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EFFICIENT STEREOSELECTIVE SYNTHESIS OF THE EPOXYACID FRAGMENT OF THE AZINOMYCINS

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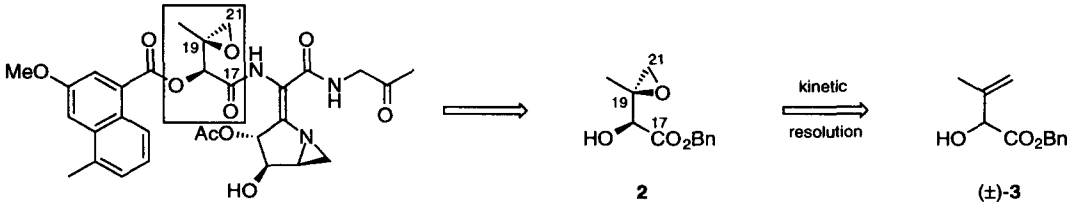
ABSTRACT: Three concise enantioselective synthetic routes to the C17-C21 epoxyacid segment of the azinomycins are presented and were based on a Sharpless asymmetric epoxidation/kinetic resolution of racemic allylic alcohol (±)-**3** that occurred with reversal of the expected sense of enantioselection. © 1997 Elsevier Science Ltd.

Azinomycins A and B are antitumor-antibiotic agents[1] that possess an intricately functionalized structure containing the unprecedented aziridino[1,2-*a*]pyrrolidine ring system.[2] Azinomycins A and B exhibit potent in vitro cytotoxic activity and promising in vivo antitumor activity;[3] the electrophilic epoxide and aziridine rings suggest that the azinomycins act by covalent cross-linking of DNA.[4] The azinomycins are attractive targets for synthetic efforts,[5] and we have reported a synthesis of the intact C8-C13 1-azabicyclo[3.1.0]hexane substructure of the azinomycins.[6,7,8] Herein, we report the stereoselective construction of **2**, the C17-C21 epoxyacid segment of the natural product. Given the substantial body of literature on syntheses of **2**,[5a,b,c,n,o] we set synthetic efficiency and high enantioselectivity as preconditions for our work. Of particular note is the effectiveness that is exhibited by our synthesis, particularly in comparison with existing routes.[5a,b,c,n,o] Our routes to **2** relied on introduction of the epoxide using a Sharpless asymmetric epoxidation/kinetic resolution of a racemic allylic alcohol (±)-**3** to provide (2*S*,3*S*)-(−)-**2**. This reaction occurred with *reversal of the expected sense of enantioselection*.

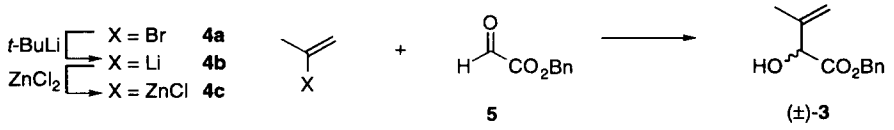


azinomycin A (**1**) **2** (±)-**3**

Existing syntheses of the five-carbon epoxide substructure of the azinomycins are lengthy and/or inefficient. A synthesis by Armstrong and co-workers[5n] required eight steps, and proceeded in only 4% overall yield. A synthesis by Shibuya, et al.[5b] starting from D-fructose required 11 steps, and a more recent publication by Shishido, et al.,[5c] which set the C18 and C19 stereogenic centers using a known Sharpless kinetic resolution of divinyl carbinol, reported a difficult four-

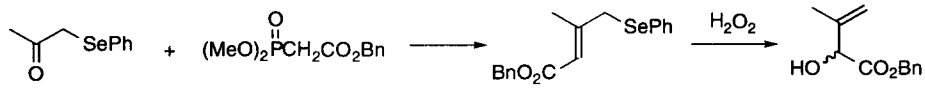
step 39% olefin-to-carboxylate conversion, one step of which took 10 days to reach completion. Konda, et al.[5a] reported a synthesis of this epoxide similar to our present work, but in low yield (< 21%) and with poor stereoselectivity (43-73% ee), which necessitated a final HPLC purification to obtain material of useful enantiomeric purity. After the completion of our work, a six-step synthesis of **2** appeared that was based on a Sharpless asymmetric dihydroxylation, and was achieved in 27% overall yield.[5o] In comparison to published work, our synthesis of the C17-C21 epoxide portion of the azinomycins reported herein is short (4 steps), effectual (40% overall yield), and proceeds with 98% enantioselectivity.

Intermediate (±)-**3** could be prepared by addition of 2-propenylzinc chloride (**4c**) to benzyl glyoxylate (**5**),[9] in a reaction that occurred with complete selectivity for the aldehyde carbonyl group. We found that treatment of glyoxylate **5** with 1 equivalent of propenyllithium **4b** (prepared from **4a** and 2 equiv *t*-BuLi) occurred with poor chemoselectivity even at –78 °C,[10] whereas zinc reagent **4c** (prepared from **4b** and 1 equiv $ZnCl_2$) added selectively to the aldehyde carbonyl group of **5** (Et_2O, 0 °C) to afford (±)-**3** as the major reaction product in 60% yield. The instability of **5** limited the effectiveness of this route.



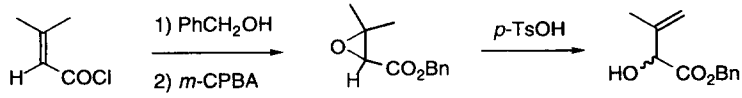
5 (±)-**3**

Alcohol (±)-**3** was also prepared effectively starting from known phenylselenoacetone (**6**)[11] by olefination (NaH, THF, 25 °C) using the phosphonate prepared from benzyl chloroacetate and trimethyl phosphite. This afforded (*E*)-**7**[12] as a single diastereomer. Oxidation of **7** (30% H_2O_2, CH_2Cl_2, 25 °C) and spontaneous [2,3] sigmatropic rearrangement of the intermediate selenoxide afforded (±)-**3** in 98% yield.



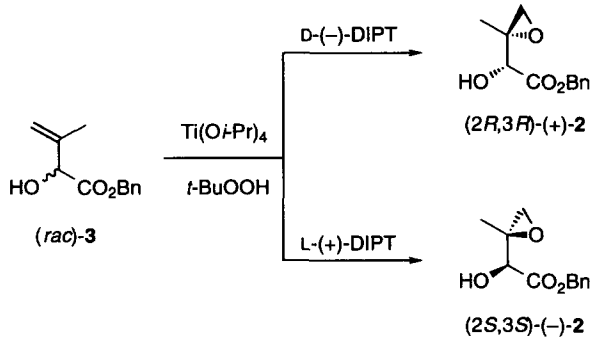
6 **7** (±)-**3**

An even simpler and more effective preparation of (±)-**3** that avoided toxic selenium reagents was achieved starting from commercially available 3,3-dimethylacryloyl chloride (**8**). Esterification by treatment with benzyl alcohol (pyridine) followed by epoxidation using *m*-chloroperbenzoic acid (CH_2Cl_2, 25 °C) afforded the racemic glycidic ester **9**[13] in 92% yield. Acid-catalyzed rearrangement of **9** by treatment with anhydrous *p*-toluenesulfonic acid in CH_2Cl_2 under carefully controlled conditions (9 mol% *p*-TsOH, benzene, reflux, 6 h) effected rearrangement to allylic alcohol (±)-**3** in 90% yield.[14]



8 **9** (±)-**3**

Sharpless asymmetric epoxidation[15] of (±)-**3** operating in the kinetic resolution mode with D-(–)-diisopropyl tartrate (DIPT) and 0.6 equiv of *t*-BuOOH proceeded smoothly to afford the epoxide. Surprisingly, the product of this reaction was demonstrated to be the (2*R*,3*R*)-epoxide (+)-**2** by comparison of the optical rotation with that reported by Shibuya and co-workers for the enantiomeric (–)-epoxide,[5b] which was prepared by a stereochemically unambiguous route starting from D-fructose. Thus, Sharpless kinetic resolution proceeded to afford the *opposite* enantiomer of epoxide **2** than that predicted using literature precedent.[15] When L-(+)-diisopropyl tartrate was used in the kinetic resolution (10 mol% Ti(O*i*-Pr)$_4$, 15 mol% (+)-DIPT, 70 mol% *t*-BuOOH, 3 Å sieves, –20 °C, 48 h), the desired (2*S*,3*S*)-epoxide (–)-**2** was obtained in 48% isolated yield with > 98% ee.[16]



Overall, the three syntheses of **2** proceeded with excellent efficiency and high stereoselectivity (98% ee) in a total of only four steps from dibenzyl fumarate (16%), isopropenyl acetate (37%), or 3,3-dimethylacryloyl chloride (40% overall yield), including the kinetic resolution step. The exceptional result obtained in the Sharpless asymmetric epoxidation is postulated to be due to coordination of the titanium by the proximal ester carbonyl,[17,18] possibly altering the aggregation state of the reactive complex. The origin of this effect is currently under investigation, and these results will be reported separately.

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