds and crystal structures for compounds **14**, **16**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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