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CALYCULIN SYNTHETIC STUDIES. 3. ENANTIOMERIC PURITY DETERMINATION FOR THE C(26)-C(32) OXAZOLE SEGMENT VIA THE SILKS-ODOM ^{77}Se NMR METHOD

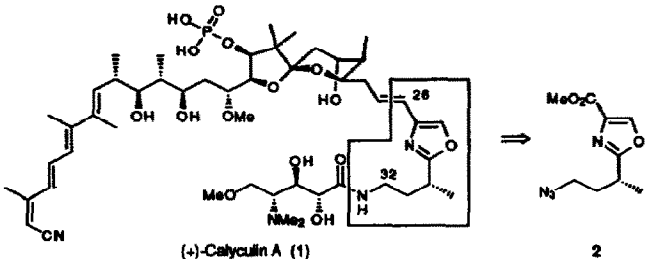
Brian A. Salvatore and Amos B. Smith, III*

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.

Summary: An improved preparation of the C(26)-C(32) oxazole subunit of calyculin A is described. The enantiomeric purity was determined via the exceptionally sensitive Silks-Odom method, which can probe remote stereocenters by ^{77}Se NMR analysis.

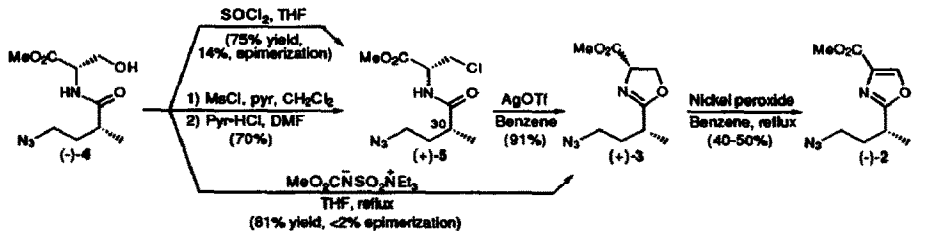
The diverse biological activity and novel architecture of the calyculins (e.g., **1**, Scheme I) have stimulated considerable interest in the synthetic community.[1,2] Herein we outline an improved route to the C(26)-C(32) oxazole building block (-)-**2**. The simple and remarkably sensitive Silks-Odom ^{77}Se NMR method was then employed in the determination of enantiomeric purity.

Scheme I



In earlier studies[1] we prepared (-)-**2** from oxazoline (+)-**3**, which in turn arose from the starting serine amide derivative (-)-**4** via the intermediacy of chloride (+)-**5** (Scheme II). Unfortunately, generation of the chloride via both the $SOCl_2$ and MsCl protocols resulted in partial epimerization at C(30). We described[1] the quantification of the chlorination via the Anderson-Shapiro procedure for measurement of enantiomeric purity;[3] this entailed condensation of the primary amine derived from **2** with a scalemic chlorophospholane, followed by ^{31}P NMR analysis of the resultant diastereomers.[4]

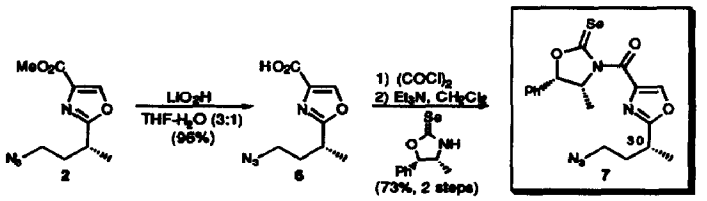
Scheme II



More recently we have explored the single-step conversion of **4** to **3** via the attractive protocol introduced by Wipf.[5] Treatment of **4** with the Burgess reagent ($MeO_2C\bar{N}SO_2\dot{N}Et_3$, THF, at reflux) did furnish **3** in 81% yield. However, as we then attempted to determine whether the Wipf procedure would also circumvent the problem of C(30) epimerization, it became clear that the Anderson-Shapiro approach employed earlier does not reliably indicate the enantiomeric purity of **2**.

We are pleased to report here that the Silks-Odom method[6] offers a highly effective alternative. As outlined in Scheme III, the carboxylic acid[7] obtained from **2** was readily converted to the oxazolidine-2-selone

Scheme III



derivative **7**.[6] The ^{77}Se NMR singlets for the resultant diastereomers were completely resolved, as expected, with $\Delta\delta$ > 2 ppm (Figure 1). Analysis of **2** prepared via thionyl chloride treatment of **4** confirmed ca. 14% epimerization at C(30), whereas the Wipf protocol furnished nearly enantiomerically pure material (<2% epimerization).

In closing, we wish to call attention to the simplicity and effectiveness of the Silks-Odom scheme for interrogating remote stereocenters; seven bonds separate the selenium atom from the C(30) position in **7**.[8] Further progress toward the total synthesis of calyculin A will be reported in due course.

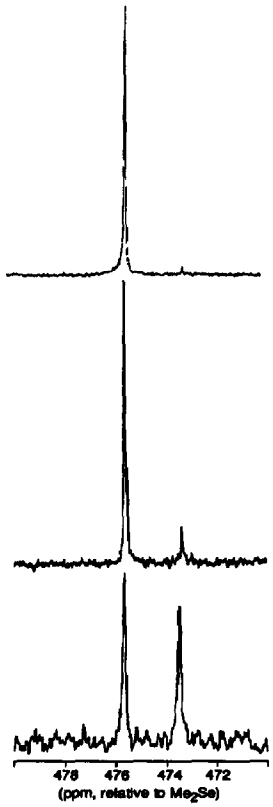


Figure 1. ^{77}Se NMR analysis of **7** and its C(30) epimer. Sources of precursor **2**: (a) authentic 1.4:1 enantiomer mixture; (b) $SOCl_2$ chlorination of **4**; (c) Wipf protocol.

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