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Isoxazole → Benzisoxazole Rearrangement Promoted Cascade Reactions Affording Stereodefined Polycycles

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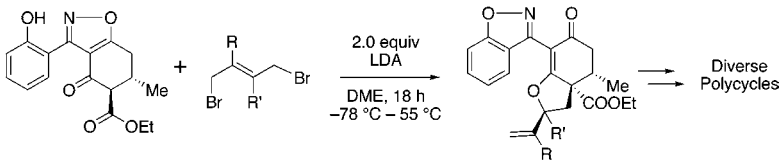
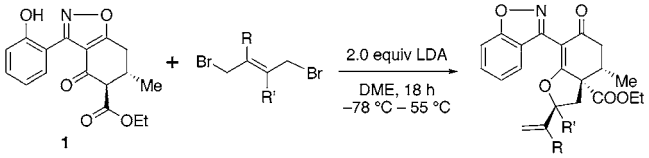
ABSTRACT



A new chemo-, regio-, and stereoselective cascade reaction features a novel isoxazole → benzisoxazole rearrangement and affords highly functionalized, differentially protected compounds. The products of this reaction are directly converted to a number of complex, structurally diverse polycyclic molecules. These transformations highlight the unique chemistry inherent to readily prepared fused isoxazoles.

In the preceding communication, we reported the efficient and regioselective synthesis of versatile, functionalized isoxazoles.[1] We now report the discovery of novel reactivity unique to these *o*-phenolic isoxazoles, of which **1** is representative. Under basic conditions, such compounds undergo an unexpected isoxazole → benzisoxazole rearrangement that, combined with biselectrophiles, promotes a tandem reaction sequence useful for the synthesis of complex stereochemically defined polycyclic products (Scheme 1).[2] The resulting compounds, interesting in their own right, are divergently converted (1−2 steps) to a variety of complex, polycyclic structures likely to be of use for the synthesis of natural products or small molecule drugs.[33]

Scheme 1



During the course of studies on the unique chemistry of *o*-phenolic isoxazoles, we uncovered unexpected reactivities.[4] Base-promoted alkylation of phenolic isoxazole **1** with simple electrophiles provided a multitude of products, far more than that expected from consideration of competing O- versus C-alkylations of the phenolic and keto-ester moieties. A breakthrough in our understanding of the origin of these complications came when we isolated an unusual cyclized product upon attempted alkylation of **1** with bis-electrophile **2** (Table 1, entry 1). A combination of spectral, degradation, and crystallographic methods was employed in assigning the structure of this cyclized compound as **4** (vida infra).

Although our initial conditions afforded this compound only in trace amounts and as a 2:1 mixture of diastereomeric

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(2) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831−844.

(3) (a) Arya, P.; Joseph, R.; Chou, D. T. H. *Chem. Biol.* **2002**, *9*, 145−156. (b) Dixon, Darren J.; Ley, S. V.; Rodriquez, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4763−4765. (c) Nicolaou, K. C.; Zong, Y.-L.; Baran, P. S.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145−2149.

(4) Isoxazole **1** was prepared in two steps from commercial material (70% overall). See Supporting Information of ref 1 for an experimental procedure.

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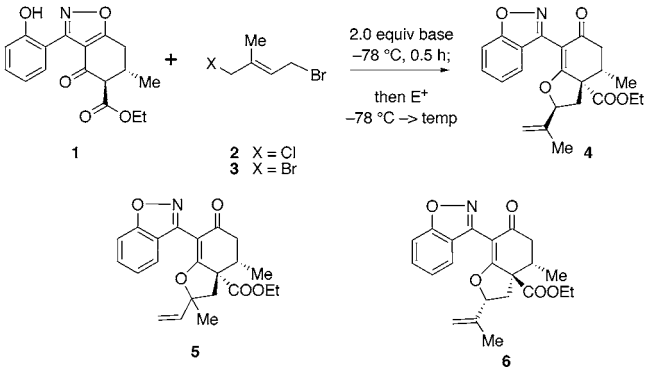
Table 1. Optimization of the Tandem Alkylation-Isoxazole Rearrangement-Cyclization Reaction[a]



entry	X	solvent	temp[b] (°C)	base	time (h)	yield (%)
1	Cl	DMF	55	Cs_2CO_3	16	10[c]
2	Cl	DMF	55	K_2CO_3	16	
3	Br	THF	40	NaHMDS	60	18
4	Br	THF	40	LDA	60	25[d]
5	Br	DME	40	NaHMDS	18	22
6	Br	Et_2O	40	LDA	48	tr
7	Br	DME	60	LDA	22	34[e]
8	Br	DME	55	LDA	36	38[e]

[a] See the Supporting Information for experimental details. [b] Refers to the final temperature of the reaction. [c] The product was isolated as a 2:1 mixture of **4** and diastereomer **6**. [d] Starting material **1** was recovered in 50% yield. [e] Regioisomer **5** was detected as a minor component; yield refers to isolated yield of pure **4**.

products, we sought to improve both the chemical yield and the stereoselectivity of this process by consideration of the reaction parameters. Use of readily prepared dibromide **3**[5] was found to be preferable to chloride **2**.[6] In particular, it was necessary to favor initial C-alkylation in exclusion to competing O-alkylation of the phenol or dicarbonyl. Following reports that low reaction temperatures and lithium bases favored the desired chemoselectivity,[7] we found the use of LDA to be beneficial. Notably, lithium (Table 1, entries 4 and 6−8) and sodium (entries 3 and 5) bases but not cesium (entry 1) or potassium (entry 2) afforded the cyclized product with high regio- and stereoselectivity. Further improvement in the chemical yield was obtained by employing DME (entry 7), in favor of THF (entry 4) or Et_2O (entry 6) as the reaction solvent. Likewise, the final temperature of the reaction showed some effect on the outcome (entries 4, 7, and 8).

Under conditions thus identified, the rearranged and cyclized product was formed in approximately 40% yield as a single diastereomer, along with a trace (>10:1) of the corresponding regioisomer **5**. Although the yield of this cyclization is modest, the products are readily isolated from the crude mixtures; the major byproducts, unidentified polymeric materials, do not elute under standard conditions for purification by column chromatography. Significantly, a remarkable number of bonds are formed, broken, or transposed in a chemo-, regio-, and stereoselective manner in a single reaction operation.

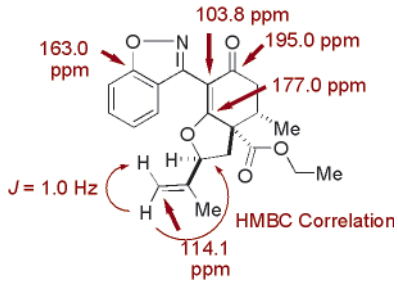
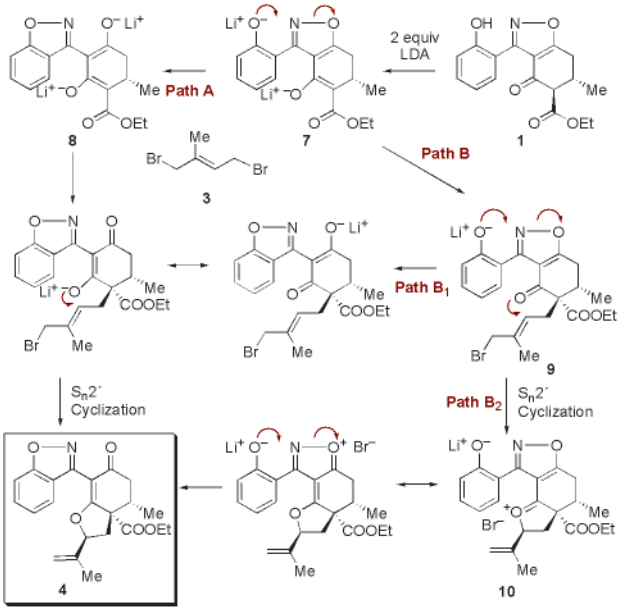


Figure 1. NMR spectral data for structural assignment of **4**, indicating key long-range HMBC correlations.

The structure of cyclized product **4** was secured by a battery of spectral methods combined with chemical transformation and X-ray crystallographic analysis. In particular, long-range C−H couplings (HMBC) demonstrated that the keto-carbon of starting material **1** and the vinyl ether carbon of the isoxazole had been transposed. The absence of exchangeable protons was apparent from both ^{1}H NMR and IR measurements, and further connectivity through the phenol via an ether linkage was ruled out by HMBC analysis. Finally, the small geminal coupling of the vinyl protons strongly suggested a terminal, exocyclic olefin moiety. The stereochemical outcome was ascertained by ^{1}H NOE differ-

Scheme 2. Possible Pathways for the Formation of Cyclized Product **4**



(5) Dibromide **3** was prepared in stereochemically pure form (>99% trans) by bromination of isoprene: Heasley, V. L.; Fyre, C. L.; Gore, R. T.; Wilday, P. S. *J. Org. Chem.* **1968**, *33*, 2342−2345.

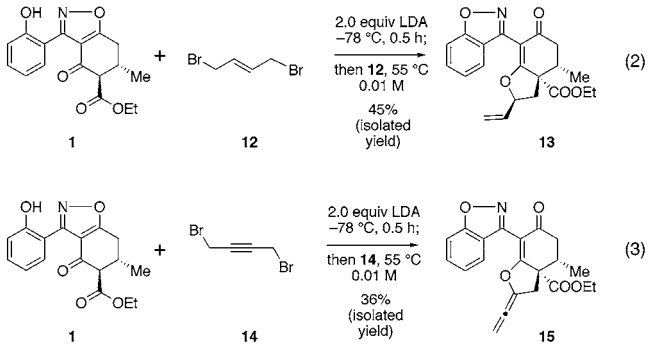
(6) Prepared from the corresponding alcohol. For a preparation of this alcohol, see: Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676−3686.

(7) Appendino, G.; Cravotto, G.; Nano, G. M.; Palmisano, G. *Synth. Commun.* **1992**, *22*, 2205−2212.

ence studies and confirmed by single-crystal X-ray analysis of **20** (vide infra).

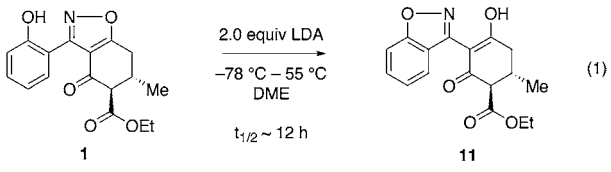
Some possible mechanisms for the formation of **4** are shown in Scheme 2. The dianion **7** is generated at low

Scheme 3



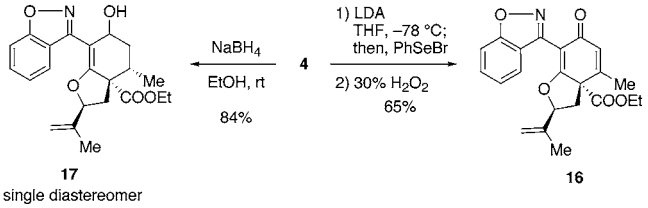
temperature from **1**. In path A, **7** undergoes base-induced isoxazole → benzisoxazole rearrangement to give **8**. Alkylation of **8** by dibromide **3** and subsequent S_N2' cyclization affords **4**. In path B, alkylation of **7** provides **9** in a chemo-, regio-, and stereoselective fashion. From **9**, two possible reaction sequences are likely. In path B_1, **9** undergoes isoxazole → benzisoxazole rearrangement and subsequent stereoselective S_N2' cyclization to provide tetracyclic product **4**. Alternatively (path B_2), the ketone carbonyl of **9** effects S_N2' substitution of the allyl bromide to give **10** prior to the heterocycle rearrangement.

Support for these mechanisms comes from both literature precedents and our own observations. Rearrangements of similar heterocyclic systems (i.e., isoxazole → isothiazole) are well-known.[8] Likewise, the synthesis of benzisoxazoles from the corresponding salicylaldoximines has been described.[9] The plausibility of a related isoxazole rearrangement operating in the present case was demonstrated by the treatment of **1** with base at elevated temperature (55 °C), which results in slow ($t_{1/2}$ ~12 h) but apparently irreversible formation of benzisoxazole **11** (eq 1). To the best of our knowledge, these are the first reported examples of an isoxazole to benzisoxazole rearrangement.



Finally, the stereo- and regioselective synthesis of related tetrahydrofurans from bis-electrophiles finds precedent in the

Scheme 4

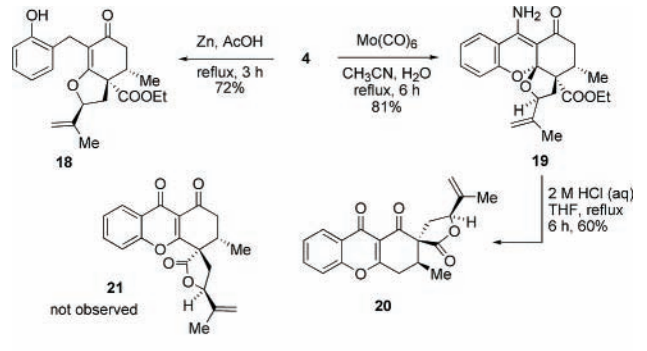


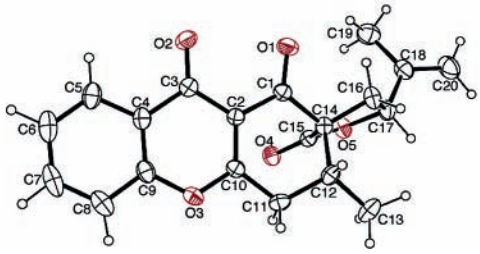
work of Zhao[10] and of Rodriguez,[11] who have described similar S_N2' cyclizations in simpler systems.

Several experiments suggested this rearrangement-cyclization process to be a general reaction for bis-electrophiles. Coupling of **1** with *trans*-1,4-dibromobut-2-ene (**7**) afforded the corresponding cyclized product **8** in 45% yield as a single compound (eq 2). Employment of 1,4-dibromobut-2-yne (**9**) delivers the interesting allenyl ether **10** (eq 3; stereochemistry assigned by analogy to **4**).[12] Although analysis of the unpurified reaction mixture showed remarkably clean formation of the desired compound, the isolated yield was compromised by its instability to silica gel chromatography.

The synthetic value of these highly functionalized precursors is enhanced by their facile and high-yielding conversion to a number of structurally distinct polycyclic compounds. The isoxazole-benzisoxazole rearrangement process has the notable advantage that the abundant functionalities do not require protection before further transformations of **4** can proceed. Indeed, polycycle **4** contains the equivalent of four differentiated carbonyl moieties, an olefin, and internally protected phenol and hydroxyl groups. This allows functionalization, such as alkylation with PhSeBr, to proceed directly from **4** (Scheme 4). Likewise, the ketone may be readily reduced in a stereoselective fashion to afford alcohol

Scheme 5





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(9) (a) Stokker, G. *J. Org. Chem.* **1983**, *48*, 2613−2615. (b) Shutske, G. M.; Setescak, L. L.; Allen, R. C.; Davis, L.; Effland, R. C.; Ranbom, K.; Kitzen, J. M.; Wilker, J. C.; Novik, W. J. *J. Med. Chem.* **1982**, *25*, 36−44.

17 as a single diastereomer (relative configuration unassigned).

In accordance with our results on less functionalized isoxazole systems, the benzisoxazole moiety provides a valuable handle for divergent transformations. Reduction of benzisoxazole compounds under a variety of conditions provided further complex, highly functionalized polycycles. Treatment of **4** with Zn in refluxing acetic acid resulted in complete reduction of the isoxazole, including loss of the benzylic oxidation to afford tricyclic compound **18**. Under milder reduction conditions with $Mo(CO)_6$,[13] tetracyclic vinylogous amide **19** was obtained in 81% yield.

Acid hydrolysis of vinylogous amide **19** resulted in yet another structural rearrangement to afford spirolactone **20** in 60% unoptimized yield. Although we originally expected the formation of **21**, single-crystal X-ray analysis of the resulting product demonstrated that **20** had been formed as the exclusive product.

In conclusion, we have described a stereoselective cascade reaction predicated upon a novel isoxazole rearrangement. This process affords complex polycyclic compounds in a single reaction step from readily available starting materials. The resulting products are notable for their plethora of functionality and their straightforward (1−2 steps) elaboration to structurally unique, stereo-defined polycyclic molecules reminiscent of natural products. This and related processes should enable the design of new pathways for the rapid preparation of highly functionalized molecules without recourse to long synthetic sequences or tedious protective group manipulations.

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Supporting Information Available: Characterization data and experimental procedures for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0272848

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