Dolastatins 23: stereospecific synthesis of dolaisoleuine[1]

George R. Pettit,* Douglas D. Burkett and Michael D. Williams

Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, Arizona 85287-1604, USA

The remarkable antineoplastic peptide dolastatin 10, isolated from the opisthobranchia mollusc *Dolabella auricularia*, is currently in clinical development and further improvements in its total synthesis have been undertaken. Major effort has been directed at devising more stereoselective routes to the dolastatin 10 amino acid units dolaisoleuine 2 and dolaproine 3, each bearing three chiral centres. We report herein highly stereoselective routes to both natural (3*R*,4*S*,5*S*)-dolaisoleuine 2 and its 3*S*,4*S*,5*S*-isomer 14 (Z replaces H) using an asymmetric aldol methodology. Key reaction steps are condensation of chiral α-(methylsulfanyl)acetyloxazolidinone 4d with (*S*)-*N*-Z-*N*-Me-isoleucinal 6 using dibutylboron triflate followed by reductive desulfurization, O-methylation and cleavage of the oxazolidinone auxiliary to complete a simple route to *N*-benzyloxycarbonyldolaisoleuine 10. By substituting chiral oxazolidinone 5d for 4d the 3*S*-isomer of *N*-benzyloxycarbonyldolaisoleuine 14 was selectively obtained.

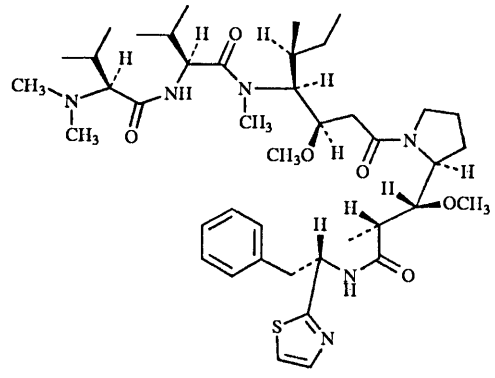
Introduction

Dolastatin 10 **1** from the Indian Ocean sea hare *Dolabella auricularia* has proven to be a remarkably potent antineoplastic substance.[2–4] Clinical development of this promising peptide is currently entering the Phase I human trials stage. In order to improve the overall yields obtained using our first[5] total synthesis of dolastatin 10, it became necessary to devise more stereoselective routes to the dolaisoleuine **2** (Dil) and dolaproine **3** (Dap) units. In our original synthesis of dolastatin 10,[5] high stereoselectivity in the aldol reaction-based routes to dolaproine and dolaisoleuine was not desirable. The absolute configuration of the natural product was not known and a path to all possible isomers was needed. Once the absolute configuration was established,[5] a highly stereoselective synthesis of dolaproine **3** was achieved using chiral oxazolidinone **4b** to control the stereochemical course of the aldol reaction.[1,6] The original route to dolaisoleuine employed a relatively nonselective aldol reaction, giving rise to similar amounts of both the 3*S*,4*S*,5*S*-isomer and the 3*R*,4*S*,5*S*-isomer.[5,7] We have now extended the stereoselective approach of dolaproine to a high-yield synthesis of dolaisoleuine.

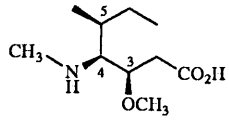
Fortunately, the mechanism and factors controlling the course of the aldol condensation have received considerable investigation over the past decade.[8] Recent advances with the Evans enolate[9] have been especially useful. Furthermore, it is now well established that the enolate geometry controls the stereochemistry of the aldol condensation.[10] More specifically, a *Z* enolate should lead exclusively to a *syn* aldol product. Conversely, an *E* enolate should give the *anti* aldol product. Also well known is that the direction of the enolate approach to the aldehyde group determines the absolute configuration of the resulting hydroxy group.[11] Thus, with chiral aldehydes such as prolinal or isoleucinal, the direction of the enolate approach controls the aldol 3,4-stereochemistry.

The chirality of the directing group along with the choice of metal and ligands determines the orientation of the molecule during enolate formation.[12] Steric effects of the groups attached to the asymmetric centres of both oxazolidinones **4** and **5** force these molecules into configurations which favour exclusive formation of the *Z* enolates.[13] With the Evans oxazolidinones, *syn* aldol products will result as long as the aldol reaction conditions are adjusted to ensure a closed transition state (*i.e.*, by using excess of Lewis base to prevent any Lewis acid from complexing with the aldehyde oxygen).[8e]

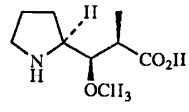
The chirality of the enolate assists in controlling the most favourable face of the enolate for approach to the aldehyde.[14] Inspection of oxazolidinones **4** and **5** shows that the enolates derived from these chiral auxiliaries will favour an approach from opposite directions. Several factors control the enolates' preference for approach on a particular side. The oxazolidinone carbonyl oxygen forms a complex with the metal co-ordinated to the enolate oxygen, effectively locking the oxazolidinone ring in place and leaving the chiral groups blocking one face of the molecule for approach to an aldehyde.[15] The size of these groups influences the degree of steric hindrance and hence the



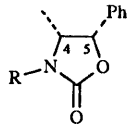
1 Dolastatin 10



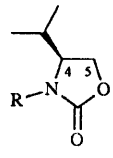
2 Dolaisoleuine



3 Dolaproine



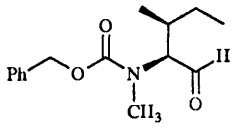
4a; R = H
4b; R = $COCH_2CH_3$
4c; R = $COCH_3$
4d; R = $COCH_2SCH_3$



5a; R = H
5b; R = $COCH_2CH_3$
5c; R = $COCH_3$
5d; R = $COCH_2SCH_3$

resulting facial preference. The choice of metal and ligand is also critical. Boron gives rise to shorter bond lengths than most metals, such as lithium, making boron and bulky ligands the most favourable choice. By studying the favoured approach of the enolate from oxazolidinones **4b–d** and **5b–d** to the aldehyde, one can determine the most likely configuration of the aldol hydroxy group.

All of the preceding requirements were successfully met in our stereoselective route[6] to Dap **3** using the oxazolidinone **4b**. We assumed the same general methodology could be applied to the synthesis of Dil **2**. However, Dil represented a more difficult exercise in stereocontrol. The lack of any substituent in the 2-position of Dil made the acetyl oxazolidinones **4c** and **5c** obvious choices. However, with two hydrogen atoms present (no heteroatom), no enolate *E* or *Z* character is present and unsatisfactory stereocontrol would result. The absence of any R^1–R^3 steric interactions[15] eliminates this aspect of the favoured transition state. Those predictions were confirmed when reaction between oxazolidinone **4c** and *N*-benzyloxycarbonyl-*N*-methylisoleucinal **6** was implemented. The 3′*S*,4′*S*,5′*S*- and 3′*R*,4′*S*,5′*S*-Dil diastereoisomers were routinely obtained in nearly equal proportions. To circumvent this problem, we utilized oxazolidinones **4d** and **5d**, known[9] to form exclusively *Z* enolates, thus ensuring *syn* stereocontrol. Theoretically these would lead to the 2′*R*,3′*S*,4′*S*,5′*S*-aldol from the oxazolidinone **4d** and the 2′*S*,3′*R*,4′*S*,5′*S*-aldol from the oxazolidinone **5d**.



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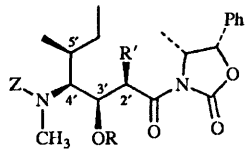
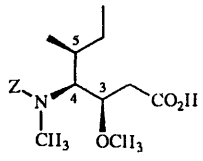
The aldol condensation was accomplished by enolate formation of oxazolidinone **4d** with dibutylboron triflate in the presence of a slight excess of diisopropylethylamine in methylene dichloride. Condensation with *N*-benzyloxycarbonyl-*N*-methyl isoleucinal at −78 °C afforded only one product. Analogous condensation with oxazolidinone **5d** again gave only one apparent product. The *N*-(methylsulfanylacetyl)oxazolidinones **4d** and **5d** both required much longer (≈5×) reaction times for enolization and condensation compared with their somewhat less hindered *N*-propionyloxazolidinone (**4d** and **5b**) counterparts.[16] The usual reaction conditions require an aq. phosphate buffer followed by a large excess of hydrogen peroxide to cleave, by oxidative degradation, the dibutylboron complexed to the product. The result was three products—the aldol along with the corresponding sulfoxide and sulfone derivatives.[17] Application of only 1.1 mole equivalent of hydrogen peroxide eliminated this problem.[16,18] Purification of the aldol product **7** was first attempted on a column of silica gel. Sephadex LH-20 was found to be a more efficient alternative owing to the unstable nature of the product on silica.

Cleavage (**7** ⟶ **8**) of the methylsulfanyl group was first attempted using Raney nickel.[19] Yields were poor even with numerous alterations in experimental conditions. In general, W-2 Raney nickel was found to be in the activity range of choice. More active nickel led to several side-products. Under the most optimal conditions found, the yield of cleavage product was only 51%. Other reductions were then evaluated. Tributyltin hydride in benzene with the free-radical initiator 2,2′-azoisobutyronitrile (AIBN) provided a clean and efficient method for cleavage of the sulfide.[20,21] By limiting the reaction time to 30 min, formation of side-products was minimized and good yields of compound **8** were routinely obtained.

Results from ^{1}H NMR (300 MHz) analysis of the cleavage products from sulfides **7** and **11** were interesting. Several of the



7 R = H, R′ = SCH_3
8 R = R′ = H
9 R = CH_3, R′ = H



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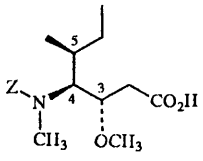

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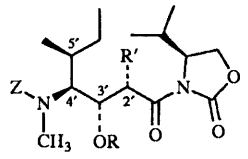
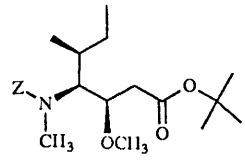


11 R = H, R′ = SCH_3
12 R = R′ = H
13 R = CH_3, R′ = H



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signals were doubled in compound **7**, including those of the N-methyl protons and the oxazolidinone 5-H atom, indicating the possibility of diastereoisomers in roughly a 3:2 ratio. The Raney nickel and the tributyltin hydride reaction products **8** gave identical ^{1}H NMR spectra. Elevated-temperature (55 °C) ^{1}H NMR analysis of compound **12** was inconclusive but indicated the possibility of conformers. Methylation of alcohols **8** and **12** using trimethyloxonium tetrafluoroborate and proton sponge was achieved in high yield using an earlier procedure.[7] Analysis by ^{1}H NMR spectroscopy, at 55 °C, of the resulting methyl ethers (**9** and **13**) showed coalescence of some signals, including those of the 4′-H hydrogen, the methoxy hydrogens and the N-methyl hydrogens—indicating the presence of conformers, not diastereoisomers.

Cleavage (and in an analogous course **13** ⟶ **14**) of the oxazolidinone amide from compound **9** employing hydrogen peroxide and lithium hydroxide followed by sodium sulfite[21] furnished carboxylic acid **10**. Comparison of the product was made with an authentic sample prepared from deprotection of *N*-Z-Dil-OBu^t **15**, which was synthesized *via* our original procedure.[5] The two samples of Z-Dil **10** were identical by ^{1}H NMR, optical rotation and IR comparison. The (3*R*,4*S*,5*S*)-*N*-Z-Dil **10** was converted into ester **15** (the intermediate currently being used in preparation of dolastatin 10) by reaction with 2-methylpropene and a catalytic amount of sulfuric acid.[22]

The preceding stereospecific synthesis of natural (3*R*,4*S*,5*S*)-*N*-Z-Dil **10** and our earlier stereocontrolled synthesis of natural Dap have considerably improved the overall synthesis of dolastatin 10 and allowed easier access to this valuable compound for clinical development.

Experimental

All reagents were used as received from Sigma-Aldrich Chemical Co. and solvents were redistilled prior to use. Reactions requiring anhydrous conditions were conducted under argon in a round-bottom flask equipped with a stir bar, sealed with a rubber septum and flame-dried under argon. Evaporation of solvents (solutions dried over anhydrous sodium sulfate) was performed under reduced pressure on a rotary evaporator at 40 °C, unless otherwise stated. The pH value of solutions was measured with a pH meter. TLC was accomplished with silica gel GHLF Uniplates (Analtech, Inc.). Column chromatography (Kieselgel 60, 0.040–0.063 mm) was performed using silica gel supplied by E. Merck (Darmstadt), unless otherwise stated.

Mps are uncorrected and were determined on an Electrothermal 9100 apparatus. Bps were determined using bulb-to-bulb distillation (*in vacuo*). Optical rotations were recorded using a Perkin-Elmer 241 polarimeter, and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were measured with a Nicolet FT-IR Model MX-1 unit. NMR spectra were recorded on a Varian Gemini 300 MHz or Unity 500 instrument for samples in deuteriochloroform containing tetramethylsilane as internal standard unless otherwise noted. *J* Values are in Hz. The EIMS mass spectra were recorded with a FINNIGAN-MAT 312 instrument (70 eV). Elemental analyses were determined by Galbraith Laboratories, Inc. (Knoxville, Tennessee).

(4*R*,5*S*)-*N*-Acetyl-4-methyl-5-phenyloxazolidin-2-one 4c

A solution of (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one **4a** (5.0 g, 28.22 mmol) in dry tetrahydrofuran (THF) (75 cm^3) was cooled to −78 °C (solid CO_2–acetone-bath) and butyllithium (17.8 cm^3, 28.22 mmol) was added (by syringe over a period of 10 min; the solution turned red with the last few drops). Acetyl chloride (2.1 cm^3, 29.6 mmol) was added and the solution was stirred for 20 min at −78 °C, then at room temperature for 20 min. Excess of acid chloride was eliminated by the addition of saturated aq. ammonium chloride (15 cm^3). The volatile material was removed and the resulting slurry was extracted with methylene dichloride (3 × 20 cm^3). The combined extracts were washed successively with 1 mol dm^{-3} sodium hydroxide (20 cm^3) and brine (20 cm^3). The solution was dried and solvent was removed. The resulting oil was purified on a column of silica gel [33 cm × 3.2 cm; gradient elution with hexane–ethyl acetate (5:1→2:1)] to give a crystalline solid[9] (5.5 g, 90%), mp 68–69 °C; $[\alpha]_D^{25}$ +45 (*c* 2.1, CH_2Cl_2); $\delta_H(CDCl_3)$ 7.40 (5 H, m), 5.67 (1 H, d, *J* 7.8), 4.77 (1 H, m), 2.56 (3 H, s) and 0.90 (3 H, d, *J* 6.7).

(4*R*,5*S*)-*N*-{(3′*R*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)-amino]-3′-hydroxy-5′-methylheptanoyl}-4-methyl-5-phenyl-oxazolidin-2-one 8 and its 3′-hydroxy diastereoisomer

A solution of (4*R*,5*S*)-*N*-acetyl-4-methyl-5-phenyloxazolidin-2-one **4c** (0.85 g, 3.9 mmol, 1.1 mol equiv.) in methylene dichloride (10 cm^3, distilled from CaH_2) was cooled to 0 °C. Triethylamine (0.75 cm^3, 5.3 mmol, 1.5 mol equiv., distilled from CaH_2) was added (by syringe) followed by dibutylboron triflate (4.6 cm^3, 4.6 mmol, 1.3 mol equiv. of a 1.0 molar solution in methylene dichloride) by syringe at such a rate as to keep the internal temperature below 5 °C. The solution was cooled to −78 °C (solid CO_2–acetone-bath) and *N*-benzyloxycarbonyl-*N*-methyl-isoleucinal **6**[5,7] was added (0.82 g, 3.5 mmol) as a solution in anhydrous methylene dichloride (2.0 cm^3). The solution was stirred at −78 °C for 30 min and at 0 °C for 60 min. Aq. phosphate buffer (5.0 cm^3; pH 7) in methanol (15 cm^3) was added followed by hydrogen peroxide (5.0 cm^3) in methanol (10 cm^3) at a rate that maintained the internal temperature below 10 °C. The solution was stirred at 0 °C for 60 min, concentrated to give an aqueous slurry, and extracted with diethyl ether (3 × 10 cm^3). The combined extracts were washed with aq. sodium hydrogen carbonate (10 cm^3 of a 5% solution), dried and concentrated to afford an oil. The product was separated from starting material by column chromatography on silica gel [hexane–ethyl acetate (3:1)] to give a viscous oil (1.15 g, 74%) which appeared as two spots by TLC. R_f 0.51, 0.57 [hexane–methylene dichloride–ethyl acetate (6:4:3)]; $\delta_H(CD_3CN)$ (diastereoisomers and conformers), 7.38 (10 H, m), 5.75 and 5.72 (1 H, s), 5.15 (2 H, m), 4.79 (1 H, m), 4.39 (1 H, m), 3.18 (1 H, m), 2.98 and 2.91 (3 H, s), 2.39 (2 H, m), 1.61 (1 H, m), 1.45 (1 H, m), 1.09 (3 H, m), 1.00 (1 H, m) and 0.90 (6 H, m).

(4*R*,5*S*)-4-Methyl-*N*-methylsulfanylacetyl-5-phenyloxazolidin-2-one 4d

To a cold (ice-bath) solution of (methylsulfanyl)acetic acid (10.0 cm^3, 14.9 g, 0.14 mol) in THF (60 cm^3) was added oxalyl dichloride (77 cm^3 of a 2 mol dm^{-3} solution in methylene dichloride, 0.15 mol) by syringe followed by dimethylformamide (0.2 cm^3). The solution was stirred at 0 °C for 30 min and then allowed to warm to room temperature. The volatile material was removed and the resulting oil was purified by vacuum distillation (bp 45 °C at ~10 mmHg) (lit.,[19b] bp 49–50 °C at 14 mmHg) to provide a clear oil (15.1 g, 88%).

A solution of amide **4a** (4.00 g, 22.57 mmol) in anhydrous THF (100 cm^3) was cooled to −78 °C (solid CO_2–acetone-bath). Butyllithium (14.8 cm^3, 22.57 mmol) was added (by syringe over a 10 min period; the solution turned red with the last few drops) followed by methylsulfanylacetyl chloride (2.07 cm^3, 1.1 mol equiv.) and the resulting solution was stirred 30 min at −78 °C. The solution was warmed to room temperature and stirred for an additional 30 min. Excess of acid chloride was eliminated by the addition of saturated aq. ammonium chloride (15 cm^3). The THF was removed under reduced pressure at 30 °C and the resulting slurry was extracted with methylene dichloride (3 × 25 cm^3). The combined extracts were washed successively with 1 mol dm^{-3} sodium hydroxide (20 cm^3) and brine (20 cm^3). The solution was dried and the solvent was removed. The resulting yellow oil was separated on a column of silica gel [gradient elution of hexane–ethyl acetate (4:1→2:1)] to give an oil[9] (5.5 g, 93%); $\delta_H(CDCl_3)$ 7.38 (3 H, m), 7.28 (2 H, m), 5.69 (1 H, d, *J* 7.4), 4.76 (1 H, q, *J* 6.8), 3.80 (2 H, s), 2.17 (3 H, 5) and 0.89 (3 H, d, *J* 6.6).

(4*R*,5*S*)-*N*-{(2′*R*,3′*S*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)-amino]-3′-hydroxy-5′-methyl-2′-(methylsulfanyl)heptanoyl}-4-methyl-5-phenyloxazolidin-2-one 7

A solution of (4*R*,5*S*)-4-methyl-*N*-[(methylsulfanyl)acetyl]-5-phenyloxazolidin-2-one **4d** (3.77 g, 14.22 mmol) in methylene dichloride (30.0 cm^3, distilled from CaH_2) was cooled to −10 °C. Dibutylboron triflate (15.64 mmol; 15.64 cm^3 of a 1.0 molar solution in methylene dichloride) was added followed by diisopropylethylamine (3.72 cm^3, 21.33 mmol, 4.8 mol equiv., distilled from calcium hydride) by syringe at such a rate as to keep the internal temperature below 0 °C. The reaction mixture was stirred at −5 °C for 90 min and then was cooled (solid CO_2–acetone-bath) to −78 °C. *N*-Benzyloxy-*N*-methylisoleucinal **6**[5] was added (3.40 g, 12.93 mmol) as a solution in anhydrous methylene dichloride (5.0 cm^3) by syringe during 5 min. The solution was stirred at −78 °C for 17 h and at about −5 °C for 90 min. Aq. phosphate buffer (10 cm^3; pH 7.2; KH_2PO_4 with NaOH) in methanol (45 cm^3) was added followed by hydrogen peroxide (1.6 cm^3 of a 30% solution, 1.1 mol equiv.) in methanol (5.0 cm^3) at a rate that maintained the internal temperature below 0 °C. The solution was stirred at 0 to −5 °C for 90 min, concentrated (under reduced pressure at 30 °C) to give an aqueous slurry, and extracted with methylene dichloride (3 × 20 cm^3). The combined extract was dried and concentrated to a yellow oil. The *title product* was separated by column chromatography on Sephadex LH-20 [hexane–methylene dichloride–acetone (5:3:2) as eluent] as a viscous oil (5.1 g, 75%), bp 270–273 °C (bath temp) (1 × 10^{-4} mmHg); $[\alpha]_D$ −19 (*c* 0.11, CH_2Cl_2); $\delta_H(CDCl_3)$ 7.35 (10 H, m), 5.78 (1 H, d, *J* 7.2), 5.32 (1 H, d, *J* 12), 5.15 (2 H, br s), 4.84 (1 H, q, *J* 8.5), 4.62 (1 H, t, *J* 6.7), 4.15 (1 H, m), 2.89 (1 H, br s, OH), 2.65 (3 H, s), 2.14 (3 H, s), 1.91 (1 H, m), 1.50 (1 H, m), 1.08 (1 H, m), 1.05 (3 H, d, *J* 6.7), 0.95 (3 H, d, *J* 7.1) and 0.89 (3 H, t, *J* 6.7); *m/z* 510, 481, 453, 409, 363, 265, 234, 190, 178, 134, 105, 91, 77 and 65 (Found: C, 63.1; H, 7.0; N, 5.1. $C_{28}H_{36}N_2O_6S$ requires C, 63.61; H, 6.86; N, 5.30%).

(4*R*,5*S*)-*N*-{(3′*R*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)-amino]-3′-hydroxy-5′-methylheptanoyl}-4-methyl-5-phenyl-oxazolidin-2-one 8

Method A. To a solution of methyl sulfide **7** (0.40 g, 0.758 mmol) in acetone (15 cm^3) was added Raney nickel (3.0 g, Aldrich W-2, washed with water to pH 7) as a 50% slurry in

water. The mixture was stirred at room temperature for 4 h and the solution was filtered through a 2 cm pad of Celite. Solvent was removed to yield an oil. The product was separated by gradient column chromatography on silica gel [hexane–ethyl acetate (4:1→2:1)] as an oil (185 mg, 51%), bp 175–178 °C (bath temp.) (*1.1* × 10^{-4} mmHg); $[\alpha]_D^{25}$ +22 (*c* 0.19, CH_2Cl_2).

Method B. To a solution of aldol product **7** (4.0 g, 7.57 mmol) in anhydrous benzene (100 cm^3) were added tributyltin hydride (2.31 cm^3, 1.1 mol equiv. of a 97% solution) and AIBN (62 mg, 0.05 mol equiv.). The solution was heated at reflux for 30 min and then allowed to cool to room temperature. Solvent was removed and the resulting oil was chromatographed on a column of silica gel [gradient elution with hexane–ethyl acetate (5:1→2:1)] to yield an oil (2.8 g, 76%); ν_{max}(neat)/cm^{-1} 3459, 2963, 1782, 1694, 1456, 1350, 1196, 1148 and 700; δ_H($CDCl_3$), two conformers: 7.40 (5 H, m), 7.29 (5 H, m), 5.69 and 5.67 (1 H, d, *J* 7.3), 5.16 (2 H, br s), 4.76 (1 H, q, *J* 6.8), 4.40 (1 H, m), 3.33 (1 H, m), 2.97 and 2.91 (3 H, s), 2.31 (2 H, m), 1.62 (1 H, m), 1.40 (1 H, m), 1.08 (1 H, m), 1.05 (3 H, d, *J* 6.7), 0.99 (3 H, d, *J* 6.8) and 0.89 (3 H, m); *m/z* 482, 464, 425, 407, 381, 363, 317, 273, 234, 190, 134, 107, 91 and 65 (Found: C, 67.5; H, 7.3; N, 5.8. $C_{27}H_{34}N_2O_6$ requires C, 67.20; H, 7.10; N, 5.80%).

(4*R*,5*S*)-*N*-{(3′*R*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)amino]-3′-methoxy-5′-methylheptanoyl}-4-methyl-5-phenyloxazolidin-2-one 9

To a solution of alcohol **8** (2.3 g, 4.77 mmol) in ethylene dichloride (7.0 cm^3, distilled from calcium hydride) were added 4 Å molecular sieves (1.5 g). The mixture was stirred for 20 min and proton sponge (2.61 g, 12.16 mmol, 2.55 mol equiv.) was added followed by trimethyloxonium tetrafluoroborate (1.76 g, 11.93 mmol, 2.5 mol equiv.). The mixture was stirred for 24 h at which time TLC indicated the reaction was only 50% complete. An additional molar equivalent of trimethyloxonium tetrafluoroborate (0.71 g) was added. The need for excess of oxonium salt was consistent with our experience indicating that the commercial material is often only 50–70% pure. The mixture was stirred for an additional 24 h. The solution was filtered through a thin pad (0.6 cm) of Celite. Removal of solvent gave a yellow oil, which was chromatographed on silica gel [30 cm × 3.2 cm, gradient elution with hexane–ethyl acetate (4:1→1:1)] to provide an oil (1.86 g, 79%), bp 150–155 °C (bath temp.) (5.2 × 10^{-5} mmHg); ν_{max}(neat)/cm^{-1} 2965, 1782, 1696, 1456, 1346, 1196, 1121 and 1041; δ_H($CDCl_3$; 500 MHz; 25 °C), two conformers: 7.40 (5 H, m), 7.30 (5 H, m), 5.70 and 5.62 (1 H, d, *J* 7.0), 5.15 (2 H, m), 4.76 and 4.70 (1 H, q, *J* 7.0), 4.06 (1 H, m), 3.40 and 3.31 (3 H, s), 3.24 (1 H, m), 3.01 (2 H, m), 2.87 and 2.79 (3 H, s), 1.79 (1 H, m), 1.41 (1 H, m), 1.11 (1 H, m), 1.00 (3 H, d, *J* 6.7), 0.95 (3 H, d, *J* 6.8) and 0.88 (3 H, t, *J* 6.8); δ_C($CDCl_3$; 300 MHz; 25 °C), two conformers: 171.71, 171.24, 157.94, 157.83, 153.71, 153.59, 137.73, 137.21, 133.93, 129.92, 129.28, 129.01, 128.79, 128.54, 128.35, 128.14, 126.28, 79.40, 79.34, 78.05, 67.90, 67.39, 57.99, 57.73, 55.30, 55.11, 37.00, 37.66, 35.06, 33.90, 26.23, 26.18, 16.22, 14.74, 14.69, 11.56 and 11.09; δ_C($CDCl_3$; 500 MHz; 55 °C), two conformers: 171.04, 170.60, 157.15, 152.96, 152.89, 137.30, 136.78, 133.54, 128.69, 128.41, 128.21, 127.90, 127.74, 127.59, 125.78, 79.00, 78.07, 67.54, 67.05, 57.53, 57.33, 54.96, 37.82, 37.71, 35.12, 33.98, 26.11, 16.13, 14.49, 11.35 and 10.92; *m/z* 496, 464, 439, 395, 363, 331, 262, 234, 190, 160 and 117 (Found: C, 67.5; H, 7.4; N, 5.6. $C_{28}H_{36}N_2O_6$ requires C, 67.72; H, 7.31; N, 5.64%).

(3*R*,4*S*,5*S*)-4-[Benzyloxycarbonyl(methyl)amino]-3-methoxy-5-methylheptanoic acid (*N*-Z-Dil) 10

Method A. To a solution of methyl ether **9** (0.10 g, 0.20 mmol) in THF (0.8 cm^3)–water (0.2 cm^3) at 0 °C was added (over a period of 10 min) 30% aq. hydrogen peroxide (0.08 cm^3). Aq. lithium hydroxide (13.5 mg in 0.4 cm^3) was added and the solution was stirred at 0 °C for 3 h. Aq. sodium sulfite (0.10 g, 0.79 mmol in 0.6 cm^3) was added, and the solution was allowed to warm to room temperature and was stirred for 2 h. The THF was removed under reduced pressure (at 25–30 °C) and the remaining slurry was washed with methylene dichloride (5 × 1 cm^3). The aqueous phase was cooled to 0 °C, acidified to pH 3 with 1 mol dm^{-3} hydrochloric acid, and extracted with ethyl acetate (5 × 1 cm^{-3}). Removal of solvent from the combined extract led to *N*-Z-Dil **10** as an oil (54 mg, 97%), bp 110–114 °C (bath temp.) (8.1 × 10^{-5} mmHg); $[\alpha]_D$ −11.4 (*c* 0.56, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2965, 2934, 1708, 1699, 1315 and 1169; δ_H($CDCl_3$; 300 MHz), two conformers: 8.35 (1 H, br s), 7.23 (5 H, m), 5.03 (2 H, br s), 4.01 (1 H, m), 3.81 (1 H, m), 3.30 and 3.20 (3 H, s), 2.69 and 2.68 (3 H, s), 2.40 (2 H, m), 1.70 (1 H, m), 1.38 (1 H, m), 1.00 (1 H, m), 0.87 (3 H, d, *J* 6.1) and 0.79 (3 H, m); *m/z* 337, 234, 190, 91, 71 and 57 (Found: C, 63.8; H, 8.1; N, 4.3. $C_{18}H_{27}NO_5$ requires C, 64.07; H, 8.06; N, 4.15%).

Method B. To a solution of *N*-Z-Dil-OBu^t **15** (see below) (20 mg, 0.05 mmol) in methylene dichloride (0.5 cm^3) at 0 °C was added trifluoroacetic anhydride (0.50 cm^3). The solution was stirred at 0 °C for 4 h. Removal of solvent left a residue, which was dissolved in toluene and reconcentrated (twice). The free acid **10** (17 mg, 99%) was obtained as an oil, from which solvent was removed *in vacuo*, $[\alpha]_D^{25}$ −12.5 (*c* 0.57, $CHCl_3$). Spectral characteristics were identical with those for acid **10** prepared *via* Method A.

(4*S*)-4-Isopropyloxazolidin-2-one 5a

To a mixture of (*S*)-valine (9.0 g, 76.80 mmol) in dry THF (25 cm^3) was added boron trifluoride–diethyl ether (10.4 cm^3, 84.50 mmol) over a period of 5 min. After the mixture had been heated at reflux for 15 min, the solid dissolved. Borane–THF complex (85.0 cm^3, 84.50 mol, 1.1 mol equiv. of a 1 mol dm^{-3} solution in THF) was added (by syringe) to the refluxing solution during 30 min and the mixture was heated at reflux for an additional 2 h. THF–water [10 cm^3 of a 1:1 mixture (v/v)] was added dropwise followed by 6 mol dm^{-3} sodium hydroxide (40 cm^3). The solution was stirred and heated at reflux for 2 h, then was allowed to cool to ambient temperature. The mixture was concentrated and extracted with diethyl ether (3 × 20 cm^3). The combined extract was dried over anhydrous potassium carbonate. The solution was filtered, and solvent was removed under reduced pressure to yield (*S*)-valinol as an oil (3.80 g, 50%); δ_H($CDCl_3$; 300 MHz), conformers: 3.63 (1 H, m), 3.30 (1 H, m), 2.57 (1 H, m), 2.05 (1 H, br s), 1.57 (1 H, m), 1.44 (1 H, s), 1.31 (1 H, s), and 0.93 (6 H, m).

To a stirred solution of (*S*)-valinol (4.0 g, 39.00 mmol) in dry toluene under argon was added diethyl carbonate (5.17 cm^3, 43.00 mmol, 1.1 mol equiv.). The flask was fitted with an efficient fractionating column and placed in a hot oil-bath (160–170 °C). The solution was heated and the azeotrope at 85 °C was removed by distillation. When the distillate reached 110 °C (pure toluene), the solution was cooled for 10 min. Sodium methoxide (0.21 g, 0.1 mol equiv.) was added and the mixture was heated at 110 °C. Ethanol (2.5 cm^3, 2 mol equiv.) was collected, the mixture was cooled to room temperature and diethyl ether (300 cm^3) was added. The solution was filtered through a pad of Celite and solvent was removed under reduced pressure. The resulting solid was washed with diethyl ether–hexane (1:5) to yield the oxazolidinone **5a** (3.2 g, 70%), mp 74–75 °C (lit.,[14] 69–70 °C); $[\alpha]_D^{25}$ +12 (*c* 15, CH_2Cl_2); δ_H($CDCl_3$; 300 MHz) 7.75 (1 H, s), 4.28 (1 H, t, *J* 8.7), 3.94 (1 H, dd, *J* 8.7 and 6.6), 3.48 (1 H, dt, *J* 8.5 and 6.5), 1.56 (1 H, m), 0.81 (3 H, d, *J* 6.6) and 0.77 (3 H, d, *J* 6.9).

(4*S*)-4-Isopropyl-*N*-[(methylsulfanyl)acetyl]oxazolidin-2-one 5d

A solution of (*S*)-4-isopropyloxazolidin-2-one **5a** (40.0 g, 31.00 mmol) in dry THF (93 cm^3) (under argon) was cooled to −78 °C (solid CO_2–acetone-bath) and butyllithium (20.3 cm^3, 32.6 mmol, 1.05 mol equiv. of a 1.6 mol dm^{-3} solution in hexane) was added over a period of 10 min. (Methylsulfanyl)-

acetyl chloride (2.84 cm^3, 34.10 mmol, 1.1 mol equiv.) was added, and the solution was stirred 40 min at −78 °C, and then at room temperature for 30 min. Oxazolidinone **5d** was isolated as summarized above for methyl sulfide **4d** (6.1 g, 89%), $[\alpha]_D$ +83 (*c* 2.0, CH_2Cl_2); δ_H($CDCl_3$; 300 MHz) 4.46 (1 H, m), 4.27 (2 H, m), 3.95 (1 H, m), 3.69 (1 H, m), 2.41 (1 H, m), 2.18 (3 H, s), 0.94 (3 H, d, *J* 7.0) and 0.92 (3 H, d, *J* 6.8).

(4*S*)-*N*-{(2′*S*,3′*R*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)-amino]-3′-hydroxy-5′-methyl-2′-(methylsulfanyl)heptanoyl}-4-isopropyloxazolidin-2-one 11

The aldol condensation between (4*S*)-4-isopropyl-3-[(methylsulfanyl)acetyl]oxazolidin-2-one **5d** [4.67 g, 21.50 mmol; in 30 ml of methylene dichloride (30 cm^3) distilled from CaH_2], dibutylboron triflate (25.8 cm^3, 25.82 mmol, 1.2 mol equiv. of a 1 mol dm^{-3} solution in methylene dichloride) and diisopropylethylamine (6.37 cm^3, 36.60 mmol, 1.7 mol equiv., distilled from CaH_2) was accomplished as described above for the aldol product **7**. The yellow oily product appeared as a single spot by TLC [hexane–toluene–ethyl acetate (6:1:1)] accompanied by a trace of starting oxazolidinone **5d**. Final purification was readily achieved by column chromatography on Sephadex LH-20 [hexane–methylene dichloride–acetone (5:3:2)] which furnished an oil (7.3 g, 70%), bp 197–200 °C (bath temp.) (1 × 10^{-4} mmHg); $[\alpha]_D^{25}$ +6.5 (*c* 0.20, CH_2Cl_2); δ_H($CDCl_3$; 300 MHz) 7.37 (5 H, m), 5.08 (2 H, br s), 4.79 (1 H, d, *J* 10.5), 4.55 (1 H, m), 4.41 (1 H, t, *J* 6.9), 4.30 (1 H, m), 4.18 (1 H, m), 4.10 (1 H, m), 2.93 (3 H, s), 2.24 (1 H, m), 2.14 (3 H, s), 1.49 (1 H, m), 1.40 (1 H, m), 1.05 (4 H, m), 0.94 (3 H, d, *J* 6.9), 0.93 (3 H, d, *J* 7.0) and 0.85 (3 H, t, *J* 7.3); *m*/*z* 462 ($M^+ - H_2O$), 405, 361, 264, 234, 190, 130, 91, 71 and 57.

(4*S*)-*N*-{(3′*S*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)amino]-3′-hydroxy-5′-methylheptanoyl}-4-isopropyloxazolidin-2-one 12

Method A. Desulfurization of methyl sulfide **11** (3.80 g, 7.66 mmol) in acetone (100 cm^3) with Raney nickel (20 g, Aldrich W-2, rinsed with water to pH 7) was accomplished as noted above (see preparation of compound **8**) to yield alcohol **12** as an oil (1.5 g, 44%); δ_H($CDCl_3$; 300 MHz), two conformers: 7.34 (5 H, m), 5.16 (2 H, br s), 4.46 (1 H, m), 4.37 (1 H, m), 4.29 (1 H, m), 4.21 (1 H, m), 4.10 (1 H, m), 3.17 (2 H, m), 2.99 and 2.97 (3 H, s), 2.38 (1 H, m), 1.50 (1 H, m), 1.41 (1 H, m), 1.05 (1 H, m), 1.03 (3 H, d, *J* 6.6), 0.91 (6 H, m) and 0.88 (3 H, m).

Method B. Aldol product **11** (4.34 g, 9.04 mmol) was dissolved in dry benzene (100 cm^3) and allowed to react with tributyltin hydride (2.63 cm^3, 9.49 mmol, 1.05 mol equiv. of a 97% solution) and AIBN (0.74 g, 0.45 mmol, 0.05 mol equiv.). In this case an aliquot (at 60 min) analysed by TLC indicated that most of the starting material remained. Additional tributyltin hydride (2.63 cm^3, 1.05 mol equiv.) was added followed by AIBN (74 mg, 0.05 mol equiv.). After 2 h of heating at reflux, no starting methyl sulfide remained. Isolation of product was completed as given above (refer to alcohol **8**, Method B) to yield alcohol **12** as an oil (1.86 g, 79%), bp 180–183 °C (bath temp.) (1 × 10^{-4} mmHg) (Found: C, 61.7; H, 8.5. $C_{23}H_{34}N_2O_6 \cdot H_2O$ requires C, 61.04; H, 8.02%).

(4*S*)-*N*-{(3′*S*,4′*S*,5′*S*)-4′-[Benzyloxycarbonyl(methyl)amino]-3′-methoxy-5′-methylheptanoyl}-4-isopropyloxazolidin-2-one 13

The procedure used to obtain methyl ether **9** was repeated with alcohol **12** [2.8 g, 6.45 mmol in ethylene dichloride (8 cm^3)], 4 Å molecular sieves (1.6 g), proton sponge (3.53 g, 16.5 mmol, 2.55 mol equiv.) and trimethyloxonium tetrafluoroborate (2.39 g, 16.1 mmol, 2.50 mol equiv.), resulting in compound **13**, an oil (2.0 g, 70%), bp 132–135 °C (bath temp.) (8.0 × 10^{-5} mmHg); $[\alpha]_D^{25}$ +19 (*c* 0.91, CH_2Cl_2); δ_H($CDCl_3$; 300 MHz) 7.36 (5 H, m), 5.07 (2 H, br s), 4.47 (1 H, m), 4.32 (1 H, m), 4.17 (1 H, m), 3.85 (1 H, m), 3.81 (1 H, m), 3.35 (3 H, s), 3.08 (2 H, m), 2.85 (3 H, s), 2.40 (1 H, m), 1.50 (1 H, m), 1.45 (1 H, m), 1.08 (1 H, m), 0.99 (3 H, d, *J* 6.6) and 0.90 (9 H, m); *m*/*z* 448, 391, 347, 276, 234, 190, 91, 71 and 58 (Found: C, 64.05; H, 8.1; N, 6.1. $C_{24}H_{36}N_2O_6$ requires C, 64.26; H, 8.09; N, 6.24%).

(3*S*,4*S*,5*S*)-4-[Benzyloxycarbonyl(methyl)amino]-3-methoxy-5-methylheptanoic acid 14

Cleavage of the oxazolidinone group was performed as given above for the preparation of *N*-Z-Dil **10**, using methyl ether **13** (0.10 g, 0.215 mmol) in THF (0.8 cm^3), water (0.2 cm^3), 30% aq. hydrogen peroxide (0.09 cm^3), lithium hydroxide (0.015 g), sodium sulfite (0.109 g), and more water (0.4 cm^3). Removal of solvent from the combined ethyl acetate extract yielded compound **14** as an oil (58 mg, 97%), bp 130–132 °C (bath temp.) (1.1 × 10^{-4} mmHg); $[\alpha]_D^{25}$ −34.5 (*c* 0.59, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3300–3000, 2967, 1699, 1454, 1314, 1169 and 1105; δ_H($CDCl_3$; 300 MHz), two conformers: 7.33 (5 H, m), 5.14 (2 H, br s), 4.03 (1 H, m), 3.94 (1 H, m), 3.36 and 3.34 (3 H, s), 2.87 (3 H, s), 2.50 (2 H, m), 1.95 (1 H, m), 1.33 (1 H, m), 1.05 (1 H, m), 0.97 (3 H, m) and 0.85 (3 H, m) (Found: C, 63.5; H, 8.1; N, 4.0. $C_{18}H_{27}NO_5$ requires C, 64.07; H, 8.06; N, 4.15%).

***tert*-Butyl (3*R*,4*S*,5*S*)-4-[benzyloxycarbonyl(methyl)amino]-3-methoxy-5-methylheptanoate 15**

A solution of (3*R*,4*S*,5*S*)-4-[benzyloxy(methyl)amino]-3-methoxy-5-methylheptanoic acid **10** (2.30 g, 6.87 mmol) in CH_2Cl_2 (60 cm^3) was added to a pressure-safe vessel fitted with a septum. Conc. sulfuric acid (0.20 cm^3, 2.0 mmol, 0.3 mol equiv.) was added. The solution was cooled to −78 °C and 2-methylpropene (2.56 cm^3, condensed at −78 °C, 27.48 mmol, 4.0 mol equiv.) was bubbled slowly into the solution. The reaction mixture was warmed to ambient temperature, stirred for 72 h, and then added to water (100 cm^3) containing sodium carbonate sufficient to neutralize the acid. The CH_2Cl_2 layer was separated, washed with water, and concentrated. The resulting yellow oil was purified using silica gel column chromatography [elution with (4:1) acetone–hexane] to afford ester **15** (1.39 g, 51%) as an oil, R_f 0.43 [(4:1) hexane–ethyl acetate]; $[\alpha]_D^{25}$ −13.0 (*c* 1.0, CH_3OH); δ_H($CDCl_3$, 300 MHz), two conformers: 7.32 (5 H, m), 5.09 (2 H, m), 4.10 (1 H, m), 3.83 (1 H, m), 3.36 and 3.25 (3 H, s), 2.75 and 2.74 (3 H, s), 2.35 (2 H, m), 1.70 (1 H, m), 1.41 (1 H, m), 1.40 (9 H, s), 1.05 (1 H, m), 0.91 (3 H, d, *J* 6.7) and 0.82 (3 H, t, *J* 7.4); ν_{max}(neat)/cm^{-1} 2968, 2827, 1734, 1701, 1454, 1367, 1313, 1153, 1101 and 846; *m*/*z* (relative intensity) 393 (M^+), 281, 234 (100), 190 and 91 (Found: C, 66.9; H, 9.05. $C_{22}H_{35}NO_5$ requires C, 67.15; H, 8.96%).

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