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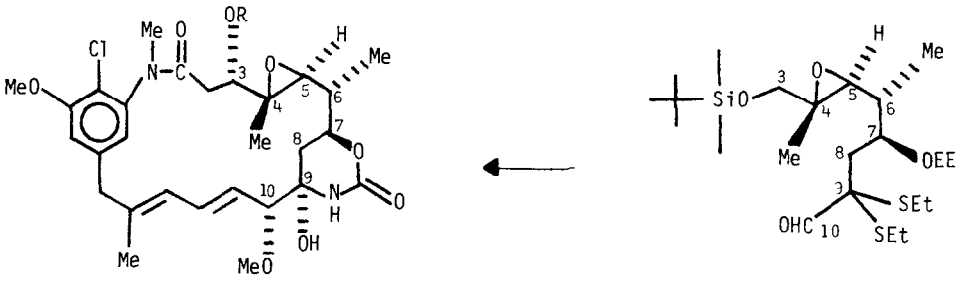
ENANTIOSELECTIVE SYNTHESIS OF C_3-C_{10} FRAGMENT (NORTHEASTERN ZONE) OF MAYTANSINOIDS WITH 4-CHIRAL CENTERS (4S,5S,6R,7S)

A. I. Meyers* and James P. Hudspeth
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

SUMMARY: The major precursor to the maytansinoids containing 4 non-racemic chiral centers has been prepared in gram quantities, suitable for further synthesis. The route to (+)-1 was accomplished in 13 steps including several highly stereocontrolled reactions which precluded resolutions or separations.

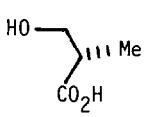
In the recently described total synthesis of maytansinoids,[1] the major fragment 1 was featured, in racemic form, as a key precursor to a variety of these interesting macrocycles. We now report that an efficient synthesis of enantiomerically pure 1 has been accomplished which, along with another described route,[2] should provide access to optically active members of the series. The sequence begins with the hydroxy acid 2[3] with S-configuration and proceeds



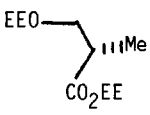
Maytansines (R = H, Acyl)

(+)-1

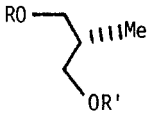
through a series of transformations to reach the R-configuration (7) necessary as the C-6 substituent in maytansines. Thus, 2 was converted to its bis-ethoxyethyl derivative 3 with ethyl vinyl ether (TsOH, 0°) and without purification was reduced ($LiAlH_4$, THF, 0°) to the alcohol 4 ($[\alpha]_D$+7.82).[4] Treatment with benzyl bromide-t-BuOK (THF, 0°) gave the benzyl ether 5 ($[\alpha]_D$ = -1.07°)[4] which was converted to the alcohol 6 by treatment with 10% HCl-THF at 25°.



S (+)-2



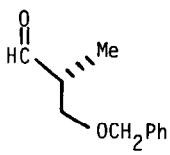
3 (crude)



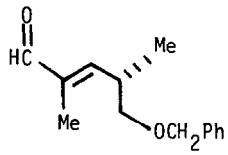
(+)-4, R = (2-ethoxyethyl), R'=H

(-)-5, R = (2-ethoxyethyl), R'=CH_2Ph

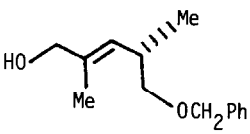
(-)-6, R=H, R'=CH_2Ph (99% ee)



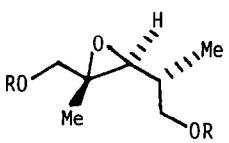
7



(+)-8



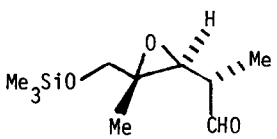
(+)-9



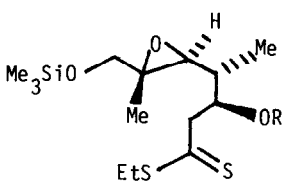
(-)-10, R = H, R' = CH_2Ph

(-)-11, R = Me_3Si, R' = CH_2Ph

(-)-12, R = Me_3Si, R' = H (99% ee)

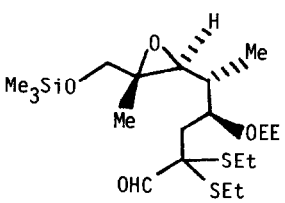


(+)-13



(+) 14, R = H (10:1 E/T)

15, R = EE



(+)-1a

(+)-1b

The alcohol ($[\alpha]_D$ -11.2°, c 16 $CHCl_3$) was esterified with α-trimethoxy-α-trifluoromethylphenylacetic acid (Mosher Ester)[5,6] and found to be >99% ee. The R-aldehyde 7[7] which is equivalent to the 6-methyl group in (+)-1, was prepared by Swern[8] oxidation (DMSO, oxalyl chloride, Et_3N, -60°) with less than 1% racemization. This was later confirmed by ee assessment on (-)-12 using diastereomeric esters (vide infra). Homologation to the α,β-unsaturated aldehyde (+)-8 ($[\alpha]_D$ +26.0) was accomplished using N-cyclohexylpropyl imine (LDA, -78°, THF) followed by oxalic acid hydrolysis. Reduction ($NaBH_4$, EtOH, 0°) gave the allyl alcohol, R-(+)-9 ($[\alpha]_D$ +13.16)[7] in 54% overall yield from 2. Epoxidation of 9 according to Sharpless[9] gave (-)-10 in 93% yield ($[\alpha]_D$ -12.05). The % ee could not be determined either by nmr or hplc and thus (-)-10 was transformed into (-)-11 (90%, t-$BuMe_2SiCl$, imidazole, 25°, $[\alpha]_D$ -4.46°) which also failed to exhibit diastereomers (hplc nmr). However, removal of the benzyl group (Na, liq. NH_3, -78°) to give (-)-12 ($[\alpha]_D$ -5.33°) gave, as the Mosher ester, >99% diastereomeric purity[10] (hplc, T_R 13.0 min, 20% ethyl acetate-hexane). When racemic 12 was similarly treated, both diastereomers were visible (T_R 12.0, 13.0 min). With the three chiral centers corresponding to 4S,5S,6R already in place, the sequence continued by chromic acid oxidation (CH_2Cl_2, -25°) to give (+)-13 ($[\alpha]_D$ +18.7°) which was treated with lithiodithioacetate (THF, -120°)[11] to give the erythro (+)-14 (Cram's Rule) in 10:1 ratio. Tlc separation gave pure (+)-14 ($[\alpha]_D$ +36.8°) in 60% yield from 9. The hydroxy group in 14 was masked (ethyl vinyl ether, TsOH) to a mixture of diastereomers 15 and treated with ethylmagnesium iodide[11] and formylated[1] to (+)-1. The latter was separated (TLC, 10% acetone-hexane) into both diastereomers (+)-1a, $[\alpha]_D$ +112.7°, (+)-1b, $[\alpha]_D$ +61.8°, but this is not necessary since the protecting group (EE) in 1 will be removed at the later stages of the synthesis. Thus, (+)-1 contains the four properly placed chiral centers which was confirmed by nmr (360 MHz) comparison with racemic 1.[1]

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REFERENCES & NOTES

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3. We thank Dr. Noal Cohen, Hoffmann-La Roche, for providing a generous source of the acid, S-(+)-2; C. T. Goodhue and J. R. Schaeffer, Biotechnol. Bioeng., 13, 203 (1971); N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, J. Org. Chem., 41, 3505 (1976). The acid contains ∿15% oligomer and was not purified prior to use.

4. Mixture (∿1:1) of diastereomers.
5. J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).
6. The racemic alcohol (±)-6, as a Mosher ester, showed (360 MHz) -OCH_2Ph singlets at δ 4.44 and δ 4.46. For (-)-6 as its Mosher ester, only the signal at δ 4.44 was visible.
7. The S-aldehydes and subsequent products derived therefrom have been reported, M. R. Johnson and Y. Kishi, Tetrahedron Letters, 2733 (1980). No rotation data are given in this paper.
8. A. J. Mancuso, S. L. Huangard and D. Swern, J. Org. Chem., 43, 2480 (1978).
9. T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).
10. (-)-12 was also prepared via the asymmetric halolactonization route described by S. Terashima [Tetrahedron Letters, 2733 (1980)].
11. A. I. Meyers, T. A. Tait, D. L. Comins, Tetrahedron Letters, 4657 (1978).

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