Tetrahedron Letters,Vol.23,No.23,pp 2355-2358,1982 0040-4039/82/232355-04$03.00/0
Printed in Great Britain

HIGHLY STEREOCONTROLLED REDUCTION OF α'-ALKOXYENONES TO GIVE EITHER THE THREO OR ERYTHRO ALLYLIC 1,2-DIOL. ASSIGNMENT OF THE THREO CONFIGURATION TO THE C-15,C-16 DIOL OF PUMILIOTOXIN B.[1]

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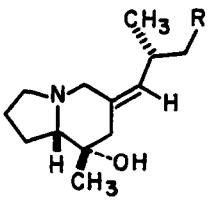
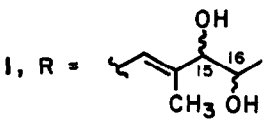
Summary: Model studies indicate that the allylic diol of pumiliotoxin B has the threo configuration, and that this functionality can be prepared with excellent stereocontrol by reduction of an α'-t-butyldiphenylsilyloxyenone.

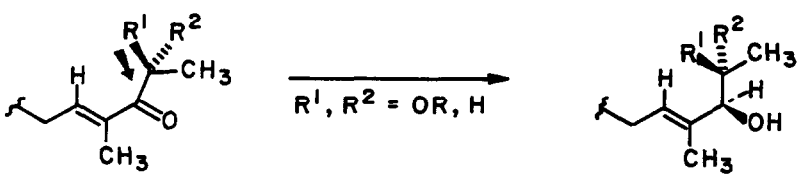
The gross structure of pumiliotoxin B (1) was reported by Daly and coworkers in 1980,[2] and last year our laboratory described[3] the first total synthesis of a member of this alkaloid class, toxin 251D (2). As a prelude to a total synthesis of pumiliotoxin B, we have been investigating stereocontrolled methods for assembling the allylic diol functionality of this toxin. In this Letter, we report that the allylic diol of pumiliotoxin B has the threo configuration, and moreover relate that the reduction of α'-alkoxyenones can be accomplished to give either threo or erythro allylic 1,2-diols with excellent (>95%) stereocontrol.





2, R = $CH_2CH_2CH_3$

Since 1,2-addition to an enone is expected to occur via a skewed[4] backside[5] trajectory which should accentuate interactions of an entering hydride with a chiral α'-carbon, we chose to explore the preparation of the pumiliotoxin B diol functionality by relative 1,2-asymmetric induction[6] as illustrated in eq 1. The model (2S,4E)-enones 3 and 4[7] were prepared from ethyl (S)-(+)-lactate in 30-40%

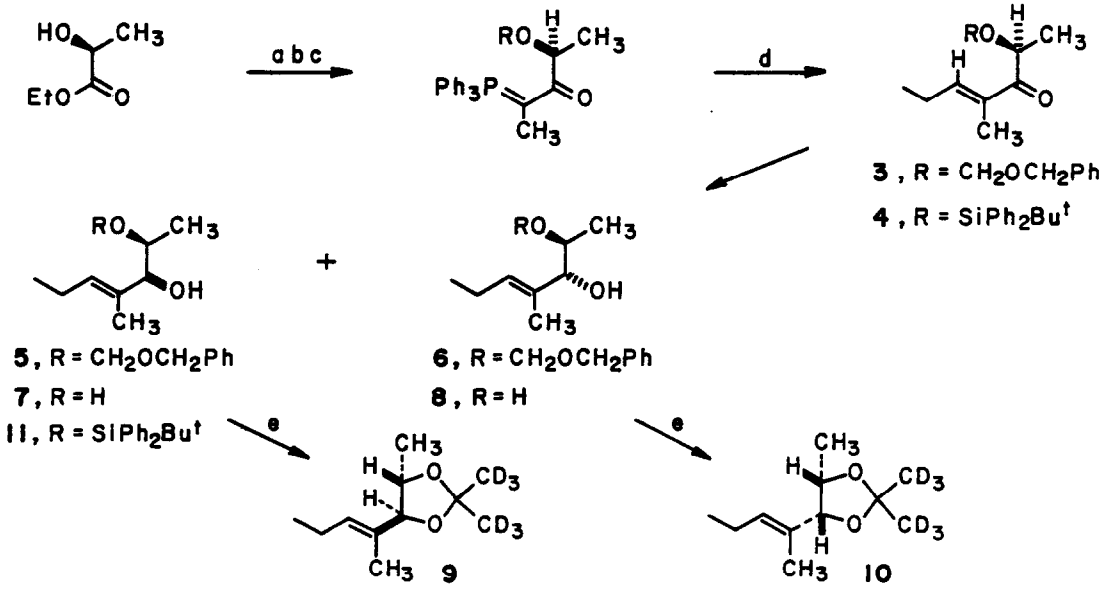


(1)

overall yield as summarized in the Scheme. Reduction of 3 with 2 equiv of diisobutylaluminum hydride (toluene, rt) gave a 3:2 mixture of diastereomeric alcohols in 80% yield. Separation by HPLC[8] gave pure samples of 5[7] (major isomer) and 6,[7] which were reductively debenzylated (Na/NH_3, -78°) in essentially quantitative yields to give the threo diol 7[7] ($[\alpha]_D^{25}$ 10.0°, C 0.5 $CHCl_3$; ^1H NMR δ 3.78, m, C_2-H;[9] δ 3.72, broadened d, J = 7.0 Hz, C_3-H; ^{13}C NMR δ 81.0, C_3; 68.8, C_2) and the erythro diol 8[7] ($[\alpha]_D^{25}$ -9.8°, C 1.5 $CHCl_3$; ^1H NMR δ 3.91, broadened d, J = 5.2 Hz, C_3-H; δ 3.85, m, C_2-H;[9] ^{13}C NMR δ 83.1, C_3; 69.2 C_2) respectively. The stereochemical assignments for 7 and 8 were made on the basis of intramolecular nuclear Overhauser experiments.[10] Thus, the threo d_6-acetonide 9 (^1H NMR δ 3.8-3.9, m, C_2-H and C_3-H) showed a strong signal (δ 3.87, d, J = 3.7 Hz) for the C_3-hydrogen in the difference NOE spectrum[10bc] when the methyl doublet at δ 1.21 was irradiated, while the erythro d_6-acetonide 10 (^1H NMR δ 4.48, d, J = 5.2 Hz, C_3-H; δ 4.38, m, C_2-H[9]) showed no detectable signal for the C_3-hydrogen under identical conditions. The 250 MHz ^1H NMR spectrum of pumiliotoxin B[2] (broadened d for the C_{15}-H at δ 3.66, J ~ 8 Hz; m for the C_{16}-H at δ 3.75) most clearly resembles the model threo diol 7.[11]

The reduction of α'-alkoxyenones of this type can be controlled to give either the threo or erythro allylic diol by the proper choice of reducing agent and alcohol protecting group; a few of the combinations examined are summarized in the Table. The high erythro selectivity (98%) obtained from the reaction of

Scheme



(a) $PhCH_2OCH_2Cl$ or Ph_2Bu^tSiCl; (b) 5% KOH, MeOH, rt; 2-pyridinethiol, DCC, rt; (c) $CH_3CH{=}PPh_3$, THF, rt; (d) CH_3CH_2CHO, 50°; (e) CD_3COCD_3, TsOH, rt.

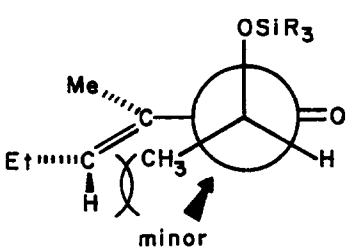
Table Stereoisomer Ratios[a] from Reduction of 2-Alkoxy-4-methyl-4E-hepten-3-ones

Enone R	Reductant	Temp, °C	Threo:Erythro
$R=CH_2OCH_2Ph$ (3)	Bu_3^iAl, pentane	25°	70:30
	Bu_3^iAl, pentane	-22°	55:45
	$LiAlH_4$, THF	-10°	30:70
	$LiAlH_4$, Et_2O	-10°	2:98
R=H	$LiAlH_4$, THF	-10°	40:60
R=Ac	Bu_3^iAl, pentane	25°	45:55
$R=SiMe_3$	Bu_3^iAl, pentane	25°	43:57
$R=SiPh_2Bu^t$ (4)	Bu_3^iAl, pentane	25°	94:6
	$LiAlH_4$, THF	-20°	95:5

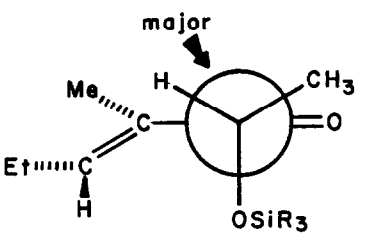
[a] From 250 MHz ^1H NMR analysis of crude products.

enone 3 with $LiAlH_4$ in ether is consistent with reduction of a chelated[6] intermediate. With many reducing agent-protecting group combinations, bad mixtures of threo and erythro diols were obtained, presumably resulting from competitive reduction of both chelated and non-chelated intermediates. When the extremely bulky t-butyldiphenylsilyl ether[12] was employed, chelation was apparently prevented, and excellent (>94%) threo selectivity was observed with both $LiAlH_4$ and triisobutylaluminum. On a preparative scale, reduction of the t-butyldiphenylsilyloxyenone 4 with Bu_3^iAl[13] followed by chromatographic purification of 11 and desilylation (Bu_4NF)[12] gave the pure chiral[14] threo diol 7 in 75% overall yield.

The excellent erythro and threo selectivities obtained from $LiAlH_4$ reduction of α'-alkoxyenones 3 and 4 are higher than selectivities recorded in the literature[6,15] for hydride reductions of α-alkoxy (and α-hydroxy)ketones, and may reflect the skewed trajectory illustrated in eq 1.[16] Since enones 3 and 4 should be effectively locked in s-trans conformations,[17] we note that the unusually high "Cram" selectivity observed with 4 may reflect also destabilization of the minor "Felkin-Ahn"[18] transition state as a result of steric interactions between the α'-methyl group and the β-hydrogen of the enone system.[16]



(erythro product)



(threo product)

Acknowledgment. We particularly wish to thank Dr. John Daly and Dr. Takashi Tokuyama for generously providing a sample of pumiliotoxin B and information concerning their parallel studies. Financial support from the National Institutes of Health (HL-25854), the Camille and Henry Dreyfus Foundation (teacher-scholar award to L.E.O.), and the NSF (instrument program) is gratefully acknowledged.

References and Notes

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7. All new compounds showed IR, 250 MHz ^{1}H NMR ($CDCl_3$), 63 MHz ^{13}C NMR ($CDCl_3$), and mass spectra which were fully in accord with their assigned structures.
8. A Dupont Zorbax PSM-60 column, 6:1 hexane:ethyl acetate eluent, and 2.0 mL/min flow rate were used for this analysis.
9. This signal was simplified to a doublet with the same coupling constant as the C_3-H when the methyl group (C_1-H) was decoupled.
10. (a) Nakanishi, K.; Schooley, D.A.; Koreeda, M.; Miura, I. J. Am. Chem. Soc. 1972, 94, 2865. (b) Hall, L.D.; Sanders, J.K.M. ibid 1980, 102, 5703. (c) Bruker Aspect-2000 NMR Software Manual, 1-A, 1981, Part 4.7.
11. A nicer comparison of a related series of phenylboronides is described in ref 1.
12. Hanessian, S.; Lavallee, P. Can. J. Chem. 1977, 55, 562.
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(Received in USA 12 March 1982)