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TOTAL SYNTHESIS OF MAYTANSINOIDS. APPROACH TO 4,6-BISDEMETHYLMAYTANSINE AND 4-DEMETHYLMAYTANSINE

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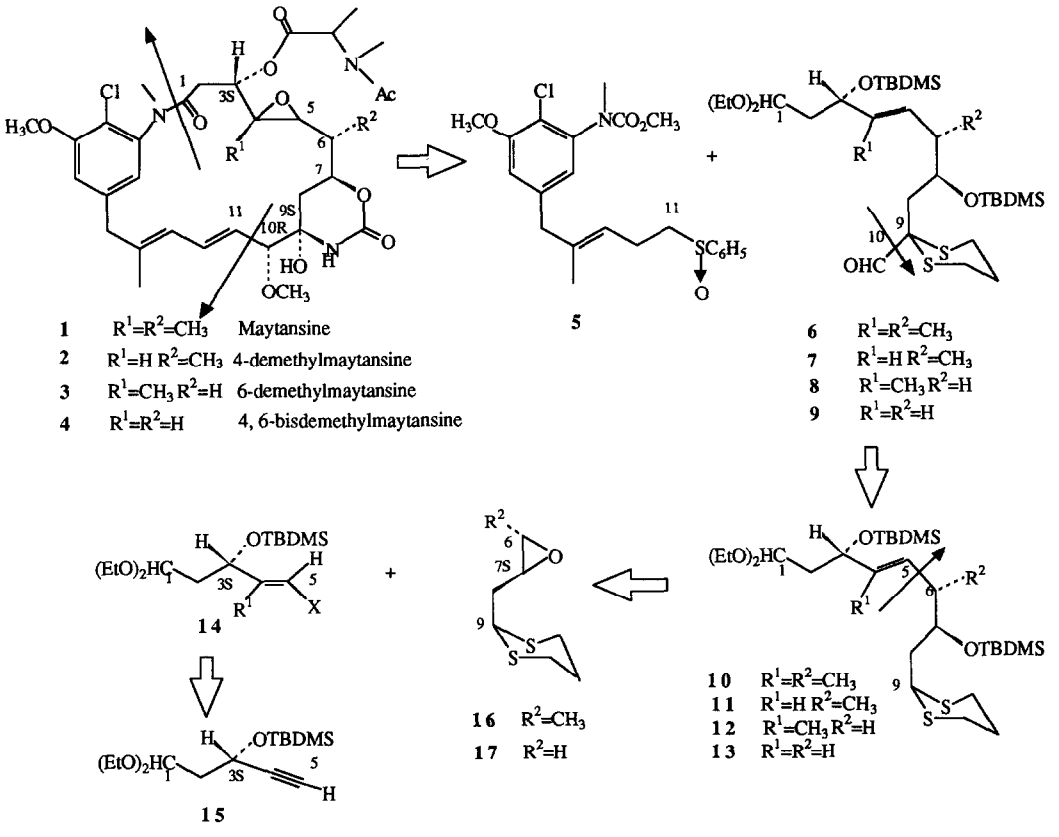
Summary: A convergent strategy was elaborated to synthesize maytansine **1** and maytansinoids modified on the carbon skeleton, especially 4-demethylmaytansine **2**, 6-demethylmaytansine **3**, 4,6-bisdemethylmaytansine **4**. In this paper, the feasibility of the project was verified by the preparation of key intermediates for the synthesis of 4, 6-bisdemethylmaytansine and 6-demethylmaytansine. The C-1-N open chain compound **18** in the 4, 6-bisdemethyl series was obtained.

Maytansine **1** is a naturally occurring ansamacrolide, isolated originally by Kupchan in 1972[1] from *Maytenus serrata*, which exhibits potent antitumor activity against various cell lines and has been the subject of extensive chemical[2] and biological[3] studies. However, its toxicity[4] in clinical use is a problem which could perhaps be overcome by replacing it with structurally related molecules. Since maytansinoids have been isolated from the fermentation broth of various *Nocardia* species,[5] the search for new products, to find a better therapeutic agent, is still carried on,[6] especially as it was found that simplified macrocycles retain some antitumoral activity.[7]

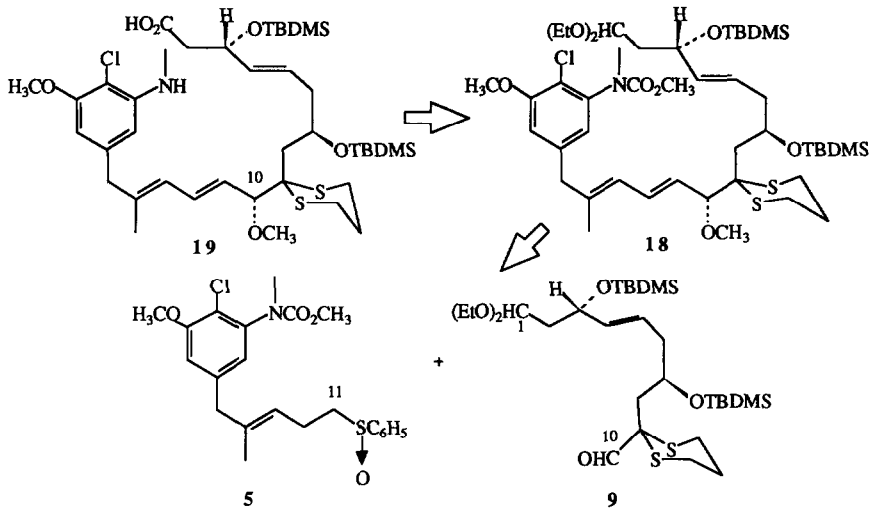
Two independant total syntheses of maytansine **1**[8] and two total syntheses of maytansinol[9] have been reported to date. We propose a new approach which could lead to modified skeleton maytansinoids. The retrosynthetic scheme we have elaborated gave the sulphoxide **5**, the chiral vinyl halide **14** or the chiral acetylene **15** and the chiral epoxides **16** or **17**, as key intermediates (scheme 1). According to this scheme, the radicals R^1 and R^2 could be H or any alkyl group, leading to maytansinoids modified at C-4 and/or C-6. We have attempted to apply this approach to the synthesis of maytansine **1** (R^1=R^2=CH_3), 4-demethylmaytansine **2** (R^1=H R^2=CH_3), 6-demethylmaytansine **3** (R^1=CH_3 R^2=H) and 4, 6-bisdemethylmaytansine **4** (R^1=R^2=H).



Scheme 1

The synthesis of the C-1-C-10 part, compounds **6** (R^1=R^2=CH_3), **7** (R^1=H R^2=CH_3), **8** (R^1=CH_3 R^2=H) or **9** (R^1=R^2=H), and their coupling with sulphoxide **5**, have been studied to investigate the feasibility of our project.

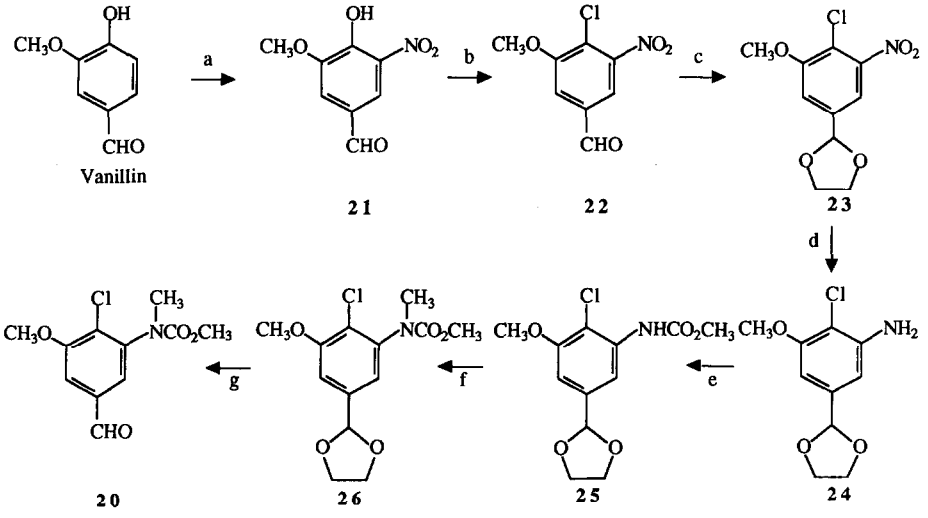
In the present paper, we report the syntheses of the two parts, sulphoxide **5** and aldehyde **9**, in the 4, 6-bisdemethylmaytansine series **4**. The coupling reaction between **9** and **5** to obtain **18** (a precursor of the amino acid **19**), as the key C1-N open-chain intermediate for the preparation of **4** will be described (scheme 2).The synthesis of compound **12**, the C1-C9 part in the 6-demethyl series, precursor of **8**, will be also studied.



Scheme 2

Synthesis of sulphoxide 5

The synthetic scheme we elaborated to prepare **5** involved the introduction of functional carbon chain on aldehyde **20**, accessible from vanillin according to the reactions which are indicated in scheme 3.

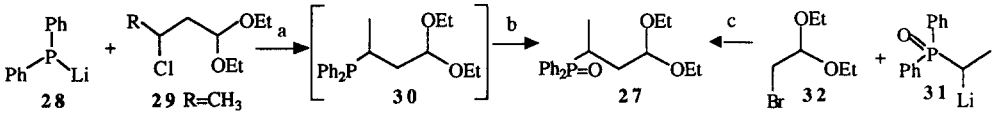


a) HNO_3, ether, 10°C then r.t. 4 h, 88%. b) LiCl, TsCl, HMPA, 80°C, 18 h, 72%. c) $HOCH_2CH_2OH$, TsOH cat., PhH, reflux, 16 h, 100%. d) H_2NNH_2. H_2O, EtOH, Raney Ni, r.t., 40 min, 99%. e) $ClCO_2CH_3$, Py, r.t, 2 h, 99%. f) HNa, THF, 0° then MeI, r.t, 3 h, 99%. g) 1N HCl, acetone, r.t, 1 h 30 min, 100%.

Scheme 3

The phenol function of nitrovanillin **21**[10] was substituted by chloride by heating at 80°, in HMPA, in the presence of *p*-toluenesulphonyl chloride and LiCl, to give **22**[11] (72% yield). After protection of the aldehyde function of **22** by dioxolanation, the nitro group of **23** was reduced with hydrazine in the presence of Raney nickel to give amine **24** which in turn was transformed to carbamate **25**. Alkylation of the sodio derivative of **25** with methyl iodide led to N-methyl derivative **26** which gave aldehyde **20** after acid hydrolysis to cleave the dioxolane protective group.

Introduction of a functional chain, starting from the aldehyde function of **20**, was effected using phosphine oxide **27** for olefination reaction according to the methodology introduced by S. Warren.[12] In this methodology, anions derived from protected β-(diphenylphosphinoyl)-aldehydes or ketones react as homoenolate equivalents with carbonyl compounds, to give protected β, γ-unsaturated aldehydes or ketones. Phosphine oxide **27** was prepared by condensation of lithium diphenylphosphide **28**, prepared from chlorodiphenylphosphine,[13] with 3-chloro-butyraldehyde diethyl acetal **29**, itself prepared from crotonaldehyde.[14] This reaction yielded phosphine acetal **30**, which was oxidised to **27**with 30% hydrogen peroxide. This scheme could be applied to various β-chloroacetals (R=H or various alkyl radicals) giving possible the access to modified maytansinoids at C-14 (for instance 14-demethylcompound) (scheme 4).

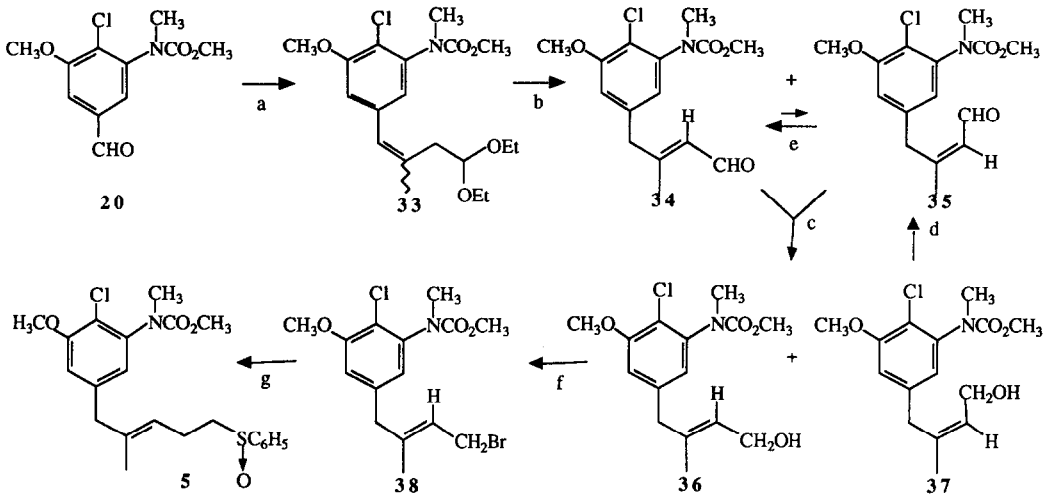


a) THF, 40°C, 16 h. b) THF, H_2O, 20°C, H_2O_2, 1 h, 58%. c) THF, hexane, HMPA, -30°C, then r.t, 15 h, 70%.

Scheme 4

Compound **27** could be also prepared by alkylation of the lithio derivative of ethyldiphenylphosphine oxide[12,15] **31** by 1-bromo-2, 2-diethoxy-ethane **32**.

Elaboration of **5** from **20** was then carried out according to the reactions indicated in scheme 5. Reaction between **20** and the lithio derivative of **27** was performed in THF. Elimination of sodium diphenylphosphinate from the intermediate addition product was effected by heating the sodio alkoxide at 60° in DMF for 1h,[12] giving a mixture of E and Z olefins **33**. Acid hydrolysis of the acetal function gave conjugate aldehydes **34** and **35**, with complete migration of the double bond.[16] Reduction with sodium borohydride gave alcohols E **36** and Z **37** separable by chromatography. The minor alcohol **37** could be transformed to **36** after oxidation, equilibration by 1N HCl into a 3:1 mixture of E and Z aldehydes,[18] reduction and further separation of the isomers. The major alcohol **36**[17,18] of E geometry was obtained in 81% combined yield and was transformed to allylic bromide **38** by PBr_3 in the presence of LiBr and collidine.[18] Coupling reaction between **38** and the anion derived from methylphenylsulphoxide led to desired compound **5** with a 68 % yield.



a) **27**, 1 eq, LDA, 1.1 eq, THF, 10 min, 0°C then -78°C, **20**, 1 eq, in THF, -78°C to r.t.; extraction, NaH, DMF, 50-60°C, 1 h, 89%. b) 1N HCl, acetone, 24 h, r.t. c) $NaBH_4$, EtOH, 0°C. d) MnO_2, CH_2Cl_2, r.t.,24 h e) 1N HCl, acetone, r.t. 90 min. f) LiBr in ether/THF, PBr_3, collidine, 0°C then r.t. 50 min, 95%. g) LDA, THF, methylphenylsulphoxide, -78°C, then HMPA, **38**, -78°C to -20°C, 90 min 68%.

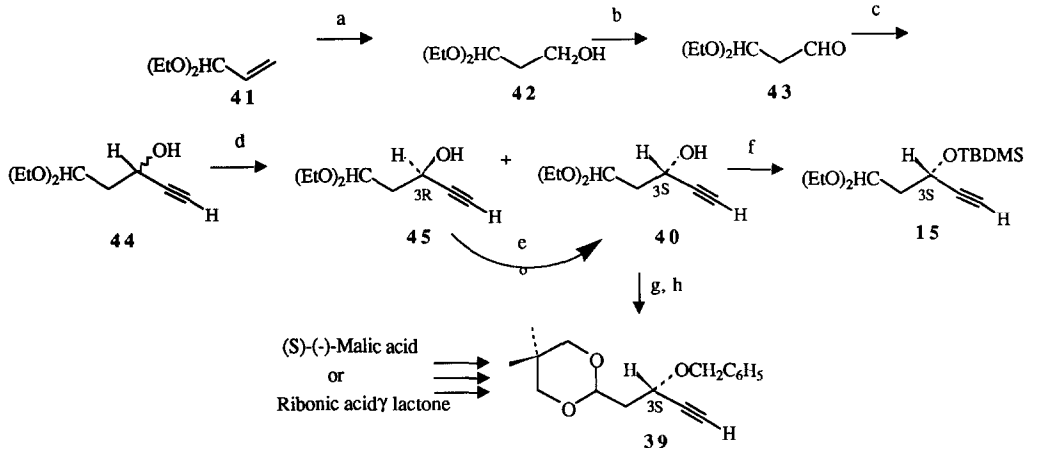
Scheme 5

Synthesis of C-1-C-10 "north-eastern" unit of 4,6-bisdemethylmaytansine 9.

The synthesis of **9**, which is the simplest derivative of this series, was studied first. According to the proposed way, **9** was obtained by formylation of the dithioacetal **13**, provided by the opening of the (7S)-epoxide **17** by an organometallic derived from the O-protected acetylene **15.**

The preparation of propargylic benzyl ether **39** of (3S)-configuration starting from (S)-(-)-malic acid and ribonic acid-γ-lactone has been published elsewhere[19], but the modest yield which was obtained and the numerous steps which were necessary, led us to investigate another route to synthesize this C-1-C-5 fragment. The synthesis of **40** and **15** bearing more suitable protective groups at C-1 and C-3 is summarized in scheme 6.

Hydroboration of acrolein diethylacetal **41** gave the primary alcohol **42**, which in turn was oxidised to malonaldehyde monodiethylacetal **43** with pyridinium dichromate in the presence of molecular sieves[20] or better with Dess-Martin's periodinane.[21] Addition of lithium acetylide[22] on **43** led to the formation of racemic alcohol **44.** Its resolution was effected by preparative high pressure chromatography of the diastereomeric (S)-phenylethyl carbamates.[23] After cleavage of the carbamate function with methanolic sodium methoxide, enantiomeric alcohols, (3S)-**40** and (3R)-**45**, were obtained. The alcohol of (3S)-configuration was identified after conversion to the known 5, 5-dimethyl-1,3-dioxane derivative **39**,[19] by refluxing in benzene,in the presence of 2, 2-dimethylpropane-1, 3-diol and catalytic p-toluenesulphonic acid, followed by benzylation. Inversion of **45** according to the Mitsunobu's procedure[24] was effected providing a new amount of **40** after saponification of the intermediate benzoate. The protection of the hydroxyl function of **40** was accomplished by silylation with *tert*-butyldimethylsilyl chloride in the presence of imidazole to yield **15**.



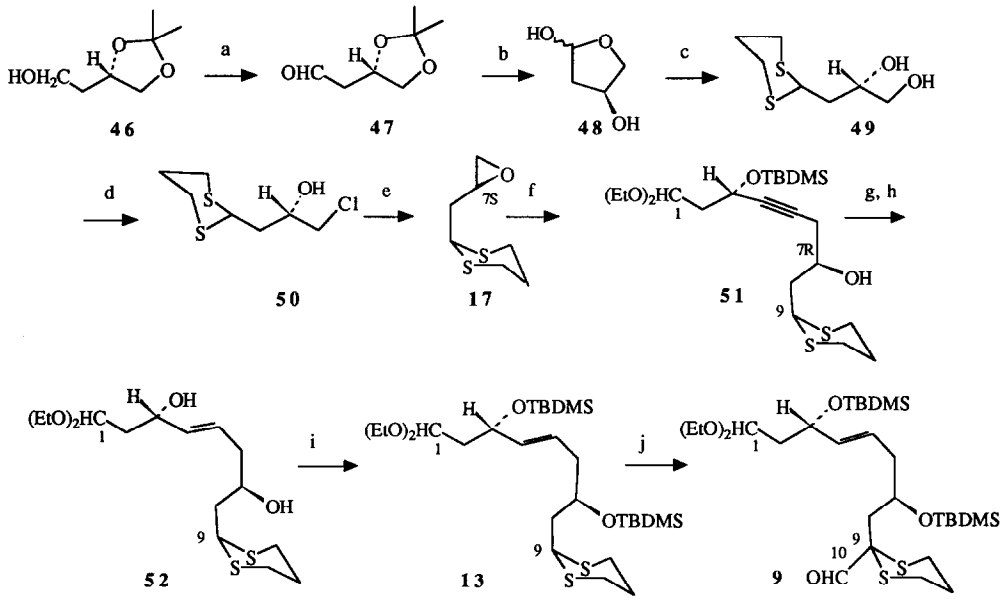
a) $BH_3.SMe_2$, 2M in THF, 0.5 eq., 0°C to r.t., 3N NaOH, then 0°C, 30% H_2O_2, 40°C, 16 h, 65%; b) PDC, 1.2 eq, 4 Å molecular sieves, CH_2Cl_2, r.t., 60%; c) lithium acetylide, THF, -78°C to r.t., 54%; d) (S)-naphtylethylisocyanate, 1.1 eq., dimethylaminoethanol, 5 moles %, $PhCH_3$, 70°C; preparative HPLC; 1M MeONa, MeOH, reflux; e) DEAD, PPh_3, $PhCO_2H$, THF, 4 h, r.t., 1N NaOH, MeOH, 86%; f) TBDMSCl, 1.2 eq., imidazole, 3 eq., DMF, 95%. g) 2, 2-dimethylpropanediol, excess, TsOH, catalytic, PhH, reflux, 98%; h) NaH, 1 eq., $BrCH_2C_6H_5$, 1.eq., THF, 90%.

Scheme 6

Epoxide **17** of (S)-configuration was prepared starting from alcohol **46** which was obtained from (S)-(-)-malic acid by reduction and acetalisation as described by Hanessian.[25] Oxidation with pyridinium dichromate[20] gave aldehyde **47**[26] transformed in acidic medium to lactol **48**. This lactol, when treated with propane-1, 3-dithiol in the presence of boron trifluoride etherate, gave dithioacetal **49** which in turn produced chlorhydrin **50** when it was reacted with carbon tetrachloride and triphenylphosphine.[27] The tosylation of the primary hydroxyl of **49**, or its transformation to bromide, led to an intramolecular alkylation with formation of useless cyclic sulfonium. After treatment with methanolic sodium methoxide, **50** provided the desired epoxide **17** with a 74% yield.

The opening of epoxide **17** by the lithium derivative of **15** was effected either at 20°C, in the presence of one equivalent of HMPA, or at -78°C, after addition of boron trifluoride etherate.[28] The coupling compound **51** was formed in both cases with a 70% yield. The hydroxyl at C-3 was deprotected before reduction of the triple bond into E- olefin with lithium aluminium hydride.[29] The diol **52** which was thus obtained, was treated with *t*-butyldimethylsilyl chloride in the presence of imidazole to afford O, O'-diprotected compound **13**.

By action of *n*-butyllithium at -20°C for 2.5 hours,[30] the anion α from the dithioacetal group of **13**, was prepared and then was reacted with dimethylformamide[31] to give formyl derivative **9**. This compound represents the C1-C10 unit of 4,6-bisdemethylmaytansine (scheme 7).

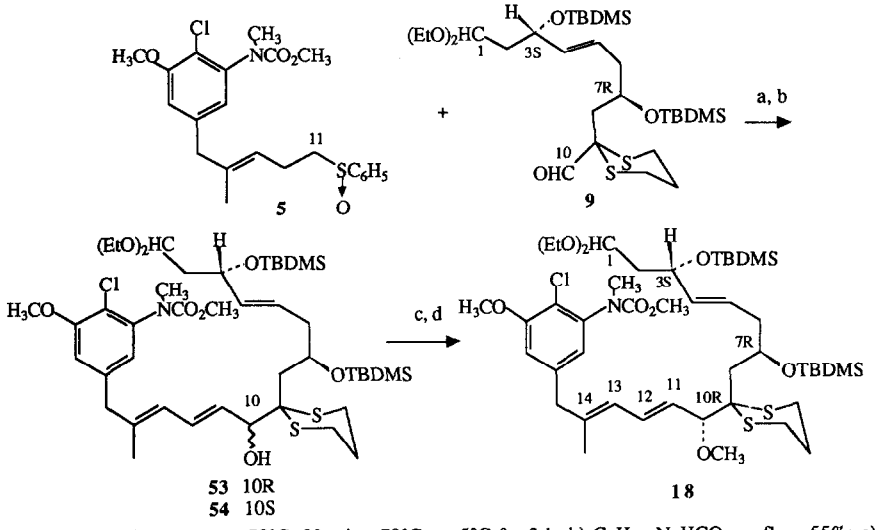


a) PDC, 1.2 eq., 3Å molecular sieves, CH_2Cl_2, 0°C to rt, 67%; b) 50% aqueous CH_3CO_2H; c) $HS(CH_2)_3SH$, 1.2 eq., $BF_3.OEt_2$, CH_2Cl_2, 48 h, r.t., 77%; d) Ph_3P, 2 eq., CCl_4, toluene, 70°C, 3 h, 66%; e) MeONa, MeOH, 15 min, r.t., 74%; f) **15**, 1 1 eq., *n*BuLi, 1.1 eq., THF, -78°C, 10 min, then $BF_3.OEt_2$, 1.eq., 10 min, then **17**, 1 eq., in THF, -78°C 30 min, 70%; g)- Bu_4NF, 1.eq., THF; h) $LiAlH_4$, 2.6 eq., THF, reflux, 47% from **51**; i) TBDMSCl, 2.4 eq., imidazole, 5 eq., DMF, 12 h, r.t., 90%; j) *n*BuLi, 1.5 eq., -20°C, 2.5 h, then -78°C, DMF, 10 eq., to -50°C, 30 min, 85%.

Scheme 7

Synthesis of the C-1-N-open chain compound 18.

The condensation reaction between **9** and **5** was then studied (scheme 8).The metallation α from sulphoxide function of **5** was effected with LDA at -78°C in DME,[32] in the presence of aldehyde **9**.[33] The reaction was not complete, as starting material remained. The reversibility of the reaction might be involved to explain that the reaction did not go to completion. *Syn*-elimination of the sulphoxide group in the adduct, performed by refluxing in benzene for 1 hour, in the presence of solid sodium hydrogencarbonate, led to a 1/1 mixture of the alcohols isomeric at C-10. Unreacted aldehyde **9** was recovered, **5** being lost during the thermolysis step. The lack of selectivity we observed for this condensation reaction, could not be overcome by using a chiral sulphoxide, as, according to Solladié,[34] , asymmetric induction was poor, when anions from chiral sulphoxides were added to aldehydes. Dienol **53** of which the (10R)-configuration was determined by Horeau's method,[35] could be separated from the (10S)-isomer **54** by preparative high pressure chromatography. Difficulties were encountered to inverse the wrong alcohol.[8] The exclusive E/E geometry of the diene in the coupling products was confirmed by examination of the olefinic protons in their ^1H NMR spectrum. Treatment of **53** with methyl iodide in the presence of sodium hydride or silver oxide afforded methoxy compound **18** (scheme 8) which represents the C1-N open chain precursor of 4,6-bisdemethylmaytansine **4**.

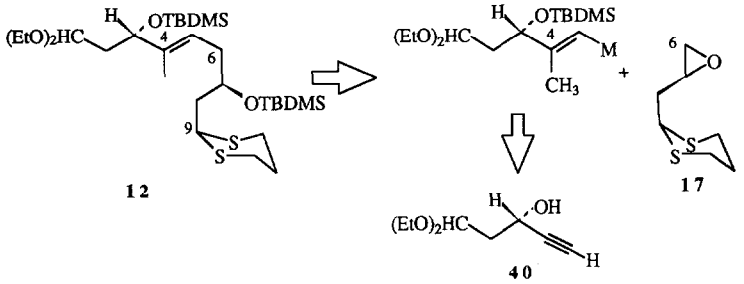


a) **5**, 1.eq., **9**, 1 eq., LDA, 3 eq., DME, -78°C, 30 min, -78°C to -5°C for 3 h; b) C_6H_6, $NaHCO_3$, reflux, 55%; c) preparative HPLC; d) MeI, excess, Ag_2O, 1 eq., ethyl acetate, 60°C, 90 min, 99%.

Scheme 8

Synthesis of the C1-C9 "north-eastern" part of 3, compound 58.

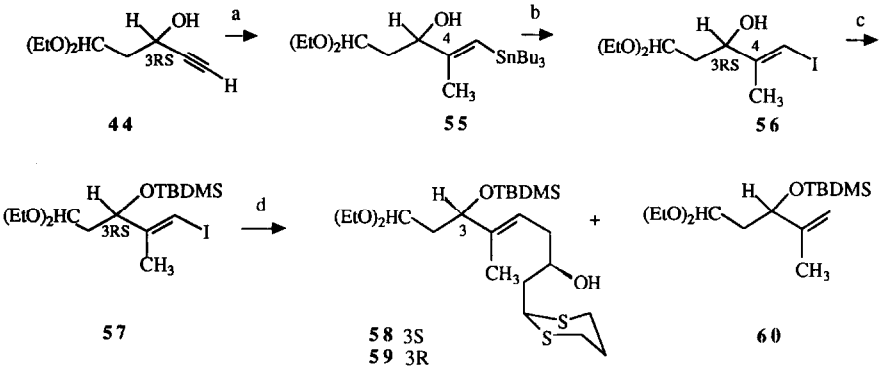
According to the former retrosynthetic scheme, the opening of epoxide **17** by an organometallic compound prepared from vinyl halide **14** (R^1=CH_3), itself obtained from acetylene **40**, could lead to **12**, the C1-C9 "north-eastern" part of 6-demethylmaytansine **3** (scheme 9).



Scheme 9

In a preliminary study of this sequence of reactions, we started from racemic acetylene **44**. Transformation of acetylene **44** to methyl vinyl iodide **56** was performed, *via* a stannylmagnesiation reaction according to Oshima's procedure[36] (scheme 10). We used this methodology as, on the one hand, methylcupration[37] led to a mixture, and on the other hand, the hydrozirconation[38] of **45** we tried, was unsuccessfull. Intermediate vinyl stannane **55** was unstable and could not be purified. Chromatography on silicagel yielded the corresponding vinyl

compound. Steric interaction between the methyl at C-4 and the tri-*n*butyltin fragment could be involved to explain this easy protonolysis. Then we chose to transform **55** directly to stable vinyl iodide **56** .The opening of epoxide **17** was effected in the presence of $BF_3.OEt_2$ by a mixed cuprate prepared from O-silylated compound **57** according to Lipshutz's work[39], the lithium derivative of **57** being formed by the action of *t*-butyllithium and treated with lithium 2-thienylcyanocuprate. The diastereomers, epimeric at C-3, **58** and **59**, were obtained in modest yield (25%), but this result showed that the opening of the monosubstituted epoxide **17** by a vinylic cuprate was possible. We recovered vinylic compound **60**, indicating that the acetal at C-1 was not cleaved by a cuprate in the presence of BF_3OEt_2. The presence of epimers at C-3 was seen only by examination of the ^{13}C NMR spectrum where the signals of C-4 and C-5 were split. Their ^1H NMR spectrum were identical. The separation of the isomers was not carried out, but this preliminary work shows that compound **12** could be accessible by this way.



a) *n*BuLi, 14.5 eq., $SnCl_2$, 4.8 eq., THF, -10°C, 150 min, then CH_3MgBr, 4.8 eq., ether, 0°C, 20 min, then CuCN, cat., then **44**, 0°C, 1 h, then -70°C, MeI, excess, -70°C to r.t.; b) I_2, 1 eq., THF, 48% from **44**; c).TBDMSCl, 1.2 eq., imidazole, 2.5 eq., THF, 18 h, r.t., 71%; d) *t*BuLi, 2 eq., THF, -78°C,15 min, then Li thienylcyanocuprate, 1.4 eq., THF, -40°C, 1 h, then -78°C, **17**, 0.9 eq., $BF_3.OEt_2$, 1 .04 eq., 90 min, 25%

Scheme 10

In conclusion, in this first paper, the feasibility of the strategy we proposed to synthesize maytansinoids, has been tested with the preparation of a C1-N open chain compound **18**, in the 4,6-*bisdemethyl* series. This product possesses the required absolute configuration at C-3, C-7 and C-10 (3S, 7R corresponding to 7S in the maytansine series, 10R), E/E geometry of the 11-13-diene, E-geometry of the 4-,5 double bond and suitable functional groups to perform macrocyclisation and cyclic carbamate elaboration. A representative fragment, compound **58**, in the 6-demethyl-series was also synthesized. This strategy has to be applied to the synthesis of maytansine and the results will be reported in following papers.

Acknowledgements. We would like to thank Professors Sir D.H.R. Barton and P. Potier for having initiated the work and providing many helpful advices.

Experimental

Melting points (mp) were determined in capillary tubes and are uncorrected. Optical rotations, $[\alpha]_D$, were measured in $CHCl_3$ with 0.5% EtOH, at 20°C, on a PERKIN-ELMER 241 polarimeter. IR spectra were recorded with a PERKIN-ELMER 257 spectrometer. ^1H NMR spectra were performed in $CDCl_3$, unless otherwise stated, with TMS as internal reference, chemical shifts δ are expressed in ppm, coupling constants J in Hz. They were recorded on Varian T-60, BRUKER WP-200, BRUKER AC-200 or BRUKER WM-400 instruments. Mass spectra (MS) were run on AEI MS-50 or AEI MS-9 spectrographs. Tetrahydrofuran was distilled from sodium-benzophenone ketyl, diethyl ether from lithium-aluminium hydride, dichloromethane from phosphorous pentoxide, toluene from sodium. Other solvents and reagents were purified by standard procedures as necessary. Numbering for ^1H assignments follows the systematic (IUPAC) nomenclature but the natural product numbering system was adopted for compounds **9, 12-15, 18** Column chromatography was performed on Merck Kieselgel 60, flash chromatography on Merck Kieselgel 60H. Preparative HPLC was performed on a 47 mm x 250 mm column filled with 37-55 μ porasil.

4-Chloro-3-methoxy-5-nitro-benzaldehyde **22.**-Anhydrous LiCl (7 g, 165 mmol), nitrovanillin **21**[10] (mp 177-178°, $C_8H_7NO_5$ calc. % C 48.74, H 3.58, N 7.10, O 40.58 found: C 48.53, H 3.62, N 7.38, O 40.30) (10 g, 50.7 mmol) and *p*-toluenesulphonyl chloride (15 g, 78.7 mmol) were stirred for 18 h at 80° in dry HMPA (40 ml) . More *p*-toluenesulphonyl chloride (5 g) was added and the mixture was stirred for 4 h at 80°. After cooling down, ether was added and the organic layer was washed well with aqueous $NaHCO_3$ and brine. Evaporation of the solvent afforded a yellow-orange solid purified by filtration through a silica gel column and crystallisation, to give **22** (7.303 g, 67%), as pale yellow crystals (ether), mp 118-119°.[11] The ethereal mother liquors were treated with saturated aqueous $NaHSO_3$ giving a precipitate which was dissolved in hot water and treated with concentrated HCl. The orange solid which was obtained after cooling, was then purified by flash chromatography and crystallisation to give a second crop of **22** (0.532 g) (total yield 72%), $C_8H_6ClNO_4$ calc. % C 44.57, H 2.81, Cl 16.44, N 6.50, O 29.67 found: C 44.70, H 2.75, Cl 16.63, N 6.31, O 29.76; IR (nujol) cm^{-1}: 1690 ($\nu_{C=O}$), 1540, 1365 (NO_2); MS EI: M^+ 215 and 217, M-1, m/z 169, 154; ^1H NMR (400 MHz) δ ppm: 4.09 (3H, *s*, OCH_3), 7.67 (1H, *d*, J=2, H-2 or H-6) 7.92 (1H, *d*, J=2, H-6 or H-2) 10.09 (1H, *s*, CHO).

2-(3-Methoxy-4-chloro-5-nitro-phenyl)-1, 3-dioxolane **23.**- Compound **22** (5.244 g, 24.3 mmol) in benzene (60 ml), ethylene glycol (2 ml, 35.8 mmol) and *p*-toluenesuphonic acid (5 mg) were refluxed in a Dean-Stark apparatus for 16 h. After cooling down, saturated aqueous $NaHCO_3$ and ether were added. The organic layers were washed, dried and evaporated to give **23**, as pale yellow crystals, (6.311 g, 100%) mp 54-55° (EtOH), $C_{10}H_{10}ClNO_5$, calc. % C 46.26, H 3.88, Cl 13.65, N 5.39, O 30.81 found: C 46.51, H 3.81, Cl 13.68, N 5.39, O 30.50; IR (nujol) cm^{-1}: 1535, 1355 (NO_2); MS EI: M^+ 259 and 261, M-1, m/z 171, 73; ^1H NMR (400 MHz) δ ppm: 4.01 (3H, *s*, OCH_3), 4.11 (4H, *m*, OCH_2CH_2O), 5.86 (1H, *s*, H-2), 7.27 (1H, *d*, J=2, H-2' or H-6'), 7.55 (1H, *d*, J=2, H-6' or H-2').

2-(3-Amino-4-chloro-5-methoxy-phenyl)-1, 3-dioxolane **24.**-98% hydrazine hydrate (1.5 ml) and a suspension of Raney nickel in EtOH were added.to a solution of **23** (3.117 g, 12 mmol) in EtOH (65 ml) The mixture was stirred for 40 min producing heat and gas evolution. After filtration, the solvent was evaporated giving a white solid residue which was purified by filtration on alumina. **24** (2.72 g, 99%), mp 85-86° (ether) was obtained, $C_{10}H_{12}ClNO_3$, calc. %: C 52.30, H 5.27, Cl 15.43, N 6.10, O 20.90 found: C 52.35, H 5.28, Cl 15.37, N 6.21, O 21.22; MS EI: M^+ 229 and 231, M-1, m/z 157, 73; ^1H NMR (400 MHz) δ ppm: 3.73 (2H, *s*, NH_2), 3.90 (3H, *s*, OCH_3), 4.08 (4H, *m*, OCH_2CH_2O), 5.72 (1H, *s*, H-2), 6.51 (1H, *d*, J=1.5, H-2' or H-6'), 6.59 (1H, *d*, J=1.5, H-2' or H-6').

Carbamate **25.**-Methyl chloroformate (1.7 ml, 22 mmol) was added dropwise to **24** (2.417 g, 10.5 mmol) in pyridine (10 ml) at 0°. An exothermic reaction occurred with the formation of a precipitate. After 2 h at room temperature, water was added and the product was extracted with ether. After usual work-up, **25** was obtained as white crystals (2.997 g, 99%), mp 99 -100° (EtOH), $C_{12}H_{14}ClNO_5$, calc. %: C 50.10, H 4.90, Cl 12.32, N 4.87, O 27.81, found: C 50.01,H 4.94, Cl 12.47, N 4.89 ,O 27.88; IR (nujol) cm^{-1}: 3280 (ν_{NH}), 1725 ($\nu_{C=0}$), 1590, 1525; MS EI: M^+ 287 and 289, M-1, 252, 180, 73; ^1H NMR (400 MHz) δ ppm: 3.82 (3H, *s*, OCH_3), 3.94 (3H, *s*, OCH_3), 4.10 (4H, *m*, OCH_2CH_2O), 5.81 (1H, *s*, H-2'), 6.84 (1H, *d*, J=2, H-4 or H-6), 7.29 (1H, *broad s*, NH), 8.02 (1H, *broad s*, H-6 or H-4).

Carbamate **26.**-A mixture of sodium hydride (480 mg of a 55% dispersion in oil, 11 mmol) and MeI (2 ml, 32 mmol) in THF (10 ml) was stirred at 0°, then **25** (2.875 g, 10 mmol) in THF (19 ml) was added. After 3 h at room temperature, extraction with ether afforded **26** as an oil, purified by chromatography through a silica gel

column (2.994 g, 99%), $C_{13}H_{16}ClNO_5$ calc.: C 51.75, H 5.35, Cl 11.75, N 4.64, O 26.51 found: C 52.04, H 5.42, Cl 11.68, N 4.59, O 26.39; IR (nujol) cm^{-1}: 1705 ($\nu_{C=O}$), 1590 (C-O) ; MS EI: M^+ 301 and 303, M-1, m/z 266, 179, 73; ^1H NMR (400 MHz) δ ppm: 3.23 (3H, *s*, OCH_3), 3.65 (major rotamer) and 3.82 (minor rotamer) (3H, 2 *s*, NCH_3), 3.96 (3H, *s*, OCH_3), 4.12 (4H, *m*, OCH_2CH_2O), 5.80 (1H, *s*, H-2'), 7.05 (1H, *broad s*, H-4 or H-6), 7.07 (1H, *d*, J=2, H-4 or H-6).

***Aldehyde* 20.**-HCl (8 ml of a 1 N aqueous solution) was added to **26** (2.905 g, 9.6 mmol) in acetone (40 ml). After 90 min, extraction with ether and usual work-up gave **20** (2.473 g, 100%), as white crystals, mp 110-111° (EtOH), $C_{11}H_{12}ClNO_4$, calc. % C 51.27, H 4.70, Cl 13.76, N 5.44, O 24.84 found: C 51.42 H 4.62 Cl 13.93 N 5.46 O 24.59; IR (nujol) cm^{-1}: 1685 ($\nu_{C=O}$), 1575 (C-O); MS EI: M^+ 257 and 259, m/z 222, 207; ^1H NMR (400 MHz) δ ppm: 3.26 (3H, *s*, OCH_3), 3.67 (major rotamer) and 3.85 (minor rotamer) (3H, 2 *s*, NCH_3), 4.02 (3H, *s*, OCH_3), 7.43 (1H, *broad s*, H-6 or H-4), 7.45 (1H, *d*, J=2, H-4 or H-6), 9.98 (1H, *s*, CHO).

(1, 1-Diethoxybutyl)-3-diphenylphosphine oxide* 27.**-1)-a)-3-chlorobutyraldehyde diethylacetal* **29.**-Chlorotrimethylsilane (150 ml, 1.2 mol) was added slowly to crotonaldehyde (35 g, 500 mmol) in anhydrous EtOH (60 ml) and dry CH_2Cl_2 (200 ml) at 15°.[14] The mixture was then refluxed for 1 h. *HCl was given off.* After cooling down, the solution was rendered neutral with solid sodium hydrogencarbonate. Extraction with CH_2Cl_2 and usual work-up gave 3-chlorobutyraldehyde diethylacetal **29** (44.7 g, 74%) bp 70°/15 mmHg;[14] MS EI: no M^+, m/z 121 and 123 (M-31), 75; ^1H NMR (60 MHz) δ ppm: 1.20 (6H, *t*, J=7, $OCH_2\underline{CH_3}$), 1.50 (3H, *d*, J=7, CH_3), 1.96 (2H, *dd*, J=6, J'=7, CH_2-2), 3.53 (4H, *m*, OCH_2), 4.08 (1H, *q*, J=7, H-3), 4.63 (1H, *t*, J=6, H-1).

-b)-THF (250 ml) and small pieces of lithium (3.5 g, 0.504 atom-gram) were introduced under argon in a round-bottomed three-neck flask with a condenser and an addition funnel. The mixture was stirred and diphenylchlorophosphine (27.5 g, 125 mmol) was added dropwise.[13] An exothermic reaction occurred and a red colour appeared. The mixture was refluxed for 5 h. After cooling down, the lithio compound was transferred through a needle, into a solution of 3-chlorobutyraldehyde diethyl acetal (22.5 g, 124.6 mmol) in THF (200 ml). The mixture was stirred at 40° for 16 h under argon. Partial decoloration of the solution was observed. After cooling down, water and a 30% solution of hydrogen peroxide (50 ml, 500 mmol) were added. The mixture was cooled to 20° and stirred for 1 h. Extraction with ether and usual work-up afforded a colourless viscous liquid which was chromatographied on silica gel column to give **27** (25.3 g, 58.4%) as a colourless oil, $C_{20}H_{27}O_3P$, calc. % C 69.35 H 7.86 O 13.86 P 8.94 found: C 69.21, H 8.09, O 14.12, P 8.87; IR cm^{-1}: 1435, 1190, 1115, 1060, 720, 700; MS EI: M^+ 346, m/z 317, 301, 201, 103, 99; ^1H NMR (400 MHz) δ ppm: 1.16 (3H, *t*, J=7, $OCH_2\underline{CH_3}$), 1.20 (3H, *t*, J=7, $OCH_2\underline{CH_3}$), 1.22 (3H, *dd*, J=16.5, J'=7, CH3), 1.73 (1H, *m*), 1.99 (1H,*m*), 2.65 (1H, *m*), 3.48 (2H, ABX_3, J= 9.5, J'=7, Δν 74.5 Hz,OCH_2), 3.51 (2H, ABX_3, J=9.5, J'=7, Δν 52 Hz,OCH_2), 4.57 (1H, *dd*, J=7.5, J'=3.5, H-1), 7.52 (6H, *m*, aromatics), 7.85 (4H, *m*, aromatics).

2)-ethyldiphenylphosphine oxide, mp 121°,[15] (9.208 g, 40 mmol) in THF (100 ml) was cooled at -10°, under argon and *n*-butyllithium (27.2 ml of a 1.5 M solution in hexane, 40.8 mmol) was added. The mixture was warmed to 0° and stirred 30 min at this temperature. The solution was cooled to -30° and 1-bromo-2-2-diethoxy-ethane **32** (6.5 ml, 42.2 mmol) in HMPA (10 ml) was added. The mixture was stirred at room temperature for 15 h. Extraction with ether and usual work-up afforded an orange oil which was chromatographied on silica gel to give **27** (9.789 g, 70%) as a colourless oil.

Compound* 33** ***(mixture of E and Z isomers)- LDA (18.6 ml of a 0.6 M solution in THF, 11.2 mmol) was added to **27** (3.510 g, 10.1 mmol) in THF (60 ml) at 0°, under argon. After stirring for 10 min at 0°, the mixture was cooled to -78° and **20** (2.577 g, 10 mmol) in THF (34 ml) was added The mixture was warmed to room temperature and the reaction was quenched with water. Extraction with CH_2Cl_2 gave a residue which was taken up in DMF (250 ml) and treated under argon with sodium hydride (700 mg of a 55% dispersion in oil, 16 mmol) at 50-60° for 1 h. After cooling down, extraction with ether and usual work-up gave an orange oil purified by chromatography on silica gel column to afford **33** (mixture of E and Z isomers) (3.432 g, 89%); IR cm^{-1}: 1700 ($\nu_{C=O}$), 1580, 1440; MS EI: M^+ 385 and 387, m/z 103, 75, 47; less polar isomer: ^1H NMR (400 MHz) δ ppm:[a] 1.17 (6H, *t*, J=7, $OCH_2\underline{CH_3}$), 1.93 (3H, *s*, CH_3) 2.57 (2H, *d*, J=6, CH_2-13), 3.19 (3H, *s*, OCH_3), 3.56 (4H, *ABq*, J=9.5, J'=7, Δν=58 Hz, OCH_2), 3.63 (major rotamer) and 3.78 (minor rotamer) (3H, 2 *s*, NCH_3), 3.91 (3H, *s*, OCH_3), 4.73 (1H, *t*, J=6, H-12), 6.33 (1H, *broad s*, H-15), 6.87 (1H, *broad s*, H-17 or H-21), 7.05 (1H, *broad s*, H-17 or H-21); more polar isomer: ^1H NMR (400 MHz) δ ppm:[a] 1.22 (6H, *t*, J=7, $OCH_2\underline{CH_3}$), 1.92 (3H, *d*, J=1, CH_3) 2.50 (2H, *d*, J=6, CH_2-13), 3.22 (3H, *s*, OCH_3), 3.64 (4H, ABX_3,

J=9.5, J'=7, Δν=64.5 Hz, OCH_2), 3.66 (major rotamer) and 3.81 (minor rotamer) (3H, 2s, NCH_3), 3.92 (3H, s, OCH_3), 4.71 (1H, *t*, J=6, H-12), 6.31 (1H, *broad s*, H-15), 6.78 (2H, *m*, H-17 and H-21) ([a] natural product numbering system).

***Alcohols* 36 *and* 37.**-HCl (15 ml of a 1 N aqueous solution) was added to **33** (3.43 g, 8.9 mmol) in acetone (60 ml). The mixture was stirred 24 h at room temperature and then extracted with ether to give an oil (mixture of E **34** and Z **35** aldehydes) which was taken up in EtOH (100 ml). Sodium borohydride (370 mg, 9.8 mmol) was added at 0° to the ethanolic solution. After stirring for 30 min at 0°C, addition of water and extraction with CH_2Cl_2 afforded an orange oil which was chromatographied on silica gel column giving **36** and **37**.

-**36**, E isomer (1.847 g, 66%) more polar, white crystals (ether), mp 91-92°,[17] $C_{15}H_{20}ClNO_4$, calc.: C 57.42, H 6.42, Cl 11.30, N 4.46, O 20.40 found: 57.16, H 6.35, Cl 11.25, N 4.63, O 20.28; IR cm^{-1}: 3420 (OH), 1680 ($\nu_{C=O}$), 1575; MS EI: M^+ 313 and 315, m/z 278, 260; ^1H NMR (400 MHz) δ ppm: 1.64 (3H, *s*, CH_3), 1.77 (1H, *s*, OH), 3.21 (3H, *s*, OCH_3), 3.32 (2H, *s*, CH_2-15), 3.65 (major rotamer) and 3.81 (minor rotamer) (3H, 2 *s*, NCH_3), 3.92 (3H, *s*, OCH_3), 4.23 (2H, *d*, J=7, CH_2OH), 5.53 (1H, *t*, J=7, H-13), 6.74 (2H, *m*, H-17 and H-21).

-**37**, Z isomer (614 mg, 22%) colourless oil, ^1H NMR (400 MHz) δ ppm: 1.71 (3H, *s*, CH_3), 1.84 (1H, *s*, OH), 3.21 (3H, *s*, OCH_3), 3.42 (2H, *s*, CH_2-15), 3.66 (major rotamer) and 3.82 (minor rotamer) (3H, 2 *s*, NCH_3), 3.92 (3H, *s*, OCH_3), 4.23 (minor rotamer) and 4.28 (major rotamer) (2H, 2 *d*, J=7, CH_2OH), 5.68 (1H, *t* J=7, H-13), 6.73 (1H, *broad s*, H-17 or H-21), 6.78 (1H, *broad s*, H-17 or H-21).

Active MnO_2 (1.7 g, 19.6 mmol) was added portionwise to **37** (614 mg, 1.96 mmol) in CH_2Cl_2 (40 ml). The suspension was stirred for 24 h and filtered through Celite. Evaporation of the solvent gave a yellow oil (615 mg) which was dissolved in acetone (16 ml) and treated with HCl (4 ml of a 1 N aqueous solution) for 90 min. Extraction with ether afforded an oil which was dissolved in EtOH (20 ml). Sodium borohydride (80 mg, 2.11 mmol) was added to this solution at 0°C. After 30 min at 0°C, standard work-up gave a residue which was chromatographied on silica gel column to give **37** (145 mg) and **36** (411 mg) (total yield 81 %).

***Allylic bromide* 38**[18].-Alcohol **36** (1.16 g, 3.71 mmol) in THF (6 ml) and ether (16 ml) was added to dry LiBr (375 mg, 4.3 mmol). The mixture was stirred and collidine (0.5 ml, 3.75 mmol) and then PBr_3 (0.35 ml, 3.72mmol) were added dropwise. A slight exothermic reaction occurred and a white precipitate was formed. The mixture was stirred at room temperature for 50 min. Extraction with ether gave **38** (1.25 g, 95%) which was used without further purification.

***Sulphoxide* 5.**-Methylphenylsulphoxide (518 mg, 3.7 mmol) in THF (3 ml) was added to LDA (4.1 ml of a 1 M solution in THF, 4.10 mmol), at - 78°. The mixture was warmed to -70° and after the addition of HMPA (3.5 ml), was stirred for 10 min and then cooled to -78°. Allylic bromide **38** (1.25 g, 3.3 mmol) in THF (10 ml) was then added. The mixture was warmed to -20° for 90 min. Quenching was effected by the addition of aqueous NH_4Cl. Extraction with ether was effected and the solvent was evaporated *without heating*. The residue was purified by flash chromatography to give **5** (980 mg, 68%), as a colourless oil, $C_{22}H_{26}ClNO_4S$; MS EI: M^+ 437 and 435, m/z 400 (M-Cl, m* 367.8), 310, 274; ^1H NMR (200 MHz) δ ppm: 1.56 (3H, *s*, CH_3), 2.38 and 2.59 (2H, 2 *m*, CH_2-11), 2.86 (2H, *t*, J=7.5, CH_2-12), 3.23 (3H, *s*, OCH_3), 3.30 (2H, *broad s*, CH_2-15), 3.66 (major rotamer) and 3.83 (minor rotamer), (3H, 2 *s*, NCH_3), 3.93 (3H, *s*, OCH_3), 5.34 (1H, *t*, J=7.5, H-13), 6.76 (2H, *m*, H-17 and H-21), 7.63 and 7.71 (5H, 2*m*, C_6H_5).

***3-Hydroxypropanal diethylacetal* 42.** $BH_3.SMe_2$ (50 ml of a 2M solution in THF, 100 mmol, 0.5 eq.) was added to a solution of acrolein diethylacetal **41** (26 g, 200 mmol) in THF (500 ml) at 0°C, under argon. The mixture was warmed to room temperature and upon completion of the reaction monitored by TLC, NaOH was added (70 ml of a 3N aqueous solution). The mixture was cooled with external ice bath and H_2O_2 (40 ml of a 30% solution) was added, producing refluxing of the solution. After 16 h. at 40°C, a white precipitate was formed. Extraction with ether gave the alcohol **42** (16.8 g, 65%), used without further purification, MS: M^+ 148.

***Malonaldehyde monodiethylacetal* 43.**-Alcohol **42** (20 g, 135 mmol) was added to a stirred suspension of PDC (60 g, 159 mmol) and 3 Å molecular sieves (70 g) in anhydrous CH_2Cl_2 (500 ml) at room temperature. Upon completion of the reaction monitored by TLC, the mixture was filtered through silicagel, elution with CH_2Cl_2 gave the aldehyde **43** (12 g, 60%) as a colourless liquid, MS: M^+ 146. 3-Ethoxyacrolein (2 g, 10%) was formed as secondary product.

***O-Protected Acetylene* 15.**-1)-Lithium acetylide (120 mmol) was prepared by slow addition of *n*-butyllithium (86 ml of a 1.4M solution in hexane) at -78°C to a saturated solution of acetylene in THF (500 ml), whereas acetylene bubbling was continued. After 30 min. at -78°C, the solution was set under argon, and the aldehyde **43** (14.6 g, 100 mmol) was added. The mixture was warmed to room temperature. Water was poured

and extraction with ether gave the racemic acetylene **44**, purified by flash chromatography (9.3 g, 54%), liquid, MS: M^+ 172.

2)-*Resolution*.- A solution of **44** (5.3 g, 30 mmol), (S)-phenylethylisocyanate (4.8 g, 33 mmol) and dimethylaminoethanol (0.133 g, 1.5 mmol, 5 mol %) in toluene (100 ml) was warmed at 70°C for 12 h. After standard work-up, the diastereomeric carbamates (9,8 g) were separated by preparative HPLC using hexane-AcOEt 95-5 as eluent. Hydrolysis of each carbamate (4 g) was performed by refluxing in 1M methanolic sodium methoxide (50 ml). After 2 h, standard work-up afforded the corresponding alcohols: **40** (1.31 g, 61%), from the less polar carbamate, oil, $[\alpha]_D$=-26° (c=1), ^{1}H NMR (200 MHz), δ ppm: 1.17 (3H, *t*, J=6, $CH_2\underline{CH_3}$), 1.19 (3H, *t*, J=6, $CH_2\underline{CH_3}$), 2.05 (2H, *t*, J=5, CH_2-2), 2.43 (1H, *d*, J=2, H-5), 3.42-3.78 (4H, *m*, 2 $O\underline{CH_2}CH_3$), 4.49 (1H, *td*, J=5.5, J'=2, H-3), 4.80 (1H, *t*, J=5.5, H-1)., **45**, from the more polar, $[\alpha]_D$=+26° (c=1).

3)-*Correlation with* ***39***- alcohol **40**, (100 mg, 0.58 mmol), was refluxed in benzene (10 ml) in the presence of 2-2-dimethylpropane-1, 3-diol (180mg, 1.74 mmol) and catalytic *p*toluenesulphonic acid. After completion of the reaction performed by TLC, standardwork-up afforded a product (105 mg, 0.57 mmol, 98%) which was treated in THF (5 ml) with sodium hydride (25 mg of 55% oil dispersion) and benzyl bromide (100 mg, 0.60 mmol). After standard work-up, the product had $[\alpha]_D$=-84° and was found to be identical to **39** [19].

4)-*Inversion of* **45**.-DEAD (2.6 g, 15 mmol) was added dropwise to a solution of **45** (2.3 g, 13.3 mmol), triphenylphosphine (3.93 g, 15 mmol) and benzoic acid (1.9 g, 15 mmol) in THF (50 ml). After 4 h, the products were extracted with $CHCl_3$. The organic layer was washed with sodium hydrogencarbonate and evaporated giving a residue which was purified by flash chromatography with toluene. The benzoate ester so obtained was treated with NaOH (20 ml of a 2N solution in MeOH-H_2O 5/1) for 20 min. at 20°. After standard work-up, a column chromatography gave pure **40** (2 g, 86%).

5)-*Silylation of* **40**.- A mixture of **40**(2 g, 11.6 mmol), imidazole (1.57 g, 23.2 mmol, 2 eq.) and TBDMSCl (2.1 g, 13.9 mmol, 1.2 eq.) in DMF (5 ml) was stirred at room temperature for 24 h. Standard work-up gave **15** (3.15 g, 95%), oil.

***Epoxide* 17**.-1)-*Dihydroxy-Dithioacetal* **49**.- Alcohol **46**[25] (20 g, 137 mmol) was added to a suspension of PDC (60 g, 160 mmol) and flame dried 3Å molecular sieves (70 g) in CH_2Cl_2 (500 ml) at 0°C. The mixture was warmed to room temperature and stirred until completion of the reaction, monitored by TLC. The suspension was filtered off through Celite giving, after evaporation of the solvent, the unstable aldehyde **47** (13.2 g, 67%) treated, without further purification, with 50% aqueous acetic acid (500 ml). Evaporation of the solution at reduced pressure gave the lactol **48** as a colourless viscous oil which was treated with propane-1,3-dithiol (12 ml, 1.2 eq.) and BF_3. OEt_2 (0.5 ml) in CH_2Cl_2 (50 ml). After 48 h, solid sodium hydrogencarbonate (2 g) was added and the mixture stirred for 1 h, then filtered through silicagel column. Elution with CH_2Cl_2-MeOH 97/3 afforded the dithioacetal **49** (13.6 g, 77%) as a colourless oil, $C_7H_{14}O_2S_2$, calc. %: C 43.27, H 7.26, O 16.47, S 33.00, found: C 43.04, H 7.29, O 16.67, S 32.75; $[\alpha]_D$=-11.48° ($CHCl_3$, c=1.2); MS EI: M^+ 194, m/z 145, 119; ^{1}H NMR (60 MHz), δ ppm 1.88 (3H, *m*, CH_2-2 and H-3'a) 2.14 (1H, *m*, H-3'b), 2.89 (4H, *m*, CH_2-2' and 4'), 3.48 and 3.67 (2H, ABX, J_{AB}=11,5, J_{AX}=7, J_{BX}=4, CH_2-4), 4.03 (1H, *m*, H-3), 4.27 (1H, *dd*, J=9, J'=5,5, H-1).

2)-*Chlorhydrin* **50**.- A mixture of the dithioacetal **49** (2.5 g, 12.9 mmol), triphenylphosphine (6 g, 22.9 mmol), CCl_4 (10 ml) in toluene (20 ml) was warmed at 70°C for 3 h. After standard work-up, flash chromatography gave the chlorhydrin **50** (1.82 g, 66%), mp 73°C (ether/hexane), unstable; MS EI: M^+ 212 (2/3) and 214 (1/3), m/z 177, 159, 119. ^{1}H NMR, (60 MHz), δ ppm: 1.92 (3H, *m*, CH_2-2 et H-3'a), 2.10 (1H, *m*, H-3'b), 2.89 (4H, *m*, CH_2-2' and 4'), 3.54 and 3.66 (2H, ABX, J_{AB}=11.5, J_{AX}=6, J_{BX}=3.5, CH_2-4), 4.17 (1H,*m*, H-3), 4.27 (1H, *dd*, J=6, J'=9, H-1).

3)-*Epoxide* **17**.- The chlorhydrin **50** (1.82 g, 8.5 mmol) was treated by methanolic MeONa (10 ml of a 1N solution) for 15 min at room temperature. The epoxide **17** was obtained after usual work-up (1.12 g, 74%), $C_7H_{12}OS_2$, calc. % C 47.69, H 6.86, O 9.08, S 36.38, found : C 47.47, H 7.09, O 9.36, S 36.28; $[\alpha]_D$=-4°4 ($CHCl_3$, c=1); MS EI: M^+176, m/z 145, 119; ^{1}H NMR (60 MHz), δ ppm: 2.0 (4H, *m*, CH_2-3' and CH_2-5), 2.60 (1H, *m*, H-1_a'), 2.86 (5H, *m*, CH_2-4, CH_2-4, H-1_b'), 3.16 (1H, *m*, H-2'), 4.26 (1H, *t*, J=6,5, H-2).

***Compound* 13**.-1)-*a*)- *n*-BuLi (1.2 ml of a 1.5 M solution in hexane, 1.8 mmol) was added to the acetylene **15** (514 mg, 1.8 mmol) in THF (5 ml) at -78°C. Were added, after 10 min, BF_3.OEt_2 (0.21 ml, 1.7 mmol) and after further 10 min, the epoxide **17** (300 mg, 1.7 mmol) in THF (3 ml). After stirring 30 min at -78°C, water was poured and standard work-up followed by flash chromatography gave **51** (581 mg, 70%).

b)- *n*-BuLi (4.3 ml of a 1.5M solution in hexane, 6.5 mmol) was added to the acetylene **15** (1.63 g, 5.7 mmol) in THF (15 ml) in the presence of HMPA (3 ml) at -78°C. After 30 min, **17** (1.02 g, 5.8 mmol) in THF (10 ml) was added. The mixture was warmed to room temperature and stirred for 24 h. After quenching with water, standard work-up followed by flash chromatography gave **51** (1.83 g, 70%).

2)- Tetrabutylammonium fluoride (5.2 ml of 1M solution on THF, 5.2 mmol) was added to **51** (2.4 g, 5.2 mmol) in THF (20 ml). After 15 min at room temperature, standard work-up afforded a diol which was refluxed in THF (10 ml) in the presence of $LiAlH_4$ (0.513 g,13.5 mmol). Usual work-up gave **52** (0.85 g, 47%), mp 61°C (acetone); $[\alpha]_D$=-2°3 (c=1.8); $C_{16}H_{30}O_4S_2$, calc. % C 54.86, H 8.57, O 18.28, found: C 55.02, H 8.73, O 18.19; MS EI: M^+ 350, m/z 332, 305, 286, 232, 119; ^1H NMR (400 MHz) δ ppm: 1.22 (3H, *t*, J=7, CH_3), 1.23 (3H, *t*, J=7, CH_3), 1.85 (4H, *m*, CH_2-8, CH_2-2), 2,10 (2H, *m* CH_2-6), 2.20 and 2.26 (2H, *m*, CH_2-3'), 2.87 (4H, *m*, CH_2-2',CH_2- 4'), 3.55 and 3.70 (4H, *m*, OCH_2), 3.97 (1H, *m*, H-7), 4.27 (1H, *t*, J=7.5, H-9), 4.33 (1H, *m*, H-3), 4.71 (1H, *t*, J=5, H-1), 5.60 (1H, A of AB*d*, J=16, J'=6, H-4), 5.70 (1H, B of AB*t*, J=16, J'=7, H-5).

3)- Imidazole (0.833 g, 5 eq.), TBDMSCl (0.864 g,2.4 eq.) and diol **52** (0.85 g, 2.45 mmol)) in DMF (8 ml) were stirred overnight at room temperature. Work-up gave **13** (1.28 g, 90%), colourless oil; $[\alpha]_D$=-22°7 (c=1); MS EI: M^+ 578, m/z 119; ^1H NMR (200 MHz) δ ppm: 0.04 (3H, *s*, $SiCH_3$), 0.05 (3H, *s*, $SiCH_3$), 0.08 (3H, *s*, $SiCH_3$), 0.10 (3H, *s*, $SiCH_3$), 0.84 (9H, *s*, *t*Bu), 0.86 (9H, *s*, *t*Bu), 1.14 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.16 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.7 (4H, *m*, CH_2-2, CH_2-8), 1.98 and 2.11 (2H, *m*, CH_2-3'), 2.11 (2H, *m*, CH_2-6), 2.69 (4H, *m*, CH_2-2', CH_2-4'), 3.23-3.61 (4H, *m*, OCH_2), 3.84 (1H, *m*, H-7), 3.94 (1H, *dd*, H-9), 4.04 (1H, *m*, H-3), 4.43 (1H, *t*, J=5, H-1), 5.17(1H, A of AB*d*, J= 16, J'=6, H-4), 5.28 (1H, B of AB*t*, J=16, J'=7, H-5); ^{13}C NMR δ ppm: -4.87, -4.67, -4.34, -3.87 (4 Si-CH_3), 15.41 (2 $OCH_2\underline{CH_3}$), 18.08 (Si-C), 18.72 (Si-C), 25.91 (6 CH_3 of 2 *t*Bu), 26.07 ($SCH_2\underline{CH_2}$), 29.95 (SCH_2), 30.56 (SCH_2), 40.47 (CH_2-6), 42.13 (CH_2-8 [a]), 42.58 (CH_2-2 [a]),43.99 (CH-9), 60.87 (OCH_2), 61.45 (OCH_2), 68.10 (CH-7), 70.38 (CH-3), 100.43 (CH-1), 125.21 (CH-5), 136.61 (CH-4).(^1H ^1H and ^1H ^{13}C correlations led to these assignments; [a] assignments could be reversed).

***Aldehyde* 9.-** *n*-BuLi (5.8 ml of a 1.5 M solution in hexane, 1.5 eq.) was added at - 20°C to **13** (3.4 g, 5.8 mmol) in THF (30 ml). After 2.5 h at -20°, the mixture was cooled to -78°C and DMF (4.23 g, 58 mmol,10 eq.) was added. The solution was stirred at -50°C for 30 min and the reaction was quenched with brine. Standard work-up followed by flash chromatography led to **9** (3.05 g, 85%), colourless oil; $[\alpha]_D$=+27°8 (c=1); $C_{29}H_{58}O_5S_2Si_2$, calc. % C 57.44, H 9.57, found: C 57.70, H 9.50; MS EI: M^+ 606; ^1H NMR (400 MHz): δ ppm 0.04 (3H, *s*, Si-CH_3), 0.05 (3H, *s*, Si-CH_3), 0.075 (3H, *s*, Si-CH_3), 0.08, (3H, *s*, Si-CH_3), 0.88 (9H, *s*, *t*-Bu), 0.89 (9H, *s*, *t*-Bu), 1.20 (3H, *t*, J=7, CH_3), 1.22 (3H, *t*, J=7, CH_3), 1.78 and 1.88 (4H, *m*, CH_2-8 and CH_2-2), 1.98 and 2.10 (2H, *m*, CH_2-3'), 2.21 (2H, *m*, CH_2-6), 2.55 and 2.69 (4H, *m*, CH_2-2', CH_2-4'), 3.50, 3.60 and 3.70 (4H, *m*, 2 OCH_2), 4.10 (1H, *m*, H-7), 3.70 (1H, *q*, J=7, H-3), 4.61 (1H, *dd*, J=7 , J'=4 , H-1), 5.47 (1H, A of AB*d*, J=16, J'=6, H-4), 5.66 (1H, B of AB*t*, J=16, J'=7, H-5), 8.9 (1H, *s*, CHO); ^{13}C NMR δ ppm: -4.80, -4.40, -3.98, -3.86 (4 Si-CH_3), 15.42 (2 $OCH_2\underline{CH_3}$),18.01 (Si-C), 18.14 (Si-C), 24.76 ($SCH_2\underline{CH_2}$), 25.96 (6 CH_3 of 2 *t*Bu), 26.49 (2 SCH_2), 40.72 (CH_2-6), 42.66 (CH_2-2), 44.04 (CH_2-8), 55.47 (C-9), 60.81 (OCH_2, 61.45 (OCH_2), 67.14 (CH-7), 70.35 (CH-3), 100.45 (CH-1), 124.45 (CH-5), 129.03 (CH-4), 187.20 (CH-10).

***Compound* 18.-**1)- LDA (8.6 ml of a 0.5 M solution in DME, 4.3 mmol) was added at -78°C to **5** (0.630 g, 1.45 mmol) and **9** (0.87 g, 1.43 mmol) in DME (10 ml). After 30 min, the mixture was warmed to - 5°C over 3 h. After addition of water, standard work-up led to a residue which was refluxed in benzene (10 ml) in the presence of solid sodium hydrogencarbonate (1 g). Thermolysis was monitored by TLC. Upon completion of the reaction, the solution was poured on silicagel column and flash chromatography afforded **9** (0.35 g, 40%) and the mixture of **53** and **54**(0.72 g, 55%) which was resolved by preparative HPLC.

Absolute configuration, Horeau' s method: **53**, (10R), recovered α-phenylbutyric acid had $[\alpha]_D$=+6°2; **54**, (10S), recovered α-phenylbutyric acid had $[\alpha]_D$=-6°6.

53- colourless oil; MS EI: M^+ 915; ^1H NMR (400 MHz) δ ppm: 0.06 (12H, *s*, Si-CH_3), 0.89 (18H, *s*, *t*Bu), 1.18 (3H, t, J=7, CH_3), 1.21 (3H, *t*, J=7, CH_3), 1.71 (3H, *s*, vinylic CH_3), 1.76 and1.88 (4H, *m*, CH_2-8 and CH_2-2), 2.05 and 2.10 (2H, *m*, CH_2-3'), 2.25 and 2.36 (2H, *m*, CH_2-6), 2.65 and 2.95 (4H, *m*, CH_2-2' and CH_2-4'), 3.19 (3H, *s*, O-CH_3), 3.33 (2H, *s*, $CH_2$15), 3.48 and 3.63 (4H, *m*, O-CH_2), 3.63 (3H, *s*, NCH_3),

3.89 (3H, *s*, OCH_3), 4.21 (2H , *m*, H-7 and H-3), 4.60 (1H, *dd*, J=7, J'=5, H-1), 4.65 (1H, *d*, J=5.5, H-10), 5.50 (1H, part A of AB*d*, J=15, J'=6, H-4), 5.60 (1H, part B of AB*t*, J=15, J'=7, H-5), 5.91 (1H, *dd*, J=15, J'=5.5, H-11), 5.96 (1H, *d*, J=11, H-13), 6.63 (1H, *dd*, J=15, J'=11, H-12), 6.68 (2H, *s*, Ar-H).

2)- A suspension of **53** (1 g, 1.09 mmol), MeI (10 ml) and freshly prepared Ag_2O (1 g) in ethyl acetate (10 ml) was stirred at 60°C for 90 min. The suspension was filtered off through silicagel column to afford **18** (1 g, 99%); MS EI: M^+ 929 ; ^1H NMR (200 MHZ) δ ppm : 0.07 (3H, *s*, Si-CH_3), 0.08 (3H, *s*, Si-CH_3), 0.12 (3H, *s*, Si-CH_3), 0.13 (3H, *s*, Si-CH_3), 0.90 (18 H, *s*, *t*Bu), 1.20 (3H, *t*, J=7, CH_3), 1.21 (3H, *t*, J=7, CH_3), 1.72 (3H, *s*, vinylic CH_3), 1.70-2.20 (6H, *m*, CH_2-2, CH_2-8, CH_2-4'), 2.25-2.35 (2H, *m*, CH_2-6), 2.50-3.0 (4H, *m*, CH_2-3', CH_2-5'), 3.20 (3H, *s*, OCH_3, 3.32 (3H, *s*, OCH_3), 3.37 (2H, *s*, CH_2-15), 3.61 (3H, *s*, NCH_3), 3.91, (3H, *s*, OCH_3), 3.47-4.01 (5H, *m*, O-CH_2, H-10), 4.22 (2H, *m*, H-7 and H-3), 4.63 (1H, *t*, J=5, H-1), 5.52 (1H, part A of AB*d*, J=15, J'=6, H-4), 5.82 (1H, part B of AB*t*, J=15, J'=7, H-5), 5.82 (1H, *dd*, J=15, J'=5.5, H-11), 6.0 (1H, *d*, J=11, H-13), 6.44 (1H, *dd*, J=I5, J'=11, H-12), 6.74 (2H, *s*, Ar-H).

***Compound* 58.-** 1)- *vinyl iodide* **56-** *n*-BuLi (84 ml of a 1.5 M solution in hexane, 126 mmol) was added to a suspension of stannous chloride (8 g, 42 mmol) in THF (50 ml) at -10°C. After 150 min, to the red solution of tributylstannyllithium thus obtained, were added methylmagnesium bromide (42 ml of 1 M solution in ether, 42 mmol) and then, after 20 min at 0°C, anhydrous CuCN (0.35 g, 3.9 mmol) followed by **44** (1.5 g, 8.7 mmol). After 1 h at 0°C, the mixture was cooled to -70°C and MeI (10 ml) was added. The mixture was warmed to room temperature overnight and quenched by addition of water. Extraction with CH_2Cl_2 afforded organic products which were dissolved in THF (10 ml) and treated with iodine (0.5 M solution in THF) until yellow colour persisted. Ether was added, the solution was washed successively with aqueous sodium thiosulfate and sodium hydrogencarbonate. The organic layer was evaporated and the residue was chromatographied on silicagel column. Elution with heptane-ethyl acetate 87/13 gave pure **56** (1.3 g, 48%), colourless oil, $C_{10}H_{19}IO_3$, calc %: C 38.23, H 6.10, O 15.28; found: C 38.51, H 6.21, O 15.02; MS EI: no M^+, m/z 197, 142, 103; ^1H NMR (200 MHz) δ ppm: 1.22 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.23 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.82 (3H, *broad s* , CH_3), 1.88 (2H, *t*, J=6, CH_2-2), 3.42-3.78 (4H, *m*, $\underline{CH_2}CH_3$), 4.37 (1H, *t*, J=6, H-3), 4.67 (1H, *t*, J=6, H-1), 6.35 (1H, *s*, H-5). Some demethyl-4 compound was also formed.

2)- Imidazole (0.56 g, 2.5 eq.) and TBDMSCl (0.57 g, 1.2 eq.) were added to **56** (1 g, 3.2 mmol) in THF (50 ml). After 18 h at 20°, standard work-up gave **57** (0.98 g, 71%), colourless oil; MS EI: no M^+, M-57, M-117, M-I; ^1H NMR (200 MHz) δ ppm: -0.01 (3H, *s*, $SiCH_3$), 0.04 (3H, *s*, $SiCH_3$), 1.19 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.22 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.77 (3H, *broad s*, vinylic CH_3), 1.77 (2H, *m*, CH_2-2) 3.40-3.74 (4H, *m*, $O\underline{CH_2}CH_3$), 4.30 (1H, *dd*, J=8, J'=5, H-3), 4.54 (1H, *dd*, J=7, J'=5, H-1), 6.21 (1H, *s*, H-5).

3)- *t*-BuLi (2.3 ml of 1M solution in pentane) was added to **57** (0.5 g, 1.15 mmol) in THF (5 ml) at -78°C. After 15 min. lithium 2-thienylcyanocuprate (1.6 ml of a 1M solution in THF, 1.6 mmol) was added. The mixture was warmed to -40°C and allowed to stand at this temperature for 1 h. After cooling to -78°C, were added **17** (0.192 g, 1 mmol) in THF (2 ml) and then $BF_3.OEt_2$ (0.15 ml, 1.2 mmol) in THF (1ml). After 90 min at -78°C, quenching was effected with aqueous NH_4Cl and ether. The suspension was filtered through celite. The organic layers were washed, dried and evaporated. A chromatography on silicagel column gave **58** and its (3R)-epimer (133 mg, 25%), which were not separated, as an oil ; MS, EI: no M^+, M-30, M-57, m/z 347, 229, 119, 103; ^1H NMR (400 MHz) δ ppm: -0.01 and 0.04 (2*s* of 3H each, Si-CH_3), 0.87 (9H, *s*, *t*-Bu), 1.18 (3H, *t*, J=7, $CH_2\underline{CH_3}$, 1.20 (3H, *t*, J=7, $CH_2\underline{CH_3}$), 1.59 (3H, *broad s*, vinylic CH_3), 1.75, 1.86 (2H, *t*, J=7, CH_2-2), 2.03 (2H, *t*, J= J=4.5, CH_2-8), 2.19 (2H, *t*, J=7, CH_2-6), 2.86 (4H, *m*, S-CH_2), 3.35-3.74 (4H, *m*, $O\underline{CH_2}CH_3$), 3.94 (1H, *m*, H-7), 4.14 (1H, *dd*, J=8, J'=4.5, H-3), 4.24 (1H, *t*, J=7, H-9), 4.55 (1H, *dd*, J=7, J'=4, H-1), 5.37 (1H, *t*, J=7, H-5); ^{13}C NMR, δ ppm: -5.0 et -4.33 (2 Si-CH_3), 11.56 (vinylic CH_3), 15. 49 (2 CH_2-$\underline{CH_3}$), 18.24 (Si-C), 25.95 (*t*Bu), 26.07 (S-$CH_2\underline{CH_2}$), 30.18 (CH_2-S), 30.46 (CH_2-S), 35.89 (CH_2-2), 40.82 (CH_2-6), 42.48 (CH_2-8), 44.39 (CH-9), 60.82 ($O\underline{CH_2}CH_3$), 61.33 ($O\underline{CH_2}CH_3$), 68.62 (CH-7), 75.20 (CH-3), 100.71 (CH-1), 120.62 and 120.76 (CH-5), 141.41 and 141.42 (C-4).

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