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A Correction of Three Reports on the Synthesis of the Epoxide Fragment of the Azinomycins.

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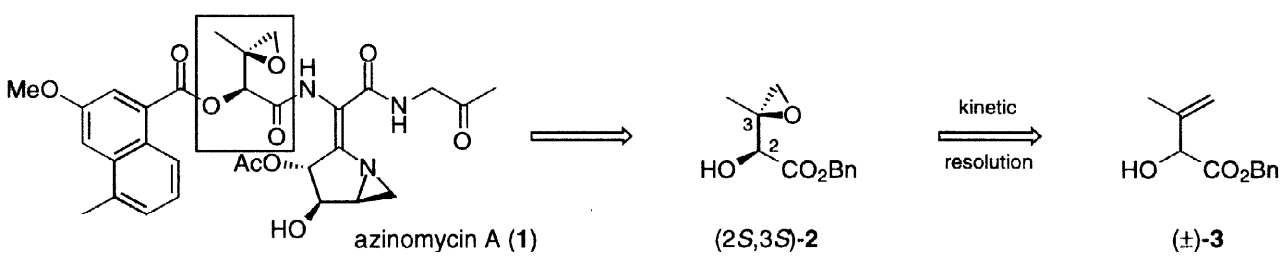
ABSTRACT: We revise our report on the Sharpless epoxidation of (±)-**3**, and correct the reported specific rotation of epoxide (2*S*,3*S*)-**2** to be dextrorotatory.

The azinomycins[1] are cytotoxic agents that exhibit promising antitumor activity.[2] These natural products are attractive targets for synthetic efforts, and we have reported a synthesis of the 1-azabicyclo[3.1.0]hexane substructure[3,4] and of the epoxyacid fragment **2** of the azinomycins.[5] Our synthesis of the epoxide **2** relied on a Sharpless kinetic resolution of a racemic allylic alcohol (±)-**3**. We originally reported this reaction to occur with reversal of the expected sense of enantioselection, but after a detailed examination of the literature on the synthesis of **2**, we have found several errors by previous workers[6,7] that led us to this mistaken conclusion. Shipman, *et al.*,[8,9] have also reported on problems with data in these publications. As a result of our use of this erroneous data, we are compelled to revise our earlier work and to correct prior reports in the literature.



We reported[5] that Sharpless kinetic resolution[10] of (±)-**3** with D-(–)-DIPT proceeds smoothly to afford the *dextrorotatory* epoxide **2**. Our material was of opposite sign compared with material of unequivocal 2*S*,3*S*-configuration that was prepared by Shibuya and co-workers[6] by a stereochemically unambiguous sequence from D-fructose. Because Shibuya reported that (2*S*,3*S*)-**2** was *levorotatory*, we concluded, logically, that we had obtained *dextrorotatory* (2*R*,3*R*)-**2** by our route. Thus, it appeared that the Sharpless kinetic resolution proceeded to afford the opposite enantiomer of epoxide **2** than that predicted using literature precedent.

In apparent confirmation of this conclusion on the sense of stereoinduction, our results agreed with those of Konda and co-workers,[7] who found that a *levorotatory* epoxide **2** was obtained with L-(+)-DET, which they assigned as (2*S*,3*S*) based on Shibuya's rotation. Konda and co-workers reportedly confirmed their results by hydrogenating the recovered (*R*)-alkene to (2*R*)-(–)-2-hydroxyisovaleric acid, of which the (*R*)-enantiomer was reported by Ourisson[11] to be levorotatory. Thus, Konda's reported measurements appeared consistent and confirmed our results. At this stage, we began an examination of the apparently anomalous Sharpless epoxidation.

In these studies, we found that the rotation reported by Shibuya and co-workers was in error both in sign and magnitude,[12,13] a fact also noted by Shipman.[8,9] Not only has the Shibuya rotation led us astray, but Konda and co-workers[7] assigned *levorotatory* epoxide **2** erroneously as (2*S*,3*S*) based on Shibuya's optical rota-

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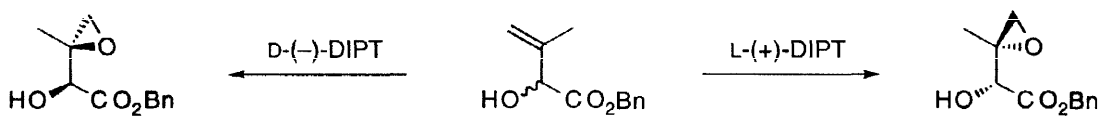
tion. It further appears that Konda, *et al.*,[7] made an error in measuring the optical rotation of the 2-hydroxyisovaleric acid produced from hydrogenation of recovered alkene **3**. As Shipman, *et al.*, reported and we have now confirmed, (2*S*,3*S*)-**2** must be *dextrorotatory*, not levorotatory as reported by Shibuya, *et al.*[6] This unfortunately means that our report[5] on the reversed sense of enantioselection in the Sharpless epoxidation of (±)-**3** was in error, although it does not change the effectiveness of our synthesis.

We offer the following evidence to support our claims. Sharpless kinetic resolution of (±)-**3** with L-(+)-DIPT afforded *levorotatory* **2** of $[\alpha]_D^{20}$ −11.10 (EtOH, *c* 1.90), 93% ee. This is opposite in sign and of the same magnitude as the rotation of (2*S*,3*S*)-(+)-**2** that was prepared by Shipman and co-workers.[14] The alkene **3** recovered from our Sharpless kinetic resolution was *dextrorotatory*, which according to Shipman's data,[8,9] confirms the absolute configuration as (*S*)-**3**. Furthermore, hydrogenation of recovered **3** (1 atm H_2, 10% Pd/C, EtOH) afforded *dextrorotatory* (2*S*)-(+)-2-hydroxyisovaleric acid, which compared in sign of rotation with authentic material prepared according to Ourisson's procedure from (*S*)-valine.[11]

In conclusion, we have found that the Sharpless kinetic resolution of (±)-**3** occurs with the *expected* sense of stereoinduction, where L-(+)-DIPT affords unnatural (2*R*,3*R*)-(−)-**2** contrary to our original report.[5] Similarly, D-(−)-DIPT affords (2*S*,3*S*)-(+)-**2** (data not shown). The remaining aspects of our synthesis, including the degree of stereoselection and overall yield remain as originally reported.



(2*S*,3*S*)-(+)-**2** (±)-**3** (2*R*,3*R*)-(−)-**2**

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12. The specific rotation reported by Shibuya[6] was is $[a]_D^{20}$ −22.4 (EtOH, *c* 0.13). This means that the actual rotation measured on a polarimeter, assuming a standard 1 dm path length, was only −0.029°, which may be of insufficient magnitude to permit reliable measurement. Shipman's specific rotation[9] of $[a]_D^{20}$ +11.5 (EtOH, *c* 1.9) for material of 95% ee was made at a much higher concentration giving an apparent measured rotation of +0.2185°, and is therefore more reliable. We feel this may be the origin of the discrepancy.
13. Shibuya and co-workers also corrected their rotation of another azinomycin intermediate. See: Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin 1* **1992**, 2053.
14. The data in the Shipman papers (references 8 and 9) are unambiguous with respect to absolute configuration since both a key intermediate and the final product were characterized by X-ray crystallography as the camphorsulfonate or phenethylamine derivatives, respectively.