Synthesis of analogues of the marine anti-tumour agent curacin A

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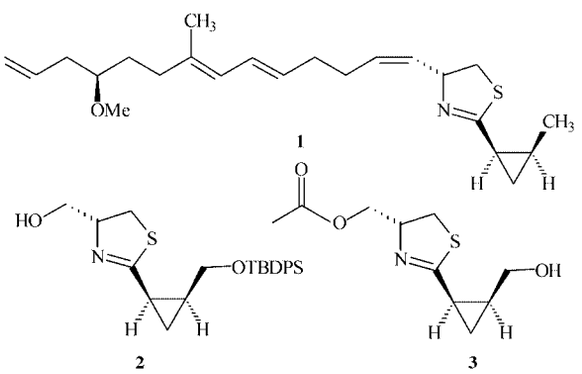
Received (in Cambridge) 2nd June 1999, Accepted 12th July 1999

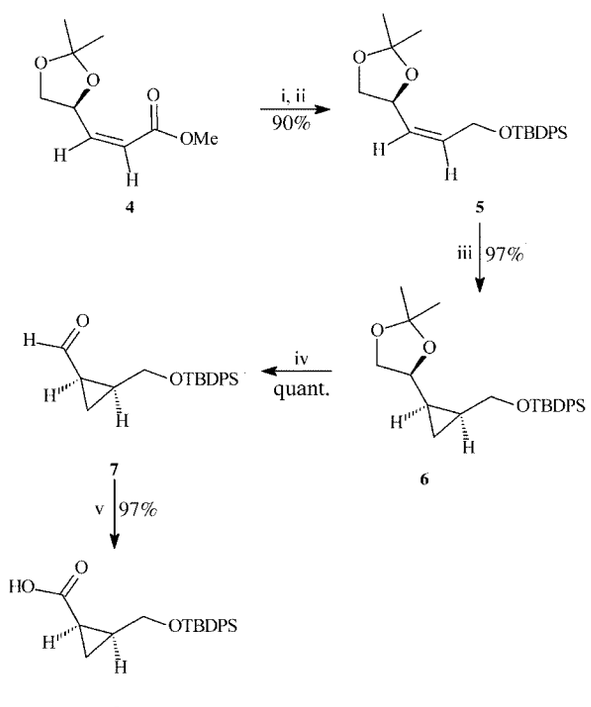
A concise, multigram synthesis of (4*R*)-2-[(1′*R*,2′*S*)-1′,2′-methano-3′-(*tert*-butyldiphenylsiloxy)propyl]-4-hydroxymethyl-4,5-dihydrothiazole has been achieved, and this compound has been used for the production of a range of analogues of the anti-mitotic agent curacin A.

Curacin A, **1**, from the marine cyanobacterium *Lyngbya majuscula*,[1] has excited the interest of chemists and biologists not least because its cytotoxic potency (at the nanogram level) is combined with a relatively simple structure. It binds to tubulin at the colchicine-binding site, which provides further fascination, since there is no obvious structural similarity between these two secondary metabolites. The possibility of devising a completely novel class of anti-cancer drugs is thus most appealing.



A number of total syntheses of curacin A have already been completed,[2] but since the compound is very sensitive to oxidation, acids and bases, and must be stored under an inert atmosphere at −80 °C, its viability as a drug is clearly compromised. Some information concerning structure–activity data for analogues has also been published,[3] with the survey by Gerwick, White and coworkers being the most extensive. They reported the activity of 23 analogues, and the main conclusions from this and the other studies were that the unsaturated side-chain and cyclopropylthiazoline† were required for optimal activity, though the relative stereochemistry of the cyclopropyl substitutents could be varied without loss of too much activity. To date no analogues with a modification to the cyclopropyl methyl group have been reported. With this in mind, we embarked upon a programme of research that would provide efficient access to the compounds **2** and **3**, which are ideally functionalised for elaboration into a wide array of analogues of this type. The successful syntheses of these key intermediates, and the production of a number of novel analogues of curacin A, are the subjects of this paper.

Our synthesis of compound **2** is shown in Schemes 1 and 2, and commenced with the Wittig product **4** from (*R*)-glyceraldehyde acetonide and methoxycarbonylmethylidene-(triphenyl)phosphorane.[4] Reduction with DIBAL-H (in hexanes), followed by protection of the hydroxy group provided the unsaturated ether **5** (overall yield 90% for the two steps) (Scheme 1). A highly stereoselective Simmons–Smith methylenation was accomplished using diethylzinc and diiodomethane at −20 °C (97% isolated yield), according to the method of Taguchi *et al.*,[5] and like these authors, we only obtained stereoisomer **6**. The isopropylidene group was removed (PTSA–aqueous MeOH, 80%) and the resultant diol cleaved to provide the aldehyde **7** ($NaIO_4$–aqueous THF, 81%). Unfortunately, the acid-catalysed step was only effective when carried out under conditions of high-dilution. More concentrated reaction mixtures inevitably led to concomitant removal of the TBDPS group. To circumvent this problem, we employed periodic acid in anhydrous ether[6] to effect removal of the isopropylidene group and oxidative cleavage of the resultant diol to provide the aldehyde **7** in essentially quantitative yield. This aldehyde was then oxidised with $KMnO_4$ to produce the desired acid **8** (97% for the three steps).

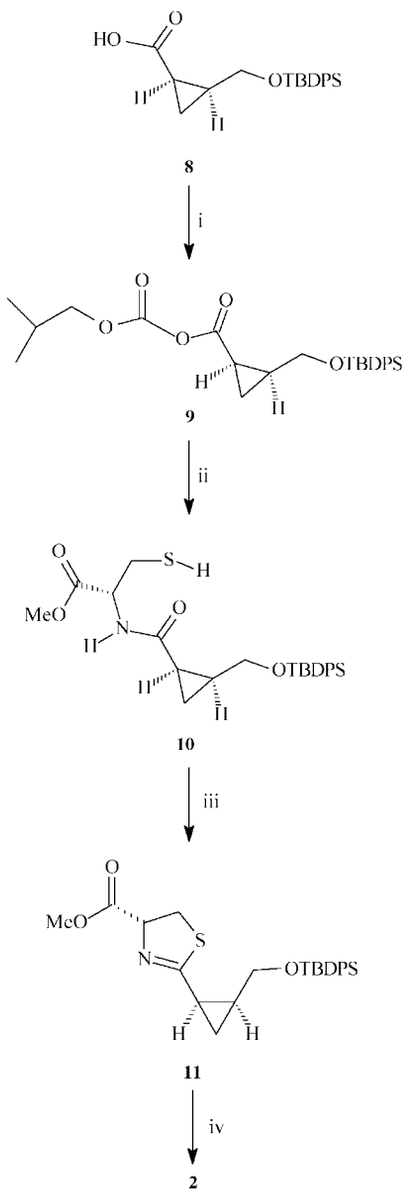


Scheme 1 *Reagents and conditions*: i, DIBAL-H; ii, TBDPS-Cl; iii, Et_2Zn–CH_2I_2, −23 °C; iv, H_5IO_6, ether, RT; v, $KMnO_4$.

In many of the reported syntheses of curacin A, a major problem has been the construction of the thiazoline ring, and

† IUPAC name: cyclopropyl-4,5-dihydrothiazole.

the synthetic sequences have either been lengthy or low-yielding. Typically, the expensive Burgess reagent[7] has been used to effect the dehydration needed for the construction of the thiazoline ring. Our solution was to prepare the mixed anhydride **9** from the acid **8** (Bu^iOCOCl–*N*-methylmorpholine, quant.) and thence the cysteinyl amide **10** (L-cysteine methyl ester·HCl–*N*-methylmorpholine, 65%) (Scheme 2). Finally,

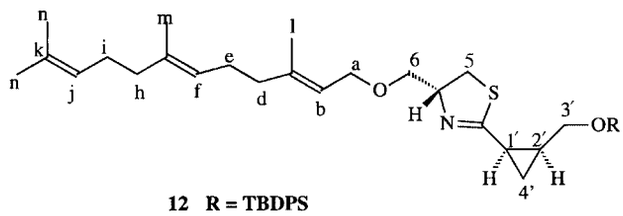


Scheme 2 *Reagents and conditions*: i, isobutyl chloroformate, *N*-methylmorpholine; ii, L-cysteine methyl ester HCl; iii, $TiCl_4$; iv, $LiAlH_4$.

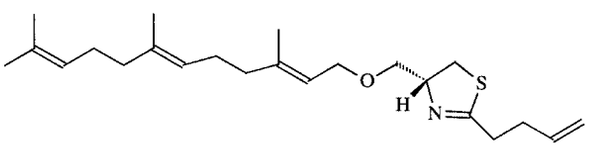
treatment of this amide with $TiCl_4$ in DCM[8] effected ring closure to provide the thiazoline ester **11** in excellent (91%) yield. Although this methodology had been used to prepare oxazoline and thiazoline rings, it had not been used to prepare thiazoline rings in delicate systems like **11**. Finally, reduction of the ester using $LiAlH_4$ provided the desired intermediate **2**, which was also converted into the alternative alcohol **3** through acetylation (Ac_2O, pyridine, quant.) and reaction with fluoride (TBAF–THF, 73%).

With multigram quantities of intermediate **2** in hand, we embarked upon the synthesis of a number of simple analogues of curacin A for biological evaluation. Since the natural product is relatively unstable due to the lability of the 4-hydrogen of the thiazoline ring, and *cis* to *trans* isomerisation of the adjacent double bond, we chose to replace the natural side-chain with a farnesyl ether to try to overcome these problems. It was our fervent hope that the farnesyl chain would have enough structural similarity to the natural chain, so that the biological effect of this substitution would be effectively 'neutral'. This would then allow us to probe the effects of introducing functionality at the cyclopropyl methyl group.

Reaction of **2** with farnesyl bromide (NaH, 18-crown-6, NaI, benzene) yielded the anticipated farnesyl ether **12** (55%), and removal of the TBDPS group (Bu_4NF, THF) produced the alcohol **13** (86%). The acetate **14** (Ac_2O, pyridine, 61%) and the hexanoate **15** (hexanoic acid, Ph_3P, DEAD, 80%) were then produced using conventional chemistry. In addition, although the methyl ether **16** could not be prepared using base and



12 R = TBDPS
13 R = H
14 R = COMe
15 R = $CO(CH_2)_4Me$
16 R = Me
17 R = CS.SMe



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methyl iodide, it could be prepared (in low yield, 25%) through the use of diazomethane on silica.[9] We also tried to reduce the hydroxy group of compound **13** *via* formation of the xanthate **17**, which could be prepared in the usual way (NaH–THF–CS_2–MeI) and in good yield (75%). However, reaction with Bu_3SnH in the presence of AIBN in toluene led to the not unexpected formation of the 2-but-3-enylthiazoline **18** *via* ring opening of the cyclopropylmethylene radical. Other attempts to convert the alcohol **13** into the bromide and tosylate led to decomposition.

Biological evaluation of compounds **13** to **16** was carried out using the Cancer Research Campaign's panel of human ovarian carcinoma cell lines: A2780, A2780 (cisplatin resistant), CH1, CH1 (cisplatin resistant), and SKOV-3; but unfortunately none of these compounds showed any cytotoxic activity at concentrations up to 25 μM. In contrast, curacin A has been reported[3] to have an IC_{50} of 0.038 μM against the human breast cancer cell line MCF-7. While it is a common finding that compounds have very different activities against different tumour cell lines, and our compounds will be tested in other systems, these results are none the less disappointing. This lack of activity may reveal that the natural unsaturated side-chain is an absolute requirement for good levels of potency, and we are presently using the key intermediates **2** and **3** to prepare analogues of compounds **13** to **16** with unsaturated side-chains that more closely resemble the one present in curacin A. It has to be admitted, however, that an increase in potency may be negated by a decrease in stability, and that analogues of curacin A that are viable clinical candidates may be impossible to prepare.

Experimental

IR spectra were recorded using a Perkin-Elmer 881 series

double beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Autospec spectrometer. Elemental analyses were carried out by Medac Ltd., Brunel University on those compounds that were stable. All compounds for which exact mass data are provided were homogeneous by TLC in three different solvent systems, and exhibited no spurious signals in their ^{1}H NMR spectra at 400 MHz. NMR spectra were recorded using JEOL EX4000, Bruker DPX 250, or Bruker WM 250 spectrometers. In ^{13}C NMR assignments ^{3}C refers to tertiary carbon. $[a]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Solvents were dried by distillation from calcium hydride (DCM, dichloromethane) or from sodium–benzophenone (ether, THF).

Methyl (4*S*)-(*Z*)-4,5-isopropylidenedioxypent-2-enoate (4)

Methoxycarbonylmethylene(triphenyl)phosphorane (61.6 g, 0.18 mol) was added in portions to a solution of (*R*)-glyceraldehyde acetonide (24 g, 0.184 mol) in methanol (AnalaR; 170 ml) at 0 °C, and the mixture was shaken for 1 h. The solvent was removed under reduced pressure and the residue extracted with warm light petroleum (bp 40–60 °C). After cooling, the extract was filtered and evaporated to dryness. The resultant colourless oil (30 g, 87%) comprised a mixture of *cis* and *trans* alkenes. The major (*cis*) product was isolated by flash chromatography on silica gel [eluent: 7:3, petroleum ether (bp 40–60 °C)–ether]. Isolated yields were *cis*-**4** (27.4 g, 80%) and *trans*-**4** (2.3 g, 7%), giving a *cis*:*trans* ratio 12:1. The spectroscopic data were in accord with the literature.[4]

Spectral data for *cis*-product (**4**): IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 1725, 1650, 1210, 1065; ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.39 and 1.45 (2 × s, 6H, 2 × Me), 3.62 (dd, 1H, J_{gem} 8.2, $J_{5,4}$ 6.9 Hz, H-5), 3.73 (s, 3H, OMe), 4.39 (dd, 1H, J_{gem} 8.2, $J_{5a,4}$ 7.0 Hz, H-5a), 5.49 (m, 1H, H-4), 5.86 (dd, 1H, $J_{2,3}$ 11.4, $J_{2,4}$ 1.8 Hz, H-2), 6.31 (dd, 1H, $J_{3,2}$ 11.4, $J_{3,4}$ 6.6 Hz, H-3); $[a]_D^{20}$ +90.8 (c = 1, $CHCl_3$).

(4*S*)-(*Z*)-1-(*tert*-Butyldiphenylsilyloxy)-4,5-isopropylidenedioxypent-2-ene (5)

The *cis*-alkene (**4**) (2.00 g, 0.011 mol) in DCM (40 ml), was treated at −78 °C with DIBAL-H (26.9 ml, 0.027 mol of a 1 M solution, 2.5 eq). After stirring the resulting solution at this temperature for 30 min the reaction was quenched by the addition of methanol (5 ml), and the mixture was warmed to room temperature, then filtered through Celite. The Celite was washed thoroughly with EtOAc, and the combined filtrates were dried and concentrated, prior to purification by silica chromatography [eluent: 3:1, petroleum ether (bp 40–60 °C)–EtOAc] to provide the required alcohol (1.65 g, 97%) as a colourless oil. To a solution of this alcohol (1.6 g, 0.010 mol) in DCM (20 ml), under an argon atmosphere at 0 °C, was added triethylamine (2 ml). After stirring for 10 min *tert*-butyldiphenylsilyl chloride (2.63 ml, 0.010 mol, 1 eq) was added and a small amount of DMAP (≈10 mg). The reaction was then quenched by addition of water followed by extraction into ether. The organic phase was washed with water, sodium bicarbonate solution and brine and then dried ($MgSO_4$) and concentrated under reduced pressure, to yield a crude oil (4.2 g) which was purified by column chromatography [eluent: 9:1, petroleum ether (bp 40–60 °C)–ethyl acetate] affording 3.7 g, 93% of the title compound (**5**).

IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 2932 (CH), 1590 (w, aromatic), 1474 (aromatic), 1113 (Si–O), 1062 (Si–O), 703 (Si–O); ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.04 (s, 9H, *tert*-butyl), 1.31 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.43 (t, 1H, J_{gem} 8.0, $J_{5,4}$ 7.6 Hz, H-5), 3.89 (dd, 1H, J_{gem} 8.0, $J_{5a,4}$ 6.2 Hz, H-5a), 4.28 (m, 1H, J_{gem} 6.2, $J_{1,2}$ 1.8 Hz, H-1), 4.32 (m, 1H, J_{gem} 6.2, $J_{1a,2}$ 1.4 Hz, H-1a), 4.62 (m, 1H, $J_{4,5a}$ 6.2, $J_{4,3}$ 1.8 Hz, H-4), 5.45 (m, 1H, $J_{3,2}$ 5.5, $J_{3,4}$ 1.8, $J_{3,1}$ 1.4 Hz, H-3), 5.81 (m, 1H, H-2), 7.32 (m, 6H, 6 × diphenyl-H), 7.66 (m, 4H, 4 × diphenyl-H); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 19.11 (^{3}C, *tert*-butyl-C), 25.85 and 26.75 (2 × CH_3, isopropylidene), 60.27 (CH_2, C-5), 69.38 (CH_2, C-1), 71.95 (CH, C-4), 109.17 [^{3}C, $C(CH_3)_2$], 127.72 (CH, diphenyl), 128.16 (CH, C-3), 129.73 (CH, diphenyl), 133.33 (CH, C-2), 133.39, 133.50, 135.56 (2 × ^{3}C, CH, remaining diphenyl-C); CI-MS *m*/*z*: 66 (17%), 130 (18), 199 (38), 251 (16), 281 (100), 339 (40), 397 (22); $C_{24}H_{32}O_3Si$ requires 397.2205, found 397.2191; $[a]_D^{20}$ −3.1 (c = 1.0, $CHCl_3$), lit.[5] $[a]_D$ −3.9 (c = 1.12, $CHCl_3$).

(1*R*,2*S*,4′*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropane (6)

Diethylzinc (61.0 ml, 0.060 mol, 1 M solution in hexane, 5 eq) and diiodomethane (9.83 ml, 0.12 mol, 10 eq) were added to the alkene (**5**) (4.84 g, 0.012 mol) in dichloromethane (60 ml, dry), under an argon atmosphere at −23 °C. The reaction was stirred vigorously overnight at −23 to 0 °C, followed by treatment with aqueous ammonium chloride and the products were extracted into ether. The organic phase was washed with saturated sodium bicarbonate solution followed by brine, and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel [eluent: 8:2, petroleum ether (bp 40–60 °C)–ether] affording the required cyclopropane (**6**) (4.88 g, 97%).

IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 3050 (C–H, cyclopropane), 2933 (C–H), 1589, 1470, 1428, 1110 (Si–O), 1064 (Si–O), 705 (Si–O), 613; ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.36 (dd, 1H, J_{gem} 10.9, $J_{3,1}$ 5.4 Hz, H-3), 0.84 (m, 1H, H-3a), 1.03 (m, 1H, $J_{1,3}$ 5.4 Hz, H-1), 1.05 (s, 9H, *tert*-butyl), 1.20 (m, 1H, H-2), 1.35 (s, 3H, acetonide-CH_3), 1.46 (s, 3H, acetonide-CH_3), 3.40 (dd, 1H, J_{gem} 11.3, $J_{5',4'}$ 9.5 Hz, H-5′), 3.78 (m, 2H, CH_2OTBDPS), 3.91 (dd, 1H, J_{gem} 11.3, $J_{5a',4'}$ 5.5 Hz, H-5′a), 4.21 (m, 1H, H-4′), 7.40 (m, 6H, 6 × diphenyl-H), 7.66 (m, 4H, 4 × diphenyl-H); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 8.17 (CH_2, C-3), 17.53 (^{3}C, *tert*-butyl), 18.361 (CH, C-1), 19.16 (CH, C-2), 25.79 (CH_3, acetonide), 26.90 (4 × CH_3, *tert*-butyl and acetonide), 64.17 (CH_2, C-5′), 70.17 (CH_2, *C*H_2OTBDPS), 108.55 (CH, C-4′), 127.66 [^{3}C, $C(CH_3)_2$], 127.70, 127.90, 129.68, 133.61, 135.49, 135.58 (12 × diphenyl-C); CI-MS *m*/*z*: 97 (30%), 155 (30), 199 (55), 295 (100), 353 (83), 411 (11); $C_{25}H_{34}O_3Si$ requires 410.2277, M + H$^+$ requires 411.2355, found 411.2301; $[a]_D^{20}$ −1.2 (c = 1.0, $CHCl_3$), lit.[5] $[a]_D$ −1.4 (c = 1.06, $CHCl_3$).

(2*R*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2,3-methanobutanal (7)

Periodic acid (1.36 g, 6 mmol, 2.5 eq) was added to the acetal (**6**) (1.0 g, 2.4 mmol) dissolved in anhydrous ether (100 ml) held at RT under an atmosphere of argon. The reaction was complete after around 10 h, and the mixture was then filtered prior to evaporation of the ether. The crude product was dissolved in chloroform, insoluble salts were removed by filtration, and the filtrate was evaporated to yield an off-white solid (0.81 g, quant.). This was used without further purification but an analytical sample was obtained by chromatography [eluent: 8:2, petroleum ether (bp 40–60 °C)–ether].

Mp 87–88 °C; IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 3049 (C–H, cyclopropane), 2930 (C–H), 2723 (*H*–*C*=O, w), 1707 (H–*C*=*O*), 1113 and 704 (Si–O); ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.03 (s, 9H, *tert*-butyl), 1.19 (m, 1H, CH_2), 1.28 (m, 1H, CH_2), 1.77 (m, 1H, H-3), 1.96 (m, 1H, H-2), 3.66 (dd, 1H, J_{gem} 11.3, $J_{4,3}$ 8.0 Hz, H-4), 3.99 (dd, 1H, J_{gem} 11.3, $J_{4a,3}$ 5.5 Hz, H-4a), 7.36–7.40 (m, 6H, 6 × diphenyl-H), 7.62–7.67 (m, 4H, 4 × diphenyl-H), 9.36 (d, 1H, $J_{1,2}$ 5.5 Hz, H-1); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 12.19 (CH_2), 19.16 (^{3}C, *tert*-butyl), 25.87 (CH, C-3), 26.77 (CH_3, 3 × CH_3, *tert*-butyl), 27.43 (CH, C-2), 62.05 (CH_2, C-4), 127.73–135.55 (2 × ^{3}C and 10 × CH, 2 × diphenyl), 200.76 (^{3}C, C-1); CI-MS *m*/*z*: 78 (20), 198 (16), 281

(60), 339 (100); $C_{21}H_{26}O_2Si$ requires 338.1702, M + H^+ requires 339.1780, found 339.1772; requires C, 74.51, H, 7.74%, found C, 74.52, H, 7.69%; $[\alpha]_D^{20}$ −11.9 (c = 1.0, $CHCl_3$).

(2*R*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2,3-methanobutanoic acid (8)

Potassium hydrogen orthophosphate buffer (40 ml, 1.25 M) was added to aldehyde (**7**) (1.561 g, 4.61 mmol) in *tert*-butyl alcohol (50 ml) to adjust the pH to 4.4. Aqueous $KMnO_4$ (48 ml, 1 M solution) was then added and the mixture was stirred vigorously for 5 min until all the aldehyde had been consumed. The reaction was quenched by addition of saturated sodium sulfite solution and acidified with cold dilute HCl (2 M) to pH 3, where the solution lost its colour. The mixture was extracted with DCM and washed with brine, the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound (**8**) (1.59 g, 97%), which was used without further purification.

IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 2600–3200 (br, OH), 3050 (CH, cyclopropane), 2931 (CH), 1695 (C=O), 1113, 824 (Si–O); ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.01 (s, 9H, *tert*-butyl), 1.02–1.06 (m, 2H, CH_2), 1.64 (m, 1H, H-3), 1.76 (m, 1H, H-2), 3.78 (dd, 1H, J_{gem} 11.0, $J_{4,3}$ 8.4 Hz, H-4), 3.94 (dd, 1H, J_{gem} 11.0, $J_{4a,3}$ 6.2 Hz, H-4a), 7.32–7.43 (m, 6H, 6 × diphenyl-H), 7.62–7.69 (m, 4H, 4 × diphenyl-H); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 12.94 (CH_2), 17.35 (^{3}C, *tert*-butyl), 19.184 (CH, C-3), 24.506 (CH, C-2), 26.719 (3 × CH_3, *tert*-butyl), 61.996 (CH_2, C-4), 127.59–135.55 (diphenyl carbons), 178.83 (^{3}C, C-1); CI-MS *m*/*z*: 94 (22%), 138 (23), 175 (19), 199 (100), 236 (21), 277 (30), 297 (49), 355 (69); $C_{21}H_{26}O_3Si$ requires M^+ 354.1651, found 354.166; requires C, 70.95, H, 7.37%, found C, 70.90, H, 7.35%; $[\alpha]_D^{20}$ +27.8 (c = 1, $CHCl_3$).

N-[(2′*R*,3′*S*)-4′-(*tert*-Butyldiphenylsilyloxy)-2′,3′-methanobutanoyl]-(*S*)-cysteine methyl ester (10)

A mixture of isobutyl chloroformate (0.60 ml, 4.65 mmol, 1 eq) and *N*-methylmorpholine (0.51 ml, 4.65 mmol, 1 eq) were added to the carboxylic acid (**8**) (1.65 g, 4.65 mmol) in DCM (100 ml) at −10 °C, and the mixture was stirred for 15 min to produce the mixed anhydride (**9**). To this mixture was added a stirred suspension of L-cysteine methyl ester hydrochloride (0.798 g, 4.65 mmol) in DCM (20 ml) and *N*-methylmorpholine (0.51 ml, 4.65 mmol, 1 eq). The mixture was stirred for 2 h at room temperature followed by addition of water, extraction with DCM, and the organic phase was washed with water and brine. The organic phase was dried ($MgSO_4$), filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel [eluent: 1 : 1, petroleum ether (bp 40–60 °C)–ether] to give the required amide (**10**) (1.43 g, 65%), as a colourless viscous oil.

IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 3318 (N–H, 2° amide stretch), 3011 (CH, cyclopropane), 2931 (CH stretches), 1744 (C=O, ester), 1655 (C=O, amide), 1526 (br, C–N stretch), 1111 (Si–O), 823 (Si–O), 792, 741, 690 (diphenyl); ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.88–1.01 (m, 1H, $J_{5',2'}$ 8.0 Hz, H-5′), 1.04 (s, 9H, *tert*-butyl), 1.37 (m, 1H, H-5′a), 1.47 (m, 1H, H-3′), 1.66 (m, 1H, $J_{2',5'}$ 8.0 Hz, H-2′), 2.87–3.01 (m, 2H, CH_2S), 3.78 (s, 3H, OMe), 3.82–3.94 (m, 2H, J_{gem} 10.9, $J_{4',3'}$ 5.5 Hz, H-4′, 4′a), 4.89–4.93 (m, 1H, CHN), 6.61 (d, 1H, J 7.3 Hz, N-H), 7.26–7.42 (m, 6H, 6 × diphenyl-H), 7.65–7.69 (m, 4H, 4 × diphenyl-H); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 10.17 (CH_2, C-5′), 19.21 (^{3}C, *tert*-butyl), 19.48 (CH, C-3′), 19.23 (CH, C-2′), 26.87 (3 × CH_3, *tert*-butyl), 27.05 (CH_2, C-4′), 52.75 (CH_3, OMe), 53.59 (CHN), 62.13 (CH_2S), 127.54–135.52 (diphenyl carbons), 170.76 (^{3}C, C-1′), 170.83 (^{3}C, CO_2Me); CI-MS *m*/*z*: 94 (10%), 122 (21), 198 (52), 278 (20), 319 (15), 348 (27), 380 (100), 414 (59), 438 (17); $C_{25}H_{33}O_4NSSi$ M^+ requires 471.1961, found 471.1957; $[\alpha]_D^{20}$ −18.4 (c = 2, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-(*tert*-butyldiphenylsilyloxy)-propyl]-4-methoxycarbonyl-4,5-dihydrothiazole (11)

Titanium tetrachloride (0.53 ml of a 1 M solution in DCM, 1 eq) was added to the amide (**10**) (0.25 g, 0.525 mmol) in DCM (20 ml) at 0 °C. The mixture was stirred for 2 h until starting material had been consumed. The reaction was quenched by the addition of sodium bicarbonate solution followed by extraction with DCM. The organic phase was washed with water and brine then dried ($MgSO_4$), followed by evaporation of solvents to afford the title compound (**11**), (0.22 g, 91%). Purification was not necessary.

IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 3011 (CH, cyclopropane), 2931 (CH), 1745 (C=O), 1614 (C=N), 1111, 1068 and 824 (Si–O), 611 and 704 (diphenyl); ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 1.04 (s, 9H, *tert*-butyl), 1.05 (m, 1H, H-4′a), 1.14 (m, 1H, J_{gem} 11.9, $J_{4',1'}$ 5.9 Hz, H-4′), 1.63 (m, 1H, H-2′), 1.99 (m, 1H, $J_{1',4'}$ 5.9 Hz, H-1′), 3.40 (dd, 1H, J_{gem} 11.0, $J_{3',2'}$ 9.4 Hz, H-3′), 3.47 (dd, 1H, J_{gem} 11.0, $J_{3a',2'}$ 9.9 Hz, H-3′a), 3.69 (dd, 1H, J_{gem} 11.0, $J_{5,4}$ 8.8 Hz, H-5), 3.77 (s, 3H, OMe), 3.83 (dd, 1H, J_{gem} 11.0, $J_{5a,4}$ 5.9 Hz, H-5a), 4.74 (m, 1H, H-4), 7.35–7.41 (m, 6H, 6 × diphenyl-H), 7.64–6.67 (m, 4H, 4 × diphenyl-H); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 11.51 (CH_2, C-4′), 19.19 (CH, C-2′), 19.26 (^{3}C, *tert*-butyl), 23.96 (CH, C-1′), 26.76 (CH_3, 3 × CH_3, *tert*-butyl), 35.74 (CH_2, C-3′), 52.62 (CH_3, OMe), 62.20 (CH_2, C-5), 77.00 (CH, C-4), 127.54–135.57 (diphenyl-C), 171.56 (^{3}C, CO_2Me), 172.79 (^{3}C, C-2); CI-MS *m*/*z*: 112 (29%), 198 (22), 278 (11), 396 (100), 454 (18); $C_{25}H_{31}O_3NSSi$ requires 453.1794, M + H^+ calculated 454.1872, found 454.1879; requires C, 66.19, H, 6.89, N, 3.09%, found C, 66.24, H, 6.93, N, 3.06%; $[\alpha]_D^{20}$ −13.5 (c = 1.0, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-(*tert*-butyldiphenylsilyloxy)propyl]-4-hydroxymethyl-4,5-dihydrothiazole (2)

Diethylamine (0.05 ml, 0.464 mmol, 1 eq) and lithium aluminium hydride (0.018 g, 0.464 mmol) were added to a solution of methyl ester (**11**) (210 mg, 0.464 mmol) in THF (10 ml). The reaction was stirred vigorously for 5 min then quenched by the addition of water (0.5 ml). The mixture was filtered followed by extraction of the filtrate with DCM, washed with brine, dried ($MgSO_4$) and then evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel [eluent: 4 : 6, petroleum ether (bp 40–60 °C)–ether] to yield the alcohol (**2**) in 82% yield.

IR (thin film in $CHCl_3$) ν_{max}/cm^{-1}: 3426 (br, OH), 3011 (CH, cyclopropane), 2931 (CH), 1614 (C=N), 1101, 1064 and 821 (Si–O), 619 and 706 (diphenyl); ^{1}H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.97 (m, 2H, H-4′, 4′a), 1.05 (s, 9H, *tert*-butyl), 1.57 (m, 1H, H-2′), 1.96 (m, 1H, H-1′), 3.13 (dd, 1H, J_{gem} 10.8, $J_{3',2'}$ 9.5 Hz, H-3′), 3.24 (dd, 1H, J_{gem} 10.8, $J_{3a',2'}$ 8.8 Hz, H-3′a), 3.60 (dd, 1H, J_{gem} 11.4, $J_{6,4}$ 5.8 Hz, H-6), 3.69 (dd, 1H, J_{gem} 11.4, $J_{6a,4}$ 8.8 Hz, H-6a), 3.83 (dd, 1H, J_{gem} 11.1, $J_{5,4}$ 5.8 Hz, H-5), 3.87 (dd, 1H, J_{gem} 11.1, $J_{5a,4}$ 4.4 Hz, H-5a), 4.37 (m, 1H, $J_{4,6a}$ 8.8, $J_{4,5}$ 5.8 Hz, H-4), 7.36–7.43 (m, 6H, 6 × diphenyl-H), 7.64–6.69 (m, 4H, 4 × diphenyl-H); ^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si): 11.27 (CH_2, C-4′), 19.12 (^{3}C, *tert*-butyl), 19.19 (CH, C-1′), 23.40 (CH, C-2′), 26.80 (CH_3, 3 × CH_3, *tert*-butyl), 34.70 (CH_2, C-5), 62.48 (CH_2, C-3′), 64.67 (CH_2, C-6), 78.44 (CH, C-4), 127.5–135.7 (phenyl-C), 171.3 (^{3}C, C-2); CI-MS *m*/*z*: 130 (21%), 199 (88), 278 (100), 336 (18), 368 (55), 426 (16); $C_{24}H_{31}O_2NSSi$ requires 425.1837, M + H^+ requires 426.1915, found 426.1950; $[\alpha]_D^{20}$ +14.1 (c = 2.0, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-(*tert*-butyldiphenylsilyloxy)propyl]-4*R*-farnesyloxymethyl-4,5-dihydrothiazole (12)

To a solution of the alcohol (**2**) (300 mg, 0.71 mmol) in dry benzene (distilled over CaH_2 under an argon atmosphere) was added sodium hydride (60% in mineral oil, 4–5 eq) under argon. The reaction mixture was stirred for one hour, then a catalytic

amount of 18-crown-6 (10%) was added. After stirring for another hour, a catalytic amount of sodium iodide was added and after a further hour, *trans*,*trans*-farnesyl bromide (201 mg, 0.71 mmol) was added dropwise. The reaction mixture was stirred overnight before adding petroleum ether (40–60 °C) then filtered to remove salts then evaporated and purified by flash column chromatography on silica gel in petroleum ether (40–60 °C)–ether (gradient: 1:0, 8:1, 5:1, 3:1, 1:1). The desired ether (**12**) was isolated as a colourless oil (246 mg, yield 55%).

IR (in paraffin oil) ν_{max}/cm^{-1}: 3071 (C–H, cyclopropane), 2925 and 2854 (C–H), 2359, 1668 (C=C, trisubstituted), 1622 (C=N), 1462 (CH_2), 1428, 1377 (CH_3, *t*-Bu), 1263 (Si–C, stretch), 1112 (Si–O), 1086 (Si–O, C–O–R), 824 (Si–O–C), 738, 701, 614 (aromatic); ^{1}H NMR δ_H (400 MHz, $CDCl_3$, Me_4Si): 0.90–1.10 (m, 2H, H-4′), 1.05 (s, 9H, 3 × CH_3, *t*-Bu), 1.60 (s, 6H, 2 × Me), 1.63 (m, 1H, H-2′), 1.66 (s, 3H, Me), 1.67 (s, 3H, Me), 1.84–2.06 (m, 9H, H-1′ and 4 × CH_2: H-d, H-e, H-h, H-i), 3.13–3.34 (m, 2H, H-5), 3.38 (t, 1H, *J* 8.4 Hz, H-6), 3.66–3.87 (m, 3H, H-6 and H-3′), 4.02 (d, 2H, *J* 6.8 Hz, H-a), 4.39–4.51 (m, 1H, H-4), 5.09 (m, 2H, H-f and H-j), 5.34 (t, 1H, *J* 6.8 Hz, H-b), 7.33–7.44 (m, 6H, Ar-H), 7.63–7.73 (m, 4H, Ar-H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, Me_4Si): 11.35 (CH_2, C-4′), 15.96 (Me-n), 16.47 (Me-m), 17.64 (Me-n), 19.17 (*t*-Bu-C and CH, C-1′), 23.36 (CH, C-2′), 25.65 (Me-l), 26.25 (CH_2, farnesyl), 26.65 (CH_2, farnesyl), 26.76 (*t*-Bu-Me), 36.25 (CH_2, C-5), 39.64 (2CH_2, farnesyl), 62.50 (CH_2, C-3′), 67.60 (CH_2, C-a), 70.98 (CH_2, C-6), 75.99 (CH, C-4), 120.55 (CH, C-b), 123.78 (CH, C-i), 124.27 (CH, C-f), 127.51 (4CH, aromatic), 129.43 (2CH, aromatic), 131.21 (^{3}C, farnesyl), 134.02 (2 ^{3}C, aromatic), 135.21 (^{3}C, farnesyl), 135.50 (4CH, aromatic), 140.31 (^{3}C, farnesyl), 170.89 (N=C–S, C-2); *m*/*z*: 630 (100%), 572 (26), 492 (7), 409 (6), 368 (29), 336 (7), 278 (19), 199 (20), 137 (16), 69 (53); $C_{39}H_{55}NO_2SSi$ requires: 630.3787, found M^+ 630.3782; $[a]_D^{20}$ +3.9 (*c* = 0.65, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-hydroxypropyl]-4-farnesyloxymethyl-4,5-dihydrothiazole (13)

To the ether (**12**) (230 mg, 0.36 mmol) in dry THF (freshly distilled under argon using Na–benzophenone, 1–2 ml) under an argon atmosphere, was added TBAF (1.0 M in THF, 2 eq, 0.730 ml) at 0 °C. After addition, the mixture was maintained at room temperature overnight. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel in petroleum ether (40–60 °C)–ether 1:1 then ether. The desired product was isolated as a colourless oil (123 mg, 86%).

IR (in paraffin oil) ν_{max}/cm^{-1}: 3396 (br, OH), 3070 (C–H, cyclopropane), 2924 and 2854 (C–H), 2360, 1668 (C=C, trisubstituted), 1616 (C=N), 1456 (CH_2), 1428, 1377, 1239, 1112, 1057 (C–O–R), 836; ^{1}H NMR δ_H (250 MHz, $CDCl_3$, Me_4Si): 0.96–1.18 (m, 2H, H-4′), 1.59 (s, 6H, 2 × Me), 1.61 (m, 1H, H-2′), 1.67 (s, 3H, Me), 1.68 (s, 3H, Me), 1.83 (m, 1H, H-1′), 1.93–2.27 (m, 8H, 4CH_2: H-d, H-e, H-h, H-i), 3.29 (m, 1H, H-5), 3.40 (m, 2H, H-5 and H-6), 3.49 (m, 1H, H-3′), 3.61 (dd, 1H, *J* 4.3 and 9.4 Hz, H-6), 3.96 (m, 1H, H-3′), 4.02 (d, 2H, *J* 6.1, H-a), 4.69 (m, 1H, H-4), 5.10 (m, 2H, H-f and H-j), 5.33 (t, 1H, *J* 7.1 Hz, H-b); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, Me_4Si): 11.75 (CH_2, C-4′), 16.02 (CH_3, Me-n), 16.53 (CH_3, farnesyl), 17.70 (CH_3, Me-n), 18.61 (CH, C-1′), 23.42 (CH, C-2′), 25.70 (CH_3, farnesyl), 26.32 (CH_2, farnesyl), 26.74 (CH_2, farnesyl), 35.84 (CH_2, C-5), 39.61 (CH_2, farnesyl), 39.71 (CH_2, farnesyl), 61.35 (CH_2, C-3′), 67.77 (CH_2, C-a), 70.38 (CH_2, C-6), 75.99 (CH, C-4), 120.49 (CH, C-b), 123.82 (CH, C-j), 124.34 (CH, C-f), 131.32 (^{3}C, farnesyl), 135.34 (^{3}C, farnesyl), 140.72 (^{3}C, farnesyl), 173.15 (N=C–S, C-2); *m*/*z*: 392 (100%), 322 (11), 254 (22), 171 (63), 112 (21), 69 (42); $C_{23}H_{37}NO_2S$ M^+ requires 391.2545, found M + H^+ 392.2632; $[a]_{20}^{D}$ −5.64 (*c* = 0.55, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-acetoxypropyl]-4-farnesyloxymethyl-4,5-dihydrothiazole (14)

To a solution of alcohol (**13**) (48 mg, 0.12 mmol) in dichloromethane (1 ml) was added at room temperature a catalytic amount of DMAP (0.1 eq). Acetic anhydride (11.6 µl, 1 eq) then pyridine (20 µl, 2 eq) were added slowly and the mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was directly purified by flash column chromatography on silica gel in petroleum ether (40–60 °C)–ether 1:1. The desired product was isolated as a colourless oil (32 mg, 61%).

IR (in paraffin oil) ν_{max}/cm^{-1}: 3070 (C–H, cyclopropane), 2924 and 2854 (C–H), 2356, 2246, 1744 (C=O), 1668 (C=C, trisubstituted), 1620 (C=N), 1456, 1368, 1236 and 1112 (C–O–C, stretch), 1060, 1027, 988, 908, 735, 648; ^{1}H NMR δ_H (250 MHz, $CDCl_3$, Me_4Si): 1.11–1.23 (m, 2H, H-4′), 1.60 (s, 6H, Me), 1.67 (s, 3H, Me), 1.68 (s, 3H, Me), 2.04 (s, 3H, Me), 1.95–2.20 (m, 10H, H-1′ and H-2′ and 4CH_2: H-d, H-e, H-h and H-i), 3.19–3.42 (m, 2H, H-5), 3.46 (m, 1H, H-6), 4.73 (dd, 1H, *J* 4.4 and 9.5 Hz, H-6), 4.05 (m, 2H, *J* 5.1, H-d), 4.15 (m, 2H, H-3′), 4.55 (m, 1H, H-4), 5.10 (m, 2H, H-f and H-j), 5.34 (t, 1H, *J* 6.6 Hz, H-b); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, Me_4Si): 11.59 (CH_2, C-4′), 16.02 (CH_3, Me-n), 16.54 (CH_3, farnesyl), 17.70 (CH_3, Me-n), 19.14 (CH, C-1′), 20.94 (C-2′ and OAc), 25.70 (CH_3, farnesyl), 26.32 (CH_2, farnesyl), 26.74 (CH_2, farnesyl), 36.54 (CH_2, C-5), 39.62 (CH_2, farnesyl), 39.71 (CH_2, farnesyl), 63.32 (CH_2, C-3′), 67.74 (CH_2, C-a), 70.96 (CH_2, C-6), 76.52 (CH, C-4), 120.66 (CH, C-b), 123.84 (CH, C-i), 124.34 (CH, C-f), 131.31 (^{3}C, farnesyl), 135.32 (^{3}C, farnesyl), 140.55 (^{3}C, farnesyl), 170.97 (2C, C=O and N=C–S, C-2); *m*/*z*: 434 (100%), 374 (11), 296 (21), 213 (51), 170 (11), 138 (28), 93 (6), 69 (33); $C_{25}H_{39}NO_3S$ requires 433.2651, found M + H 434.2731; $[a]_D^{20}$ −2.8 (*c* = 0.60, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-methoxypropyl]-4-farnesyloxymethyl-4,5-dihydrothiazole (16)

The alcohol (**13**) (100 mg, 0.25 mmol) was added to 770 mg of silica gel (Kieselgel 60, 0.063–0.200 nm) in 2.5 ml of dry ether under argon. After cooling to 0 °C, a solution of diazomethane in ether (20 eq, freshly prepared from 2 g of Diazald in 12 ml of ether) was added dropwise over 45 min. After stirring for 5 h at 0 °C, the mixture was warmed to room temperature. The reaction mixture was then filtered, concentrated and the crude product purified by column chromatography on silica gel in petroleum ether (40–60 °C)–ether 1:1 then ether to furnish the methyl ether as a colourless oil (27 mg, 26%).

IR (in paraffin oil) ν_{max}/cm^{-1}: 3070 (C–H, cyclopropane), 2968 and 2861 (C–H), 2361, 2338, 1653 (C=C, trisubstituted), 1617 (C=N), 1456, 1385, 1261, 1197, 1093, 1055 (C–O–R), 985, 823; ^{1}H NMR δ_H (250 MHz, $CDCl_3$, MeSi): 1.10 (m, 2H, H-4′), 1.55 (m, 1H, H-2′), 1.60 (s, 6H, 2 × Me), 1.67 (s, 6H, 2 × Me), 1.90–2.13 (m, 9H, 4CH_2: H-d, H-e, H-h, H-i and H-1′), 3.19 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,5'}$ 12.5 Hz, H-5), 3.31 (s, 3H, OMe), 3.35 (dd, 1H, $J_{4,5}$ 7.5, $J_{5,5'}$ 12.5 Hz, H-5), 3.41–3.48 (dd, 1H, $J_{6,6'}$ 17.5, $J_{6,4}$ 5.0 Hz, H-6), 3.45 (d, 2H, *J* 7.5 Hz, H-3′), 3.74 (dd, 1H, $J_{6',4}$ 10.0 Hz, H-6), 4.05 (d, 2H, $J_{a,b}$ 7.5 Hz, H-a), 4.55 (m, 1H, H-4), 5.09 (m, 2H, H-f and H-j), 5.35 (t, 1H, *J* 7.5 Hz, H-b); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, TMS): 11.55 (CH_2, C-4′), 16.03 (CH_3, Me-n), 16.55 (CH_3, farnesyl), 17.70 (CH_3, Me-n), 19.00 (CH, C-2′), 20.36 (CH, C-1′), 25.70 (CH_3, farnesyl), 26.35 (CH_2, farnesyl), 26.76 (CH_2, farnesyl), 36.58 (CH_2, C-5), 39.65 (CH_2, farnesyl), 39.73 (CH_2, farnesyl), 58.43 (OCH_3), 70.93 (CH_2, C-3′), 67.78 (CH_2, C-a), 71.13 (CH_2, C-6), 76.66 (CH, C-4), 120.73 (CH, C-b), 123.86 (CH, C-j), 124.37 (CH, C-f), 131.31 (^{3}C, farnesyl), 135.35 (^{3}C, farnesyl), 140.52 (^{3}C, farnesyl), 170.11 (N=C–S, C-2); *m*/*z*: 406 (100%), 336 (13), 268 (33), 185 (72), 112 (62), 81 (37); $C_{24}H_{39}NO_2S$ requires 405.2712, found M + H 406.2780; $[a]_D^{20}$ +17.1 (*c* = 0.55, $CHCl_3$).

(4*R*)-2-[(1′*R*,2′*S*)-1′,2′-Methano-3′-hydroxypropyl]-4-acetoxymethyl-4,5-dihydrothiazole (3)

To a solution of alcohol (**2**) (500 mg, 1.175 mmol) in dry methylene chloride (10 ml) at room temperature was added 4-dimethylaminopyridine (15 mg, 0.1 eq). Acetic anhydride (111 µl, 1 eq) then pyridine (190 µl, 2 eq) were added slowly and the mixture was stirred at room temperature until starting material had disappeared. Water was added, the organic phase was separated, washed with water and brine then dried ($MgSO_4$) and evaporated. The acetate was isolated as a colourless oil (550 mg, 100%) and was used without further purification.

To a sample of this acetate (732 mg, 1.56 mmol) in dry THF (distilled under argon using Na–benzophenone, 20 ml) under an argon atmosphere was added TBAF (1.0 M in THF, 2 eq, 3.13 ml) at 0 °C. After the addition, stirring was maintained at room temperature for 2 h. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel in petroleum ether (40–60 °C)–ether 1 : 1 then ether. The desired product (**3**) was isolated as a colourless oil (260 mg, 73%).

IR (in paraffin oil) ν_{max}/cm^{-1}: 3382 (br, OH), 3073 (C–H, cyclopropane), 3006, 2948 and 2879 (C–H), 1737, 1615 (C=N), 1441, 1382, 1365, 1229, 1118, 1044 (C–O–R), 979, 913, 836; ^{1}H NMR δ_H (250 MHz, $CDCl_3$, Me_4Si): 1.00 (m, 1H, H-4′), 1.15 (m, 1H, H-4′), 1.63 (m, 1H, H-2′), 1.84 (m, 1H, H-1′), 2.08 (s, 3H, OAc), 3.15 (dd, 1H, $J_{4,5}$ 6.9, $J_{5,5'}$ 11.2 Hz, H-5), 3.42 (dd, 1H, $J_{4,5'}$ 8.9 Hz, H-5′), 3.49 (m, 1H, H-3′), 3.97 (dd, 1H, $J_{2',3'}$ 4.0 Hz, H-3′), 4.12 (dd, 1H, $J_{4,6}$ 6.2, J_{gem} 11.1 Hz, H-6), 4.23 (m, 1H, H-6), 4.42 (m, 1H, H-4); ^{13}C NMR δ_C (100 MHz, $CDCl_3$, Me_4Si): 11.98 (CH_2, C-4′), 18.59 (CH, C-1′), 20.80 (CH_3), 23.55 (CH, C-2′), 35.27 (CH_2, C-5), 61.31 (CH_2, C-3′), 64.74 (CH_2, *C-6), 74.61 (CH, C-4), 170.85 (C*=O), 173.82 (N=C–S, C-2); *m/z*: $C_{10}H_{15}NO_3S$ requires 229.0773, found M + H 230.0851; $[\alpha]_D^{20}$ +23.3 (*c* = 1, $CHCl_3$).

Acknowledgements

We thank the Association for International Cancer Research for generous financial support; Dr Lloyd Kelland of the CRC Centre for Cancer Therapeutics for the biological evaluations; and the EPSRC Mass Spectrometry Service at Swansea for numerous high resolution spectra.

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