New approach to AI-77B: stereoselective construction of a potential precursor of the amino acid side chain

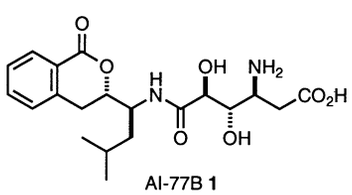
Chisato Mukai,* Motonori Miyakawa and Miyoji Hanaoka*

Faculty of Pharamaceutical Sciences, Kanazawa Univesity, Takara-machi, Kanazawa 920, Japan

A potential precursor of the amino acid side-chain derivative of antiulcerogenic antibiotic AI-77B is prepared in a highly stereoselective manner from the *anti*-aldol product 3, obtained from the reaction of the chiral benzaldehydechromium(0) complex 2.

Introduction

AI-77B **1**, a representative to the group of antibiotics known as the AI-77s, has been isolated from *Bacillus pimilus*[1] and shown to possess potent antiulcerogenic action against stress ulcer in rats without any anticholinergic, antihistaminergic or central suppressive effects.[2] Several groups[3] have so far accomplished total synthesis of AI-77B **1** *via* the coupling reaction



AI-77B **1**

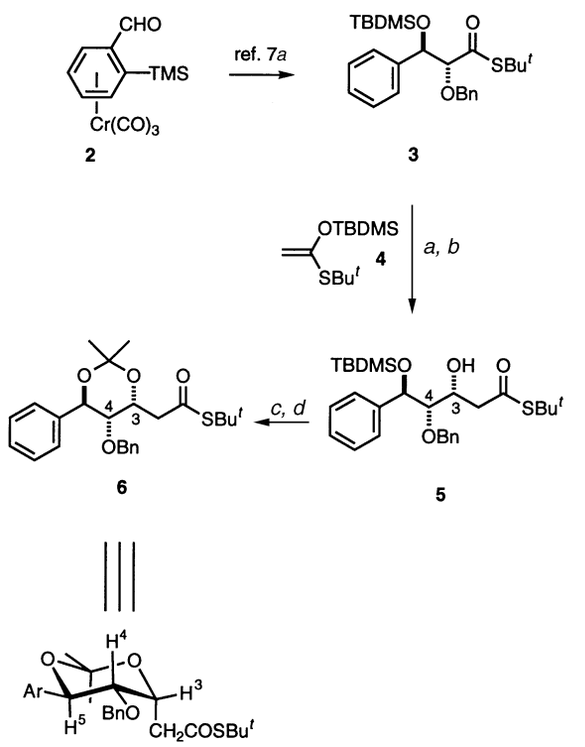
between a dihydroisocoumarin moiety and an amino side-chain portion. Some alternative methods for the preparation of both dihydroisocoumarin derivatives[4] and the protected amino acid tethers[5] have also been developed.

Recent efforts from this laboratory[6] have explored highly *anti*-selective aldol reactions of the chiral tricarbonyl[η^6-*o*-(trimethylsilyl)benzaldehyde]chromium(0) complex **2** with enolsilanes or titanium enolates. By taking advantage of these highly stereoselective aldol reactions as a crucial step, we have completed syntheses of several bioactive compounds.[6b,7] Here we describe an additional example, namely the successful application of the newly developed *anti*-selective aldol reaction to a highly stereocontrolled construction of an amino acid side-chain analogue of AI-77B.

Results and discussion

At the inception of this program, highly stereoselective two-carbon elongation of the *anti*-aldol products **3**,[7a] prepared from the aldol reaction of aldehyde **2**, was first investigated by employing racemic *erythro* thioester **3**. Treatment of (±)-**3** (*anti* : *syn* = 95 : 5) with diisobutylaluminium hydride (DIBAL-H) gave the corresponding aldehyde, which was subsequently exposed to aldol reactin with the *O*,*S*-ketal **4** under chelation-controlled conditions[8] in the presence of tin(IV) chloride ($SnCl_4$) to produce (±)-3,4-*syn*-aldol product **5** in 53% yield as expected (Scheme 1). The formation of the desired 3,4-*syn*-product **5** from substrate **3** can be interpreted in terms of the chelation-controlled transition state on the basis of a Felkin–Anh chelated model[9] as shown in Fig. 1.

In order to confirm the relative stereochemistry of product **5**, we transformed it into the corresponding six-membered acetonide **6**. Desilylation of compound **5** with sodium iodide and boron trifluoride–diethyl ether ($BF_3{\cdot}OEt_2$) provided the diol,



Scheme 1 *Reagents*: *a*, DIBAL-H, CH_2Cl_2; *b*, $SnCl_4$, **4**; *c*, NaI, $BF_3{\cdot}OEt_2$, CH_3CN; *d*, $Me_2C(OMe)_2$, PPTS

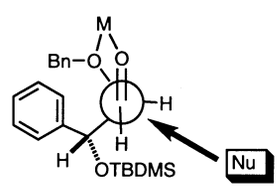
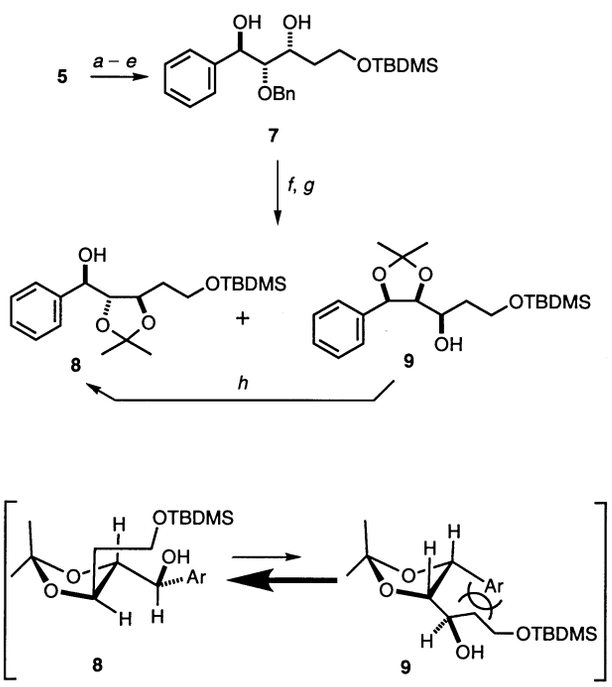


Fig. 1

which was converted into the acetonide (±)-**6** in 71% overall yield on treatment with 2,2-dimethoxypropane and pyridinium toluene-*p*-sulfonate (PPTS). A careful examination of the ^1H NMR spectrum of compound **6** disclosed that the coupling constant between H^3 and H^4 is 4.4 Hz, while that between H^4 and H^5 is 7.3 Hz. This observation obviously indicated that the smaller coupling constant should be due to equatorial–axial or equatorial–equatorial coupling, and that the larger one should be attributed to axial–axial coupling. This diagnostic analysis of coupling constants is in good accord with the preferred conformation of compound **6**. Chemical modification of alcohol **5**

into acetonide **6** enabled us to establish the relative stereochemistry of compound **5** unambiguously.

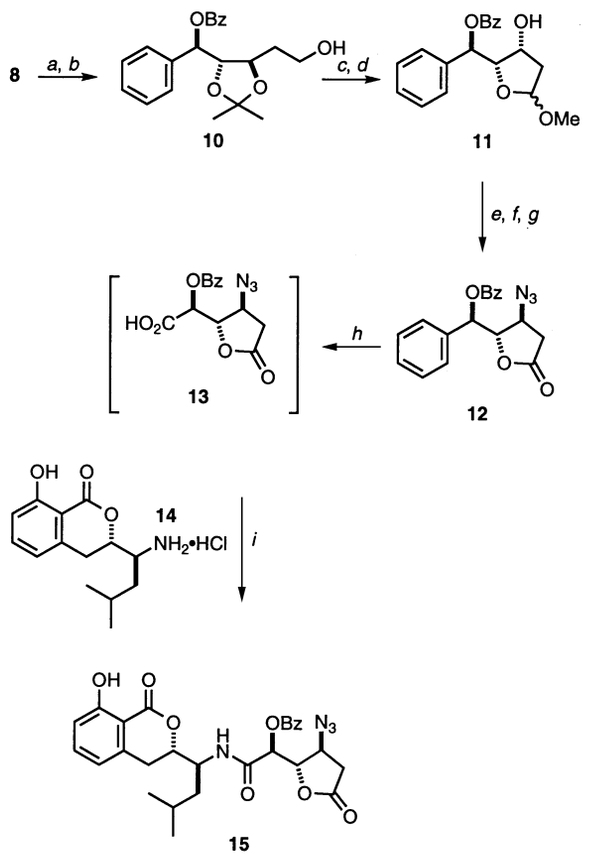
According to the procedure that resulted in a series of racemates, we next synthesized optically pure (−)-**5**[10] in 58% overall yield from the non-racemic starting material **3** (*anti* : *syn* = 95 : 5). Direct reduction of the thioester group of compound **5** with several hydride reagents such as $LiAlH_4$, $LiAlH(OMe)_3$ and $LiBH_4$ was troublesome and gave the desired primary hydroxy compound in only poor yield and/or as an intractable mixture. We tentatively surmised that these results might result from the free β-hydroxy functionality of compound **5**. Therefore, the free hydroxy group of compound (−)-**5** was first protected with a trimethylsilyl (TMS) group to afford the TMS derivative, which was consecutively exposed to the following reactions: (i) reduction with DIBAL-H, (ii) reduction with sodium borohydride ($NaBH_4$), (iii) desilylation, (iv) introduction of a *tert*-butyldimethylsilyl (TBDMS) group on the resulting primary hydroxy functionality to yield diol (−)-**7** in 91% overall yield from **5**. Upon treatment under Birch conditions, diol **7** underwent debenzylation to produce the triol, acetalization of which with 2,2-dimethoxypropane and PPTS for 2 h at room temperature gave the acetonides **8** and **9** in 56 and 21% yield, respectively (Scheme 2). Thermodynamic consideration of these acetonides



Scheme 2 *Reagents*: *a*, TMS–imidazole, CH_2Cl_2; *b*, DIBAL-H, CH_2Cl_2; *c*, $NaBH_4$, MeOH; *d*, TBAF, THF; *e*, TBDMSCl, Et_3N, CH_2Cl_2; *f*, Na, liq. NH_3; *g*, $Me_2C(OMe)_2$, PPTS, DMF; *h*, PTTS, CH_3CN

8 and **9** led to the insight that isomer **8** would be thermodynamically preferred over **9** because there is an unfavourable non-bonding interaction between two *cis*-oriented substituents on a fixed five-membered ring in structue **9**. However, this would not be the case in isomer **8** where two appendages on a fixed five-membered ring are *trans*. As a result, easy isomerization of **9** to **8** would be expected. Actually, treatment of crude compound **9** under similar acetalization conditions for a prolonged reaction time (8 h) provided isomer **8** in 83% yield. Thus, exclusive formation *arabino* of isomer **8** from diol **7** was attained in 73% overall yield.

Successive protection of the hydroxy moiety with a benzoyl group and removal of the TBDMS group of compound **8** furnished primary alcohol (+)-**10** in 73% yield. Tetrahydrofuran (THF)-ring formation was achieved by oxidation of the primary alcohol of compound **10**, followed by deacetalization in methanol to give acetal **11** in 81% yield as a mixture of two diastereoisomers. Introduction of amino functionality at the C-4 position of **11** with inversion of configuration was undertaken as follows. The tetrahydrofuran derivative **11** was converted into the corresponding mesyl ester, which was then exposed to sodium azide in dimethylformamide (DMF) to afford the azido derivative with inverted stereochemistry at the C-4 position. Treatment of the resulting azido compound with *m*-chloroperbenzoic acid (MCPBA) in the presence of $BF_3 \cdot OEt_2$[11] effected generation of the γ-lactone moiety to provide derivative **12** in 66% yield (Scheme 3).



Scheme 3 *Reagents*: *a*, BzCl, Et_3N, CH_2Cl_2; *b*, TBAF-HF, THF; *c*, $Py \cdot SO_3$, DMSO, Et_3N, CH_2Cl_2; *d*, 10% HCl, MeOH; *e*, MsCl, Et_3N, CH_2Cl_2; *f*, NaN_3, DMF; *g*, MCPBA, $BF_3 \cdot OEt_2$, CH_2Cl_2; *h*, RuO_2, $NaIO_4$, aq. CH_3CN, AcOEt; *i*, DCC, HOBt, DMF

The final requirement for synthesis of the target amino acid derivative **13** is transformation of a phenyl moiety into a carboxylic acid functionality. Oxidative cleavage of the benzene ring of compound **12** was performed under Sharpless conditions[12] with ruthenium tetraoxide[13] producing the desired carboxylic acid derivative **13**. Owing to the relative difficulty of its isolation, acid **13** was, without isolation, condensed with the dihydroisocoumarin derivative **14**[3a] to yield amide (−)-**15** in 38% overall yield from compound **12**. It should be mentioned that amide **15** has all the carbon framework with the proper stereochemistry required for AI-77B, although we have not carried compound **15** any further.[14]

Thus, we have developed a new procedure for the construction of the amino acid side-chain analogue of AI-77B by taking advantage of the two chiral stereogenic centres of the *anti*-aldol product derived from a highly selective aldol reaction of the chiral tricarbonyl[η^6-*o*-(trimethylsilyl)benzaldehyde]-chromium(0) complex **2**.

Experimental

Mps were determined on a Yanagimoto micro melting-point

apparatus and are uncorrected. IR Spectra were measured on samples in $CHCl_3$ with a JASCO A-102 spectrometer; mass spectra with Hitachi M-80 and JEOL JMS-SX 102 A mass spectrometers; ^{1}H NMR spectra with JEOL EX-270 and JEOL JNM-GX 500 spectrometers for samples in $CDCl_3$, using either tetramethylsilane as an internal standard for compounds that have no silyl group or $CHCl_3$ (δ 7.26) for compounds possessing the silyl group; ^{13}C NMR spectra with JEOL EX-270 and JEOL JNM-GX 500 spectrometers for sample in $CDCl_3$ with $CDCl_3$ (δ_C 77.0) as an internal reference. All *J* values are in Hz and $[\alpha]_D$ values in 10^{-1} deg dm^2 g^{-1}.

Methylene dichloride was freshly distilled from P_2O_5, and THF from sodium–benzophenone prior to use. All reactions were carried out under nirogen. Silica gel (silica gel 60, 230–400 mesh, Nacalai Tesque) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

S-*tert*-Butyl (3*R,4*S**,5*R**)-4-benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-5-phenylpentanethioate (±)-5**

DIBAL-H in toluene (1.00 mol dm^{-3}; 0.28 cm^3, 0.28 mmol) was added to a solution of compound (±)-**3**[7a] (a mixture of *anti*:*syn* = 95:5; 51.0 mg, 0.11 mmol) in dry methylene dichloride (1.0 cm^3) at −78 °C. After being stirred for 15 min, the reaction mixture was qenched by addition of saturated aq. Rochelle salt (1.5 cm^3) and passed through a short pad of Celite. The organic layer was washed successively with water and brine, dried and concentrated to dryness. The residue was dissolved in dry methylene dichloride (1.5 cm^3), to which the *O*,*S*-acetal **4**[15] (30.0 mg, 0.12 mmol) was added. A solution of $SnCl_4$ in methylene dichloride (1.0 mol dm^{-3}; 0.12 cm^3, 0.12 mmol) was added dropwise to the solution at −78 °C. The reaction mixture was stirred for 10 min at the same temperature, then quenched by addition of saturated aq. ammonium chloride (1.5 cm^3) and diluted with methylene dichloride. The organic layer was washed successively with water and brine, dried and concentrated to leave a residual oil, which was chromatographed with hexane–ethyl acetate (15:1) to give title compound (±)-**5** (30.0 mg, 53%) as an oil, ν_{max}/cm^{-1} 3500 (OH) and 1675 (CO); δ_H 7.38 (2 H, d, *J* 6.8, ArH), 7.34 (1 H, t, *J* 6.8, ArH), 7.30–7.25 (5 H, m, ArH), 7.08–7.06 (2 H, m, ArH), 4.82 (1 H, d, *J* 7.3, 5-H), 4.39 (1 H, ddd, *J* 2.0, 5.4 and 8.3, 3-H), 4.22 and 4.00 (2 H, AB-q, *J* 10.7, benzylic H), 3.34 (1 H, dd, *J* 2.0 and 7.3, 4-H), 2.75 (1 H, dd, *J* 8.3 and 14.7, 2-H), 2.56 (1 H, dd, *J* 5.4 and 14.7, 2-H), 1.45 (9 H, s, Bu^t), 0.88 (9 H, s, Bu^t), 0.08 (3 H, s, Me) and −0.20 (3 H, s, Me); δ_C 198.4, 142.2, 137.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.3, 83.9, 74.6, 73.9, 67.8, 49.0, 48.1, 29.8, 25.8, 18.0, −4.6 and −5.2; *m*/*z* (fast-atom bombardment) (FAB) 503 (M^+ + 1, 1.7%), 221 (59), 161 (8) and 91 (100).

S-*tert*-Butyl (3*R,4*S**,5*R**)-4-benzyloxy-3,5-isopropylidenedioxy-5-phenylpentanethioate (±)-6**

To a solution of compound **5** (50.9 mg, 0.10 mmol) and sodium iodide (46.0 mg, 0.30 mmol) in dry acetonitrile (1.0 cm^3) was added a solution of BF_3·OEt_2 in dry methylene dichloride (1.00 mol dm^{-3}; 0.20 cm^3, 0.20 mmol) at 0 °C and the reaction mixture was stirred for 15 min before being diluted with ethyl acetate, and the mixture was washed successively with water and brine, dried and concentrated to dryness. The residue was dissolved in 2,2-dimethoxypropane (1.0 cm^3), PPTS (1.9 mg, 0.01 mmol) was added at room temperature, and the mixture was stirred for 1 h before being quenched by addition of saturated aq. $NaHCO_3$, diluted with water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried and concentrated to dryness. Chromatography of the residual oil with hexane–ethyl acetate (15:1) afforded *title compound* (±)-**6** (30.2 mg, 71%) as an oil (Found: C, 70,1; H, 7.3. $C_{25}H_{32}O_4S$ requires C, 70.1; H, 7.6%); ν_{max}/cm^{-1} 1675 (CO); δ_H 7.44–7.11 (10 H, m, ArH), 4.63 (1 H, d, *J* 7.3, 5-H), 4.59 (1 H, ddd, *J* 4.4, 6.3 and 7.3, 3-H), 4.26 and 4.05 (2 H, AB-q, *J* 11.2, benzylic H), 3.18 (1 H, dd, *J* 4.4 and 7.3, 4-H), 2.91 (1 H, dd, *J* 7.3 and 15.6, 2-H), 2.85 (1 H, dd, *J* 6.3 and 15.6, 2-H), 1.46 (12 H, s, Bu^t and Me) and 1.41 (3 H, s, Me); δ_C 198.1, 140.7, 137.7, 128.6, 128.2, 128.1, 127.9, 127.6, 127.4, 101.5, 82.6, 75.4, 73.6, 68.1, 48.1 and 44.3; *m*/*z* (FAB) 429 (M^+ + 1, 15%), 393 (30), 371 (24), 349 (26), 307 (28), 211 (24) and 161 (39).

S-*tert*-Butyl (3*R*,4*S*,5*R*)-4-benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-5-phenylpentanethioate (−)-5

According to the procedure described for the preparation of racemate (±)-**5**, compound (−)-**5** (542 mg, 58%) was obtained from the optically active substrate **3** (a mixture of *anti*:*syn* = 95:5; 858 mg). *Product* (−)-**5** was an oil (Found: C, 66.9; H, 8.4. $C_{28}H_{42}O_4SSi$ requires C, 67.1; H, 8.4%); $[\alpha]_D^{22}$ −23.4 (*c* 0.51, $CHCl_3$).

(1*R*,2*S*,3*R*)-2-Benzyloxy-5-(*tert*-butyldimethylsiloxy)-1,3-dihydroxy-1-phenylpentane (−)-7

To a solution of thioester (−)-**5** (852 mg, 1.47 mmol) in dry methylene dichloride (15 cm^3) was added TMS-imidazole (0.25 cm^3, 1.47 mmol) at room temperature. The reaction mixture was stirred for 15 min, diluted with methylene dichloride, washed with water, dried and concentrated to dryness. The residue was dissolved in dry methylene dichloride (15 cm^3), to which a solution of DIBAL-H in toluene (1.00 mol dm^{-3}; 3.3 cm^3, 3.30 mmol) was added at −78 °C. After being stirred for 15 min, the reaction mixture was qenched by addition of saturated aq. Rochelle salt (1.5 cm^3) and passed through a short pad of Celite. The organic layer was washed successively with water and brine, dried and concentrated to dryness. $NaBH_4$ (56.0 mg, 1.47 mmol) was added to a solution of the residue in methanol (15 cm^3) and the reaction mixture was stored for 30 min at room temperature. Methanol was evaporated off and the residue was taken up in methylene dichloride, which was washed with water, dried and the solution was concentrated to dryness. The residue was dissolved in THF (15 cm^3). A solution of tetrabutylammonium fluoride (TBAF) in THF (1.00 mol dm^{-3}; 4.0 cm^3, 4.00 mmol) was added to the solution at room temperature. After being stirred for 30 min, the reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated to leave a residual oil, wich was dissolved in methylene dichloride (5.0 cm^3). Triethylamine (0.60 cm^3, 4.4 mmol), 4-(dimethylamino)pyridine (DMAP) (12.5 mg, 0.1 mmol) and TBDMSCl (332 mg, 2.2 mmol) were successively added to the solution at room temperature. The reaction mixture was kept for 8 h and then were washed successively with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (15:1) afforded *title compound* (−)-**7** (622 mg, 91%) as an oil (Found: C, 69.2; H, 8.7. $C_{24}H_{36}O_4Si$ requires C, 69.2; H, 8.8%); $[\alpha]_D^{19}$ −11.9 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3450 (OH); δ_H 7.41 (2 H, d, *J* 7.3, ArH), 7.35 (2 H, d, *J* 7.3, ArH), 7.33–7.27 (4 H, m, ArH), 7.16–7.15 (2 H, m, ArH), 5.00 (1 H, d, *J* 6.4, 1-H), 4.45 and 4.36 (2 H, AB-q, *J* 11.2, benzylic H), 4.07–4.04 (1 H, m, 3-H), 3.88–3.84 (1 H, m, 2-H), 3.75–3.71 (1 H, m, 5-H), 3.41 (1 H, dd, *J* 2.9 and 6.4, 5-H), 2.00–1.93 (1 H, m, 4-H), 1.67–1.60 (1 H, m, 4-H), 0.84 (9 H, s, Bu^t), 0.04 (3 H, s, Me) and 0.03 (3 H, s, Me); δ_C 142.0, 137.7, 128.3, 128.2, 128.1, 127.8, 126.7, 82.6, 73.9, 72.8, 71.4, 62.1, 34.8, 25.8, 18.1, −5.3 and −5.6; *m*/*z* (FAB) 417 (M^+ + 1, 20%), 381 (4), 235 (9), 189 (100) and 131 (100).

(1*R*,2*R*,3*R*)-5-(*tert*-Butyldimethylsiloxy)-1-hydroxy-2,3-isopropylidenedioxy-1-phenylpentane (−)-8

To a solution of diol (−)-**7** (620 mg, 1.49 mmol) in THF (5.0 cm^3) were added liquid ammonia (*ca*. 10 cm^3) and sodim metal (200 mg, 8.70 mmol) at −78 °C. The reaction mixture was stored for 30 min at the same temperature. Solid ammonium chloride (100 mg) was added to the reaction mixture, which was then gradually warmed to room temperature. The residue was

taken up in ethyl acetate, which solution was washed successively with water and brine, dried and concentrated to dryness. The residue was dissolved in DMF (2.0 cm^3), and 2,2-dimethoxypropane (2.0 cm^3) and PPTS (32.5 mg, 0.15 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 2 h, quenched by addition of water and extracted with ethyl acetate. The extract was washed successively with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–ethyl acetate (10:1) to afford acetonides (−)-**8** (306 mg, 56%) and **9** (115 mg, 21%). *Isomer* (−)-**8** was an oil (Found: C, 65.6; H, 9.35. $C_{20}H_{34}O_4Si$ requires C, 65.6; H, 9.3%); $[\alpha]_D^{19}$ −7.6 (*c* 0.43, $CHCl_3$); ν_{max}/cm^{-1} 3400 (OH); δ_H 7.37 (2 H, d, *J* 7.3, ArH), 7.34 (2 H, d, *J* 7.3, ArH), 7.28 (1 H, t, *J* 7.3, ArH), 4.93 (1 H, d, *J* 4.4, 1-H), 4.13 (1 H, td, *J* 2.9 and 8.3, 3-H), 3.93 (1 H, dd, *J* 4.4 and 8.3, 2-H), 3.64–3.55 (2 H, m, 5-H_2), 1.47–1.40 (1 H, m, 4-H), 1.39 (6 H, s, Me × 2), 1.18–1.12 (1 H, m, 4-H), 0.87 (9 H, s, Bu^t), 0.00 (3 H, s, Me) and −0.01 (3 H, s, Me); δ_C 139.01, 128.3, 127.8, 127.4, 126.2, 108.5, 83.9, 73.6, 72.6, 59.9, 37.0, 27.4, 26.9, 25.9, 25.8, 18.3, −5.4 and −5.5; *m*/*z* 366 (M^+, 0.2%), 348 (4), 273 (15), 233 (16), 145 (39), 131 (100) and 101 (58).

Compound **9** was an oil; ν_{max}/cm^{-1} 3450 (OH); δ_H 7.50 (2 H, d, *J* 6.8, ArH), 7.34 (2 H,d, *J* 6.8, ArH), 7.27 (1 H, t, *J* 6.8, ArH), 4.57 (1 H,d, *J* 7.3, 1-H), 4.06 (1 H, ddd, *J* 3.9, 5.4 and 9.3, 3-H), 3.88 (1 H, dd, *J* 3.9 and 7.3, 2-H), 3.84 (1 H, td, *J* 4.4 and 10.8, 5-H), 3.66 (1 H, td, *J* 2.4 and 10.8, 5-H), 2.11–2.03 (1 H, m, 4-H), 1.86–1.80 (1 H, m, 4-H), 1.48 (3 H, s, Me), 1.42 (3 H, s, Me), 0.87 (9 H, s, Bu^t), 0.07 (3 H, s, Me) and 0.05 (3 H, s, Me); δ_C 141.1, 128.3, 127.4, 126.2, 101.2, 75.4, 74.6, 70.5, 60.0, 31.8, 25.8, 24.5, 24.1, 18.1 and −5.6.

The crude product **9** (115 mg, 0.31 mmol) was treated with PPTS (3.3 mg, 0.015 mmmol) in dry acetonitrile (1.5 cm^3) at room temperature for 8 h to furnish isomer (−)-**8** (95 mg, 83%). Thus, the total yield of (−)-**8** from (−)-**7** was 73%.

(1*R*,2*S*,3*R*)-1-Benzoyloxy-5-hydroxy-2,3-isopropylidenedioxy-1-phenylpentane (+)-10

To a solution of silyl ether (−)-**8** (244 mg, 0.67 mmol) in dry methylene dichloride (4.0 cm^3) were added triethylamine (0.28 cm^3, 0.20 mmol), DMAP (12.5 mg, 0.10 mmol) and benzoyl chloride (0.12 cm^3, 1.00 mmol) at room temperature. The reaction mixture was stored at the same temperature for 8 h, washed successively with water and brine, dried and concentrated to dryness. The residue was dissolved in THF (4.0 cm^3) and a solution of TBAF and hydrofluoric acid in aq. THF (0.5 cm^3, prepared from 1.8 cm^3 of 1.0 mol dm^{-3} TBAF in THF solution and 0.1 cm^3 of 47% hydrofluoric acid) was added to the solution. The reaction mixture was stirred at room temperature, diluted with ethyl acetate, washed successively with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–ethyl acetate (3:2) to afford *title compound* (+)-**10** (174 mg, 73%) as an oil (Found: C, 70.1; H, 6.8. $C_{21}H_{24}O_5$ requires C, 69.7; H, 6.9%); $[\alpha]_D^{22}$ +23.0 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3550 (OH) and 1720 (CO); δ_H 8.11 (2 H, d, *J* 7.3, ArH), 7.61–7.29 (8 H, m, ArH), 6.21 (1 H, d, *J* 5.4, 1-H), 4.29 (1 H, td, *J* 3.2 and 7.8, 3-H), 4.19 (1 H, dd, *J* 5.4 and 7.8, 2-H), 3.74–3.71 (2 H, m, 5-H_2), 1.76–1.68 (1 H, m, 4-H), 1.65–1.58 (1 H, m, 4-H), 1.41 (3 H, s, Me) and 1.27 (3 H, s, Me); δ_C 165.3, 136.5, 133.5, 133.3, 130.1, 129.8, 129.7, 128.6, 128.5, 128.4, 127.0, 109.7, 82.7, 77.1, 75.1, 60.6, 35.9, 27.4 and 26.7; *m*/*z* 365 (M^+, 1%), 343 (13), 213 (6), 179 (16), 165 (100) and 151 (9).

(2*S*,3*R*,5*R*,1′*R*)- and (2*S*,3*R*,5*S*,1′*R*)-2-(1′-Benzoyloxy-1′-phenylmethyl)-3-hydroxy-5-methoxytetradrofuran 11

To a solution of acetonide (+)-**10** (163 mg, 0.46 mmol) in dry methylene dichloride (5.0 cm^3) were added triethylamine (0.26 cm^3, 1.84 mmol), dimethyl sulfoxide (DMSO) (0.5 cm^3) and sulfur trioxide–pyridine complex (Py·SO_3) (221 mg, 1.38 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 15 min, washed with water, dried and concentrated to dryness. The residue was dissolved in methanol (4.0 cm^3). 10% Aq. hydrochloric acid (0.10 cm^3) was added to the solution and the reaction mixture was kept at room temperature for 8 h. Methanol was evaporated off to leave a residual oil, which was taken up in ethyl acetate. The ethyl acetate solution was washed successively with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–ethyl acetate (3:1) to afford title compound **11** (123 mg, 81%, as a mixture of two diastereoisomers in the ratio 73:27) to afford title compound **11** (123 mg, 81%, as a mixture of two diastereoisomers in the ratio 73:27) as an oil; ν_{max}/cm^{-1} 3500 (OH) and 1720 (CO); δ_H 8.06 (2 H, dd, *J* 0.7 and 7.3, ArH), 7.61–7.32 (8 H, m, ArH), 6.20 (1 H, d, *J* 9.2, 1′-H), 5.17 (73/100 H, dd, *J* 3.4 and 5.9, 5-H), 5.03 (27/100 H, d, *J* 4.3, 5-H), 4.43–4.26 (2 H, m, 2- and 3-H), 3.34 (81/100 H, s, OMe), 3.18 (219/100 H, s, OMe) and 2.34–2.05 (2 H, m, 4-H_2).

(3*S*,4*S*,1′*R*)-3-Azido-4-(1′-benzoyloxy-1′-phenylmethyl)-4-butanolide (+)-12

To a solution of acetal **11** (123 mg, 0.37 mmol) in dry methylene dichloride (4.0 cm^3) were successively added triethylamine (0.10 cm^3, 0.80 mmol) and methanesulfonyl chloride (0.04 cm^3, 1.56 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min, diluted with methylene dichloride, washed successively with water and brine, dried and concentrated to dryness. The residue was dissolved in DMF (4.0 cm^3). Sodium azide (247 mg, 3.70 mmol) was added to the solution and the reaction mixture was heated at 130 °C for 8 h. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed successively with water and brine, dried and concentrated to dryness. To a solution of the residue and MCPBA (71 mg, 0.40 mmol) in dry methylene dichloride (4.0 cm^3) was added a solution of BF_3·OEt_2 in dry methylene dichloride (1.00 mol dm^{-3}; 0.40 cm^3, 0.40 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min, diluted with methylene dichloride, washed successively with saturated aq. $NaHCO_3$, water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–ethyl acetate (3:1) to afford *title lactone* (+)-**12** (82.0 mg, 66%) as an oil (Found: C, 64.1; H, 4.5; N, 12.5. $C_{18}H_{15}N_3O_4$ requires C, 64.2; H, 4.6; N, 12.3%); $[\alpha]_D^{24}$ +55.0 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 2100 (N_3, 1790 (CO) and 1720 (CO); δ_H 8.06 (2 H, d, *J* 7.3, ArH), 7.62 (1 H, t, *J* 7.3, ArH), 7.50–7.38 (7 H, m, ArH), 6.27 (1 H, d, *J* 3.9, 1′-H), 4.80 (1 H, dd, *J* 3.4 and 3.9, 4-H), 4.40 (1 H, ddd, *J* 3.4, 3.9 and 8.3, 3-H), 2.70 (1 H, dd, *J* 8.3 and 18.6, 2-H) and 2.50 (1 H, dd, *J* 3.9 and 18.6, 2-H); δ_C 172.9, 165.0, 134.0, 133.8, 129.8, 129.7, 129.3, 129.2, 129.1, 128.7, 126.6, 85.4, 74.7, 57.1 and 34.5; *m*/*z* 337 (M^+, 0.5%), 308 (1), 248 (14), 211 (52), 172 (38) and 105 (100).

(3*S*)-3-[(1′*S*)-1′-{(2″*S*)-2″-[(2‴*S*,3‴*S*)-3‴-Azido-5‴-oxotetrahydrofuran-2‴-yl]-2″-benzoyloxyacetamido}-3′-methylbutyl]-3,4-dihydro-8-hydroxy-1*H*-2-benzopyran-1-one (−)-15

Ruthenium dioxide (1.2 mg, 9.0×10^{-3} mmol) was added to a two-phase solution of compound (+)-**12** (31.0 mg, 0.09 mmol) and $NaIO_4$ (288 mg, 1.35 mmol) in ethyl acetate (1.0 cm^3), acetonitrile (1.0 cm^3) and distilled water (1.5 cm^3) under vigorous stirring. Stirring was continued for 48 h at room temperature. The reaction mixture was diluted with ethyl acetate, and was washed successively with water and brine, dried and passed through a short pad of Celite. The filtrate was concentrated to dryness and the residue was dissolved in DMF (1.0 cm^3). *N*,*N*-Dicyclohexylcarbodiimide (DCC) (28.0 mg, 0.14 mmol) and 1-hydroxybenzotriazole (HOBt) (24.5 mg, 0.18 mmol) were added to the solution. The reaction mixture was stirred for 30 min at room temperature and the resulting precipitate was filtered off by suction. Compound **14** (30.0 mg, 0.12 mmol) and triethylamine (0.02 cm^3, 0.14 mmol) were added to the filtrate and the reaction mixture was stirred for 2 h at

room temperature before being diluted with ethyl acetate, washed successively with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–ethyl acetate (3:1) to afford *title amide* (−)-**15** (18.5 mg, 38%) as an oil (Found: C, 60.7; H, 5.3; N, 10.5. $C_{27}H_{28}N_4O_8$ requires C, 60.4; H, 5.3; N, 10.4%); $[a]_D^{19}$ −72.2 (*c* 0.10, $CHCl_3$); ν_{max}/cm^{-1} 2100 (N_3), 1790 (CO), 1730 (CO), 1670 (CO) and 1620 (CO); δ_H 10.64 (1 H, s, OH), 7.93 (2 H, d, *J* 7.8, ArH), 7.65 (1 H, t, *J* 7.8, ArH), 7.47 (2 H, t, *J* 7.8, ArH), 7.42 (1 H, t, *J* 8.3, ArH), 6.87 (1 H, d, *J* 8.3, ArH), 6.70 (1 H, d, *J* 8.3, ArH), 6.41 (1 H, d, *J* 9.8, NH), 5.63 (1 H, d, *J* 2.4, 2″-H), 4.90 (1 H, ddd, *J* 4.4, 4.9 and 8.3 3‴-H), 4.75 (1 H, dd, *J* 2.4 and 4.4, 2‴-H), 4.58–4.75 (1 H, m, 3-H), 4.38–4.33 (1 H, m, 1′-H), 3.07 (1 H, dd, *J* 8.3 and 18.1, 4‴-H), 3.04–3.01 (1 H, m, benzylic H), 2.82–2.78 (1 H, m, benzylic H), 2.62 (1 H, dd, *J* 4.9 and 18.1, 4‴-H), 1.86–1.81 (1 H, m, 2′-H), 1.63–1.60 (1 H, m, 3′-H), 1.47–1.44 (1 H, m, 2′-H), 0.95 (3 H, d, *J* 6.3, Me) and 0.92 (3 H, d, *J* 6.3, Me); δ_C 173.1, 169.6, 165.9, 162.9, 162.3, 138.6, 136.1, 135.8, 135.1, 130.9, 129.5, 128.2, 119.9, 118.6, 107.1, 83.8, 80.1, 73.7, 56.8, 49.9, 41.1, 35.0, 30.0, 25.1, 24.6 and 21.6.

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