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A STEREO CONTROLLED ROUTE TO A KEY INTERMEDIATE FOR THE SYNTHESIS OF MAYTANSINE

M. Samson, P. De Clercq, H. De Wilde and M. Vandewalle*
State University of Ghent, Department of Organic Chemistry,
Laboratory of Organic Synthesis,
Krijgslaan, 271 (S.4), B-9000 Gent (Belgium).

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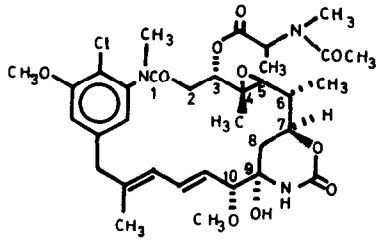
Recently a number of approaches have been published[1] towards the synthesis of various parts of maytansine (1), a novel type ansa macrolide, which shows significant antitumor activity[2].

In this paper we wish to describe the stereocontrolled synthesis of the building blocks 2a and 2b, corresponding to the "eastern zone" of the title molecule and containing carbon atoms 5 to 9; both synthons possess the correct stereochemistry at C-6 and C-7 and allow further elaboration at both ends, as shown by their transformation into respectively 7a and 7b, which are potential acylanion equivalents.



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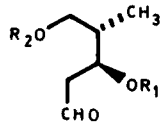
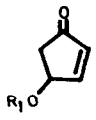
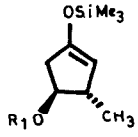


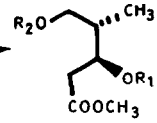
2 a; R_1 = CMe_2Ph; R_2 = $SiMe_2t.Bu$
b; R_1 = $SiMe_2t.Bu$; R_2 = CH_2SCH_3



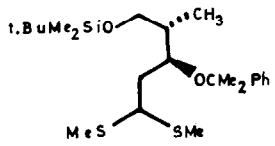
3 a; R_1 = CMe_2Ph
b; R_1 = $SiMe_2t.Bu$



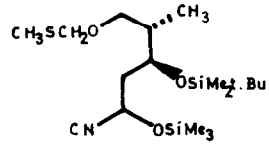
4 a; R_1 = CMe_2Ph
b; R_1 = $SiMe_2t.Bu$



5 a; R_1 = CMe_2Ph; R_2 = H
b; R_1 = $SiMe_2t.Bu$; R_2 = H
6 a; R_1 = CMe_2Ph; R_2 = $SiMe_2t.Bu$
b; R_1 = $SiMe_2t.Bu$; R_2 = CH_2SCH_3



7a



7b

The efficiency of the present approach is based on the easy synthesis of the five carbon unit by oxidative cleavage of functionalised cyclopentenes such as 4a and 4b. Treatment of the readily available 4-cumyloxy-2-cyclopentenone 3a[3] with dimethylcopper lithium (1.5 eq, ether, -78°) followed by addition of chlorotrimethylsilane-pyridine (2 eq, -78° and allowed to warm up to r.t.) gave the silylenolether 4a[4] [ν(neat) : 1650, 1250, 860, 765 and 705 cm^{-1}; δ(CCl_4) : 7.38 (5H, m), 4.40 (1H, q, ^3J = 1.8 Hz; ^4J = -1.8 Hz), 3.48 (1H, dt, X of ABX, Σ^3J = 17 Hz), 2.70 (1H, m), 2.35 (2H, dt, AB of ABX, ^4J = -1.8 Hz), 1.58 (6H, s), 0.88 (3H, d, ^3J = 6.9 Hz), 0.20 (9H, s)].

Product 4a was directly treated with ozone (1 eq, CH_2Cl_2, CH_3OH, -78°); subsequent reduction of the ozonide with sodium borohydride and esterification with diazomethane yielded 5a (49 % from 3a). [ν(neat) : 3500, 1745, 1610 and 1500 cm^{-1}]. Protection of the hydroxylgroup with t.butyldimethylsilylchloride[5] (1.05 eq, imidazole, 25°, 3 h) afforded the silylether 6a [ν(neat) : 2870, 1745, 1610, 1500, 1250, 840 and 765 cm^{-1}; δ(CCl_4) : 7.42 (5H, m), 4.23 (1H, d of X part of ABX, ^3J = 3.0 Hz, $|J_{AX}+J_{BX}|$ = 12.6 Hz), 3.62 and 3.50 (2H, CD of CDY, ^2J = -10.4 Hz), 3.58 (3H, s), 2.43 and 2.30 (2H, AB of ABX, ^2J = -15.3 Hz, ^3J = 7.2 Hz and 5.4 Hz), 1.69 (1H, m), 1.65 (3H,s), 1.58 (3H,s), 0.99 (9H,s), 0.94 (3H, d, ^3J = 6.6 Hz), 0.12 (6H, s)]. Treatment with diisobutylaluminium hydride (1 eq, -78°, toluene) yielded the aldehyde 2a [ν(neat) : 1730 cm^{-1}; δ(CCl_4) : 9.57 (t, ^3J = 1.1 Hz)]. The conversion of the aldehyde function to a potential acylanion equivalent was effected by treatment with trimethylorthothioborate under neutral conditions[6], yielding 7a (80 % yield). [δ(CCl_4) : 7.45 (5H, m), 4.01 (1H, dt, X of ABX, Σ^3J = 15.0 Hz), 3.60 and 3.45 (2H, CD of CDY, ^2J = -10.2 Hz), 3.30 (1H, t, ^3J = 7.2 Hz), 1.96 (6H, s), 1.65 and 1.58 (ss, 6H), 0.96 (9H, s), 0.91 (3H, d, ^3J = 6.9 Hz), 0.12 (6H, s)].

In a similar way 4-t.butyldimethylsilyloxy-2-cyclopentenone[7] (3b) led to the alcohol 5b, which was protected as a methylthiomethoxymethyl ether[8] (DMSO, HOAc, NaOAc, 24 hr, r.t.) yielding (45 % from 3b) the ester 6b [ν(neat) : 1745, 1250, 835 and 770 cm^{-1}; δ($CDCl_3$) : 4.73 and 4.68 (2H, ^2J = -11.7 Hz), 4.35 (1H, dt, ^3J = 3.3 Hz and 6.6 Hz), 3.82 (3H, s), 3.61 and 3.48 (2H, AB of ABX, ^2J = -9 Hz, ^3J = 6.6 Hz and 6.6 Hz), 2.57 (2H, d, ^3J = 6.6 Hz), 2.24 (3H, s), 1.98 (1H, d of sextuplet,

X of ABX, ^3J = 6.6 Hz and 3.3 Hz, 1.02 (3H, d, ^3J = 6.6 Hz), 0.97 (9H, s), 0.18 (6H, s)]. Reduction with diisobutylaluminium hydride (1 eq, -78°, toluene) gave quantitatively the aldehyde 2b [ν(neat) : 2720, 1720, 1250, 835 and 770 cm^{-1}; δ(CCl_4) : 9.91 (1H, t, ^3J = 2.1 Hz), 4.70 and 4.65 (2H, ^2J = -11.7 Hz), 4.40 (1H, dt, X of ABX, Σ^3J = 15.9 Hz), 3.53 (2H, d, ^3J = 6 Hz), 2.66 (2H, AB of ABX), 2.23 (3H, s), 1.97 (1H, m), 1.05 (3H, d, ^3J = 6.6 Hz), 1.00 (9H, s), 0.18 (6H,s)]. In the present case the formation of another potential acylanion equivalent was investigated; treatment with trimethylsilylcyanide[9] yielded (95 %) the protected cyanohydrin 7b as a mixture of two diastereoisomers [δ(CCl_4) : 4.66 (2H, s), 4.54 (1H, m), 4.0 (1H, m), 3.53 (2H, m), 2.22 (3H, s), 1.99 (2H, m), 1.83 (1H, m), 1.06 and 1.03 (3H, d), 1.01 (9H, s), 0.18-0.05 (15H)].

Both synthons 7a and 7b are synthetically equivalent and allow the introduction of the "southern zone" of the title compound as has been shown by others[1c].

In summary we have shown the easy and short construction of the carbon chain 5 to 9 with the correct stereochemistry by oxidative cleavage of an adequately substituted cyclopentene precursor. Since (S)-(+)-4-hydroxy-2-cyclopentenone (3, R_1 = H) has been shown to be readily available from (R,R)-(+)-tartaric acid[10]; this approach should proof ideal for a chiral synthesis of the "eastern zone"[11]. Further work is in progress.

ACKNOWLEDGEMENT

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11. An optically active "eastern zone" has been obtained by resolution; see reference 1d.