Tetrahedron Letters, Vol.32, No.51, pp 7535-7538, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

FROM DISUBSTITUTED ACETYLENES TO TRISUBSTITUTED OLEFINS. AN APPLICATION

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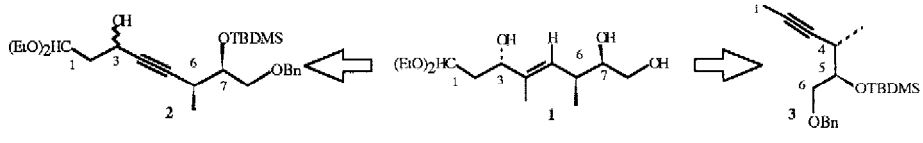
Summary: The transformation of disubstituted acetylenes to trisubstituted olefins was studied in order to obtain precursors of the north-eastern part of maytansine. Depending on the starting material, a *trans* or a *cis* stannylation reaction could lead to the olefin of the desired stereochemistry

In a previous paper,[1] we studied the opening of *trans*-2, 3-epoxybutanol derivatives with organometallic reagents and found that the use of acetylenic alanes or acetylenic alanates in the presence of BF_3:OEt_2 could lead to reactions with high yield and regioselectivity.

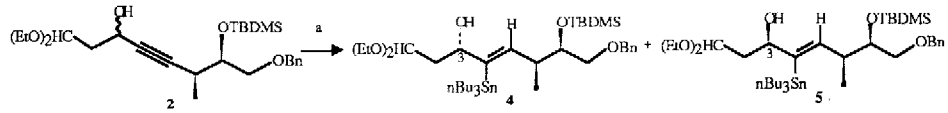
In our synthetic endeavours toward the C-1-C-9 North-Eastern part of maytansine, it was necessary for the next step to transform the disubstituted acetylenes we had obtained, to trisubstituted olefins .

Two approaches were considered for the synthesis of the 3S, 6R, 7R, E-olefin **1**, from either acetylene **2**, product with a functionalized chain, or **3**, product with an alkyl side chain (Scheme 1).



Scheme 1

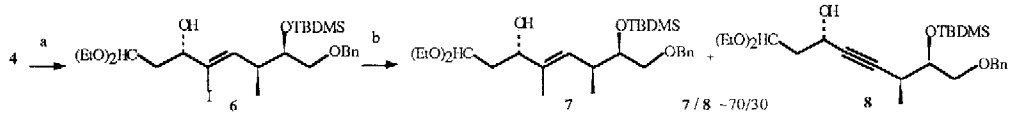
Compound **2**,[1] prepared as a mixture of diastereomers at C-3, was transformed to the corresponding tin derivatives by treatment at 80°C with tri-*n*-butyltin hydride, in the presence of AIBN, leading regio and stereoselectively to the *trans*-addition products (Scheme 2).[2] At this stage, the diastereomers were easily separable and compounds **4**[3] and **5**[4] were obtained in pure form.[5]



a)-nBu3SnH 2 eq., AIBN cat., 80°, 80%

Scheme 2

To effect the alkylation of compound **4** of the 3S, 6R, 7R stereochemistry,[5] the alkyltin group was converted to the iodo derivative **6**[6] and was submitted to the conditions described by Corey,[7] by treatment with dimethylcuprate followed by addition of excess methyl iodide. However, the best results obtained in these conditions, were an unseparable 70/30 mixture of **7**, alkylation product, and **8**, elimination product (Scheme 3).

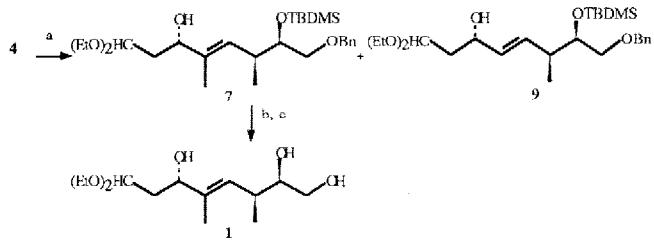


a)-I_2, slight excess, THF, rt, quantitative; b)-Me_2CuLi, THF, 4°C, 72 h, then excess ICH_3 , 0°C, 75%.

Scheme 3

Therefore, the hydrostannylated compound **4** was transformed to a higher order cuprate, with lithium dimethylcyanocuprate, according to the procedure by Lipschutz,[8] which, upon addition of excess methyl iodide, afforded trisustituted alkene **7** in a 70% yield plus *ca* 5% of the vinyl compound **9**. In the case where the 3-hydroxyl group of **6** was protected as its dimethyl-*t*-butylsilyl ether, a complex mixture was obtained upon attempted alkylation whereby cleavage of the C3-O bond took place.

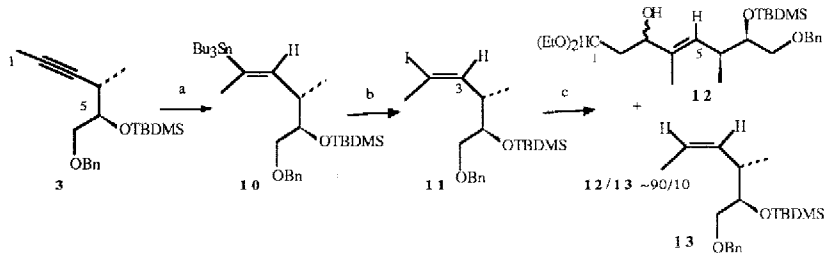
Desilylation of **7**, followed by cleavage of the benzyl group with lithium in ethylamine afforded **1**.[9]



a)- lithium dimethylcyanocuprate 3 eq., THF, -10° then ICH_3 , 5 eq, -78° then **4** or **5**, -78°C to -25°C,.19 h, 70%.b)-nBu_4NF, THF, r.t, 90%; c)- $EtNH_2$, Li°, excess, 0°C, 80%..

Scheme 4

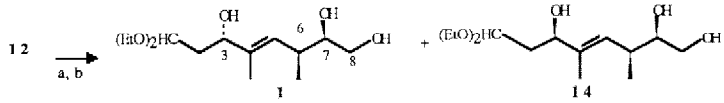
In our second approach, the acetylenic compound **3**,[10] resulting from the opening of 1-benzyloxy-2(S), 3(S)-epoxybutane with lithium propynyltrimethylalanate in the presence of $BF_3.OEt_2$, was submitted to a reaction of *cis*-hydrostannylation, according to conditions described by Zhang et al.[11], with tri-n-butyltin hydride in the presence of Pd[0]. Compound **10** was obtained regio and stereoselectively which in turn, was transformed to the iodo derivative **11.**[12] This compound, when treated with *t*-butyllithium followed by malonaldehyde monodiethyl acetal,[13] gave **12** as a mixture of diastereomers and reduced product **13** (Scheme 5).



a)-*n*Bu_3SnH, 1.5 eq., $PdCl_2(PPh_3)_2$, catalytic, 0°C, 70%; b)- I_2, slight excess, THF, -78°C quantitative; c)- *t*BuLi, 2.1 eq. -78°C, 10 min. then malonaldehyde diethylacetal 1.5 eq., -100° to -40°C, 1h , 65%.

Scheme 5

The diastereomeric mixture could easily be resolved by chromatography after removal of the C-7 and C-8 hydroxy protecting groups, furnishing compounds **1**[9] and **14**[14] (Scheme 6). Using Mitsunobu's procedure,[15] the 3R epimer could be inversed after protection of the vicinal diol of **14**.[16]



a)-nBu_4NF, 1eq., THF, 1h, 90%. b)- $EtNH_2$, Li° excess, -10°C,.80%

Scheme 6

In conclusion, we have in hand, good methodology to synthesize trisubstituted olefins of definite stereochemistry, starting from disubstituted acetylenes by the use of either *cis* or *trans* hydrostannylation procedure.[17]

Acknowedgement: T. Skrydstrup is grateful for a Maxwell postdoctoral fellowship from the Académie des Sciences.

References and Notes

1 Skrydstrup, T.; Bénéchie, M.; Khuong-Huu, F. *Tetrahedron Letters*, **1990**, *31*, 7145.

2 Nativi, C.; Taddei, A.; *J. Org. Chem.* **1988**, *53*, 820.

3 **4**- colourless oil, $C_{38}H_{72}O_5SiSn$, $[\alpha]_D$=+21 ($CHCl_3$, c=0.7), MS EI: no M^+, M-57; ^1H NMR 200 MHz δ ppm: 0.02 (3H, *s*, Si-CH_3), 0.03 (3H, *s*, Si-CH_3), 0.88 9H, *s*, *t*Bu) 0.85- 0.98 (18H, 6 CH_3), 1.20-1.89 (20H, *m*, CH_2), 2.23 (1H, *m*, H-6), 2.88 (1H, *d*, J=2 Hz, OH), 3.39, 3.55 and 3.70 (7H, *m*, H-7, CH_2-8 and 2 CH_2-O), 4.32 (1H, *m*, H-3), 4.44 and 4.54 (2H, *AB*, J=12 Hz, CH_2-Ar), 4.67 (1H, *dd*, J=5 Hz, J'=7 Hz, H-1), 6.18 (1H, *d*, J=10 Hz, H-1), 7.33 (5H, *s*, C_6H_5); ^{13}C NMR δ ppm: -4.50 (Si-C), -3.92 (Si-C), 11.46 (Sn-CH_2-CH_2-$\underline{CH_2}$) 13.73 (3 CH_3 of *n*-Bu), 15.19 (CH_3-9), 15.39 (CH_3), 15.50 (CH_3), 18.38 (Si-C), 26.12 (*t*Bu), 27.56 (3 Sn-CH_2-$\underline{CH_2}$), 29.39 (3 Sn-CH_2), 41.59 (CH-6), 41.87 (CH_2-2), 61.40 (O-$\underline{CH_2}$-CH_3), 62.34 (O-$\underline{CH_2}$-CH_3), 73.30 (CH_2-8), 73.71 (CH_2-Ar), 75.01 (CH-7), 76.41 (CH-3), 102.40 (CH-1), 127.47, 127.65 and 128.27 (5 aromatic CH), 138.56 (C aromatic), 144.01 (CH-5), 146.67 (C-4).

4 **5**- colourless oil, $[\alpha]_D$=+1 ($CHCl_3$, c=1), $C_{38}H_{72}O_5SiSn$, calc.%: C 60.93, H 9.63 found: C 60.69, H 9. 80; MS EI: no M^+, m/z 711 (M-57); ^1H NMR 200 MHz δ ppm: 0.02 (3H, *s*, Si-CH_3), 0.03 (3H, *s*, Si-CH_3), 0.88 (9H, *s*, *t*Bu), 0.85-0.98(18H, 6 CH_3), 1.18-1.87 (20H, CH_2), 2.23 (1H, *m*, H-6) 3.02 (1H, *d*, J=2 Hz, OH), 3.36, 3.55 and 3.70 (7H, *m*, H-7, CH_2-8 and 2 CH_2-0), 4.32 (1H, *m*, H-3), 4.44 and 4.54 (2H, *AB*, J=12 Hz, CH_2-Ar), 4.68 (1H, *t*, J=6 Hz, H-1), 6.20 (1H, *d*, J=10 Hz, H-5), 7.33 (5H, *s*, C_6H_5); ^{13}C NMR δ ppm: -4.59 (Si-CH_3), -3.93 (Si-CH_3), 11.40 (3 Sn-CH_2-CH_2-$\underline{CH_2}$), 13.71 (3 CH_3 of *n*-Bu), 15.01 (CH_3-9), 15.36 (CH_3), 15.47 (CH_3), 18.34 (Si-C), 26.08 (*t*-Bu), 27.52 (3 Sn-CH_2-$\underline{CH_2}$), 29.35 (3 Sn-CH_2), 41.59 (CH-6), 41.59 (CH_2-2) , 61.49 (O-$\underline{CH_2}$-CH_3), 62.26 (O-$\underline{CH_2}$-CH_3), 73.30 (CH_2-8), 73.71 (O-CH_2-Ar), 75.01 (CH-7), 76.42 (CH-3) 102.40 (CH-1), 127.47, 127.65 and 128.27 (5 aromatic-CH), 138.56 (C aromatic), 144.01 (CH-5), 146.67 (C-4).

5 Structural assignment was effected, after further transformations, by comparison with a product obtained starting from 3*S* - acetylene **2**..Resolution of **2** was effected by chromatography of the corresponding naphtylethyl carbamates. The 3*S* alcohol was identified after transformation to the product obtained from *S*-malic acid as described in Barton, D.H.R.;Bénéchie, M; Khuong-Huu, F.; Potier, P.; Reyna-Pinedo, V. *Tetrahedron Letters*, **1983**, *23*, 651.

6 **6**- colourless oil, turns yellow upon standing; ^1H NMR 200 MHz δ ppm: 0.05 (3H, *s*, Si-CH_3), 0.06 (3H, *s* ,Si-CH_3), 0.93 (*t*Bu), 1.01 (3H, *d*, J=7 Hz, CH_3-9), 1.26 (6H, *t*, J=7 Hz, CH_2-$\underline{CH_3}$), 2.0 (2H, *ABXY*, CH_2-2), 2.76 (1H, *m*, H-6), 3.43-3.83 (7H, *m*, H-7, CH_2-8 and 2 CH_2-O), 4.06 (1H, *m*, H-3), 4.50 and 4.60 (2H, *AB*, J=12 Hz, CH_2 Ar), 4.70 (1H, *t*, J=6 Hz, H-1), 6.0 (1H, *d*, J=9 Hz, H-5), 7.35 (5H, *s*, aromatiques).

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8 Behling, J.R.; Babiak, K.A.; Nguyen, J.S.; Campbell, A.L.; Moretti, R.; Koerner, M.; Lipshutz, B.H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

9 triol **1**, oil, $C_{14}H_{28}0_5$, $[\alpha]_D$= -18 ($CHCl_3$, c=1), ^{1}HNMR 200 MHz δppm: 1.01 (3H, *d*, J=7 Hz, CH_3-6), 1.21 and1.23 (6H, 2*t*, J=7 Hz, $OCH_2\underline{CH_3}$), 1.63 (3H, *d*, J=0.1, CH_3-4), 1.83 (2H, *m*, CH_2-2), 2.54 (1H, *m*, H-6), 2.80 (3H, broad *s*, OH)), 3.60 (5H, *m*, H-7, $O\underline{CH_2}CH_3$), 4.16 (1H, *dd*, J=7 Hz, J'=8 Hz, H-3), 4.65 (1H, *t*, J=6 Hz, H-1), 5.26 (1H, *d*, J=10, H-5).

10 **3**- oil, ^{1}HNMR 200 MHz δ ppm: 0.13 (3H, *s*, $SiCH_3$), 0.16 (3H, *s*, $SiCH_3$), 0.96 (9H, *s*, tBu), 1.20 (3H, *d*, J=7 Hz, CH_3-4), 1.80 (3H, *d*, J=2 Hz, CH_3-1), 2.66 (1H, *m*, H-4), 3.53 and 3.56 (2H, *ABX*, J_{AB}=10 Hz, J_{AX}=6 Hz, J_{BX}=4 Hz, CH2-6), 3.80 (1H, *m*, H-5), 4.58 (2H, *s*, CH_2-Ar), 7.40 (5H, broad *s*, C_6H_5).

11 Zhang, H.X.; Guibé, F., Balavoine, G. *J. Org. Chem.* **1990**, 55, 1857.

12 **11**- oil, ^{1}HNMR, 200 MHz, δ ppm: 0.02 (3H, *s*, Si-CH_3), 0.05, (3H, *s*, Si-CH_3), 0.83 (9H, *s*, *t*Bu), 0.90 (3H, *d*, J=7 Hz, CH_3 en 4), 2.33 (3H, *d*, J=1.5 Hz, CH_3-1), 2.62 (1H, *m*, H-4), 3.29 and 3.37 (2H, *ABX*, J_{AB}=10 Hz, J_{AX}=J_{BX}=5 Hz, CH_2-6), 3.60 (1H, *q*, J=5 Hz, H-5), 4.42 and 4.51 (2H, *AB*, J=12 Hz, CH_2-Ar), 6.01 (1H, *dq*, J=11 Hz, J'=1.5 Hz, H-3).

13 Bénéchie, M.; Delpech, B.; Khuong-Huu, F. submitted to *Tetrahedron*

14 triol **14**, oil, $C_{14}H_{28}0_5$, $[\alpha]_D$=-29 ($CHCl_3$, c=0.6), ^{1}HNMR 200 MHz δppm: 1.05 (3H, *d*, J=7 Hz, CH_3-6), 1.23 (6H, *t*, J=7 Hz, $OCH_2\underline{CH_3}$), 1.64 (3H, *d*, J=0.1, CH_3-4), 1.85 (2H, *m*, CH_2-2), 2.52 (1H, *m*, H-6), 2.80 (3H, broad *s*, OH)), 3.60 (5H, *m*, H-7, $O\underline{CH_2}CH_3$), 4.17 (1H, *dd*, J=7 Hz, J'=8 Hz, H-3), 4.67 (1H, *t*, J=6 Hz, H-1), 5.3 (1H, *d*, J=10, H-5).

15 Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Japan* **1971**, *44*, 3427.

16 Compound **14** was transformed to 7-8 epoxide derivative useful for the next steps of the synthesis. Using Mitsunobu's procedure, complete inversion was obtained, giving a 70% yield after hydrolysis of the intermediate benzoate and purification.

17 In this preliminary work, the reactions were carried out on a 5-10 mmol-scale.

(Received in France 11 September 1991)