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Stereoselective synthesis of (−)-cytoxazone

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Abstract—The stereoselective synthesis of the cytokine modulator (−)-cytoxazone in enantiopure form is described. Key steps of the process are a *syn*-stereoselective aldol addition of a chiral ketone mediated by chlorodicyclohexylborane, and a Curtius rearrangement.

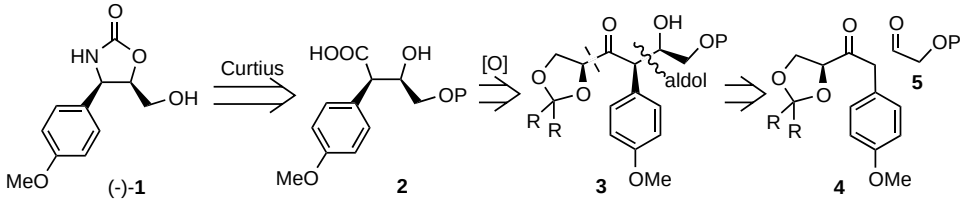
1. Introduction

During screening for chemical immunomodulators from microbial sources, the novel cytokine modulator cytoxazone (−)-**1** has been recently isolated from cultures of a *Streptomyces* species.[1] It was found to inhibit the signaling pathway of Th2 cells but not that of Th1 cells. Because of these biological properties, several total syntheses of (−)-**1** and of its *trans*-diastereoisomer (4-*epi*-cytoxazone) have been published in the last three years. Three of these syntheses relied on asymmetric dihydroxylations as the source of chirality[2] whereas another made use of a precursor from the chiral pool.[3] Two further syntheses led to racemic cytoxazone, which was then resolved via chemical[4] or enzymatic[5] procedures. Herein, we present our synthetic approach to (−)-**1**, based on our recently developed, stereoselective aldol methodology.[6] The retrosynthetic scheme is shown below and includes the Curtius degradation of acid **2**, the oxidative cleavage of the acetal ring[6] in **3** and the *syn*-stereoselective boron aldol addition of chiral ketone **4** to a suitably protected glycolic aldehyde **5**.

2. Results and discussion

The homochiral ketone **6** [≡**4**, R,R = $(CH_2)_5$] was readily prepared from L-erythrulose cyclohexylidene acetal **7**[7] in 49% overall yield (Scheme 1). Reduction of **7** with LAH yielded diol **8** as a mixture of diastereoisomers. The formation of the epoxide ring to give **9** (diastereoisomeric mixture) was best achieved via tin acetal methodology.[8] Epoxide ring opening in **9** was performed with an organocopper derivative[9] prepared from 4-methoxyphenyl magnesium bromide. This provided a mixture of diastereoisomeric alcohols **10**, which was finally oxidised to ketone **6** by means of the Dess–Martin procedure.[10] An interesting feature of the process is that all four carbon atoms of the chiral precursor, L-erythrulose, are used (full atom economy).[11]

Aldol additions of ketone **6** with three protected derivatives of glycolic aldehyde (hydroxy acetaldehyde) **5** were then investigated (Scheme 2, P = TBS, TPS, Bn).[12] All three reactions worked efficiently to furnish the expected *syn–syn* aldol adducts **11a–c**. Oxidative cleav-



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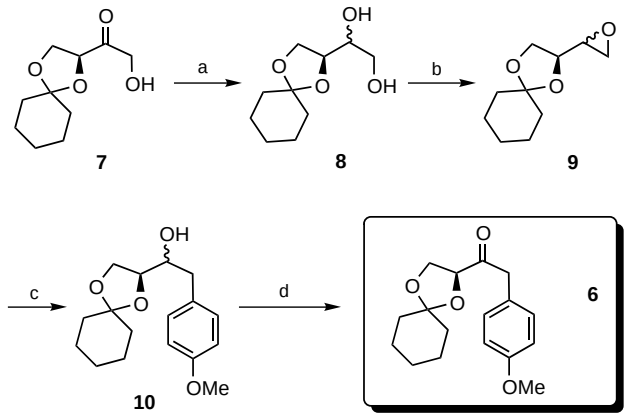


Scheme 1. Preparation of ketone **6** from L-erythrulose cyclohexylidene acetal **7**. *Reagents and conditions*: (a) LAH, THF, 74%. (b) TsCl, Et_3N, cat. Bu_2SnO; NaH, THF, 90% overall. (c) 4-Methoxyphenyl magnesium bromide, CuI, 83%. (d) Dess–Martin periodinane, 88%.

age of the acetonide ring using periodic acid hydrate (H_5IO_6)[13] proceeded well when P = TPS or Bn but not when P = TBS, as the latter group proved too sensitive to the acidic reaction conditions. As previously observed in related cases,[6] oxidative cleavage of the aldols with H_5IO_6 gave intermediate β-formyloxy acids, which were then converted into the corresponding β-hydroxy acids **12a**–**b** via mild alkaline hydrolysis. Curtius rearrangement of the latter compounds was performed with the aid of diphenyl phosphoryl azide (DPPA).[14] This furnished oxazolidinones **13a**–**b** directly through in situ intramolecular capture of the isocyanate group by the free hydroxyl function.[15] Cleavage of the protecting group in **13a**–**b** led finally to cytoxazone (−)-**1**.

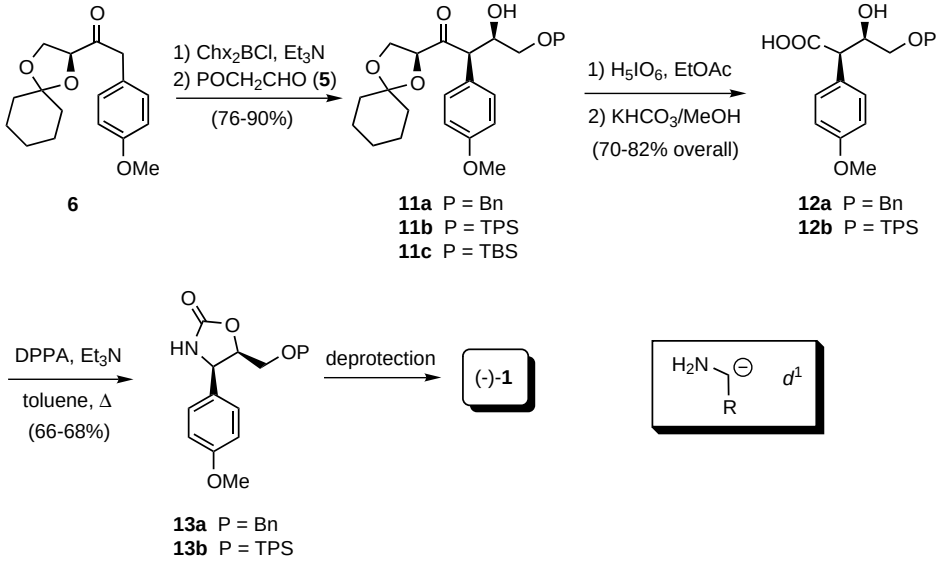
Among the previous syntheses of *non-racemic* cytoxazone, only one involved the formation of a C–C bond.[3] A characteristic feature of the present synthesis is that the two stereogenic centres of the target molecule were simultaneously created in the course of an aldol addition with complete relative as well as absolute stereocontrol by the stereogenic centre resident in the starting homochiral precursor **6**. This stereocentre was later sacrificed, once his control role had been accomplished. Ketone **6** and structurally related compounds may therefore be considered as chiral equivalents of the d^1 synthon type depicted in Scheme 2 (R = alkyl, aryl). They should thus prove very useful for the synthesis of many naturally occurring, nitrogen-containing molecules, such as amino acids, amino polyols, alkaloids, etc., in enantiopure form. Efforts in this direction are underway and will be reported in due course.

3. Experimental

3.1. General methods

^1H NMR spectra (400 or 500 MHz) and ^{13}C NMR spectra (100 or 125 MHz) were measured at 22°C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Multiplicity assignments of ^{13}C NMR signals were made with the DEPT pulse sequence. Mass spectra were run in a VG AutoSpec mass spectrometer using either the electron impact mode (EIMS, 70 eV) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix). Samples for IR spectral measurements were prepared as oily films on NaCl plates (oils) or KBr pellets (solids). Optical rotations were measured at 22°C.

Column chromatography (CC) was performed on silica gel Süd-Chemie AG (60–200 μm). Experiments which required an inert atmosphere were carried out under dry argon (Ar) in a flame-dried glassware. THF and Et_2O were freshly distilled from sodium/benzophenone ketyl and were transferred via syringe. Toluene was



Scheme 2. Synthesis of (−)-cytoxazone from chiral ketone **6**.

freshly distilled from sodium wire. Methylene chloride was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Commercially available reagents (Aldrich or Fluka) were used as received. If not detailed otherwise, the work-up of the reactions was consistently performed in the following manner: the reaction mixture was poured into brine and extracted twice with solvent (Et_2O, CH_2Cl_2 or EtOAc), the organic layer was washed with diluted aq. NH_4Cl and then washed again with brine, the organic layer was dried over anhydrous $MgSO_4$ or Na_2SO_4, and the solvent was eliminated with a rotary evaporator at aspirator pressure.

3.2. Preparation of ketone 6

Lithium aluminum hydride (1.14 g, 30 mmol) was suspended under Ar in dry THF (30 mL). After cooling in an ice bath, a solution of ketone **7**[7] (5 g, ca. 25 mmol) in dry THF (30 mL) was slowly added dropwise (10 min). When the addition was complete, the ice bath was removed, and the reaction mixture was stirred at room temperature for 16 h. After recooling in an ice bath, water (2 mL) was *slowly* added dropwise (**caution: evolution of H_2!**). After this, 1 M aq. NaOH (2 mL) and again water (10 mL) were added, the cooling bath was removed, and the mixture was stirred at room temperature for 3 h. Filtration through Celite was followed by concentration under reduced pressure and column chromatography on silica gel (hexanes–EtOAc 1:1, then 1:2) to yield diol **8** as a mixture of diastereoisomers (3.74 g, 74%).

Diol **8** (3.03 g, 15 mmol) was dissolved under Ar in dry CH_2Cl_2 (30 mL) and treated with nBu$_2$SnO (75 mg, 0.3 mmol), *p*-toluenesulphonyl chloride (3.15 g, 16.5 mmol) and triethylamine (2.6 mL, 18 mmol). The mixture was stirred at room temperature and stirred for 3 h, then filtered through Celite and evaporated under reduced pressure. The oily residue was then dissolved in dry THF (150 mL) and added dropwise to a suspension of NaH (30 mmol of the base) in dry THF (40 mL). The reaction mixture was stirred at room temperature for 3 h. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc 4:1) gave epoxide **9** as a mixture of diastereoisomers (2.49 g, 90%).

Copper iodide (4.95 g, 26 mmol) was dried by means of gentle heating under vacuum. It was then suspended under Ar in dry Et_2O (200 mL). The mixture was cooled to −10°C and treated with *p*-methoxyphenyl magnesium bromide (0.5 M solution in THF, 104 mL, 52 mmol). After stirring at −10°C for 1 h, a solution of epoxide **9** (2.40 g, ca. 13 mmol) in dry Et_2O (30 mL) was added dropwise to the organocopper reagent solution. The cooling bath was removed, and the reaction mixture was stirred at room temperature. for 16 h. Satd aq. NH_4Cl (50 mL) and 30% aq. NH_3 (10 mL) were sequentially added to the reaction mixture. The organic layer was then poured onto brine, washed once again with satd aq. NH_4Cl, dried and evaporated under reduced pressure. Column chromatography of the oily residue on silica gel (hexanes–EtOAc 9:1, then 4:1 and 7:3) afforded alcohol **10** as a mixture of diastereoisomers (3.16 g, 83%).

Alcohol **10** (2.92 g, 10 mmol) was dissolved under Ar in dry CH_2Cl_2 (100 mL). After cooling in an ice bath, $NaHCO_3$ (2.52 g, 30 mmol) and Dess–Martin periodinane (12.72 g, 30 mmol) were successively added. The orange red reaction mixture was then stirred for 16 h at room temperature, diluted with Et_2O (250 mL) and poured onto satd aq. $Na_2S_2O_3$. The organic layer was then stirred for 15 min, separated from the aqueous layer, washed again with satd aq. $NaHCO_3$, dried and evaporated under reduced pressure. Column chromatography of the residue on silica gel (hexanes–EtOAc 9:1, then 4:1) afforded ketone **6** as an oil (2.55 g, 88%): $[\alpha]_D^{22}$ −99.3 (*c* 0.5, $CHCl_3$), ^{1}H NMR (500 MHz) δ 7.15 (2H, d, J=8.5 Hz, aromatic), 6.89 (2H, d, J=8.5 Hz, aromatic), 4.53 (1H, dd, J=7.5, 5.7 Hz, C$\underline{H}$OR), 4.16 (1H, dd, J=8.5, 7.5 Hz, C$\underline{H}_2$OR), 4.02 (1H, dd, J=8.5, 5.7 Hz, C$\underline{H}_2$OR), 3.96 (1H, d, J=16 Hz, ArC$\underline{H}_2$), 3.83 (1H, d, J=16 Hz, ArC$\underline{H}_2$), 3.80 (3H, s, OMe), 1.80–1.45 (10H, br m, cyclohexane protons). ^{13}C NMR (125 MHz) δ 208.2 (C=O), 158.6, 130.6, 125.3, 114.0 (aromatic), 111.6 (acetal carbon), 79.5 (C$\underline{H}$OR), 66.1 (C$\underline{H}_2$OR), 55.2 (OMe), 44.5 (ArC$\underline{H}_2$), 35.7, 34.5, 25.1, 24.0, 23.8 (cyclohexane carbons). IR ν_{max} 2935, 2859, 1721, 1611, 1584, 1563, 1515, 1464, 1449, 1369, 1333, 1301, 1249, 1178, 1161, 1096, 1037, 924, 847, 829, 774 cm^{-1}. HR EIMS m/z (% rel. int.) 290.1514 (M^+, 32), 141 (92), 121 (100). Calcd for $C_{17}H_{22}O_4$, 290.1518. Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found, C, 70.50; H, 7.80%.

3.3. Aldol additions of ketone 6

Chx$_2$BCl (800 μL, ca. 3.6 mmol) and Et_3N (560 μL, 4 mmol) were dissolved under Ar in anhydrous Et_2O (8 mL) and cooled to −78°C. Ketone **6** (580 mg, ca. 2 mmol) was dissolved in anhydrous ether (6 mL) and added dropwise via syringe to the reagent solution. After 10 min, the reaction mixture was warmed to 0°C, stirred for 1 h at this temperature and then recooled to −78°C. After 10 min stirring, a solution of aldehyde **5** (10 mmol) in ether (6 mL) was added dropwise. The stirring was continued for 10 min, the reaction mixture was then warmed up to 0°C and further stirred for 5 h (**5**, P=Bn or TBS) or 7 h (**5**, P=TPS). For the work-up, phosphate pH 7 buffer solution (15 mL) and MeOH (15 mL) were added at 0°C, followed by 30% aq. H_2O_2 (8 mL). After stirring for 1 h at room temperature, the mixture was poured onto brine and extracted with Et_2O. The organic layer was then dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the residue on silica gel (hexanes–EtOAc, 19:1, then 9:1 and 4:1) provided aldols **11a** (670 mg, 76% yield), **11b** (1.06 g, 90%) and **11c** (743 mg, 79%).

3.3.1. (2*S*,4*R*,5*R*)-1,2-*O*-Cyclohexylidene-6-*O*-benzyl-1,2,5,6-tetrahydroxy-4-(4-methoxyphenyl)hexan-3-one, 11a.

Oil: $[\alpha]_D^{22}$ +83.6 (*c* 5, $CHCl_3$). ^{1}H NMR (500 MHz) δ 7.35–7.25 (5H, m, aromatic), 7.25 (2H, d, J=8.5 Hz,

aromatic), 6.88 (2H, d, $J=8.5$ Hz, aromatic), 4.56 (1H, d, $J=11.8$ Hz, benzyl C$\underline{H}_2$), 4.52 (1H, d, $J=11.8$ Hz, benzyl C$\underline{H}_2$), 4.50–4.40 (2H, m, C$\underline{H}$OR), 4.35 (1H, d, $J=7.1$ Hz, ArC$\underline{H}$), 4.07 (1H, t, $J=8.1$ Hz, C$\underline{H}_2$OR), 3.80 (3H, s, OMe), 3.75 (1H, dd, $J=8.1$, 6.5 Hz, C$\underline{H}_2$OR), 3.53 (1H, dd, $J=9.6$, 5.1 Hz, C$\underline{H}_2$OBn), 3.44 (1H, dd, $J=9.6$, 5.1 Hz, C$\underline{H}_2$OBn), 2.45 (1H, br s, OH), 1.70–1.40 (10H, br m, cyclohexane protons). ^{13}C NMR (125 MHz) δ 209.1 (C=O), 159.2, 137.9, 130.7, 128.3, 127.9, 125.7, 114.2 (aromatic), 111.6 (acetonide *C*), 79.7, 73.3, 71.5, 71.2, 66.1, 55.2 (*C*-OR), 55.1 (OMe), 35.2, 34.6, 24.9, 23.9, 23.7 (cyclohexane carbons). IR ν_{max} 3480 (br), 2934, 2861, 1709, 1610, 1511, 1452, 1368, 1250, 1179, 1161, 1099, 1035, 924, 827, 737 cm^{-1}. HR FAB MS m/z 441.2262 (M+H$^+$). Calcd for $C_{26}H_{33}O_6$, 441.2277. Anal. calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found, C, 71.00; H, 7.50%.

3.3.2. (2*S*,4*R*,5*R*)-1,2-*O*-Cyclohexylidene-6-*O*-(*tert*-butyldiphenylsilyl)-1,2,5,6-tetrahydroxy-4-(4-methoxyphenyl)hexan-3-one, 11b. Oil: $[\alpha]_D^{22}$ +33.2 (*c* 5.7, $CHCl_3$). ^{1}H NMR (500 MHz) δ 7.70 (4H, m, aromatic), 7.50–7.40 (6H, m, aromatic), 7.26 (2H, d, $J=8.5$ Hz, aromatic), 6.89 (2H, d, $J=8.5$ Hz, aromatic), 4.52 (1H, d, $J=6.8$ Hz, ArC$\underline{H}$), 4.48 (1H, dd, $J=7.6$, 6.5 Hz, C$\underline{H}$OR), 4.36 (1H, m, C$\underline{H}$OH), 4.09 (1H, dd, $J=8.5$, 7.5 Hz, C$\underline{H}_2$OR), 3.81 (3H, s, OMe), 3.70–3.65 (2H, m, C$\underline{H}_2$OR, C$\underline{H}_2$OTPS), 3.60 (1H, dd, $J=10.2$, 5.7 Hz, C$\underline{H}_2$OTPS), 2.60 (1H, br s, OH), 1.65–1.40 (10H, br m, cyclohexane protons), 1.13 (9H, s, *t*BuSi). ^{13}C NMR (125 MHz) δ 209.7 (C=O), 159.3, 135.6, 135.5, 133.2, 133.1, 130.9, 130.1, 129.9, 129.8, 127.8, 127.7, 125.7, 114.1 (aromatic), 111.7 (acetonide *C*), 79.9, 72.3, 66.4, 65.1 (*C*-OR), 55.2 (OMe), 54.6 (Ar*C*H), 35.3, 34.7, 25.0, 23.9, 23.7 (cyclohexane carbons), 26.9, 19.2 (*t*BuSi). IR ν_{max} 3430 (br, OH), 3071, 2932, 2857, 1707, 1610, 1511, 1463, 1449, 1428, 1368, 1251, 1179, 1161, 1112, 1038, 924, 824, 740, 703 cm^{-1}. HR FAB MS m/z 589.3001 (M+H$^+$). Calcd for $C_{35}H_{45}O_6Si$, 589.2985. Anal. calcd for $C_{35}H_{44}O_6Si$: C, 71.39; H, 7.53. Found, C, 71.30; H, 7.59%.

3.3.3. (2*S*,4*R*,5*R*)-1,2-*O*-Cyclohexylidene-6-*O*-(*tert*-butyldimethylsilyl)-1,2,5,6-tetrahydroxy-4-(4-methoxyphenyl)hexan-3-one, 11c. Oil: $[\alpha]_D^{22}$ +58.6 (*c* 7.7, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.20 (2H, d, $J=8.5$ Hz, aromatic), 6.84 (2H, d, $J=8.5$ Hz, aromatic), 4.49 (1H, dd, $J=7.6$, 6.5 Hz, C$\underline{H}$OR), 4.31 (1H, d, $J=7.1$ Hz, ArC$\underline{H}$), 4.22 (1H, m, C$\underline{H}$OH), 4.07 (1H, dd, $J=8.4$, 7.6 Hz, C$\underline{H}_2$OR), 3.77 (3H, s, OMe), 3.69 (1H, dd, $J=8.4$, 6.5 Hz, C$\underline{H}_2$OR), 3.56 (1H, dd, $J=10.1$, 5.1 Hz, C$\underline{H}_2$OTBS), 3.49 (1H, dd, $J=10.1$, 5.3 Hz, C$\underline{H}_2$OTBS), 2.50 (1H, br s, OH), 1.60–1.30 (10H, br m, cyclohexane protons), 0.90 (9H, s, *t*BuSi), 0.05 (3H, s, Me_2Si), 0.04 (3H, s, Me_2Si). ^{13}C NMR (100 MHz) δ 209.5 (C=O), 159.2, 130.8, 125.8, 114.1 (aromatic), 111.7 (acetonide *C*), 79.9, 72.5, 66.3, 64.4 (*C*-OR), 55.2 (OMe), 54.9 (Ar*C*H), 35.3, 34.7, 25.0, 23.9, 23.8 (cyclohexane carbons), 25.9, 18.3 (*t*BuSi), −5.3 ($\underline{Me}_2$Si), −5.4 ($\underline{Me}_2$Si). IR ν_{max} 3580 (br), 2936, 2859, 1708, 1610, 1511, 1464, 1369, 1253, 1179, 1161, 1113, 1037, 909, 837, 779 cm^{-1}. HR EIMS m/z (% rel. int.) 407.1890 (M$^+$−*t*Bu, 16), 290 (72), 141 (100), 117 (89). Calcd for $C_{25}H_{40}O_6Si$-*t*Bu, 407.1890. Anal. calcd for $C_{25}H_{40}O_6Si$: C, 64.62; H, 8.68. Found, C, 64.77; H, 8.53%.

3.4. Oxidative cleavage of aldols 11a–c with periodic acid hydrate

The aldol **11a** (661 mg, 1.5 mmol) was dissolved in an Et_2O–EtOAc 1:1 mixture (30 mL) and treated with H_5IO_6 (1.2 g, ca. 5.25 mmol). The mixture was then stirred at room temperature until consumption of the starting material (6.5–7 h, TLC monitoring!). Solid sodium thiosulphate pentahydrate (500 mg, ca. 2 mmol) was added to the reaction mixture, which was then stirred for 15 min, filtered through Celite (the Celite pad was additionally washed with 30 mL of EtOAc) and evaporated under reduced pressure. The oily residue was dissolved in MeOH (20 mL) and treated with $KHCO_3$ (400 mg, ca. 4 mmol). After stirring the mixture at room temperature for 2 h, satd. aq. NH_4Cl (2 mL) was added, followed by filtration through Celite (the Celite pad was additionally washed with 30 mL of MeOH) and evaporation under reduced pressure. The residue was then subjected to column chromatography on silica gel (EtOAc:AcOH, 99:1) to yield **12a** (389 mg, 82%). Acid **12b** was obtained in 70% yield from aldol **11b** using the same procedure. Aldol **11c** decomposed under these conditions.

3.4.1. (2*R*,3*R*)-4-Benzyloxy-3-hydroxy-2-(4-methoxyphenyl)butanoic acid, 12a. Oil: $[\alpha]_D^{22}$ +20 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz) δ 7.40–7.30 (7H, m, aromatic), 6.90 (2H, d, $J=8.5$ Hz, aromatic), 4.55 (2H, s, benzyl C$\underline{H}_2$), 4.45 (1H, m, C$\underline{H}$OH), 3.82 (1H, overl. m, ArC$\underline{H}$), 3.81 (3H, s, OMe), 3.53 (1H, dd, $J=9.7$, 5.9 Hz, C$\underline{H}_2$OBn), 3.49 (1H, dd, $J=9.7$, 4.8 Hz, C$\underline{H}_2$OBn). ^{13}C NMR (125 MHz) δ 177.7 (C=O), 159.3, 137.7, 130.4, 130.2, 128.4, 127.8, 127.7, 126.2, 114.1 (aromatic), 73.4, 71.4, 70.7 (*C*H$_2$OR), 55.2 (OMe), 52.9 (Ar*C*H). IR ν_{max} 3430 (br), 2934, 2860, 1726, 1612, 1513, 1452, 1367, 1248, 1179, 1099, 1035, 927, 807, 740 cm^{-1}. HR EIMS m/z (% rel. int.) 316.1308 (M$^+$, 4), 166 (100), 121 (40), 91 (73). Calcd for $C_{18}H_{20}O_5$, 316.1310. Anal. calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found, C, 68.49; H, 6.50%.

3.4.2. (2*R*,3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-2-(4-methoxyphenyl)butanoic acid, 12b. Oil: $[\alpha]_D^{22}$ +26.3 (*c* 4, $CHCl_3$). ^{1}H NMR (500 MHz) δ 7.70 (4H, m, aromatic), 7.50–7.40 (6H, m, aromatic), 7.34 (2H, d, $J=8.5$ Hz, aromatic), 6.90 (2H, d, $J=8.5$ Hz, aromatic), 4.39 (1H, dT, $J=6.6$, 5.5 Hz, C$\underline{H}$OH), 3.90 (1H, d, $J=6.6$ Hz, ArC$\underline{H}$), 3.81 (3H, s, OMe), 3.71 (1H, dd, $J=10.4$, 5.5 Hz, C$\underline{H}_2$OTPS), 3.65 (1H, dd, $J=10.4$, 5.5 Hz, C$\underline{H}_2$OTPS), 1.10 (9H, s, *t*BuSi). ^{13}C NMR (125 MHz) δ 177.9 (C=O), 159.2, 135.8, 133.2, 130.7, 130.1, 130.0, 128.1, 128.0, 126.8, 114.3 (aromatic), 72.0, 65.1 (*C*-OR), 55.2 (OMe), 52.7 (Ar*C*H), 26.8, 19.2 (*t*BuSi). IR ν_{max} 3430–2800 (br, COOH), 3071, 2932, 2858, 1706 (br, C=O), 1610, 1588, 1512, 1463, 1441, 1428, 1252, 1179, 1106, 1064, 1036, 825, 740, 703 cm^{-1}. HR EIMS m/z (% rel. int.) 407.1334 (M$^+$−*t*Bu, 13), 361 (35), 328 (50), 241 (41), 198 (100), 121 (72). Calcd for $C_{27}H_{32}O_5Si$-*t*Bu, 407.1315. Anal. calcd for $C_{27}H_{32}O_5Si$: C, 69.80; H, 6.94. Found, C, 69.60; H, 6.79%.

3.5. Curtius rearrangement of acids 12a–b with DPPA

A solution of acid **12a** (316 mg, 1 mmol) and triethylamine (175 μL, 1.25 mmol) in dry toluene (10 mL) containing activated 4 Å molecular sieves was treated under Ar with DPPA (240 μL, ca. 1.1 mmol) and heated overnight under reflux. After cooling to room temperature, the mixture was poured into a glass separation funnel containing water (40 mL) and CH_2Cl_2 (40 mL). The organic layer was separated, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the residue on silica gel (hexanes–EtOAc, 1:3) afforded oxazolidinone **13a** (213 mg, 68%) as a yellowish oil. Compound **13b** was similarly obtained from acid **12b** in 66% yield.

3.5.1. (4*R*,5*R*)-5-Benzyloxymethyl-4-(4-methoxyphenyl)-oxazolidin-2-one, 13a. Oil: $[\alpha]_D^{22}$ −44.8 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz) δ 7.30 (5H, m, aromatic), 7.20 (2H, d, J=8.5 Hz, aromatic), 6.90 (2H, d, J=8.5 Hz, aromatic), 6.00 (1H, br s, NH), 4.96 (2H, m, H-4, H-5), 4.33 (1H, d, J=11.8 Hz, benzyl C$\underline{H}_2$), 4.23 (1H, d, J=11.8 Hz, benzyl C$\underline{H}_2$), 3.83 (3H, s, OMe), 3.36 (1H, dd, J=10.5, 6.2 Hz, C$\underline{H}_2$OBn), 3.15 (1H, dd, J=10.5, 5.2 Hz, C$\underline{H}_2$OBn). ^{13}C NMR (125 MHz) δ 160.0 (C=O), 159.3, 138.2, 137.4, 128.4, 128.3, 127.8, 127.7, 127.6, 114.1 (aromatic), 79.0, 73.4, 68.7, 57.8 (C-OR), 55.3 (OMe). IR ν_{max} 3300 (br, NH), 3051, 2928, 2853, 1746 (C=O), 1606, 1514, 1453, 1404, 1252, 1178, 1080, 1010, 845, 736, 701 cm^{-1}. HR EIMS m/z (% rel. int.) 313.1314 (M^+, 20), 207 (100), 162 (62), 135 (84), 91 (93). Calcd for $C_{18}H_{19}NO_4$, 313.1314. Anal. calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11. Found, C, 68.79; H, 6.20%.

3.5.2. (4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one, 13b. Oil: $[\alpha]_D^{22}$ −27.3 (*c* 5.9, $CHCl_3$). ^{1}H NMR (500 MHz) δ 7.52 (2H, m, aromatic), 7.45–7.30 (8H, m, aromatic), 7.18 (2H, d, J=8.5 Hz, aromatic), 6.88 (2H, d, J=8.5 Hz, aromatic), 6.35 (1H, br s, NH), 4.99 (1H, d, J=8.2 Hz, C$\underline{H}$N), 4.89 (1H, ddd, J=8.2, 6.2, 5.5 Hz, C$\underline{H}$O), 3.82 (3H, s, OMe), 3.54 (1H, dd, J=11.2, 5.5 Hz, C$\underline{H}_2$OTPS), 3.39 (1H, dd, J=11.2, 6.2 Hz, C$\underline{H}_2$OTPS), 1.02 (9H, s, *t*BuSi). ^{13}C NMR (125 MHz) δ 159.8 (C=O), 159.5, 135.5, 135.4, 132.7, 132.6, 129.7, 129.6, 128.4, 128.1, 127.7, 127.6, 114.0 (aromatic), 80.1, 61.9, 57.9 (C-OR), 55.2 (OMe), 26.6, 18.9 (*t*BuSi). IR ν_{max} 3400 (br), 1679, 1596, 1578, 1491, 1450, 1387, 1263, 1207, 1093, 1069, 978, 929, 833, 755 cm^{-1}. HR EIMS m/z (% rel. int.) 404.1338 (M^+−*t*Bu, 2), 361 (80), 253 (24), 121 (100). Calcd for $C_{27}H_{31}NO_4Si$-*t*Bu, 404.1318. Anal. calcd for $C_{27}H_{31}NO_4Si$: C, 70.25; H, 6.77. Found, C, 70.35; H, 6.79%.

3.6. Deprotection of oxazolidinones 13a and 13b to cytoxazone, (−)-1

By hydrogenolysis: a solution of oxazolidinone **13a** (157 mg, 0.5 mmol) in absolute EtOH (4 mL) was mixed with $Pd(OH)_2$ (20% on charcoal, Degussa type, 50 mg) and hydrogenated in a pressure vessel (500 psi) with efficient stirring for 24 h. After filtration through Celite [the Celite pad was additionally washed with EtOH (10 mL)] and removal of volatiles under reduced pressure, the oily residue was chromatographed on silica gel (EtOAc) to yield (−)-**1** (87 mg, 78%).

By desilylation: oxazolidinone **13b** was desilylated with TBAF as reported previously[2b] to yield (−)-**1**.

3.6.1. (4*R*,5*R*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-oxazolidin-2-one, (−)-cytoxazone, (−)-1. White solid, mp 122–124°C, lit.[1] mp 118–121°C, lit.[5] mp 122–123°C; $[\alpha]_D$ −74.6 (*c* 1.1; MeOH), lit.[1] $[\alpha]_D$ −71 (*c* 0.1; MeOH), lit.[2b] $[\alpha]_D$ −75.7 (*c* 1; MeOH); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.25 (2H, d, J=8.8 Hz, aromatic), 6.93 (2H, d, J=8.8 Hz, aromatic), 6.90 (1H, br s, NH), 5.02 (1H, d, J=8 Hz, H-4), 4.81 (1H, dt, J=8, 4 Hz, H-5), 3.79 (3H, s, OMe), 3.78 (1H, m, OH), 3.22 (1H, ddd, J=12, 8, 5 Hz, C$\underline{H}_2$OH), 3.27 (1H, dd, J=12, 6.3, 4 Hz, C$\underline{H}_2$OH); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 160.7 (C=O), 159.5, 130.2, 129.0, 114.6 (aromatic), 81.5 (C-5), 62.6 (C$\underline{H}_2$OH), 57.8 (C-4), 55.6 (OMe).

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