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SYNTHESIS OF SUBSTITUTED 3-HYDROXY-4-ALKOXYCARBONYL-2-AZETIDINONES

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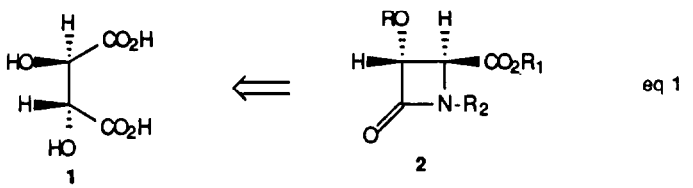
Summary: A short chemical process is described for the synthesis of optically active 3-hydroxy-4-alkoxycarbonyl-2-azetidinones (β-lactams) from L-tartaric acid.

Tartaric acid is an extremely useful and versatile member of the chiral pool. Since nearly any type of β-hydroxy acid can be converted to a β-lactam (2-azetidinone) by the hydroxamate method,[1] tartaric acid was considered an attractive precursor of important optically active derivatives of 3-hydroxy-4-alkoxycarbonyl-2-azetidinones **2**. The main problem with the utilization of tartaric acid derivatives for the synthesis of β-lactams was anticipated to be the differentiation of the two carboxylic acid and two hydroxyl groups. A recent report on the the synthesis of β-lactams from tartaric acid required enzymatic methods for this differentiation.[2] Herein we describe a totally chemical approach to the complete differentiation of all of the functional groups of L-(2R,3R)-(+)-tartaric acid and the application to the synthesis of optically active substituted 3-hydroxy-4-alkoxycarbonyl-2-azetidinones.



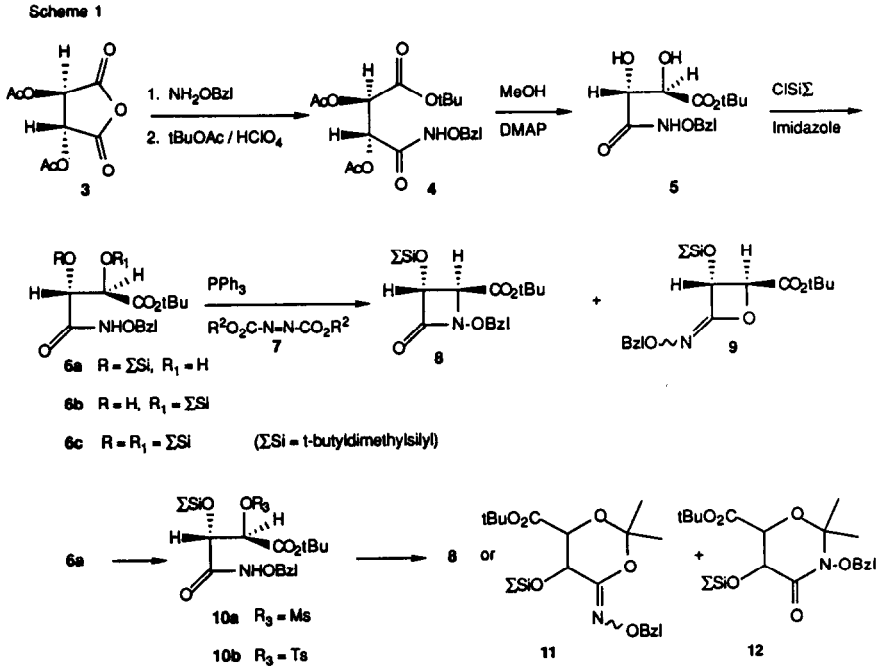
1 **2** eq 1

L-Tartaric acid **1** was converted to the diacetoxysuccinic anhydride **3** as described.[3] Since **3** has an axis of symmetry, differentiation of the two carbonyl groups was easily accomplished. Reaction of **3** with O-benzylhydroxylamine followed by conversion of the remaining carboxyl group to the t-butyl ester (t-butyl acetate / perchloric acid)[4] provided the optically pure hydroxamate ester **4**[5,6] in 75% overall yield (90% overall yield when the intermediates were not individually purified). Methanolysis of **4** in the presence of DMAP[5] removed the two acetyl groups to provide the diol **5**[5] in essentially quantitative yield.[7] In order to employ the usual cyclization methods[1] for conversion of **5** to a β-lactam, an efficient method for differentiation of the two hydroxyl groups was now necessary. Interestingly, treatment of **5** with 100 mole % of t-butyldimethylsilylchloride and 200 mole % of imidazole provided the desired α-silyloxy-β-hydroxy hydroxamate **6a**[5] exclusively. Alternatively, repetition of the same reaction with only 100 mole % of imidazole resulted in exclusive formation of the α-hydroxy-β-silyloxy hydroxamate **6b**.[5] Subsequent treatment of **6b**

with an additional 100 mole % of imidazole resulted in rearrangement to **6a**. Not suprisingly, reaction of **5** with 200 mole % each of t-butyldimethylsilylchloride and imidazole produced the bissilylated product **6c**.[5] The ready availability of the desired β-hydroxy hydroxamate **6a** encouraged studies related to its cyclization.

Cyclization of **6a** to the corresponding β-lactam 8[5] under the usual Mitsunobu conditions (azodicarboxylate, **7** / triphenylphosphine)[1,8] was not straight-forward. The yield of the β-lactam was remarkably dependent on the azodicarboxylate used. Thus, while use of dimethyl azodicarboxylate (**7**, R^2=Me) resulted in formation of β-lactam 8 in 40% yield, variation of the azodicarboxylate ester (R^2 of **7**) was detrimental. Use of diethyl azodicarboxylate (**7**, R^2=Et) produced 8 in only 22% yield along with a small amount (5.5%) of the O-alkylated material **9**[5], as a mixture of the E and Z isomers. Use of diisopropyl azodicarboxylate (**7**, R^2=iPr) resulted in formation of a 1:1 ratio of **8** to **9** with only a 14% yield of the β-lactam **8**. This is the first example we have encountered of competitive O-alkylation during the attempted formation of β-lactams.[9]

Scheme 1



Alternative cyclizations of **6a** were also studied. Conversion of **6a** to the corresponding mesylate **10a**[5] was essentially quantitative. Treatment of **10a** with 100 mole% of powdered KOH or K_2CO_3 in a benzene / DMSO mixture (10:1) at 50-60°C for 30 min, reproducibly provided the β-lactam 8 in 50-60% yield. Contrary to some literature precedent,[2] similar attempts to cyclize the tosylate **10b** proceeded slowly (over 48 h) and produced the β-lactam 8 in only 20% yield. Other conditions used to cyclize **10a** or **10b** were less effective. Especially interesting was the attempted cyclization of **10b** with K_2CO_3 in acetone, conditions which work extemely well for the synthesis of monobactams.[10] In this case, only a mixture of the acetonides **11** and **12** were generated. Again this unusual result

may reflect the steric constraints inherent in hydroxamates **6** and **10.**

Although some improvement of the cyclization step might be realized, the overall process described here provides a direct preparation of optically pure 3-hydroxy-4-alkoxycarbonyl-2-azetidinones which are useful precursors for the preparation of a variety of β-lactams.[11]

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References and Notes.

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5. Representative characterization data includes: **4**: oil; ^{1}HNMR ($CDCl_3$, 90 MHz) δ 1.43 (s, 9H), 2.07 (2s, 6H), 4.9 (s, 2H), 5.53 (m, 1H), 5.84 (d, 1H, J = 3Hz), 7.42 (s, 5H), 9.33 (br s, 1H); IR (neat) 3200, 1730, 1670 cm^{-1}; ms (CI with isobutane) m/e 396 (M+1); $[\alpha]_D$ = +8.0 (c. = 4.5, CH_2Cl_2). **5**: mp 116-117°C; ^{1}HNMR ($CDCl_3$) δ 1.5 (s, 9H), 3.53 (m, 1H), 3.95 (m, 1H), 4.52 (m, 2H), 4.9 (s, 2H), 7.4 (s, 5H), 9.5 (br s, 1H); IR (nujol) 3500, 3390, 3275, 1725, 1670 cm^{-1} ms (CI with argon) 312 (M+1); $[\alpha]_D$ = +28.5 (c = 2), THF). Anal. calcd. for $C_{15}H_{21}NO_6$: C(57.88%), H(6.75%), N(4.50%). Found: C(58.00), H(6.48), N(4.56). **6a**: oil; ^{1}HNMR ($CDCl_3$, the dimethyl silyl group is not reported for all of the compounds containing the t-butyldimethylsilyl group) δ 0.87 (s, 9H), 1.43 (s, 9H), 3.36 (d, 1H, J = 7Hz), 4.33 (m, 1H), 4.66 (d, 1H, J = 1.5 Hz), 4.9 (s, 2H), 7.36 (s, 5H), 9.33 (s, 1H); IR (neat) 3290, 3390, 1740, 1670 cm^{-1} ms (CI with isobutane) 426 (M+1); $[\alpha]_D$ = +93.3 (c = 0.7, CH_2Cl_2). Anal. calcd. for $C_{21}H_{35}NO_6Si$: C(59.29), H(8.24), N(3.29). Found: C(59.19), H(8.11), N(3.21). **6b**: oil; ^{1}HNMR ($CDCl_3$) δ 0.77 (s, 9H), 1.46 (s, 9H), 3.46 (d, 1H, J = 9 Hz), 4.24 - 4.36 (m, 1H), 4.5 (d, 1H, J = 1.5 Hz), 4.94 (s, 2H), 7.4 (m, 5H), 8.87 (s, 1H); IR (neat) 3390, 3290, 1730, 1675 cm^{-1}; ms (CI with isobutane) 426 (M+1); $[\alpha]_D$ = +51.2 (c = 0.95, CH_2Cl_2). **6c**: oil; ^{1}HNMR ($CDCl_3$) δ 0.73 (s, 9H), 0.9 (s, 9H), 1.46 (s, 9H), 4.4 (d, 1H, J = 1.5 Mz), 4.55 (d, 1H, J = 1.5 Hz), 4.96 (d, 2H, J = 4 Hz), 7.36 (s, 5H), 8.69 (s, 1H); IR (neat) 3400, 1745, 1700 cm^{-1}; ms 540 (M^+); $[\alpha]_D$ = +91.2 (c = 5.6, CH_2Cl_2). **8**: oil; ^{1}HNMR ($CDCl_3$) δ 0.9 (s, 9H), 1.5 (s, 9H), 3.86 (d, 1H, J = 1.5 Hz), 4.56 (d, 1H, J = 1.5 Hz), 5.1 (s, 2H), 7.42 (s, 5H): IR (neat) 1795, 1740 cm^{-1}; ms m/e 408 (M^+1); $[\alpha]_D$ = 45.7 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{21}H_{33}NO_5Si$: C(61.92), H(8.11), N(3.44). Found: C(61.85), H(8.06), N(3.70). **9**: (oil, mixture of E and Z isomers); ^{1}HNMR ($CDCl_3$) δ 0.85 (2s, 9H), 1.33 (s, 9H), 4.15 (2d, 2H, J = 8 Hz), 4.83 (s, 2H), 7.3 (s, 5H); IR (neat) 1780, 1740 cm^{-1}; ms m/e 408 (M^+1) $[\alpha]_D$ = +47.5 (c = 1.1, CH_2Cl_2). **10a**: oil; ^{1}HNMR ($CDCl_3$) δ 0.87 (s, 9H), 1.5 (s, 9H), 2.97 (s, 3H), 4.68 (d, 1H J= 2 Hz), 4.95 (s, 2H), 5.33 (d, 1H, J = 2 Hz), 7.4 (s, 5H), 9.25 (s 1H); ms (CI with argon) m/e 448 (M -56);