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A FACILE ENTRY TO 3-(1-HYDROXYETHYL)-2-AZETIDINONES FROM METHYL (R)-3-HYDROXYBUTANOATE BASED ON THE ESTER ENOLATE–ALDIMINE CONDENSATION

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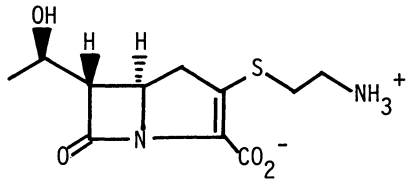
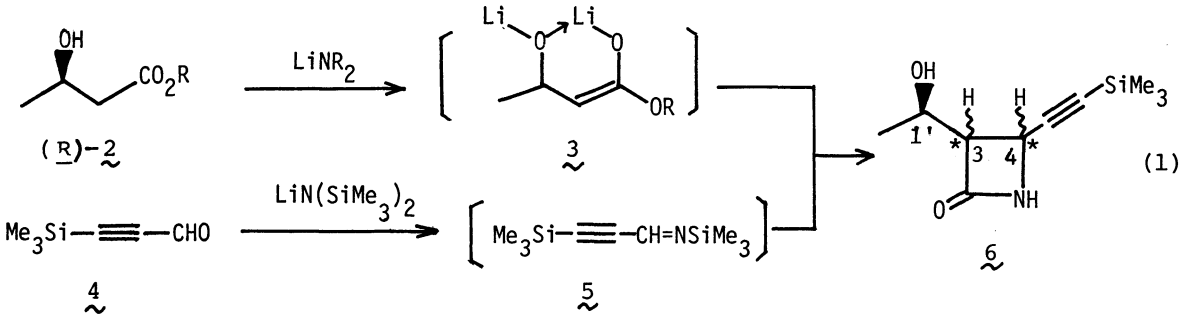
The reaction of the dianion of methyl (R)-3-hydroxybutanoate with the N-silylimine generated from trimethylsilylpropynal afforded (3R, 4S)-3-[(R)-1-hydroxyethyl]-4-trimethylsilylethynyl-2-azetidinone as the major product, of which the stereochemistry was assigned through its stereospecific conversion to the (+)-4-acetoxy derivative.

Thienamycin (1) has attracted increasing interest as the synthetic target, and hence several synthetic routes to (+)-1 and its chiral precursors have been developed.[1] As part of a program aimed at the development of a new route to (+)-1, we have now investigated the feasibility of the condensation of the dianion of the (R)-3-hydroxybutanoate (2) with the N-silylimine generated in situ from the silylpropynal (4) according to Hart's procedure[2] (Eq. 1). Of particular interest and importance in this specific enolate–imine condensation is its stereochemical outcome which is associated with both the internal and relative asymmetric induction over the three contiguous chiral centers.[3] Disclosed here are preliminary results of our studies, including the stereochemical outcomes.



(+)-1



(1)

Initial experiments were carried out on the racemic ester (±)-2 (R=CH_3, C_2H_5) to optimize conditions and examine the relative stereochemistry on the β-lactam rings formed (Eq. 2). Thus, a solution of N-silylimine 5 in tetrahydrofuran (THF),

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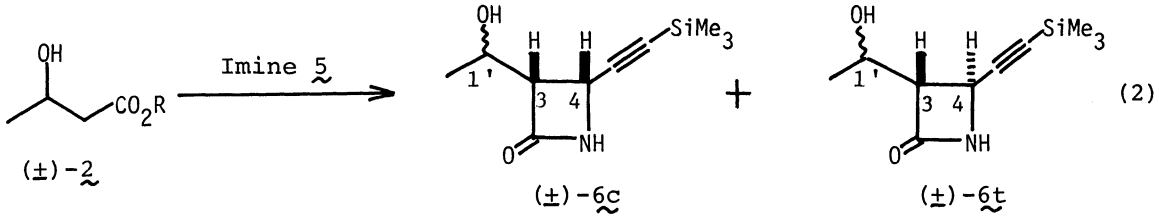
prepared in situ from aldehyde 4 and lithium hexamethyldisilylamide (LHDS) according to the reported method,[2] was added at -75– -65 °C to a solution of enolate 3 generated from (±)-2 with LHDS or lithium diisopropylamide (LDA) in either THF or 23 vol% hexamethylphosphoramide (HMPA)-THF. After stirring at -70 °C for 1.5 h, the mixture was allowed to warm to room temperature, and further stirred for 1.5 h. The resulting mixture was poured into a mixture of 10% hydrochloric acid and ethyl acetate. The organic layer was separated, washed with brine, dried, and concentrated. The residual brown oil was chromatographed (silica gel, 30% ethyl acetate in hexane) to give the pure (±)-(3,4)-cis-β-lactam 6c[4] and a mixture consisting mainly of (±)-6t.[5] The cis and trans assignments were made



(2)

from the magnitude of the coupling constants ($J_{3,4}$): 6.0 Hz for 6c and ca. 2.0 Hz for 6t. Although the relative configuration at C-1' and C-3 in each product was not assignable at this stage, NMR analyses clearly indicate that (±)-6c is a single stereoisomer[6] as revealed by only one doublet due to the 1'-methyl, whereas (±)-6t is a 1 : 1 mixture of (1',3)-syn and -anti isomer[7] as indicated by the two methyl-doublets with nearly equal integration. Table 1 summarizes the representative results thus obtained.

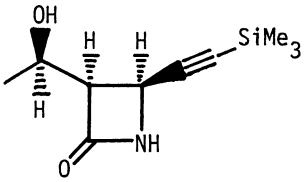
Several trends are evident from the data in Table 1. (1) The present condensation provides a moderate degree of diastereoselection over C-3 and C-4. (2) The enolization in THF leading to the chelated (Z)-enolate 3[8] as depicted in Eq. 1 resulted in the preferential formation of the cis-β-lactam (6c),[9] whereas the enolization in HMPA-THF led to a reversal in diastereoselection, along with lower yields. (3) In terms of the product yields, the methyl ester 2a (R=CH_3) is superior to the ethyl ester as the ester partner, and LHDS is superior to LDA as the base for the enolization.

With the reaction conditions optimized and the relative stereochemistry of the lactam ring established, our effort was next directed to the establishment of the overall stereochemistry over the three contiguous chiral centers of the cis-β-lactam (6c) using an optically active ester (-)-(R)-2a (R=CH_3). Thus, the condensation of commercially available (R)-2a of 70% optical purity with imine 5 was carried out under the optimal conditions (entry 3, Table 1) to afford (-)-6c ($[\alpha]_D^{16}$ -11.8° (c 1.12, EtOH) as the major product.[10] The absolute stereochemistry of (-)-6c was assigned to (1'R, 3R, 4S) as indicated in the next page through its stereospecific conversion to the (+)-4-acetoxy derivative 7c[10, 11] ($[\alpha]_D^{20}$ +22.4° (c 0.90, EtOH), of which the absolute configuration was assignable to (1'R, 3S, 4R) because the (+)-product was apparently different from the (-)-(1'R, 3R, 4S)-isomer (7c') previously prepared from D-allo-threonine.[12] The conversion of (-)-6c to (+)-7c was carried out by a three-step sequence,[13] i.e., O-silylation

Table 1. The Condensation of Enolate (±)-3 with Imine 5

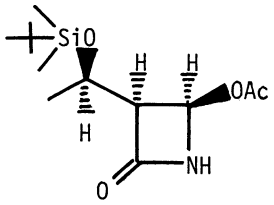
Entry	Starting ester (±)-2	Base for enolization	Solvent for enolization	Cis : trans for (±)-6[a]	Combined yield / %[b]
1	R=C_2H_5	LDA	THF	3 : 1	50
2		LHDS	THF	3 : 1	66
3	R=CH_3	LHDS	THF	3 : 1	75
4		LDA	HMPA-THF	1 : 1.3	52
5	R=C_2H_5	LDA	HMPA-THF	1 : 1.7	49

a) Determined by NMR analysis after column chromatography. Note that (±)-6c is a single stereoisomer, while (±)-6t is a mixture of the two stereoisomers (see the text). b)Based on the product isolated by column chromatography.



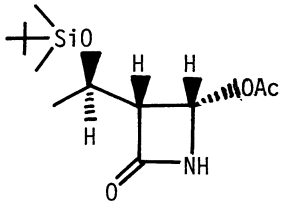
(-)-6c

(1'R, 3R, 4S)



(+)-7c

(1'R, 3S, 4R)



(-)-7c'

(1'R, 3R, 4S)

(t-$BuMe_2SiCl$, imidazole, N,N-dimethylformamide), hydration to the (-)-4-acetyl derivative[10, 14] (conc. H_2SO_4 (trace), $HgSO_4$ (cat.)/$(NH_4)_2SO_4$, aq. MeOH), and the Baeyer-Villiger oxidation (m-chloroperbenzoic acid, AcOEt). Thus, the established stereochemistry of (-)-6c reveals that the present condensation leading to the cis-β-lactam exhibits a high anti(threo)-selection over C-1' and C-3; this sense of stereoselection is in accord with similar stereoselections reported for the reactions of the chiral enolate (R)-3 with various electrophiles.[8, 15]

In conclusion, the stereochemical results of this work establish the sense and degree of both the internal and relative asymmetric induction involved in the present enolate–imine condensation.[16] Although the overall stereochemistry of (-)-6c is, unfortunately, not fully consistent with that of the framework of thienamycin (1) (*i.e.*, opposite in configuration at C-3), we still believe that (-)-6c is a potentially useful intermediate for the synthesis of (+)-1 and related carbapenems in view of the easy accessiblity and the naturally occurring (S)-configuration at C-4, coupled with the ethynyl functionality at C-4 equipped for further synthetic elaborations. We are now investigating the stereocontrolled transformation of (-)-6c to a well-established key precursor to (+)-1. The results will be reported shortly.

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References

1) For recent reviews: T. Kametani, Heterocycles, 17, 463 (1982); M. Shibuya, J. Synth. Org. Chem., Jpn., 41, 62 (1983). For more recent examples: P. J. Reider and E. J. J. Grabowski, Tetrahedron Lett., 23, 2293 (1982); M. Shibasaki, A. Nishida, and S. Ikegami, J. Chem. Soc., Chem. Commun., 1982, 1324; M. Shibasaki, A. Nishida, and S. Ikegami, Tetrahedron Lett., 23, 2875 (1982); H. Yanagisawa, A. Ando, M. Shiozaki, and T. Hiraoka, ibid., 24, 1037 (1983); T. C. Smale, ibid., 25, 2913 (1984), and references cited therein.

2) D. J. Hart, K. Kanai, D. G. Thomas, and T.-K. Yang, J. Org. Chem., 48, 289 (1983). The Hart's paper has described a similar condensation of ethyl α-phenylthiopropionate with imine 4 leading to the β-lactam. After completion of this work, the condensation of the dianion of (±)-2 with benzilideneaniline has been reported: G. I. Georg, Tetrahedron Lett., 25, 3779 (1984).

3) For a general discussion of the internal asymmetric induction in the enolate–imine condensations: D. A. Evans, J. V. Nelson, and T. R. Taber, "Topics in Stereochemistry," Vol. 13, John Wiley & Sons, Inc., New York (1982), p.1.

4) Mp 95-97 °C; IR (nujol), 3360, 3190, 1775 cm^{-1}; NMR ($CDCl_3$, TMS), δ 0.10 (br. s, Me_3Si), 1.37 (d, J=6.9 Hz, 3H), 2.87 (br. s, OH), 3.40 (d,d, J=6.0 and 7.2 Hz, 3-H), 4.06-4.40 (m, 1'-H), 4.43 (d, J=6.0 Hz, 4-H), 6.43 (br. s, NH).

5) IR (nujol), 3300, 1770 (sh.), 1720 cm^{-1}; NMR ($CDCl_3$), δ 0.10 (s, Me_3Si), 1.00-1.50 (2d, J= *ca.* 7.0 Hz, 3H), 2.25 (br. s, OH), 3.00-3.50 (m, 3-H), 4.00-4.50 (m, 1'- and 4-H), 6.60 (br. s, NH).

6) This means that (±)-6c possesses either the (1', 3)-syn or -anti configuration by virtue of an extremely high diastereoselectivity over C-1' and C-3.

7) The two isomers were not separable by usual chromatographic techniques.

8) For the presumed structure of enolate 3: D. Seebach and E. Hungerbühler, "Modern Synthetic Methods," ed by R. Schefford, Otto Sale Verlag, Frankfurt (1980), Vol. 2, p.91.

9) This sense of diastereoselection over C-3 and C-4 formally corresponds to the erythro-selection generally observed for the aldol condensations involving (Z)-enolates. For the stereochemistry of aldol process: Ref. 3.

10) The optical purity of this compound has not been determined yet; attempted NMR analyses using chiral shift reagents have been unsuccessful so far.

11) IR (nujol), 3250, 1780, 1720 cm^{-1}; NMR ($CDCl_3$), δ 0.10 (s, Me_2Si), 1.00 (s, t-BuSi), 1.33 (d, J=6.6 Hz, 1'-CH_3), 2.16 (s, CH_3CO_2), 3.27-3.53 (m, 3-H), 4.17-4.53 (m, 1'-H), 5.97 (d, d, J=5.5 Hz, 4-H), 6.67 (br. s, NH).

12) M. Shiozaki, N. Ishida, T. Hiraoka, and H. Yanagisawa, Tetrahedron Lett., 22, 5205 (1981).

13) The overall yield was *ca.* 30%; efforts are in progress to improve the yield.

14) $[\alpha]_D^{20}$ -98.7° (c 1.56, EtOH); IR (nujol), 2950, 1760, 1720 cm^{-1}; NMR ($CDCl_3$), δ 1.37 (d, J=6.9 Hz, 1'-CH_3), 2.43 (s, CH_3CO), 4.27 (d, J=6.0 Hz, 4-H).

15) G. Fráter, Helv. Chim. Acta, 62, 2825, 2829 (1979); D. Seebach and D. Wasmuth, ibid., 63, 197 (1980), references cited therein.

16) The mechanistic aspects of the stereochemical outcomes will be discussed in a full paper.

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