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RESOLUTION AND ABSOLUTE CONFIGURATIONAL ASSIGNMENTS TO 1-OXA- AND 1-THIA-6-KETOSPIRO[4.4]NONANYL PLATFORMS†

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Abstract - A convenient chiral sulfoxide mediated protocol for resolving the heterocyclic spiro[4.4]nonanes (**3**, **7**, and **10)** is described, along with crystallographic substantiation of their absolute configuration.

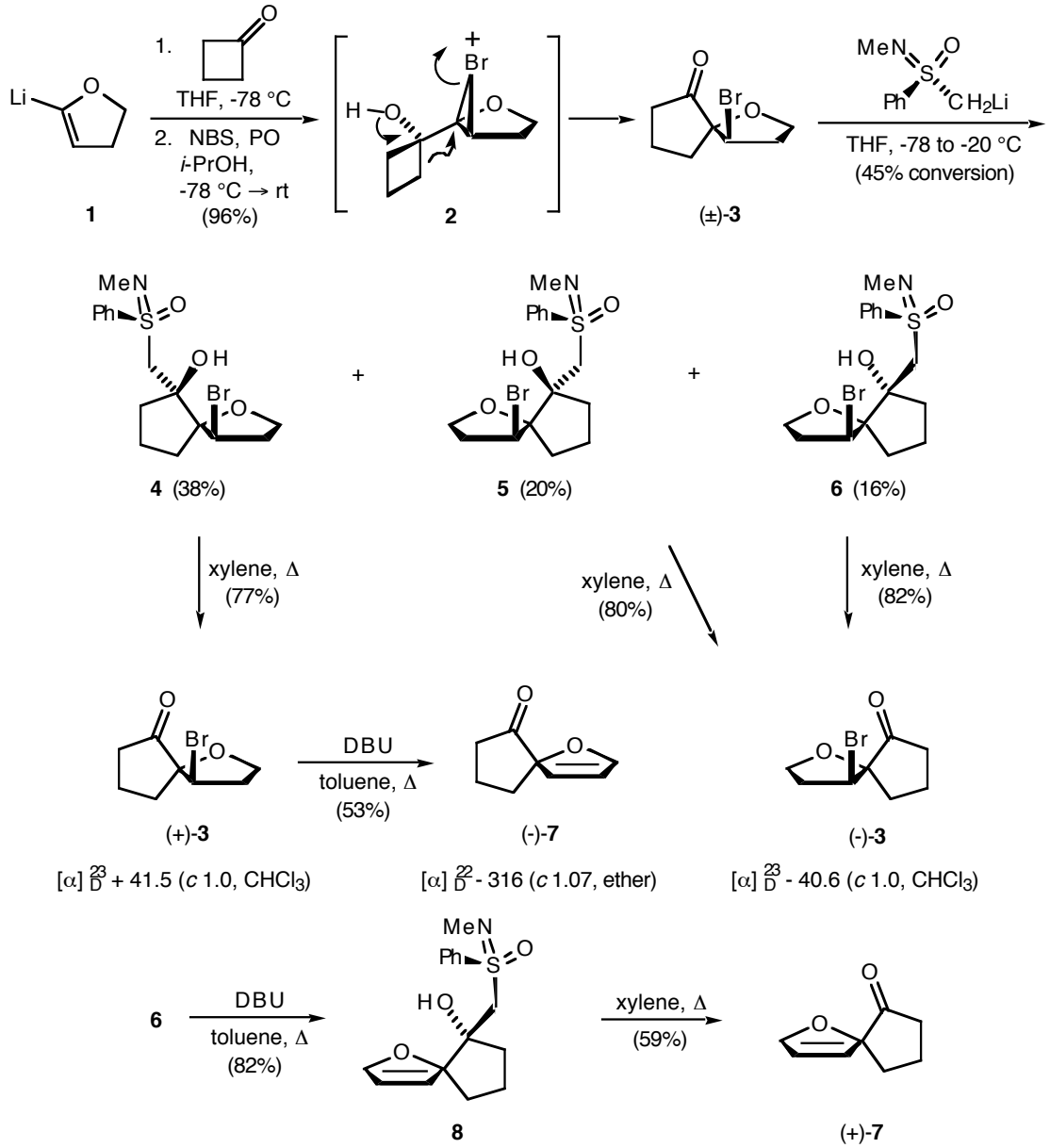
The recognition that spiro[4.4]nonanes such as fredericamycin A[2] and the gloiosiphones[3] are produced in nature has focused increasing attention on this class of compounds. In addition, the demonstration that the enantiomerically pure *cis,cis*-1,6-diols and derivatives thereof are capable of inducing enantioselectivity in various types of important chemical transformations holds considerable promise in the arena of asymmetric synthesis.[4] In the light of these results, it is not surprising that the resolution of these molecules has attracted the concern of several research groups.[5]

In contrast, heterocyclic spiro[4.4]nonanes have not been resolved despite their ready accessibility[6,7] and their potential application as useful building blocks[8] and molecular probes.[9,10] Here we present our effort to rectify this deficiency by defining the absolute configuration of exemplary 1-oxa- and 1-thia-6-keto systems.

Structural assembly began with the addition of 5-lithio-2,3-dihydrofuran (**1**) to cyclobutanone followed by the exposure of the sensitive allylic carbinol to *N*-bromosuccinimide and propylene oxide (PO) in isopropyl alcohol at low temperature (Scheme 1). The presence of PO was to guard against the buildup of adventitious acid that would catalyze independent rearrangement. The high degree of diastereoselectivity observed in the production of racemic **3** can be rationalized in terms of the concerted electronic shift depicted in **2**, or a stepwise process with the identical stereochemical alignment.[11] Coupling of (±)-**3** with the lithium anion of the (*S*)-(+)-sulfoximine according to Johnson's protocol[12] gave the three chromatographically separable diastereomers (**4**, **5**, and **6)** (ratio 2:1:1) in good yield at

†This paper is dedicated with great personal and professional admiration to Professor Shô Itô as he celebrates his 77th birthday.

Scheme 1

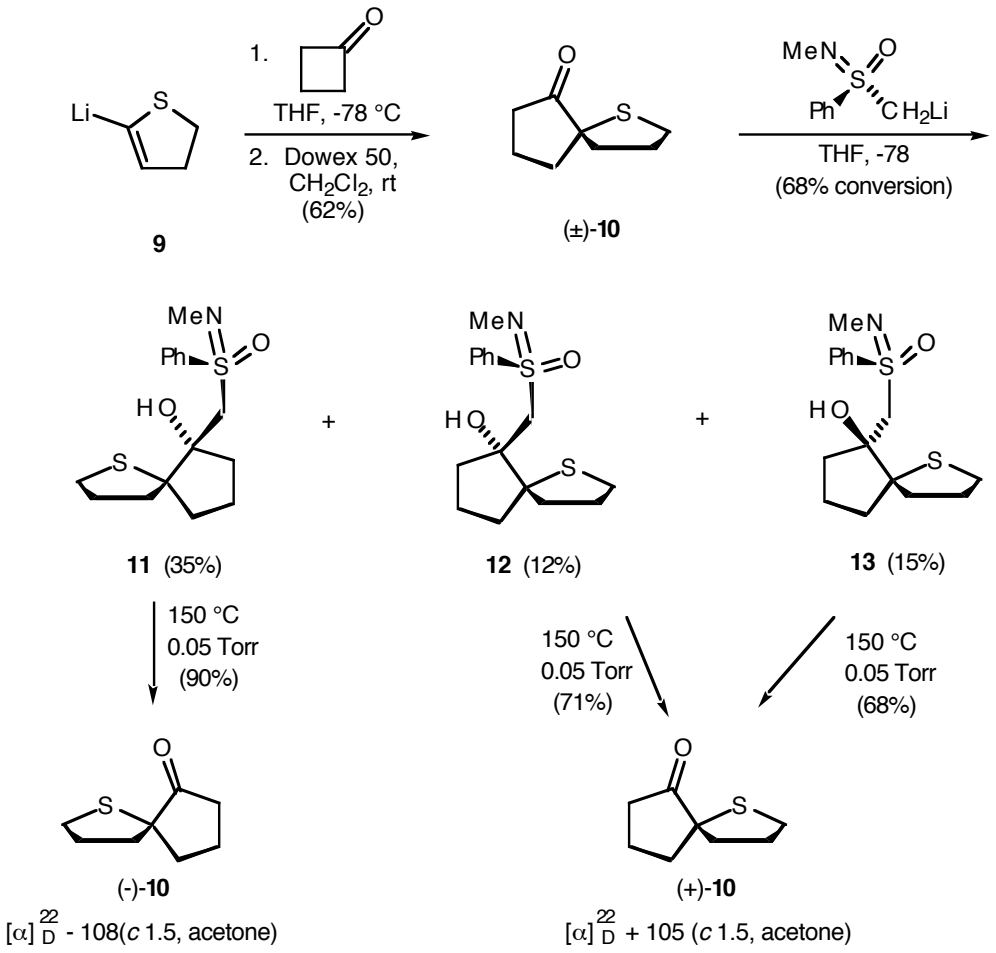


44-50% conversion.[13] Identification of the major adduct as **4** was achieved by X-Ray crystallography (Figure 1). When concentrated solutions of **4** in xylene were refluxed overnight, smooth conversion to (+)-**3** was observed alongside efficient recovery of the chiral auxiliary. Comparable processing of **5** and **6** gave rise to (-)-**3**, the absolute configuration of which was now equally apparent.

Although **6** underwent smooth dehydrobromination to **8** when heated with DBU in toluene, the subsequent thermal retrogression to give (+)-**7** proceeded with lower efficiency because of the thermal sensitivity of the product enone. This same instability was noted in the conversion of (+)-**3** to (-)-**7** under comparable conditions.

Next to be explored was the π-facial diastereoselectivity with which the previously described racemic ketone (**10**)[7] would be attacked by the same lithiated sulfoximine. In the event, a 62% yield of a 3:1:1 mixture of diastereomers was obtained at 68% conversion (Scheme 2). The three crystalline products

Scheme 2



proved entirely amenable to chromatographic separation, and the major one, shown to be **11** by X-Ray diffraction measurements (Figure 2), was heated neat under vacuum at 150 °C in a Kugelrohr apparatus. No difficulties were experienced, and (-)-**10** was isolated in 90% yield along with recovered sulfoximine. Entirely comparable pyrolysis of **12** and **13** gave rise efficiently to the dextrorotatory enantiomer of **10**. Thus, the α-thia spiro ketone displays a kinetic preference for nucleophilic attack *anti* to the hetero atom in conformance to the established pattern.[9]

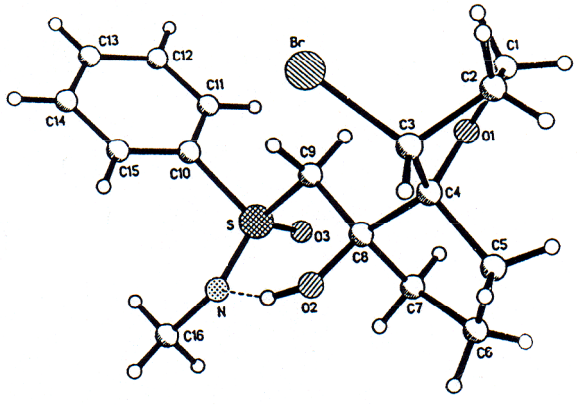


Figure 1. ORTEP diagram

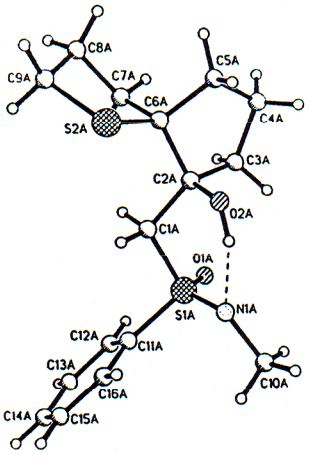


Figure 2. ORTEP diagram

The chemistry described above illustrates one straightforward means for effecting the resolution of several 1-hetero [4.4]spirononan-6-ones. Integration of the equally available (*R*)-(-)-sulfoximine[11] provides an alternative for addressing a reversal in the relative quantities of spiranone end products if desired. The one drawback to the overall scheme is the inability to force the coupling reaction to completion. For this reason, alternative tactics for resolving these useful intermediates continue to be pursued in this laboratory.

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13. More advanced conversion was not achieved due to competitive enolization.