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AN UNEXPECTED REVERSAL OF STEREOCHEMISTRY IN A MODIFICATION OF THE RYCHNOVSKY CYANOHYDRIN ALKYLATION

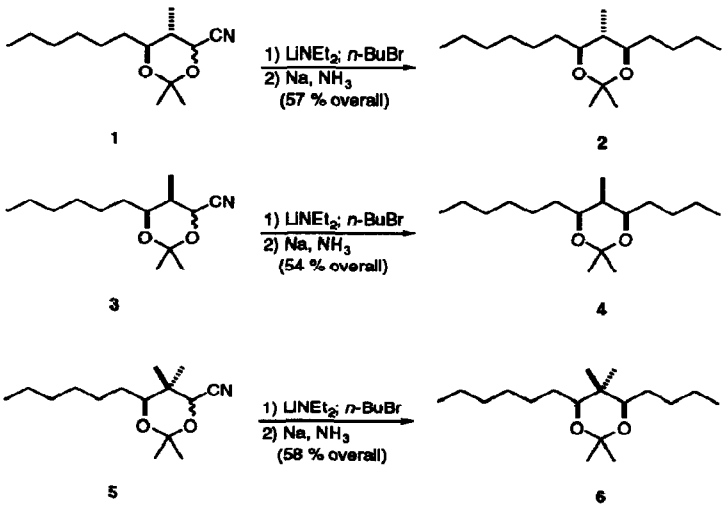
Linda Joy Brzezinski, Dinah D. Levy and James W. Leahy*

Department of Chemistry, University of California, Berkeley, CA 94720-1460

Abstract: Alkylation of cyanohydrin 1,3-acetonides with unsaturated substitution at the 2-position is described. The stereochemistry of the products obtained from this reaction was opposite to that anticipated.

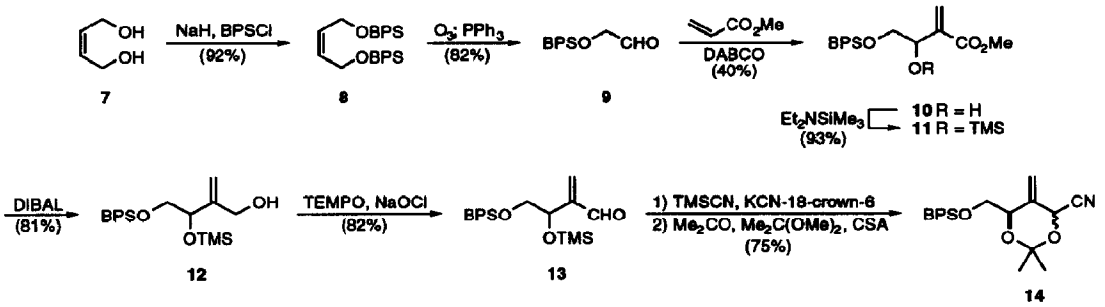
The ubiquitous nature of polyacetates and polypropionates in natural products has prompted a number of groups to expend considerable efforts toward the stereoselective synthesis of 1,3-diols.[1] Recently, Rychnovsky and coworkers have demonstrated the utility of cyanohydrin 1,3-acetonides in the controlled construction of alternating polyol chains.[2] In an elegant study, they were able to demonstrate that alkyl substituents at the 2-position did not affect the course of the reaction, and the stereochemical triads **2** and **4** as well as the quaternary **6** were generated with equal proficiency (Scheme I).[2b] In every case examined, the less sterically demanding nitrile group assumed an axial orientation, and reductive decyanation led to the formation of the desired 1,3-diol systems.[2]

Scheme I



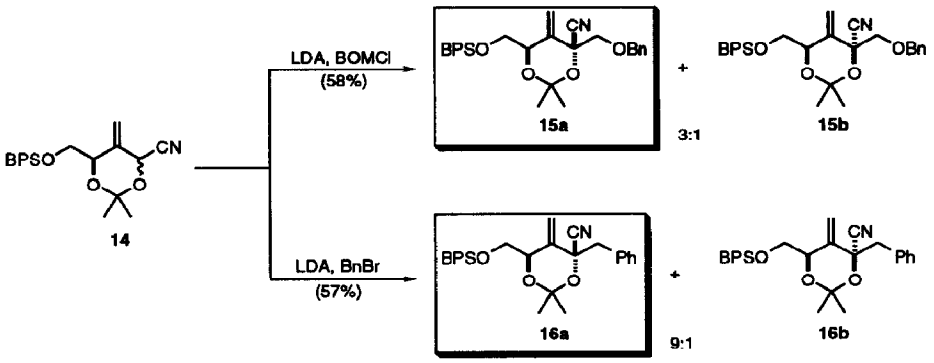
In our efforts toward the total synthesis of the hypocholesterolemic natural product zaragozic acid A/squalestatin 1, we required a convenient source of a syn 1,3-diol that contained a methylene substituent at the 2-position.[3,4,5] We therefore sought to extend the methodology of Rychnovsky in order to evaluate the feasibility of incorporating this modification. Toward this end, the requisite cyanohydrin was prepared from *cis*-2-buten-1,4-diol (**7**, Scheme II). Silylation of **7** with *t*-butyldiphenylsilyl chloride followed by ozonolytic cleavage of the olefin gave aldehyde **9**.[6] Baylis-Hillman addition of methyl acrylate to **9** afforded allylic alcohol **10**,[7,8] which was then silylated with Et_2NSiMe_3. Transformation of **11** to the corresponding aldehyde was best accomplished by the two step process of DIBAL reduction followed by TEMPO oxidation.[9] Finally, the cyanohydrin was then formed from **13** via the Rychnovsky protocol.[2]

Scheme II



The cyanohydrin **14** was deprotonated with LDA, then alkylated with BOM chloride provided a 3:1 mixture of two diastereomers (Scheme III).[4] We were surprised to obtain a mixture at this point, since all previous alkylations had given exclusively the axial nitrile.[2,10] Other electrophiles were added to the anion of **14**, and the greatest diastereoselectivity was observed with benzyl bromide (9:1). In order to ascertain the

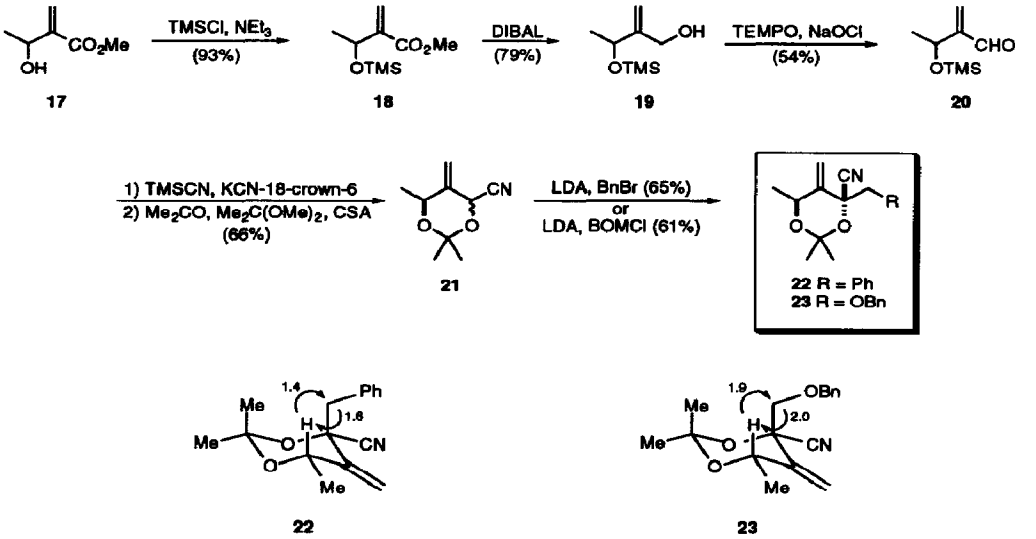
Scheme III



stereochemical outcome of these reactions, we separated the mixtures and undertook a spectroscopic evaluation of the dioxolanes. While analysis of the ^{13}C acetonide chemical shifts of the separated isomers of **15** and **16** did not readily lend themselves to elucidation of the structure,[11] examination of the nOe spectra revealed that the major isomers in fact possessed the nitrile in the unexpected equatorial position. Specifically, irradiation of the methine proton of **16a** resulted in a 2.1% enhancement of the benzylic protons (as well as a 4.0% enhancement in the methyl protons) while irradiation of the benzylic protons generated a 3.3% enhancement in the methine proton. The minor isomer did not display either of these nOe characteristics. This enhancement could only be rationalized if the benzyl group was cis to the methine proton, which is opposite to that predicted from all previous results. Similarly, the major isomer **15a** showed enhancement between the methine proton and the proximal side chain protons, while the minor isomer did not give any enhancement between these protons.

In an effort to simplify the study of this surprising reversal of selectivity, we examined the same reaction on the methyl derivative **21** (Scheme IV). Exposure of the known **17**[12] to similar conditions to those above resulted in the formation of cyanohydrin 1,3-acetonide **21**. Alkylation of the anion of **21** with benzyl bromide and BOM chloride proceeded to generate exclusively **22** and **23** respectively. The stereochemical outcome of these reactions was confirmed via nOe enhancement experiments.

Scheme IV



In conclusion, we have observed a surprising reversal in the selectivity of the Rychnovsky cyanohydrin alkylation when an unsaturated substituent is present at the 2-position. Efforts are underway to maximize the selectivity of this reaction and to utilize these results in our synthetic pursuit of the zaragozic acids/squalestatins.

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10. Professor Scott Rychnovsky has informed us that in the numerous systems under investigation in his laboratories, including saturated 1,3-dioxanes and tetrahydropyrans, he has typically observed selectivities on the order of 200:1 for alkylation products with the nitrile in the axial position and has never seen this inversion of selectivity (Rychnovsky, S. D. personal communication).
11. A convenient method for the determination of syn and anti 1,3-diol acetonides has been developed by Rychnovsky. a) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511. b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. However, the unsaturation at the 2-position apparently distorts the ring so that the products do not lie in distinct chair and twist-boat conformations. The relavent ^{13}C data are as follows: **15a** (δ 25.8, 27.6, 102.1), **15b** (δ 24.0, 29.5, 100.4), **16a** (δ 26.4, 26.7, 101.8), **16b** (δ 24.0, 29.4, 100.0), **22** (δ 26.5, 26.8, 101.9), **23** (δ 26.0, 27.1, 101.9). While this clearly follows the trend predicted by Rychnovsky and Evans, the Δδ's of the acetonide shifts were not pronounced enough to allow us to assign the structures of these products.
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