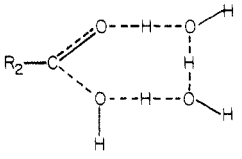
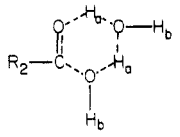


2

R value the interaction of water with the AOT head groups is stronger than its autoassociation.[12]

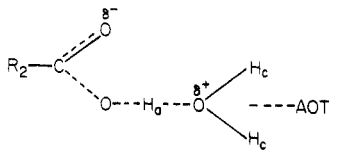
The results at $R = 11.1$ suggest that $\nu > 1$; i.e., several protons contribute to the solvent isotope effect. Curve fitting according to TS **2**, i.e., using $\nu = 3$, gave $\phi_a^* = 0.67$ which is outside the range expected for this type of reaction ($\phi \simeq 0.5$).[5] Additionally, the computed curvature function, γ, was different from the one derived from the experimental results.[13] A symmetrical TS containing two water molecules (**3**) gave $\phi_a^* = 0.53$ which is in the expected



3

range. However, the energetically favorable linear donor–proton-acceptor arrangement cannot be accommodated in a six-membered-ring TS without considerable strain.[14] Also, the computed γ value (0.53) was not in agreement with that derived from the rate data. Analysis of the results according to a nonsymmetrical cyclic TS, hence a less strained one, using a two-term version of eq 2 gave a bad fit.[16]

In line with the TS structure proposed for $R = 1.3$, an acyclic TS containing two, or more, water molecules seems more likely. In TS **4** the proton bridge H_a contributes a



4

primary isotope effect, H_b apparently does not contribute, whereas H_c of the "general base" water produces secondary effects. For this TS eq 2 becomes eq 3 and the quality of

$$k^n = k^0 (1 - n + n\phi_a^*)(1 - n + n\phi_c^*)^2 \qquad (3)$$

the fit can be seen in Figure 1. The best fit was obtained using $\phi_a^* = 0.49 \pm 0.02$ and $\phi_c^* = 0.77 \pm 0.01$, in good agreement with the values of 0.51 and 0.77 calculated based on the γ method.[5]

The reaction activation parameters[17] substantiate the change in the TS structure at the higher R value. Thus, when R was increased from 1.3 to 11.1, $\Delta H^{\ddagger}$ decreased from 58 to 26 kJ mol^{-1}, probably due to the participation of the "general base" water, whereas there was a large decrease in $\Delta S^{\ddagger}$ (from −111 to −199 J K^{-1} mol^{-1}) due to the presence of this extra water molecule. At a comparable water concentration (2.22 M, $R = 11.1$), the micellar rate constant is 266 times faster than that in water–dioxane.[11] This rate enhancement is clearly due to an entropy increase (72 J K^{-1} mol^{-1}) since $\Delta H^{\ddagger}$ for the reaction in AOT is 6.5 kJ mol^{-1} higher than that in water–dioxane.[18] The higher $\Delta S^{\ddagger}$ value for the former reaction can be easily rationalized if TS **4**, which is acyclic and contains less water molecules, is assumed.

In conclusion, differences between the structure of the TS of a micellar reaction and that occurring in a reference solvent can affect the activation parameters which, in favorable cases, entails a rate enhancement.

Acknowledgment. Financial support for this work from the CNPq and FAPESP Research Foundations is gratefully acknowledged. We thank Dr. J. L. Hogg for reading this manuscript, and Hoechst of Brazil for help.

(12) Wong, M.; Thomas, J. K.; Nowak, T. *J. Am. Chem. Soc.* **1977**, *99*, 4730.

(13) According to Albery,[5] γ is a function of the curvature in the (ln k^n/k^0) vs. n plots. If the observed isotope effect is due to protons with the same ϕ value (e.g., the protons in flight of TS **2** designated A) γ will be given by $\gamma \simeq \Lambda_A^2/a$, where a is the number of the protons involved, and Λ_A is given by $\Lambda_A = (a \ln \phi_A)/\ln (k^1/k^0)$. Using $\phi_A = 0.67$ and ln $(k^1/k^0) = -1.231$, we obtained $\gamma = 0.32$.

(14) On the other hand, a seven- or eight-membered-ring TS can support this linear arrangement.[15] At the present stage, however, we feel that more results are needed before TS **3** can be ruled out unambiguously.

(15) Gandour, R. D. *Tetrahedron Lett.* **1974**, 295. Litvinenko, L. M.; Oleinik, N. M. *Russ. Chem. Rev.* **1978**, *47*, 401.

(16) In this case the standard deviation in ϕ was equal to, or higher than, ϕ itself.

(17) At $R = 1.3$, the rate constants k^0_h at 18, 25, 30, and 38 °C were 2.95, 6.16, 8.72, and 15.05 × 10^{-4} s^{-1}, and for $R = 11.1$, k^0_h at 18, 25, and 38 °C was 51.3, 66.5, and 109.4 × 10^{-4} s^{-1}, giving $\Delta H^{\ddagger} = 58$ and 26 kJ mol^{-1} and $\Delta S^{\ddagger} = -111$ and −199 J K^{-1} mol^{-1}, for $R = 1.3$ and 11.1, respectively.

(18) Bell, R. P.; Sorensen, P. E. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1740.

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Received August 13, 1980

(2*S*,3*S*,4*R*)-4-Amino-3-hydroxy-2-methylvalerate. Synthesis of an Amino Acid Constituent of Bleomycin from L-Rhamnose

Summary: (2*S*,3*S*,4*R*)-4-Amino-3-hydroxy-2-methylvalerate, an amino acid constituent of the antitumor antibiotic bleomycin, has been prepared from L-rhamnose. This approach to a chiral 3-hydroxy-2-methylcarboxylate constitutes an alternative to the stereoselective aldol condensation.

Sir: The bleomycins are a family of glycopeptide-derived antibiotics elaborated by *Streptomyces verticillus*.[1] A mixture of bleomycins, consisting primarily of bleomycin A_2 (**1**), is used clinically for the treatment of certain neoplasms, including squamous cell carcinomas and malignant lymphomas.[2] As part of a synthesis of the tetrapeptide S moiety of bleomycin we recently described[3] the preparation of (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvaleric acid (**2**) by modification of the method of Yoshioka et al.[4] Although affording a much higher yield of the desired isomer than the reported procedure, we noted that some

(1) Umezawa, H. *Lloydia* **1977**, *40*, 67.

(2) (a) Crooke, S. T. "Bleomycin: Current Status and New Developments"; Carter, SK., Crooke, S. T., Umezawa, H., Eds.; Academic Press: New York, 1978; p 1 ff. (b) Carter, S. K. ref 2a, p 9 ff.

(3) (a) Levin, M. D.; Subrahamanian, K.; Katz, H.; Smith, M. B.; Burlett, D. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1452. (b) Hecht, S. M.; Burlett, D. J.; Mushika, Y.; Kuroda, Y.; Levin, M. D. "Bleomycin: Chemical, Biochemical and Biological Aspects"; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 48 ff.

(4) Yoshioka, T.; Hara, T.; Takita, T.; Umezawa, H. *J. Antibiot. (Tokyo)* **1974**, *27*, 356.

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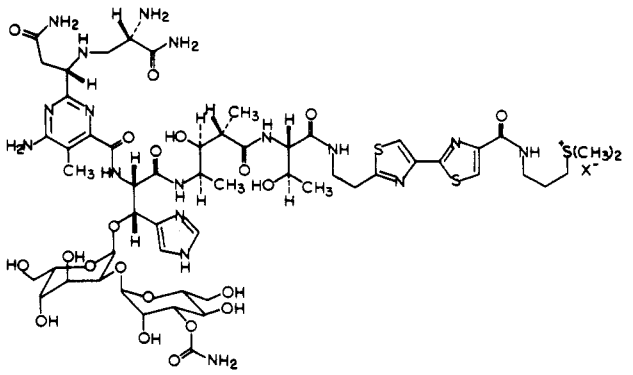

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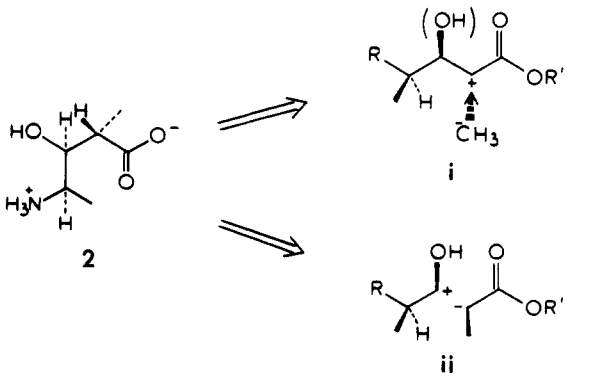
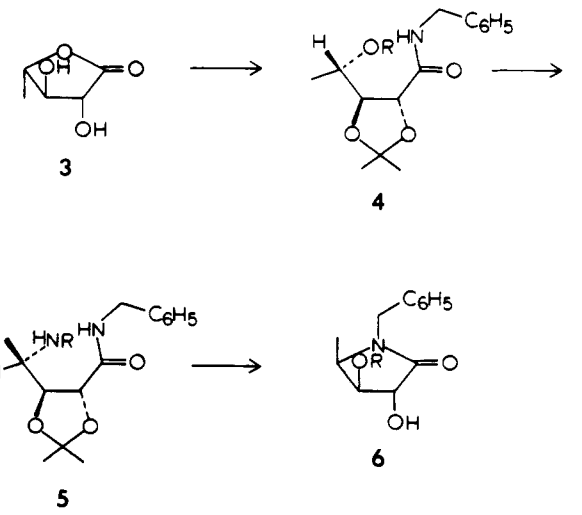
batches of material derived from the modified procedure had undergone partial racemization.[5] Reported herein is a stereospecific synthesis of optically pure (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvaleric acid from L-rhamnose. A key feature in the synthesis was the use of Mg^{2+} to *deactivate* a reactive OH group, permitting highly selective acylation of another OH group. This approach (i) constitutes an alternative to the stereoselective aldol condensation (ii) for the construction of chiral 3-hydroxy-2-methylcarboxylates.[6]



2 i ii

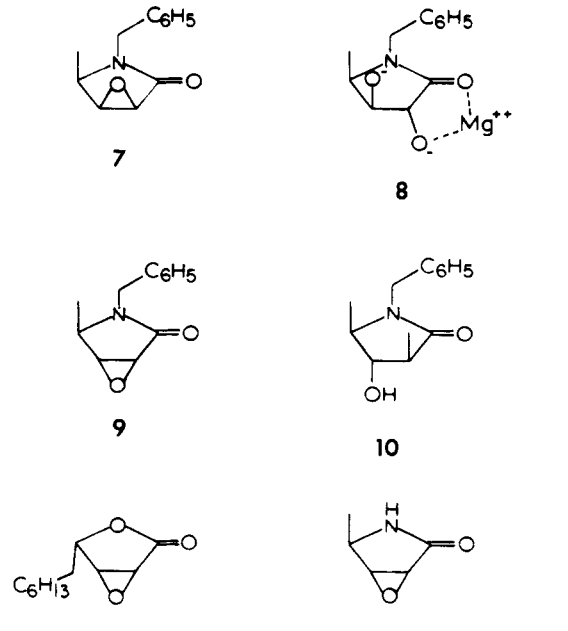
5-Deoxy-L-arabono-γ-lactone (**3**) was accessible in high yield from L-rhamnose, as described.[7,8] Treatment of **3** with excess benzylamine in methanol (reflux, 12 h, 0.6 equiv of Hünig's base) afforded the respective *N*-benzylamide as colorless prisms (82%, mp 185 °C). After conversion (acetone, p-$CH_3C_6H_4SO_3H$) to the oily acetonide (**4**, R = H; 96%), the corresponding 4-methanesulfonate derivative (**4**, R = SO_2CH_3) was obtained as a heavy reddish syrup in quantitative yield (CH_3SO_2Cl, pyridine, −20 → 0 °C, 5 h). Displacement of the mesylate (NaN_3, DMF, 100 °C, 20 h) produced the 4-azido *N*-benzylamide as a yellow syrup in 92% yield. Transformation to key intermediate **6** (R = H) was then accomplished by hydrogen-



3 4 5 6

olysis of the azide, reductive amination of benzaldehyde to afford **5** (R = $CH_2C_6H_5$), and ring closure, giving lactam **6** (R = H) as colorless crystals:[10] mp 94–95 °C; NMR (D_2O) δ 1.20 (3 H, d, J = 7.0 Hz), 3.70 (1 H, m), 4.25 (1 H, t, J = 7.2 Hz), 4.50 (1 H, J = 7.2 Hz), 4.28, 4.82 (2 H, AB q, J = 15 Hz), 7.45 (5 H, m); mass spectrum, m/e 221 (M^+). The overall yield of **6** (R = H) from **3** was 61%.

Conceptually, the preparation of amino acid **2** was to involve conversion of **6** selectively to epoxy lactam **9** and regioselective introduction of a methyl group at C-2 with concomitant opening of the epoxide ring. Hydrogenolysis and hydrolysis of **10** would then afford **2**. However, as



7 8 9 10 11 12

expected, treatment of a THF solution of **6** (R = H) with 2 equiv of CH_3SO_2Cl in the presence of a suspension of NaH gave exclusively lactam **7** ($J_{3,4}$ = 2.6 Hz), presumably via initial acylation of the more acidic 2-OH group, followed by proton abstraction from the 3-OH group and epoxide formation. The obvious alternative, pretreatment

(5) Presumably, this was a consequence of epimerization at C-4 during borohydride reduction of (4*R*)-ethyl 3-oxo-2-methyl-4-phthalamidovalerate to afford a mixture of eight isomers, from which the partially racemized species was isolated.

(6) See, e.g.: (a) Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 8109; (b) Meyers, A. I.; Reider, P. J. *J. Am. Chem. Soc.* **1979**, *101*, 2501; (c) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, 2225; (d) Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937; (e) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Ibid.* **1979**, 4029; (f) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120; (g) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066 and references therein; (h) Pirrung, M. C.; Heathcock, C. H. *Ibid.* **1980**, *45*, 1727.

(7) Taylor, E. C.; Jacobi, P. A. *J. Am. Chem. Soc.* **1976**, *98*, 2301.

(8) Andrews, P.; Hough, L.; Jones, J. K. N. *J. Am. Chem. Soc.* **1955**, *77*, 125.

(9) Satisfacotry spectral and analytical data were obtained for the new compounds reported.

(10) Hydrogenolysis of the azide (10% Pd/C, H_2, absolute CH_3OH, 5h) afforded **5** (R = H) as a thick yellow syrup in quantitative yield. A benzene solution of the amine was stirred (25 °C, 13 h) with 1 equiv of benzaldehyde, and the imine so derived was treated with $NaBH_4$ in absolute C_2H_5OH, giving **5** (R = $CH_2C_6H_5$) as a syrup in 93% yield. Subsequent treatments with CH_3OH–hydrogen chloride (reflux, 48 h) and then with 1 M $NaOCH_3$ in CH_3OH (25 °C, 2 h) afforded **6** (R = H) in 86% yield.

of **6** (R = H) with n-C_4H_9Li (2.5–5.0 equiv, −20 °C, 1:1 $(C_2H_5)_2O$–THF), followed by addition of 1.2–2.5 equiv of CH_3SO_2Cl, gave **6** (R = SO_2CH_3) in variable yields up to 40%, isolable by careful chromatography on silica gel. A much better yield of **6** (~70%, R = SO_2CH_3) was obtained by pretreatment with 4.4 equiv of isopropylmagnesium bromide (THF, 0 °C). The clear solution became turbid immediately upon addition of C_3H_7MgBr and 2.3 equiv of CH_3SO_2Cl was then added. After the reaction was complete (18 h, 0 → 25 °C) extractive workup afforded **6** (R = SO_2CH_3) as a thick syrup: NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.22 (3 H, d, J = 6.0 Hz), 3.12 (3 H, s), 3.72 (1 H, m), 4.55 (1 H, d, J = 7.8 Hz), 4.92 (1 H, t, J = 7.8 Hz), 4.01, 4.09 (2 H, AB q, J = 15 Hz), 7.20–7.40 (5 H, m); mass spectrum, m/e 299 (M^+). Although no direct evidence has been obtained concerning the nature of the intermediate(s) that resulted in selective acylation on O-3, Mg^{2+} chelate **8** may constitute a reasonable representation of the relevant species. Consistent with the interpretation that the C-2 alkoxide was deactivated toward acylation by participation in a Mg^{2+} complex[11,12] was its observed inability to mediate subsequent epoxide ring formation, even at ambient temperature, as had been found for the corresponding acylated Na^+ alkoxide intermediate. Treatment of **6** (R = SO_2CH_3) with $K^+{}^-OC(CH_3)_3$ (THF, 25 °C, 40 min) effected clean conversion to epoxide **9**, isolated as a syrup by preparative TLC (silica gel, development with 3% methanol in CH_2Cl_2, 78% yield): NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.20 (3 H, d, J = 7.0 Hz), 3.50–3.70 (3 H, m), 4.00, 4.85 (2 H, AB q, J = 15 Hz), 7.20–7.30 (5 H, br s); mass spectrum, m/e 203 (M^+), 188, and 112.

The conversion **9** → **10**, although without close precedent, bears superficial analogy to several reported transformations. For example, reaction of epoxy lactone **11** with lithium n-heptanethiolate gave a single product resulting from nucleophile attack at C-2;[13] however, other nucleophiles preferentially cleaved the lactone.[13,14] Regioselective epoxide opening with "alkyl anion" equivalents has also been observed for certain conformationally rigid carbohydrate epoxides[15] and acyclic epoxides;[16] both steric and electronic effects may contribute to regiochemistry. Treatment of epoxide **9** with 5 equiv of $(CH_3)_2CuLi$ (ether, −78 → 5 °C, 4 h) gave **10** as colorless needles (mp 100 °C, 57%) after purification by preparative TLC and crystallization from toluene; none of the isomeric (2-OH, 3-CH_3) lactam could be detected. Interestingly, analogous treatment of **12** gave an approximately equal mixture of products formed by nucleophilic attack at C-2 and C-3, respectively, emphasizing the importance of electronic effects on regioselectivity in the present case.[17] As anticipated, successive treatments of lactam **10** with Na/liquid NH_3 and 2 N HCl (reflux, 4 h) effected debenzylation and hydrolysis, in respective yields of 84% and >95%. Compound **2** was obtained as a colorless solid: mp 160–161 °C[18] (from ethanol–ether) (lit.[4,19] mp 144–146 °C); $[\alpha]^{25}_D$ +12.1° (c 1.03, H_2O) [lit.[19] $[\alpha]^{23}_D$ +10.7° (c 7.25, H_2O)]; $[\alpha]^{25}_D$ +13.6° (c 1.17, H_2O) (HCl salt); NMR (D_2O) δ 1.40 (6 H, dd), 2.70 (1 H, m), 3.70 (1 H, m), 4.00 (1 H, dd, J = 9.0, 3.0 Hz).

The construction of **2** outlined here is of interest in the context of stereospecific aldol condensations for the elaboration of 3-hydroxy-2-methylcarboxylates.[6] In the present case the erythro product, which is the typical product of the stereospecific aldol condensation,[6] is formed exclusively.[20] Significantly, while the use of chiral aldehydes in the aldol process generally affords mixtures of products whose composition can be predicted,[21] in the approach discussed here it is anticipated that the stereochemistry of the substituent at C-4 has little effect on formation of the *erythro*-3-hydroxy-2-methylcarboxylate. It seems reasonable to suggest that the approach described herein may find application in the elaboration of complex natural products from carbohydrates.[22]

Acknowledgment. We thank Professor Glenn J. McGarvey for a helpful discussion during the course of this work. This investigation was supported by research Grant CA-27603 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

(11) See, e.g.; Baker, S. R.; Crombie, L. *J. Chem. Soc., Chem. Commun.* **1980**, 213.

(12) See also: (a) Nagabhushan, T. L.; Cooper, A. B.; Turner, W. N.; Tsai, H.; McCombie, S.; Mallams, A. K.; Rane, D.; Wright, J. J.; Reichert, P.; Boxler, D. L.; Weinstein, J. *J. Am. Chem. Soc.* **1978**, *100*, 5253; (b) Hanessian, S.; Patil, G. *Tetrahedron Lett.* **1978**, 1035.

(13) Boeckman, R. K., Jr.; Thomas, E. W. *J. Am. Chem. Soc.* **1979**, *101*, 986.

(14) (a) Jakubowski, A. A.; Guziec, F. S., Jr.; Tishler, M. *Tetrahedron Lett.* **1977**, 2399. (b) Corey, E. J.; Williams, D. R. *Ibid.* **1977**, 3847. (c) Ohrui, H.; Emoto, S. *Ibid.* **1978**, 2095. (d) Pougny, J. R.; Sinaÿ, P. *Ibid.* **1978**, 3301. (e) Pietraszkiewicz, M.; Sinaÿ, P. *Ibid.* **1979**, 4741.

(15) (a) Hanessian, S.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 1111. (b) Hanessian, S.; Rancourt, G. *Pure Appl. Chem.* **1977**, *49*, 1201.

(16) (a) Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 4978. (b) Herr, R. W.; Johnson, C. R. *Ibid.* **1970**, *92*, 4979. (c) Hartman, B. C.; Livinghouse, T.; Rickborn, B. *J. Org. Chem.* **1973**, *38*, 4346. (d) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343.

(17) Presumably, treatment of **12** with excess $(CH_3)_2CuLi$ results in initial deprotonation of the amide, which deactivates C-2 toward nucleophilic displacement.

(18) Compound **2** had the same melting point as synthetic samples prepared in our laboratory by two different routes;[3,4] the ^1H NMR spectra of the synthetic samples were all identical with that reported[19] for a sample of the same material derived from bleomycin.

(19) Takita, T.; Muraoka, Y.; Maeda, K.; Umezawa, H. *J. Antibiot. (Tokyo)* **1968**, *19*, 79.

(20) One may anticipate the formation of threo products by treatment of suitable derivatives of **6** (e.g., acylated on 0-2, blocked on 0-3) with "alkyl anion" equivalents.

(21) (a) Cram, J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828, 5851. (b) Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2737. (c) Leitereg, T. J.; Cram, D. J. *Ibid.* **1968**, *90*, 4019.

(22) See also: Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159.

(23) National Cancer Institute Career Development Awardee, 1975–1980.

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Received October 24, 1980