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A simple three-step method for preparing homochiral 5-trityloxymethyl-2-oxazolidinones from optically active 3-hydroxy-γ-butyrolactones

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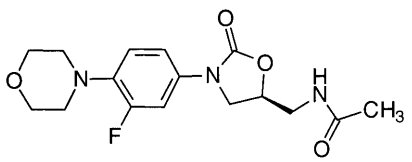
Abstract

A simple high-yield three-step route to *O*-tritylated optically active 5-hydroxymethyl oxazolidinones from optically active 3-hydroxy-γ-butyrolactones is described. The key intermediate is the 4-*O*-trityl ether of homochiral 3,4-dihydroxybutyramide, which is obtained in quantitative yield from 3-hydroxy-γ-butyrolactone by treatment with ammonia. It is readily transformed to the oxazolidinone by Hoffmann rearrangement in a two-phase system. The carbonyl group in the oxazolidinone is derived from C-1 of the amide, and a separate carbonylation reaction is not required. Oxazolidinones are key compounds in drug synthesis especially in the areas of antibacterials and behavior disorder therapy.

Oxazolidinones have emerged as a very important class of compounds in drug development especially in the areas of antimicrobials[1–7] and behavioral disorders.[8,9] They are thought to function by the inhibition of protein synthesis and are especially active against some of the most resistant human pathogens including vancomycin-resistant *enterococci*, methicillin-resistant *Staphylococcus aureus*, cephalosporin-resistant *Streptococcus pneumoniae* and several organisms that display penicillin resistance. Of the clinically important oxazolidinones, the one that has perhaps the most prominence is Linezolid.[3–7,10–13] This compound **1** was recently approved for the treatment of infections from antibiotic-resistant bacterial strains especially those that are resistant to vancomycin.



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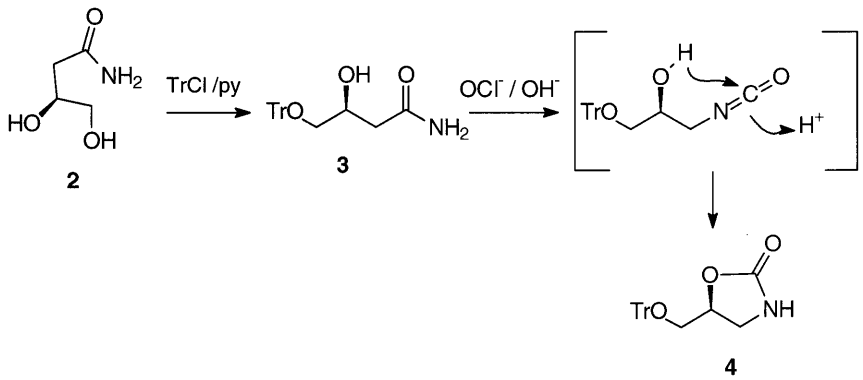
Homochiral oxazolidinones can, of course, be obtained by carbonylation of vicinal amino alcohols obtained from the reduction of amino acids with reagents such as phosgene, ethyl chloroformate and carbonyl imidazole. More recently,[14] an interesting carbonylation reaction involving palladium mediated carbonylation of amino alcohols was described. Oxazolidinones derived from amino acids are, however, limited in structure not just with respect to the position of the side chain (which must be adjacent to the ring nitrogen), but also by the type of side chain.

A common strategy for synthesizing optically active oxazolidinones is to incorporate the three-carbon core from an optically active glycidol or equivalent. This was, in fact, the strategy used in the synthesis of Linezolid.[15] In this case the source was glycidyl butyrate and the synthesis involved the alkylation of this substrate with *N*-lithioarylcarbamates. The synthesis required several steps for forming the oxazolidinone ring. Optically active 3,4-dihydroxybutanoic acids and their γ-lactones are important sources of chirality. They can be obtained from carbohydrates such as starch, lactose, maltodextrins, cellulose and arabinose by oxidative degradation.[16,17] In previous studies,[18] we explored the synthesis of amino propane diols by Hoffman degradation of the isopropylidene acetals of optically active 3,4-dihydroxybutyric acid amide. This reaction proceeded smoothly to yield the desired product. Because an isocyanate that is hydrolyzed with water is an intermediate species in the Hoffman rearrangement, in principle a vicinal hydroxyl group can act as a nucleophile resulting in cyclization to form an oxazolidinone system. In this case, a separate carbonylation reaction using phosgene, ethyl chloroformate or some similar reagent would be avoided. This is illustrated for the 4-trityl ether of (*S*)-3,4-dihydroxybutyric acid amide in Scheme 1. Similar trapping of an intermediate isocyanate in related reactions involving migration to electron-deficient nitrogen centers have been observed before.[19–21]



Scheme 1.

This process involves essentially only two steps. The first is the preparation of the trityl ether from the dihydroxybutyric acid amide **2**.[22] The amide is obtained in quantitative yield by treating the 3-hydroxy-γ-butyrolactone with aqueous ammonia at room temperature.[18] The second step is the rearrangement of the trityl ether under conditions where the intermediate isocyanate is protected from water allowing the neighboring hydroxyl group to participate. Hoffman rearrangement using a two-phase solvent system, in this case tetrahydrofuran/water,[23] gave the protected hydroxymethyl oxazolidinone **4** directly in >90% isolated yield and in >99%

enantiomeric excess.[24] This represents a tremendous economy in the synthesis of an important, homochiral protected 5-(hydroxymethyl)-2-oxazolidinone in essentially four steps from starch, maltose, lactose or similar 4-linked carbohydrate source. The trityl group can be selectively removed allowing the hydroxymethyl function to be transformed into a wide variety of substituents. The ring nitrogen can certainly be alkylated and should also be a good candidate for arylation. The *N*-arylation of related functional groups such as lactams[25,26] and acyclic amides[26] is well known. The more recent iteration of this variant of the Buchwald method is applicable even to electron-rich aromatic compounds and to carbamates and sulfonamides. The applicability to carbamates is of special relevance to the *N*-arylation of oxazolidinones. The potential functionalizability of these compounds should allow ready access to a large spectrum of possible drug candidates.

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22. (*S*)-3,4-Dihydroxybutyramide (11.9 g, 0.10 mol) was dissolved in 50 ml of tetrahydrofuran and 50 ml of dimethylformamide and 10 ml of pyridine followed by 30.6 g (0.11 mol) of trityl chloride were added to the flask. A drying tube filled with calcium chloride was used to exclude moisture. The reaction mixture was stirred at room temperature for 36 hours. After this period of time, it was filtered to remove the solid. The liquid was concentrated under reduced pressure to remove most of the solvent. The solution was poured into ice water, stirred for half an hour and the water layer was removed from the trityl protected amide. The product which was obtained as a viscous liquid was dried under vacuum. The excess trityl chloride was washed away

by trituration with hexane. The yield was 33.0 g (91%). Physical data: mp 59.0–60.0°C. (from solvent dichloromethane:hexane:acetone = 6:3:0.5) $[\alpha]_D^{25} = -53.5$ ($c = 0.5$, methanol). ^{1}H NMR (300 MHz, $CDCl_3$) ppm, 7.50–7.20 (m, 15 H), 6.17 (s, 1H), 5.62 (s, 1H), 4.19 (m, 1H), 3.17 (d, 2H, $J = 5.7$ Hz), 2.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) ppm, 174.8, 143.5, 128.3, 127.5, 126.7, 86.3, 67.4, 39.2 (one carbonyl carbon was not observable). FTIR cm^{-1} 3345, 1667, 1600, 1490, 1448, 1218, 1074, 763, 703.

23. Preparation of the (*S*)-5-trityloxymethyl-2-oxazolidinone **4**: The (*S*)-4-trityloxy-3-hydroxybutyramide **3** (3.61g, 0.01 mol) was dissolved in 30 ml THF. 13% Sodium hypochlorite solution (15 ml) was added to the solution and the mixture was stirred vigorously and then 1.6 g of sodium hydroxide dissolved in 10 ml of water was added. The reaction was stirred at 55–60°C for 8 hours after which time the rearrangement was completed as indicated by TLC and ^{1}H NMR spectroscopy. The THF layer was separated from the water layer. The water layer was extracted three times with THF. The combined organic layer was concentrated to remove solvent. The residue was taken up in dichloromethane and the solution dried over sodium sulfate. It was concentrated to remove solvent again and oxazolidinone was obtained as a white crystalline product (3.4 g, yield 95%). This crude product normally did not need further purification. Mp (solvent: chloroform:hexane:acetone = 6:3:1), 206.0–207°C. $[\alpha]_D^{25} = +35.5$ ($c = 1.0$, methanol). ^{1}H NMR (300 MHz, $CDCl_3$) ppm, 7.50–7.20 (m, 15 H), 5.88 (s, 1H), 4.75 (m, 1H), 3.61 (m, 1H), 3.45 (m, 1H), 3.40 (dd, 1H, $J = 10.2$, 4.5 Hz), 3.23 (dd, 1H, $J = 10.2$, 4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) ppm, 159.8, 143.4, 128.6, 127.9, 127.2, 86.8, 75.4, 64.2, 42.6. IR cm^{-1} 3272, 1753, 1489, 1448, 1085, 748.5, 705.5. MS (electron impact) m/z 105, 165, 183, 243, 258, 259, 282, 359. HRMS: MH^+ $C_{23}H_{22}NO_3$, 360.1590, theoretical molecular mass 360.1600.
24. The enantiomeric excess of the product was >99.9% e.e. based on GC analysis of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) derivatives.
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