Stereoselective Synthesis of 1,2-Diols by the Cycloadditive Strategy: Total Synthesis of (±)-*exo*-Brevicomin and (±)- and (−)-Pestalotin†

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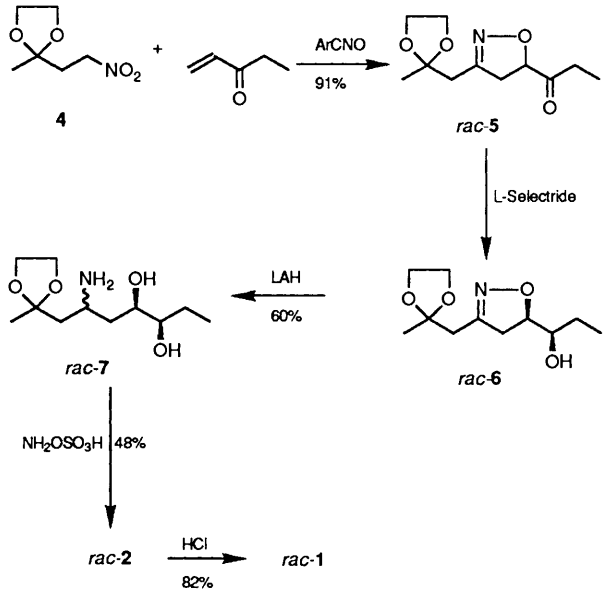
Highly selective reductions of 5-acyl-2-isoxazolines and conversion of the resulting *syn*-5-hydroxyalkyl-2-isoxazolines into *syn*-diols are key steps in concise syntheses of (±)-*exo*-brevicomin, and (±)-pestalotin. With an asymmetric nitrile oxide as starting material, cycloaddition with the acrylate derivative of Oppolzer's camphor sultam leads to a synthesis of (−)-pestalotin.

In the preceding paper,[1] we described a general route to *anti*- and *syn*-hydroxyalkyl-2-isoxazolines **II**,§ as summarized in eqn. (1). By appropriate choice of a 5-acyl- or 5-formyl-2-isoxazoline **I** and addition of either a Grignard reagent or L-Selectride, either stereoisomer of **II** could be formed in a predictable fashion with modest (85:15) to excellent (>98/2) selectivity. Isoxazolines **II** are readily converted into β,γ-dihydroxy carbonyls **III**, which are important synthetic intermediates. To extend this work, we sought to couple these methods to control relative stereochemistry with our methods to control absolute stereochemistry,[2] and also to show that isoxazolines like **II** are useful precursors for other functional groups besides dihydroxy carbonyls. Rather than demonstrate these points on model compounds, we chose to synthesize two simple natural products: (±)-*exo*-brevicomin, and (±)- and (−)-pestalotin.

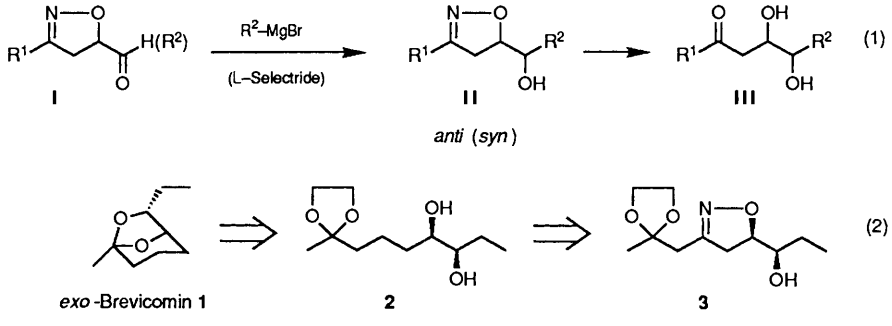
exo-Brevicomin **1** has been synthesized many times,[3] and it has become a proving ground for stereoselective methods to prepare 1,2-diols.[4] The epimer of *exo*-brevicomin (*endo*-brevicomin) is also well known.[3] Our strategy for the synthesis of *rac*-**1**,¶ outlined in eqn. (2), calls for the preparation of the diol *rac*-**2** from the isoxazoline *rac*-**3**. This requires the complete removal of the isoxazoline nitrogen atom.

The synthesis of *rac*-**1** is outlined in Scheme 1. Standard cycloaddition of a known nitro ketal **4** [2b] and ethyl vinyl ketone by the Mukaiyama method [5] provided the isoxazoline *rac*-**5** in 91% isolated yield. Reduction of *rac*-**5** with L-Selectride (THF, −78 °C) provided *rac*-**6** as essentially a single stereoisomer (>98:2) according to GC and ^{1}H NMR analysis. This selectivity is even higher than that observed with related model isoxazolines bearing 3-phenyl and 3-*tert*-butyl substituents.[1]

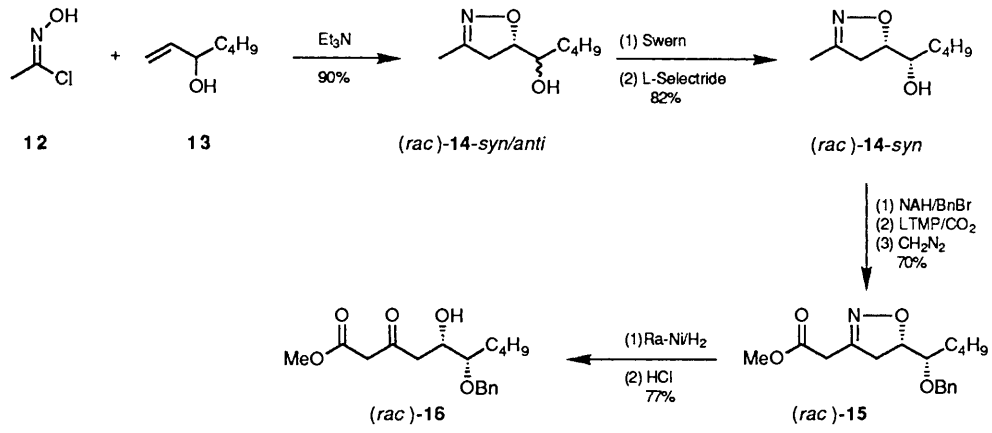


Scheme 1

syn-Isomer **6** cannot be obtained with good selectivity by direct nitrile oxide cycloaddition of **4** with an appropriate allylic ether (moderate *anti* selectivity expected) or alcohol (very low *syn* selectivity expected).[6] Reduction of *rac*-**6** with lithium aluminium hydride,[7] followed by non-aqueous work-up and recrystallization, provided the amine *rac*-**7** in 68% yield. From the crude ^{1}H NMR spectrum of the product, it was clear that this reduction was highly stereoselective. Related reductions have been extensively studied by Jäger, and normally *syn* amino alcohols are formed.[7] However, the presence of the hydroxy group in *rac*-**7** (a potential directing group), makes assignment of configuration risky. Even though we do not assign the configuration of **7**, our results show that this method should nicely integrate into Jäger's [7] isoxazoline-based approach to amino sugars. Deamination of *rac*-**7** was a difficult reaction, but



† Submitted to commemorate the 150th anniversary of the Chemical Society/Royal Society of Chemistry.
‡ Dreyfus Teacher-Scholar (1986–91), National Institutes of Health Research Career Development Awardee (1987–92).
§ The prefixes *syn* and *anti* are used as defined by S. Masamune, Sk. A. Ali, D. L. Suitman and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 557.
¶ The prefix *rac* indicates that the compound is racemic. All compounds without prefixes are the indicated enantiomers.

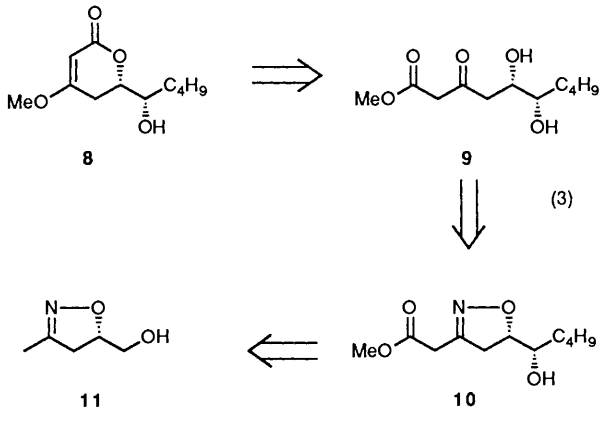


12 13 (*rac*)-**14**-*syn*/*anti* (*rac*)-**14**-*syn* (*rac*)-**16** (*rac*)-**15**

Scheme 2

modifications of a literature reduction[8] with hydroxylamino-*O*-sulphonic acid finally produced *rac*-**2** in reproducible yields of *ca.* 48%. Exposure of **2** to HCl formed racemic *exo*-brevicomin in 82% yield. Our sample was identified by comparison with a sample kindly provided by Prof. T. Cohen. *endo*-Brevicomin (also provided by Prof. Cohen) could not be detected in the sample of *rac*-**1**.

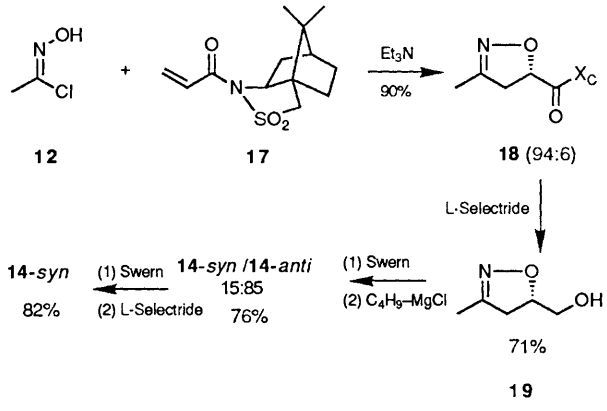
This synthesis illustrates how simple *syn*-diols can be prepared by the cycloadditive strategy. It seems certain that *endo*-brevicomin could be prepared (albeit with somewhat lower selectivity) by addition of ethylmagnesium bromide to the appropriate 5-formyl-2-isoxazoline. It is also certain that either enantiomer of *exo*-brevicomin could be prepared by a suitable modification of the route (we have already prepared the requisite optically pure isoxazoline[1b]); however, we chose to illustrate this modification in the pestalotin synthesis instead.



8 **9** **11** **10**

Eqn. (3) summarizes the strategy for the preparation of pestalotin **8**.[9] This synthesis shows how *anti*-5-hydroxyalkyl-2-isoxazolines or *syn*/*anti* mixtures can be converted into pure *syn*-5-hydroxyalkyl-2-isoxazolines, and it also shows how our strategy for preparation of optically active 5-hydroxymethyl-2-isoxazolines[2] can be incorporated into the diol synthesis.

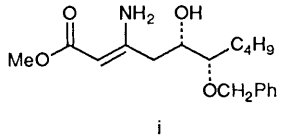
Scheme 2 illustrates the synthesis of (±)-pestalotin (*rac*-**8**). Cycloaddition of acetohydroximoyl chloride **12** with allyl alcohol **13** provided *rac*-**14** as a. 1:1 mixture of *syn* and *anti* isomers. Following the Ireland/Norbeck procedure,[1,10] Swern oxidation directly followed by addition of excess of L-Selectride provided *rac*-**14** but now as a 99:1 mixture of *syn* and *anti* isomers. The pure *syn* isomer was isolated in 82% yield after chromatography. The free alcohol of *rac*-**14** was benzylated,[11] and this was followed by *exo* deprotonation of the isoxazoline **14**,[12] carboxylation and treatment of the resulting acid with diazomethane. This sequence produced *rac*-**15** in 70% yield alongside a small amount (ratio ≈10:1) of the *endo* carboxylated regioisomer (not shown). Reduction of *rac*-**15** with Raney Ni and hydrogen gas in aqueous methanol[13] (but *without* acid*), followed by brief exposure† of the crude reduction product to HCl, provided the keto ester **16**. This keto ester is an intermediate in Professor Hagiwara's synthesis of pestalotin,[9a] and he kindly provided us with comparison spectra and samples. Following Hagiwara's procedure,‡ *rac*-**16** was lactonized under basic conditions, and this lactone was *O*-



12 **17** **18** (94:6) **14**-*syn* **19**

Scheme 3

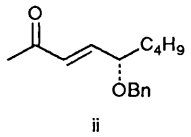
* Reduction in the presence of boric acid formed a product tentatively assigned structure i, which was inert to treatment with mild acid.



i

For related reductions see: D. P. Curran and D. H. Singleton, *Tetrahedron Lett.*, 1983, **24**, 2079.

† Prolonged exposure resulted in formation of compound ii. This compound also formed on storage of **16**.



ii

‡ We thank Professor H. Hagiwara for providing us with experimental procedures for the reactions described in reference 9*a*.

methylated, and debenzylated to give racemic pestalotin (*rac*-**8**) in 56% overall yield.

Scheme 3 shows the needed modifications to prepare (−)-pestalotin. We first prepared **19** according to our published procedure.[2] Cycloaddition of **12** and the acrylate derivative of Oppolzer's camphor sultam **17** gave **18** and its diastereoisomer (not shown) in virtually quantitative yield in a ratio of 94:6. Pure **18** was isolated in 90% yield, and was then cleaved with L-Selectride to provide optically pure **19** (71%) and recovered sultam auxiliary. Swern oxidation of **19**, followed by direct addition of butylmagnesium bromide, provided a mixture of **14** rich in the incorrect isomer for the pestalotin synthesis (*syn*/*anti*, 15:85). This mixture was epimerized by Swern oxidation and direct L-Selectride reduction to provide **14**-*syn* as a single isomer,* which was isolated in 82% yield. (−)-Pestalotin **8** was then prepared by following the steps of the racemic synthesis, as outlined in Scheme 2.

These two syntheses illustrate just a few of the possible strategies revolving around the isoxazoline that can now be implemented in the stereocontrolled syntheses of oxygenated acyclic molecules.

Experimental

General Details.—See preceding paper in this issue.

3-(2-*Methyl*-1,3-*dioxolan*-2-*ylmethyl*)-5-*propionyl*-4,5-*dihydroisoxazole rac*-**6**.—To a dry benzene solution (150 ml) of ethyl vinyl ketone (3.19 ml, 32.0 mol) and the nitroalkane **4** (4.3 g, 26.7 mmol) was added *p*-chlorophenyl isocyanate (10.26 g, 66.7 mmol) and a catalytic amount of triethylamine (0.2 ml). The reaction mixture was stirred at 25 °C for 16 h, and then diluted with water (5 ml). After 30 min, the mixture was filtered through Celite to remove the solids, and the filtrate was diluted with water and extracted with ether (3 × 60 ml). Evaporation of the extract under reduced pressure and flash chromatography of the residue with 6:1 hexane–EtOAc gave *rac*-**5** (5.54 g, 91%) as a clear oil: $\delta_H(CDCl_3)$ 4.85 (1 H, dd, *J* 11.3, 6.3), 3.94 (4 H, m), 3.29 (1 H, dd, *J* 17.8, 11.3), 3.21 (1 H, dd, *J* 17.8, 6.3), 2.68 (4 H, m), 1.32 (3 H, s) and 1.07 (3 H, t, *J* 7.1); $\delta_C(CDCl_3)$ 210.5, 129.1, 121.9, 108.3, 83.3, 64.5, 40.3, 36.9, 32.1, 24.0 and 7.1; ν_{max}(neat)/cm^{-1} 2982, 2939, 2889, 1716, 1495, 1458, 1402, 1350, 1381, 1217, 1120, 951 and 871; *m*/*z* 212 (M^+), 140, 126, 87 (Found: M^+, 212.0923. Calc. for $C_{10}H_{14}NO_4$: *M*, 212.0923).

syn-3-(1-*Methyl*-1,3-*dioxolan*-2-*ylmethyl*)-5-(1-*hydroxypropyl*)-4,5-*dihydroisoxazoline rac*-**6**.—Compound **5** (4.03 g, 17.8 mmol) was dissolved in dry THF (85 ml) and the solution was cooled to −78 °C. A THF solution of L-Selectride (21.4 ml, 21.4 mmol) was added slowly to the reaction mixture which was then stirred at −78 °C for 6 h. After this, aqueous NaOH (1 mol dm^{-3}; 22 ml) and 30% H_2O_2 (22 ml) were cautiously added to the mixture which was then warmed to 25 °C and stirred for 30 min. The mixture was then extracted with ether (4 × 50 ml) and the extract concentrated under reduced pressure to afford the crude product. A diastereoisomeric ratio of >99:1 in favour of the *syn* isomer was determined by both GC and ^{1}H NMR analyses. The crude product was then purified by chromatography with 4:1 hexane–EtOAc to give pure **6** as a clear oil (3.67 g, 92%): $\delta_H(CDCl_3)$ 4.49 (1 H, m), 3.97 (4 H, m), 3.38 (1 H, m), 3.07 (1 H, dd, *J* 17.5, 6.7), 2.92 (1 H, dd, *J* 17.5, 7.9), 2.70 (2 H, *J*, 18.6, 4.6), 1.61 (2 H, m), 1.36 (3 H, s) and 1.01 (3 H, t, *J* 7.4); $\delta_C(CDCl_3)$ 156.1 (s), 108.4 (s), 82.4 (d), 74.4 (d), 64.6 (m), 40.0 (t), 37.2 (t), 26.4 (t), 23.9 (q) and 10.0 (q); ν_{max}(thin film)/cm^{-1} 3454, 2934, 2880, 1623, 1440, 1381, 1224, 1216, 1128, 951, 925 and 875; *m*/*z* 214 (M − CH_3), 156, 126, 98, 87, 69 and 57 [Found: *m*/*z*, 214.1080. Calc. for $C_{10}H_{16}NO_4$: (*M*-CH_3), 214.1080].

6-*Amino*-8-(1,3-*dioxolan*-2-*yl*)*nonane*-3,4-*diol rac*-**7**.—To a stirred solution of compound **6** (0.26 g, 1.13 mmol) in THF (20 ml) was cautiously added a THF solution of LAH (3.95 ml, 3.95 mmol). Upon completion of the reaction (TLC), water (0.19 ml), aqueous NaOH (3 mol dm^{-3}; 0.19 ml) and water (0.57 ml) were added (**Caution:** exothermic) to the reaction mixture which was then stirred for 6 h to give a white precipitate. Filtration of the reaction mixture through Florisil, washing of the solid with EtOAc, and evaporation of the filtrate afforded a yellow solid. This was recrystallized from hexane–EtOAc to give **7** as a white solid (0.179 g, 68%): m.p. 81–82 °C; $\delta_H(CDCl_3)$ 3.98 (4 H, m), 3.80 (1 H, m), 3.53 (1 H, m), 3.25 (1 H, m), 1.9–1.4 (6 H, m), 1.34 (3 H, s) and 0.99 (3 H, t, *J* 7.4); $\delta_C(CDCl_3)$ 109.9 (s), 76.5 (d), 71.5 (d), 65 (t), 64.3 (t), 45.8 (d), 43.9 (t), 38.5 (t), 26.3 (t), 24.3 (q) and 10.3 (q); ν_{max}(thin film)/cm^{-1} 3368, 3302, 2963, 2878, 1375, 1225, 1126, 1039 and 976; *m*/*z* 234 ($M + H)^+$, 216, 204, 188, 174, 153, 132, 114, 103, 97, 87, 72 and 59 [Found: *m*/*z* 234.1075. Calc. for $C_{11}H_{24}NO_4$: (M + H), 234.1075].

8-(1,3-*Dioxolan*-2-*yl*)*nonane*-3,4-*diol rac*-**2**.—The amino alcohol **7** (236 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (4 ml), and aqueous NaOH (2.5 mol dm^{-3}; 2 ml) and NH_2OSO_3H (284 mg, 2.5 mmol) were added successively at 0 °C. After 3 min, additional portions of aqueous NaOH (2.5 mol dm^{-3}; 2 ml) and NH_2OSO_3H (284 mg, 2.5 mmol) were added to the reaction mixture which was then stirred at 25 °C for 2 h. After this it was quenched with water and extraction with CH_2Cl_2 (4 × 15 ml). Purification of the crude product by flash chromatography with 3:1 hexane–EtOAc afforded the oily diol **2** (105 mg, 48%); $\delta_H(CDCl_3)$ 3.94 (4 H, m), 3.44 (1 H, m), 3.35 (1 H, m), 1.8–1.5 (8 H, m), 1.32 (3 H, s) and 0.99 (3 H, t, *J* 7.5); $\delta_C(CDCl_3)$ 110.1, 75.9, 74.0, 64.7, 39.0, 33.7, 26.5, 23.8, 20.2 and 10.0; ν_{max}(thin film)/cm^{-1} 3428, 2959, 2934, 1462, 1377, 1217, 1043 and 949; *m*/*z* 159 (M − $C_4H_7O_2$), 141, 135, 127, 115, 97, 87, 71, 59 and 43 [Found: *m*/*z* 159.1020. Calc. for $C_8H_{15}O_3$: (*M*-$C_4H_7O_2$), 159.1021].

(±)-exo-*Brevicomin rac*-**1**.—A solution of the diol **2** (21.8 mg, 0.1 mmol) in ether (5 ml) containing HCl (3 mol dm^{-3}; 3 drops), was stirred at room temperature for 1 h with close monitoring of the reaction by GC. Upon completion, the ethereal solution was washed with brine, dried ($MgSO_4$), and carefully evaporated (*exo*-brevicomin is volatile). Quick chromatography of the residue with ether afforded a clear oil (12.8 mg, 82%). Both GC and ^{1}H NMR analyses of the crude product confirmed that only the *exo*-isomer was present; $\delta_H(CDCl_3)$ 4.13 (1 H, br s), 3.93 (1 H, t, *J* 5.7), 1.95–1.42 (8 H, m), 1.41 (3 H, s) and 0.91 (3 H, t, *J* 7.5); $\delta_C(CDCl_3)$ 107.7, 81.2, 78.3, 35.0, 29.7, 28.6, 25.1, 17.2 and 10.9; ν_{max}(thin film)/cm^{-1} 2940, 2878, 1458, 1381, 1257, 1238, 1196, 1172, 1032, 1003, 968 and 852; *m*/*z* 156 (M^+), 149, 142, 138, 135, 127, 114, 98, 85, 81, 57 and 43 (Found: M^+, 156.1150. Calc. for $C_9H_{16}O_2$: *M*, 156.1150).

Acetohydroximoyl Chloride **12**.—To a DMF solution (130 ml) of acetaldehyde oxime (7.09 g, 120 mmol) was added NCS (20.8 g, 156 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was extracted with ether (5 × 50 ml), and the combined extracts were washed with water and brine and evaporated under reduced pressure to afford the title compound as a clear liquid

* In the Swern oxidation/L-selectride reduction of *rac*-**14**, a small amount of **14**-*anti* was detected by both ^{1}H NMR and GC. However, in the same reaction with optically active **14**, only **14**-*syn* was detected. We conclude that in the racemic series, the Swern oxidation was incomplete, and the trace of **14**-*anti* observed was the result of the incomplete oxidation.

(5.43 g, 90%). Since this proved unstable, it must be used shortly after preparation; $\delta(CDCl_3)$ 8.1 (1 H, s) and 2.38 (3 H, s).

4-{5'-[(5S)-3-*Methyl*-5-*oxomethyl*-4,5-*dihydroisoxazolyl*]}-(7R)-10,10-*dimethyl*-5-*thia*-4-*azatricyclo*[5.2.1.$0^{3,7}$]*decane* 5,5-*Dioxide* **18**.[2b]—To a solution of acetohydroximoyl chloride **12** (0.60 g, 6.42 mmol) and acrylate **7** (1.57 g, 5.8 mmol) in benzene (50 ml) was added triethylamine (0.90 ml, 6.42 mmol) and the reaction mixture was stirred at 25 °C for 12 h. Filtration through Celite removed the solid triethylamine hydrochloride and evaporation of the solvent under reduced pressure afforded the crude cycloadducts. ^1H NMR analysis of the products showed a ratio of 94:6 in favour of **18**. Purification by flash chromatography with 3:1 hexane–EtOAc gave pure **18** as white crystals (1.77 g, 90%): m.p. 141–143 °C; $[\alpha]_D$ + 75.5 (*c* 2.3, $CHCl_3$); $\delta_H(CDCl_3)$ 5.49 (1 H, dd, *J* 10.8, 7.0), 3.92 (1 H, dd, *J* 7.7, 5.0), 3.52 (1 H, d, *J* 13.7), 3.48 (1 H, d, *J* 13.7), 3.30 (1 H, dd, *J* 17.7, 6.9), 3.24 (1 H, *J*, 17.7, 6.4), 2.15 (2 H, m), 2.03 (3 H, s), 1.92 (3 H, m), 1.46 (2 H, m), 1.18 (3 H, s) and 0.98 (3 H, s); ν_{max}(thin film)/cm^{-1} 2961, 2886, 1699, 1456, 1437, 1333, 1275, 1238, 1167, 1136, 1070, 916, 860 and 731 cm^{-1}; *m/z* 326 (M^+), 295, 242, 179, 135, 93, 84, 69 and 56 (Found: M^+, 326.1300. Calc. for $C_{15}H_{22}N_2O_4S$: *M*, 326.1300).

(5S)-5-*Hydroxymethyl*-3-*methyl*-4,5-*dihydroisoxazole* **19**.[2b]—To a stirred solution of compound **18** (3.60 g, 10.6 mmol) in THF (100 ml) at −78 °C was added L-Selectride in THF (1 mol dm^{-3}; 23.4 ml, 23.4 mmol) and the reaction mixture was stirred at −78 °C for 8 h, and then NaOH (3 mol dm^{-3}; 23 ml) and 30% H_2O_2 (23 ml) were added to the reaction mixture at 0 °C. After being stirred at 25 °C for 2 h, the reaction mixture was extracted with EtOAc (4 × 60 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography with 1:1 hexane–EtOAc afforded the recovered L-camphor sultam and the desired alcohol **19** as a clear oil (0.89 g, 69%): $[\alpha]_D$ + 91.4 (*c* 3.0, $CHCl_3$); $\delta_H(CDCl_3)$ 4.67 (1 H, m), 3.75 (1 H, dd, *J* 12.1, 2.8), 3.56 (1 H, dd, *J* 12.0, 3.9), 2.99 (1 H, dd, *J* 17.0, 10.5), 2.28 (1 H, dd, *J* 17.0, 7.7), 2.0 (1 H, br s) and 1.98 (3 H, s); $\delta_C(CDCl_3)$ 156.0, 80.2, 63.5, 40.0 and 13.0; ν_{max}(thin film)/ cm^{-1} 3358, 2926, 1539, 1437, 1387, 1215, 1097, 912 and 868; *m/z* 115 (M^+), 84, 69 and 56 (Found: M^+, 115.0634. Calc. for $C_5H_9NO_2$: *M*, 115.0633).

(5S)-5-[(1R)-1-*Hydroxypentyl*]-3-*methyl*-4,5-*dihydroisoxazole* **14**-*anti*.—To a solution of oxalyl chloride (0.227 ml, 2.44 mmol) in THF (22 ml) at −78 °C was added dimethyl sulphoxide (0.188 ml, 2.68 mmol). The solution was warmed to −35 °C for 5 min and then recooled to −78 °C. A solution of **19** (0.260 g, 2.22 mmol) in THF (15 ml) was added and the resulting solution was then warmed to −35 °C and stirred for 15 min. Triethylamine (1.52 ml, 11.10 mmol) was added slowly to the reaction mixture which was then warmed to 25 °C for 20 min and then recooled to −78 °C. A THF solution of butylmagnesium bromide (5.6 ml, 11.2 mmol) was added to the vigorously stirred reaction mixture. After 4 h at −78 °C, water (3 ml) was added cautiously to the solution which was then poured into saturated aqueous NH_4Cl (100 ml); this was then extracted with ether (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Both GC and ^1H NMR analyses indicated an 85:15 ratio in favour of the *anti* isomer. Flash chromatography of the residue with 4:1 hexane–EtOAc afforded an oily mixture of **14**-*anti*/**14**-*syn* (0.292 g, 76%): $\delta_H(CDCl_3)$ for **14**-*anti* 4.49 (1 H, m), 3.86 (1 H, m), 3.00 (1 H, dd, *J* 16.2, 8.0), 2.83 (1 H, dd, *J* 16.2, 11.0), 1.96 (3 H, s), 1.45 (6 H, m) and 0.90 (3 H, t, *J* 7.4); ν_{max}(thin film)/cm^{-1} 3414, 2930, 2860, 1635, 1558, 1506, 1437, 1273, 1130 and 927; *m/z* 171 (M^+), 153, 149, 138, 134, 128, 87, 69 and 57 (Found: M^+, 171.1259. Calc. for $C_9H_{17}NO_2$: *M*, 171.1259).

Preparation of Racemic Compound **14**.—To a 0 °C solution of acetohydroximoyl chloride **12** (5.3 g, 56 mmol) and 3-hydroxyhept-1-ene (7.7 g, 67 mmol) in benzene (200 ml) was added slowly triethylamine (7.8 ml, 56 mmol). The reaction mixture was stirred at 25 °C for 16 h after which it was filtered and evaporated. Purification of the residue by chromatography with 4:1 hexane–EtOAc afforded a clear oil (8.7 g, 90%) which was an equimolar mixture of *rac*-**14**-*syn* and *rac*-**14**-*anti*.

(5S)-5-[(1S)-1-*Hydroxypentyl*]-3-*methyl*-4,5-*dihydroisoxazole* **14**-*syn*.—To a solution of oxalyl chloride (60.5 μl, 0.69 mmol) in THF (3 ml) at −78 °C was added dimethyl sulphoxide (53.4 μl, 0.75 mmol). The solution was warmed to −35 °C for 5 min and then was recooled to −78 °C. A solution of compound **14** (*syn*/*anti* mixture) (100 mg, 0.58 mmol) in THF (5 ml) was added to the reaction mixture which was then warmed to −35 °C and stirred for 15 min. Triethylamine (0.40 ml, 2.9 mmol) was added slowly to the reaction mixture which was then warmed for 20 min. The reaction mixture was recooled to −78 °C and a THF solution of L-Selectride (2.9 ml, 2.9 mmol) was added to it. After 6 h at −78 °C, NaOH (3 mol dm^{-3}; 2.9 ml) and 30% H_2O_2 (2.9 ml) were added successively to the mixture at 0 °C with caution. The reaction mixture was then warmed to 25 °C and stirred for 2 h. The mixture was extracted with ether and the extract concentrated under reduced pressure; purification of the residue by chromatography with 4:1 hexane–EtOAc afforded **14**-*syn* as a clear oil (82 mg, 82%). Both GC and ^1H NMR analyses of the crude product showed only one isomer: $[\alpha]_D$ +87.7 (*c* 2.1, $CHCl_3$); $\delta_H(CDCl_3)$ 4.50 (1 H, m), 3.48 (1 H, m), 2.99 (1 H, dd, *J* 17.1, 10.6), 2.82 (1 H, dd, *J* 17.1, 7.8), 1.99 (3 H, s), 1.50 (6 H, m) and 0.91 (3 H, t, *J* 7.0); $\delta_C(CDCl_3)$ 156.0 (s), 82.7 (d), 73.3 (d), 41.2 (t), 33.4 (t), 27.8 (t), 22.7 (t), 14.3 (q) and 13.1 (q); ν_{max}(thin film)/cm^{-1} 3414, 2930, 2860, 1635, 1558, 1506, 1437, 1273, 1130 and 927; *m/z* 171 (M^+), 153, 149, 138, 134, 128, 87, 69 and 57 (Found: M^+, 171.1259. Calc. for $C_9H_{17}NO_2$: *M*, 171.1259).

(5S)-5-[(1S)-*Benzoyloxypentyl*]-3-*methyl*-4,5-*dihydroisoxazole*.—To a solution of **14**-*syn* (77 mg, 0.445 mmol) and tetrabutylammonium iodide (16.4 mg, 0.04 mmol) in THF (15 ml) were added 60% NaH (23 mg, 0.58 mmol) and benzyl bromide (75 μl, 0.623 mmol) successively. The reaction mixture was stirred at 25 °C for 6 h and then quenched with water and extracted with ether (3 × 20 ml). The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography with 8:1 hexane–EtOAc gave the benzyl ether as a clear oil (0.114 g, 98%): $[\alpha]_D$ +42.4 (*c* 3.5, $CHCl_3$); $\delta_H(CDCl_3)$ 7.30 (5 H, m), 4.70 (1 H, d, *J* 12.0), 4.65 (1 H, m), 4.61 (1 H, d, *J* 12.0), 3.45 (1 H, m), 2.87 (1 H, dd, *J* 17.1, 10.8), 2.74 (1 H, dd, *J* 17.1, 8.6), 1.97 (3 H, s), 1.50 (6 H, m) and 0.89 (3 H, t, *J* 7.1); $\delta_C(CDCl_3)$ 155.3, 138.4, 128.9, 127.7, 81.9, 79.9, 72.8, 40.5, 29.9, 27.9, 22.8, 14.1 and 13.2; ν_{max}(thin film)/cm^{-1} 3030, 2955, 2930, 1436, 1327, 1072, 871 and 736; *m/z* 262 (M^+), 204, 177, 147, 105, 91 and 84 [Found: *m/z*, 204.1025. Calc. for $C_{12}H_{14}NO_2$: (M − Bu), 204.1025].

Methyl (5S)-5-[(1S)-*Benzoyloxypentyl*]-4,5-*dihydroisoxazol*-3-*ylacetic Acid* **15**.—Lithium tetramethylpiperidine (0.87 ml, 0.70 mmol) in THF was added slowly to a solution of the above benzyl ether (122 mg, 0.467 mmol) in THF (9 ml) at −90 °C. The reaction mixture was stirred at −90 °C for 4 h after which dry carbon dioxide gas was delivered to the solution for 15 min; the reaction mixture was then allowed to warm to 25 °C. Water (2 ml) and HCl (3 mol dm^{-3}; 3 ml) were then successively added dropwise with caution to the reaction mixture which was then extracted with ether (3 × 15 ml). The combined organic extracts were treated with an excess of ethereal diazomethane at 25 °C. The solution was then stirred at room temperature for 1 h

with exposure to the air to evaporate the excess of diazomethane. The ether solution was then washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by chromatography with 5:1 hexane–EtOAc gave compound **15** as a clear oil (104 mg, 71%). Analysis of the crude products showed that **15** was present with its *endo* carboxylated regioisomer in a ratio of 10:1. Although the two regioisomers were separable by chromatography, the minor product was not isolated: $[\alpha]_D$ +45.2 (*c* 5.2, $CHCl_3$); $\delta_H(CDCl_3)$ 4.76 (1 H, m), 4.70 (1 H, d, *J* 11.5), 4.60 (1 H, d, *J* 11.5), 3.71 (3 H, s), 3.48 (1 H, m), 3.42 (2 H, s), 3.03 (1 H, dd, *J* 17.2, 10.8), 2.89 (1 H, dd, *J* 17.2, 8.5), 1.50 (6 H, m) and 0.89 (3 H, t, *J* 7.9); $\delta_C(CDCl_3)$ 169, 153, 139, 129, 128, 127, 83, 80, 73, 52, 38, 33, 30, 28, 23 and 14; ν_{max}(thin film)/cm^{-1} 3030, 2931, 2862, 1743, 1362, 1237 and 1095; *m/z* 288 (M − OCH_3), 260, 233, 204, 177, 142, 110 and 91 [Found: *m/z*, 288.1615. Calc. for $C_{17}H_{22}NO_3$: (M-OCH_3), 288.1615].

Methyl (5S,6S)-5-*Benzyloxy*-6-*hydroxy*-8-*oxodecanoate* **16**.—Compound **15** (200 mg, 0.63 mmol) was dissolved in a solution of 15:1 MeOH–H_2O (10 ml) in the presence of a catalytic amount of Raney Ni. The reaction system was flushed with H_2 gas five times through a three-way stopcock which was attached to a hydrogen balloon. The reaction mixture was stirred at 25 °C for 20 min after which TLC (4:1 hexane–EtOAc) showed that the starting material had disappeared. The reaction mixture was then filtered through Celite, and the filtrate was treated with 10% HCl (0.5 ml) and stirred at room temperature for 15 min. The solution was then extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by flash chromatography with 4:1 hexane–EtOAc gave compound **16** as a clear oil (156 mg, 77%): $[\alpha]_D$ +65 (*c* 0.4, $CHCl_3$); $\delta_H(CDCl_3)$ 7.29 (5 H, m), 4.63 (1 H, d, *J* 11.5), 4.48 (1 H, d, *J* 11.5), 4.11 (1 H, m), 3.72 (3 H, s), 3.48 (2 H, s), 3.34 (1 H, m), 2.71 (2 H, m), 2.59 (1 H, d, *J* 5.4), 1.8–1.3 (6 H, m) and 0.90 (3 H, t, *J* 6.8); $\delta_C(CDCl_3)$ 202.7, 138.3, 128.5, 128.0, 127.8, 80.9, 72.3, 68.4, 52.4, 49.7, 46.1, 29.4, 27.7, 22.9 and 14.0; ν_{max}(thin film)/cm^{-1} 3512, 3302, 3030, 2958, 2926, 1794, 1732, 1597, 1495, 1454, 1313 and 1149; *m/z*(NH_3, CI) 340 (M + NH_4), 323 (M + H), 305, 291, 273, 247, 215, 197, 177, 145, 122, 108 and 91 [Found: *m/z*, 198.1256. Calc. for $C_{11}H_{18}O_3$: (M-$C_5H_6O_3$), 198.1256].

(6S)-6-[(1S)-1-*Benzyloxylbutyl*]-4-*methoxypyran*-2-*one*.—To a solution of **16** (144 mg, 0.447 mmol) in ether (5 ml) was added NaOH (4 mol dm^{-3}; 0.5 ml). The reaction mixture was stirred at 25 °C for 45 min after which dilute HCl was added to it until the pH was *ca.* 4. The solution was then extracted with ether (3 × 15 ml) and the combined ether extracts were washed with water and brine and evaporated to afford the crude lactone (122 mg), which was used without purification: $\delta_H(CDCl_3)$ 7.31 (5 H, m), 4.73 (1 H, m), 4.58 (1 H, d, *J* 11.1), 4.43 (1 H, d, *J* 11.1), 3.43 (3 H, m), 2.76 (1 H, dd, *J* 17.1, 5.6), 2.58 (1 H, dd, *J* 17.1, 4.8), 1.8–1.4 (6 H, m) and 0.91 (3 H, t, *J* 6.8).

To a slurry of sodium carbonate (102 mg) and methyl sulphate (61 μl) in acetone (1 ml) was added the crude lactone in acetone (3 ml). The mixture was stirred at 25 °C for 40 h after which it was diluted with water and extracted with ether (3 × 20 ml). The combined organic layers were washed with water and brine, evaporated and the residue flash chromatographed with 6:1 hexane–EtOAc to afford the *O*-methylated product (156 mg, 77% for two steps): $[\alpha]_D$ −43 (*c* 1.2, $CHCl_3$); $\delta_H(CDCl_3)$ 7.31 (5 H, m), 5.13 (1 H, d, *J* 1.4), 4.66 (1 H, d, *J* 11.5), 4.61 (1 H, d, *J* 11.5), 4.52 (1 H, dt, *J* 12.8, 4.1), 3.74 (3 H, s), 3.60 (1 H, m), 2.68 (1 H, m), 2.26 (1 H, dd, *J* 17.1, 3.7), 1.8–1.3 (6 H, m) and 0.90 (3 H, t, *J* 6.7); $\delta_C(CDCl_3)$ 173.3, 167.0, 138.1, 128.4, 127.9, 127.8, 90.2, 79.0, 76.3, 72.9, 56.1, 29.3, 28.4, 27.9, 22.7 and 14.0; ν_{max}(thin film)/cm^{-1} 3030, 2953, 2884, 1713, 1624, 1496, 1454, 1377, 1226, 1072 and 997; *m/z* 218, 198, 177, 155, 127, 105, 91, 77 and 67.

(−)-*Pestalotin* **8**.[17]—A solution of the above lactone (18 mg, 0.059 mmol) in ethyl acetate (3 ml) was stirred with 5% Pd–C under an atmosphere of hydrogen for 26 h at 25 °C. The reaction was monitored by TLC (5:1 hexane–EtOAc). Upon completion of the reaction, the catalyst was removed by passing the solution through a layer of Florisil. Evaporation of the filtrate under reduced pressure and purification of the crude product by flash chromatography with 4:1 hexane–EtOAc afforded (−)-pestalotin **8** (9.2 mg, 72.9%); $[\alpha]_D$ −79.2 (*c* 0.5, $CHCl_3$); $\delta_H(CDCl_3)$ 5.14 (1 H, d, *J* 1.7), 4.29 (1 H, dt, *J* 13.0, 3.9), 3.75 (3 H, s), 2.82 (1 H, m), 2.80 (1 H, ddd, *J* 17.0, 12.9, 1.7), 2.24 (1 H, dd, *J* 17.0, 3.7), 2.16 (1 H, d, *J* 7.0), 1.70–1.30 (6 H, m) and 0.91 (3 H, t, *J* 7.1); $\delta_C(CDCl_3)$ 173, 167, 91, 79, 73, 56, 33, 30, 28, 23 and 14; ν_{max}(thin film)/cm^{-1} 3422, 3098, 2953, 1711, 1622, 1444, 1388, 1282, 1140, 1063, 997, 918, 862 and 821; *m/z* 214 (M^+), 182, 172, 157, 140, 127, 99, 95 and 67 (Found: M^+, 214.1025. Calc. for $C_{11}H_{18}O_4$: *M*, 214.1205).

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