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A SYNTHETIC APPROACH TO (+)-THIENAMYCIN FROM METHYL (R)-3-HYDROXYBUTANOATE. A NEW ENTRY TO (3R, 4R)-3-[(R)-1-HYDROXYETHYL]-4-ACETOXY-2-AZETIDINONE

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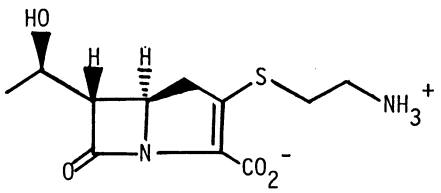
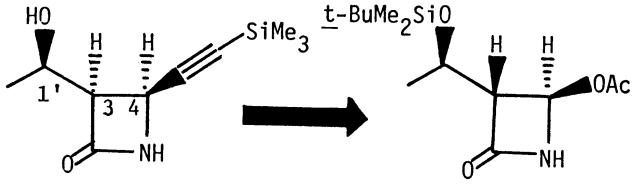
A new entry to the O-silylated form of the title azetidinone, a well-established key intermediate for thienamycin synthesis, is described which relies on the stereocontrolled transformation of the 2-azetidinone obtained via the condensation of methyl (R)-3-hydroxybutanoate with the N-silylimine of trimethylsilylpropynal.

Considerable effort has currently been devoted to the asymmetric and total synthesis of (+)-thienamycin (1) because of its unprecedented biological activities.[1] In an effort to develop a new synthetic route to (+)-1, we have recently reported that the condensation of the dianion of methyl (R)-3-hydroxybutanoate (2) with the N-silylimine (3) generated *in situ* from trimethylsilylpropynal results in the direct and selective formation of (-)-(3R, 4S)-3-[(R)-1-hydroxyethyl]-4-trimethylsilylethynyl-2-azetidinone (4).[2] Quite recently Hart and co-workers have also reported a similar condensation of ethyl 3-hydroxybutanoate with 3 leading to (±)-4 as the major product.[3] Apparently, however, (-)-4 is not well qualified as a chiral precursor of (+)-1 because of its wrong configuration at C-3. Thus, our effort has now been directed to the stereochemical adjustment to establish the requisite stereochemisty. Herein we wish to report a facile scheme for the stereocontrolled transformation of (-)-4 to the O-silylated form of the title azetidinone (5) which has been well established as a key intermediate for the chiral synthesis of (+)-1.[4,5]



(+)-1



(-)-4 (+)-5

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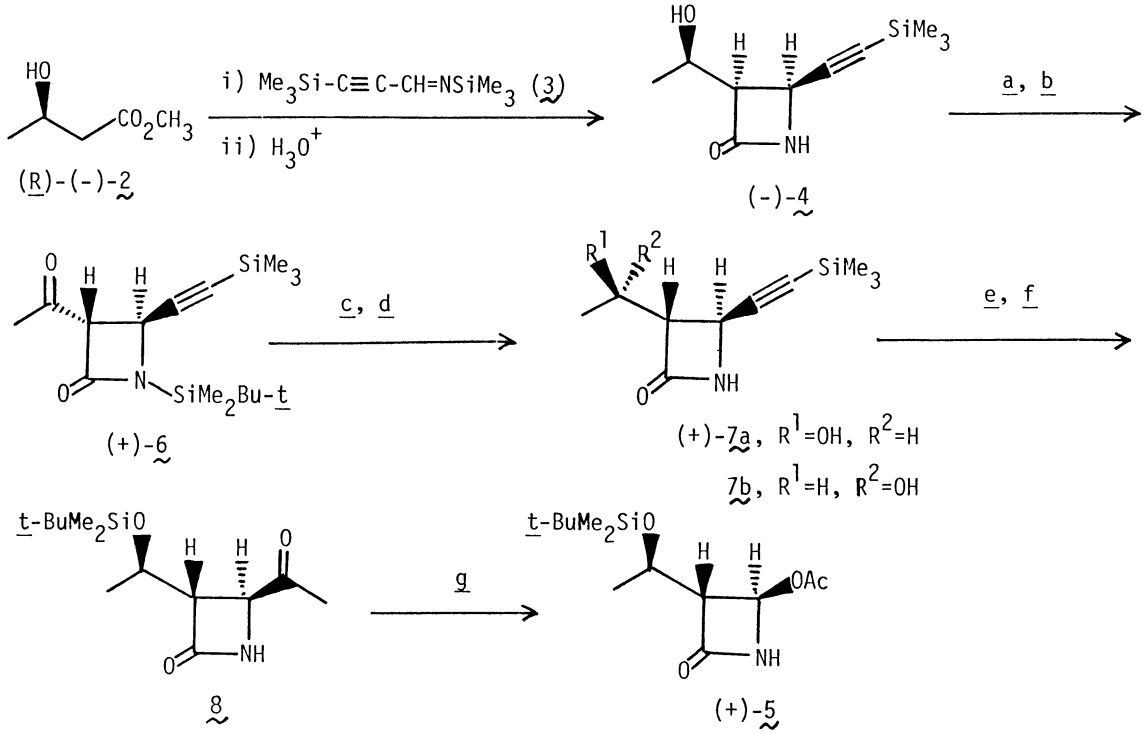
The complete transformation is depicted in Scheme 1. We first prepared the starting azetidinone 4 ($[\alpha]_D^{16}$ -11.8°(c 1.12, EtOH)) from commercially available (R)-(-)-2 of 79% optical purity according to the procedure described in our previous paper.[2] The selective NH-protection of (-)-4 by t-butyldimethylsilyl group followed by oxidation with activated manganese dioxide afforded 80% yield of the trans-3-acetylazetidinone 6 ($[\alpha]_D^{24}$ +7.3° (c 1.70, $CHCl_3$)).[6] The trans-configuration was assigned from the coupling constant ($J_{3,4}$=2.7 Hz), indicating that the oxidation simultaneously brought about complete epimerization at C-3 leading to the desired S configuration. The crucial reduction of (+)-6 was best accomplished with K-Selectride[7] to provide a diastereomeric mixture of 7a and 7b in a ratio of 9 : 1. Deprotection followed by recrystallization from hexane gave pure 7a ($[\alpha]_D^{25}$ +47.2° (c 0.72, $CHCl_3$))[8] in 62% yield from 6. It should be noted that the overall stereochemistry of (+)-7a is fully consistent with that of the framework of (+)-1. The selective OH-protection of (+)-7a by t-butyldimethylsilyl group followed by hydration of the silylethynyl group afforded the 4-acetylazetidinone 8[5f] which was subjected to the Baeyer-Villiger oxidation to furnish the desired 4-acetoxyazetidinone 5[5] ($[\alpha]_D^{25}$ +34.5° (c 0.24, $CHCl_3$)) in 30% yield from 7a.[9] The melting point and spectral data (IR and NMR) were in agreement with those of an authentic sample which was prepared from 6-aminopenicillanic acid

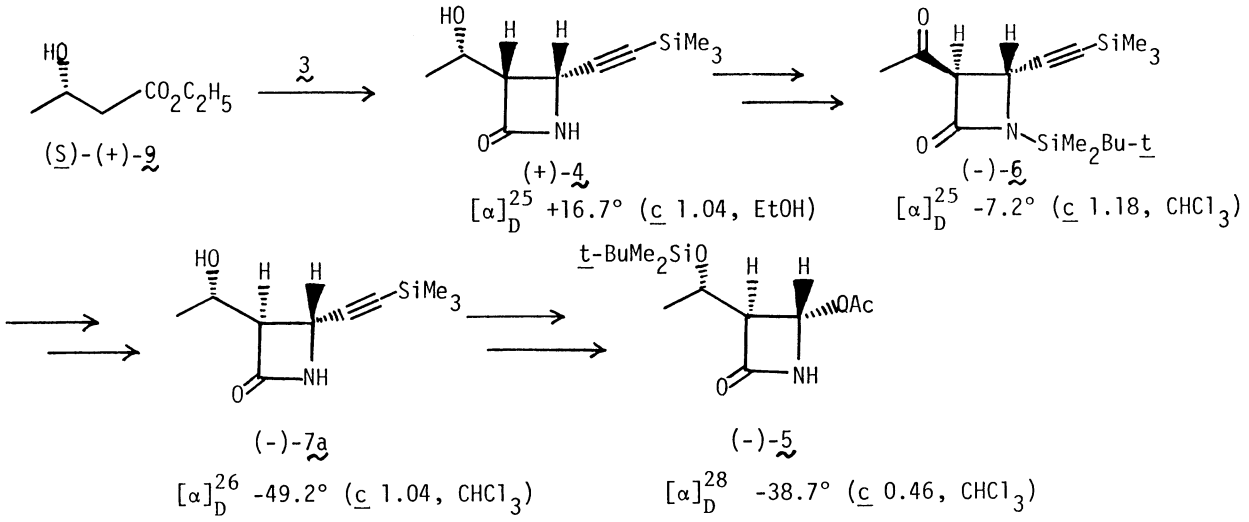


Scheme 1.

a, $LiN(SiMe_3)_2$, t-$BuMe_2SiCl$, THF; b, MnO_2(activated), AcOEt, 25 °C; c, K-Selectride, Et_2O. 25 °C; d, 10% HCl-MeOH, 25 °C; e, t-$BuMe_2SiCl$, imidazole, DMF, 40 °C; f, H_2SO_4 (trace)-$HgSO_4$ (cat.), aq. THF, 25 °C; g, m-chloroperbenzoic acid, EtOAc, 25 °C.

by using the method reported by the Merck group.[5e] The optical purity of (+)-5 thus obtained was '69%,[10] as judged from the highest literature $[\alpha]_D$-value (+50.0° ($CHCl_3$)).[5e] Thus, the present synthesis of (+)-5 from (R)-2 constitutes a new, formal synthesis of (+)-1.

Using the same reaction sequence as described above, we also carried out the synthesis of (1'S, 3S, 4S)-5, the enantiomer of (+)-5, starting from (S)-(+)-9 (90% ee) which was easily obtainable via reduction of ethyl acetoacetate with baker's yeast[11] (Scheme 2). The $[\alpha]_D$-value for (-)-5 and the intermediates thus obtained are shown in Scheme 2.



Scheme 2.

In summary, we have now completed a synthetic scheme for (+)-5, a well-secured synthetic intermediate for (+)-1, from inexpensive (R)-2. Thus, the newly developed method compares quite favorably with the existing methods[5] in terms of simplicity, flexibility, and availability of the starting material. Furthermore, it is worth noting that intermediate (+)-7a obtained above could serve as a new, more direct precursor to (+)-1 in virtue of its silylethynyl functionality well equipped for further elaborations. Further works along this line as well as the improvement of the present method are in progress in our laboratory.

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6) NMR ($CDCl_3$, TMS), δ 4.27 (d, J=2.7 Hz, 3-H), 4.50 (d, J=2.7 Hz, 4-H).

7) F. A. Bouffard and B. G. Christensen, J. Org. Chem., 46, 2208 (1981). We found that reduction of (+)-6 with $NaBH_4$ gave a 1 : 4 mixture of 7a and 7b, respectively.

8) NMR ($CDCl_3$, TMS), δ 1.30 (d, J=6.6 Hz, 1'-Me), 3.23-3.46 (m, 3-H), 4.30 (d, J=2.7 Hz, 4-H).

9) The yield has not been optimized yet; efforts are in progress to improve the yield.

10) This means that the enantiomeric purity of (+)-5 is lower (ca. 10%) than that of (-)-2. We are extensively examining the origin of the unexpected loss in enantiomeric purity.

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