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Stereoselective Synthesis of 3-(1-Hydroxyethyl)-2-azetidinones from 3-Hydroxybutyrates

Gunda I. Georg

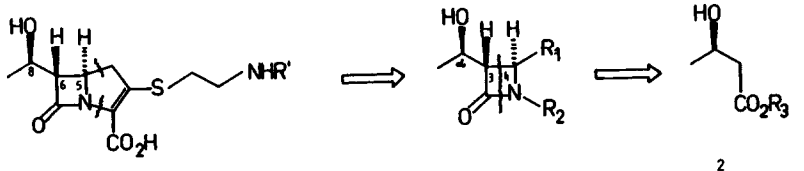
Department of Medicinal Chemistry
University of Kansas
Lawrence, KS 66045-2500

Summary: Addition of dianions of 3-hydroxybutyrates to benzylideneaniline results in direct formation of trans S*-3-(1-hydroxyethyl)-1,4-diphenyl-2-azetidinone with 95% diastereoselectivity. Inversion of the configuration at C_α gives the desired trans R*-2-azetidinone in high yield.

A major difficulty in the total synthesis[1] of (+)-thienamycin **1** is the control of the relative and absolute stereochemistry of the three contiguous chiral centres. Several multistep approaches for the synthesis of chiral 3-(1-hydroxyethyl)-2-azetidinone precursors have been described in the literature.[2]

Retrosynthetic analysis of thienamycin **1** (scheme I) suggests that readily available chiral esters[3] of 3-hydroxybutyric acid **2** could eventually be used for the synthesis of **1** and related β-lactam antibiotics.

Scheme I

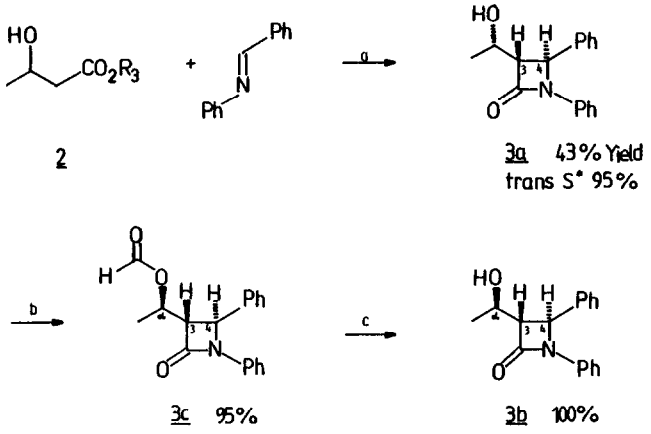


1 **2**

Herein, preliminary results of a study are described, outlining a new, and highly diastereoselective method to synthesize 3-(1-hydroxyethyl)-2-azetidinones generating the trans S* configuration at three centres in a one step process.

It is well known that the dianion of esters of 3-hydroxybutyric acid **2** can be α-alkylated to yield threo products with 95% diastereoselectivity.[4] In a novel approach to utilize this reaction, the dianions of racemic **2** (R_3 = ethyl or tert.-butyl) and benzylideneaniline were stirred at -20°C to r.t., generating directly 3-(1-hydroxyethyl)-1,4-diphenyl-2-azetidinone in 43% yield (scheme II).[5] In a one flask process the enolate not only added to the imine, but the resulting intermediate underwent an intramolecular ring closure to form the β-lactam ring system. The major isomer **3a** (95%) was assigned the trans S* (αSR, 3SR, 4RS), and the minor isomer **3b** (5%) the

Scheme II



R_3 = Et, t-Bu

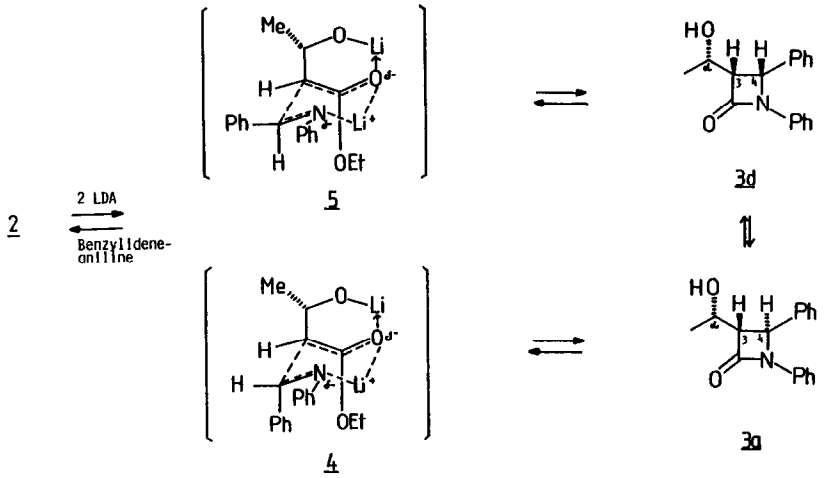
a 2 LDA/1.5 HMPA in THF; -20 to r.t., 6h. b PPh_3, DEAD, HCO_2H; 1.5h r.t.
c MeOH/HCl; 1.5h r.t.

trans R* (αRS, 3SR, 4RS) configuration.[6] No cis isomer was detected under these reaction conditions. After inversion of the configuration at C_α, the desired isomer trans R* **3b** was obtained from **3a** via **3c** according to the Mitsunobu procedure[7] (scheme II).

The reaction temperature during the dianion imine cycloaddition influenced the stereochemistry of the resulting products. Quenching the reaction mixture at -20°C after 7 h gave a 60:40 ratio of trans S* **3a** and cis S* **3d** (yield 41%). After formation of the inverted formyl esters (Mitsunobu), **3c** and the formyl ester cis R* **3e** could be separated by column chromatography. Hydrolysis of **3e** gave quantitatively αR*-cis-3-(1-hydroxy-ethyl)-1,4-diphenyl-2-azetidinone **3f**.

The influence of the reaction temperature on the stereoselectivity of the reaction suggests that kinetic and thermodynamic factors play an important role for the consequential stereochemistry. During the first step of the reaction, carbon-carbon bond formation, the oxygen of the enolate and the imide nitrogen are presumably both disposed in the direction of the lithium cation (scheme III). This leads to a six centred transition state, in which the phenyl-group of the imine and the ethoxy group of the enolate are either close (transition state **4**) or remote (transition state **5**) from each other.[9] Under kinetic control transition state **5** should be favoured, which leads to the formation of cis S* **3d**. Assuming that carbon-carbon bond formation is a reversible process and that the intermediate leading to product **3a** is thermodynamically preferred, trans S* **3a** should be the product. Another possible mechanism for the formation of **3a** would involve a cis-trans isomerisation via enolisation of cis S* **3d** or the ring open β-aminoester prior to β-lactam formation.

Scheme III



This newly discovered approach to the stereoselective synthesis of 3-(1-hydroxyethyl)-2-azetidinones is extremely advantageous over existing methods, due to its brevity and its utilization of inexpensive starting materials.

The syntheses of chiral precursors, which subsequently allow the total synthesis of thienamycin **1** are currently under active investigation.

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REFERENCES

(1) For reviews:
(a) Morin, R. B.; Gorman, M. "Chemistry and Biology of β-Lactam Antibiotics", Academic Press: New York, 1982.
(b) Kametani, T. Heterocycles, **1982**, 17, 463.
(c) Hoppe, D. Nachr. Chem. Techn. Lab. **1982**, 30, 25.
(2) (a) Bouffard, F. A.; Christensen, B. G. J. Org. Chem. **1981**, 46, 2208.
(b) Hamlet, B.; Durst, T. Cand. J. Chem. **1983**, 61, 411.
(c) Karady, S.; Amato, J. S.; Raemer, R. A.; Weinstock, L. M. J. Am. Chem. Soc. **1981**, 103, 6767.
(d) Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y. F.; Izawa, T. J. Am. Chem. Soc. **1981**, 103, 2405.
(e) Takano, S.; Kasahara, C.; Ogasawara, K. Chemistry Lett. **1983**, 175.

(f) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. Tetrahedron Lett. **1983**, 24, 3009.
(g) Okana, K.; Izawa, T.; Ohno, M. Tetrahedron Lett. **1983**, 24, 217.
(h) Shiozaki, M.; Hiraoka, T. Tetrahedron Lett. **1980**, 21, 4473.
(i) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Yanagisawa, H. Tetrahedron Lett. **1981**, 22, 5205.
(j) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. Tetrahedron **1983**, 39, 2399.
(k) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. Heterocycles **1983**, 20, 279.
(l) Yanagisawa, H.; Ando, A.; Shiozaki, M.; Hiraoka, T. Tetrahedron Lett. **1983**, 24, 1073.

(3) (a) Seuring, B.; Seebach, D. Helv. Chim. Acta **1981**, 60, 1175.
(b) Seebach, D.; Zueger, M. Helv. Chim. Acta **1982**, 65, 495.
(R)-3-Hydroxybutyric acid and ethyl (S)-3-hydroxybutyrate are commercially available from Fluka.

(4) (a) Frater, G. Helv. Chim. Acta **1979**, 62, 2825.
(b) Idem, Ibid. **1980**, 63, 1383.
(c) Idem, Tetrahedron Lett. **1981**, 22, 425.
(d) Sutter, H. A.; Seebach, D. Lieb. Ann. Chem. **1983**, 939.
(e) Hungerbuehler, E.; Seebach, D.; Wasmut, D. Helv. Chim. Acta **1981**, 64, 1467.
(f) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. J. Am. Chem. Soc. **1981**, 103, 1224.
(g) Kramer, A.; Pfander, H. Helv. Chim. Acta **1982**, 65, 293.

(5) Addition cyclization reactions between enolates and imines have been described before.
(a) Ojima, I.; Inaba, S.; Yoshida, K. Tetrahedron Lett. **1977**, 3643.
(b) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. J. Org. Chem. **1980**, 45, 3413.
(c) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yank, T. K. J. Org. Chem. **1983**, 48, 289.

(6) Otto, H. H.; Mayrhofer, R.; Bergmann, C. J. Lieb. Ann. Chem. **1983**, 1152. The spectroscopic data of **3a** and **3b** were identical with those reported.

(7) (a) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. Tetrahedron Lett. **1981**, 22, 913.
(b) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. Tetrahedron Lett. **1980**, 21, 2783.

(8) Compounds **3a-3f** were purified either by column chromatography or recrystallization. Their spectroscopic data were in agreement with their structures.

(9) The Zimmermann-Traxler transition state has been suggested for the stereoselective aldol condensation.
Heathcock, C. H. in "Asymmetric Reactions and Processes in Chemistry", Editors: Eliel, E. L., Otsuka, S. ACS Symposium Series 185:Washington, D.C., 1982; pp. 55-72.

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