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Short synthesis of both enantiomers of cytoxazone using the Petasis reaction

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Abstract—Both enantiomers of cytoxazone, (−)-**1** and (+)-**1**, were synthesized using the Petasis reaction of DL-glyceraldehyde **2**, 4-methoxyphenylboronic acid **3** and (*R*)-1-(1-naphthyl)ethylamine **7**, following formation of an oxazolidin-2-one ring.

1. Introduction

Over the course of screening for chemical immunomodulators that inhibit type 2 cytokine production in Th2 cells, the RIKEN group found (−)-cytoxazone (−)-**1** (Fig. 1) as a novel cytokine modulator produced by the *Streptomyces* species.[1] (−)-Cytoxazone (−)-**1** shows cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells but not Th1 cells.

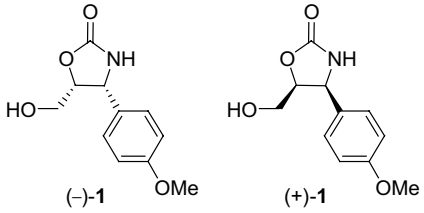
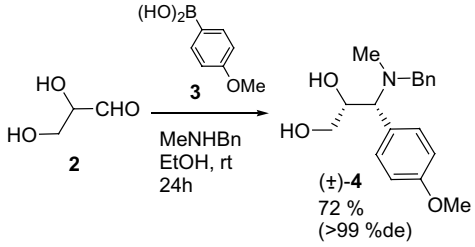


Figure 1. (−)-Cytoxazone (−)-**1** and (+)-cytoxazone (+)-**1**.

Due to the potent biological activity and the simple structure, the synthesis of (−)-**1** has been well investigated. The racemic product of cytoxazone (±)-**1** has been synthesized and then separated.[2,3] Acylation of (±)-**1** with (−)-camphanic chloride gives a mixture of two corresponding esters, and both esters can be easily separated into their diastereomers.[2] The kinetic resolution of (±)-**1** is performed by acetylation with vinyl acetate catalyzed by *Penicillium camemberti* lipase.[3] These methods require two extra steps: acylation of enantiomeric mixtures and hydrolysis of the acyl groups after separation. Several groups have also synthesized (−)-cytoxazone (−)-**1** using asymmetric reactions.[4] Madhan et al. developed the total synthesis of (−)-**1**, which involved the stereoselective addition of *p*-methoxyphenylmagnesium bromide to a benzylimine of (*S*)-2,3-*O*-isopropylidene glyceraldehyde to give the protected 3-amino-1,2-propanediol derivative, as well as subsequent regioselective cyclization to give an oxazolidin-2-one ring.[4d] A similar 3-amino-1,2-propanediol derivative (±)-**4** has been synthesized using the Petasis three-component coupling reaction;[5,6] DL-glyceraldehyde **2** reacted with 4-methoxyphenylboronic acid **3**[5] and *N*-methylbenzylamine in ethanol to give a (2*RS*,3*RS*)-3-amino-1,2-propanediol derivative (±)-**4** (Scheme 1).



Scheme 1. An example of the Petasis three-component coupling reaction.

Several optically active oxazolidin-2-ones possessing α-methylbenzyl and 1-(1-naphthyl)ethyl groups on the

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nitrogen have been synthesized,[7–11] with the diastereomers of the corresponding 5-bromomethyl-,[7] 5-phenyl-,[8] 5-chloromethyl-,[7] 5-iodomethyl-[9] and 5-vinyloxazolidin-2-ones[10] easily separable on silica gel column chromatography. Therefore, we expected that the diastereomers of oxazolidin-2-ones **5a**, **6a**, **5b** and **6b** (Fig. 2), each of which would be a precursor for the total synthesis of optically active cytoxazones (−)-**1** or (+)-**1**, could be separated on silica gel column chromatography.

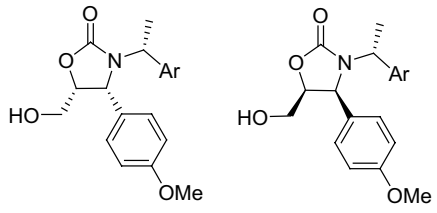


Figure 2. Proposed precursors for cytoxazones.

To synthesize cytoxazones from the intermediates **5a**, **6a**, **5b** and **6b**, the α-methylbenzyl groups and the 1-(1-naphthyl)ethyl groups must be removed. We have developed mild reaction conditions to remove *N*-α-methylbenzyl and *N*-1-(1-naphthyl)ethyl groups from oxazolidin-2-ones using methanesulfonic acid (MsOH) and anisole.[7,8] These reaction conditions do not influence the 4-phenyloxazolidin-2-one rings,[8] which are cleaved by general debenzylation conditions such as Li/NH_3[12] and Na/NH_3,[13] and the yield of removal of the *N*-1-(1-naphthyl)ethyl group using MsOH is much better than that of the *N*-α-methylbenzyl group.[7]

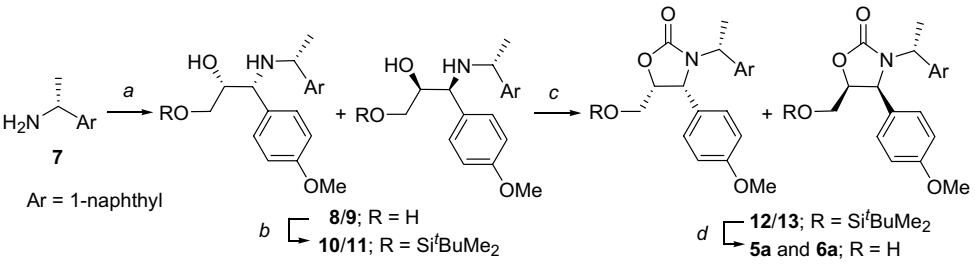
On the basis of these findings, we investigated a short synthesis of (−)- and (+)-cytoxazones (−)-**1** and (+)-**1**, respectively from DL-glyceraldehyde **2**, 4-methoxyphenylboronic acid **3** and (*R*)-1-(1-naphthyl)ethylamine **7b** as starting materials.

2. Results and discussion

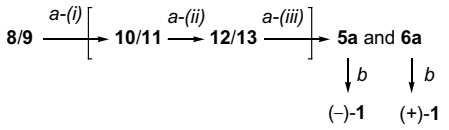
According to the procedure[5,6] reported by Petasis et al., we synthesized 3-amino-1,2-propanediols **8** and **9** by reactions of (*R*)-1-(1-naphthyl)ethylamine **7** with DL-glyceraldehyde **2** and 4-methoxyphenylboronic acid **3** (Scheme 2). This reaction proceeded very slowly at room temperature compared to the reaction[5] shown in (Scheme 1). Even in refluxing ethanol, the reaction required a long reaction time to afford a diastereomeric mixture (dr, ca. 1:1) of **8** and **9** (reaction time: one day, 28% yield; three days, 50% yield). A reaction using (*R*)-α-methylbenzylamine instead of **7** was also slow; however, it proceeded at room temperature to give a mixture of the corresponding amino alcohols (dr, ca. 1:1) in 56% yield (reaction time, three days). Amino alcohols **8** and **9** were silylated to protect the primary hydroxyl groups selectively to give silyl ethers **10** and **11**. After the formation of oxazolidin-2-ones **12** and **13** using *N*,*N*′-succinimidyl carbonate (DSC) in acetonitrile, the silyl groups were removed with tetrabutylammonium fluoride (TBAF) in THF to give oxazolidin-2-ones **5a** and **6a**. The R_f values of **5a** and **6a** were 0.20 and 0.12 (hexane/AcOEt, 1:1), respectively, and as we had expected, **5a** and **6a** were easily separated using silica gel column chromatography. Although a diastereomeric mixture of **5b** and **6b** (Fig. 2) was also synthesized from (*R*)-α-methylbenzylamine according to the procedure described above, the mixture **5b** and **6b** proved difficult to separate on silica gel column chromatography.

To simplify this synthetic procedure, we investigated the one-pot synthesis of **5a** and **6a** from **8** and **9** as follows (Scheme 3): (i) after selective protection of the primary hydroxyl groups in **8** and **9** with TBDMSCl in dichloromethane, (ii) the reaction mixture containing silyl ethers **10** and **11** was treated with 1,1-carbonyl bis-1*H*-imidazole (CDI) to afford oxazolidin-2-ones **12** and **13** and then (iii) was treated with 10% hydrochloric acid for desilylation to give the desired oxazolidin-2-ones **5a** and **6a**. In the one-pot procedure, we used CDI for the formation of oxazolidin-2-one rings instead of DSC owing to the low solubility in dichloromethane, and we used hydrochloric acid for desilylation instead of TBAF because desilylation of **12** and **13** with TBAF gave **5a** and **6a** accompanied by undesired by-products.

Absolute configurations of **5a** and **6a** were deduced by a comparison of the ^1H NMR chemical shift values of the 1-(1-naphthyl)ethyl moieties based on the empirical rule[8] that methyl protons of (4*S*,α*S*)-3-(α-methylbenzyl)-4-phenyloxazolidin-2-one derivatives **14**[8] absorb at a higher field (1.16–1.22 ppm) than the corresponding



Scheme 2. Stepwise synthesis of the precursors of cytoxazones. Reagents and conditions: (a) **2**, **3**, EtOH, reflux, three days (50%); (b) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 5 h; (c) DSC, Et_3N, MeCN, rt, 6 h (66% from **8** and **9**); (d) TBAF, THF, rt, 63 h and SiO_2 column chromatography (**5a**; 59%, **6a**; 26%).



Scheme 3. One-pot synthesis of the precursors and removal of the 1-naphthylethyl group. Reagents and conditions: (a) (i) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 30 h, (ii) CDI, rt, four days, (iii) aq HCl 23 h and SiO_2 column chromatography (**5a**; 29%, **6a**; 16 %); (b) MsOH, anisole, $MeNO_2$, 50 °C, 6 h [(−)-**1**; 90%, (+)-**1**; 86%].

protons of (4*S*,α*R*)-derivatives **15**[8] (1.75–1.84 ppm), and the benzylic proton of **14** absorbs at a lower field (5.27–5.35 ppm) than that of **15** (4.48–4.55 ppm) (Fig. 3). We found identical ^{1}H NMR spectral characters between the oxazolidin-2-ones **5a** and **6a**. The C-methyl protons of **5a** absorb at a higher field (1.34 ppm) compared to those of **6a** (1.86 ppm), and the benzylic-type proton (NC*H*Me) of **5a** absorbs at a lower field (5.88 ppm) compared to that of **6a** (5.68 ppm). Therefore, we predicted that the relative configuration of **5a** would be identical to that of **14**. After removal of the 1-naphthylethyl groups of **5a** and **6a**, we confirmed that this deduction was correct.

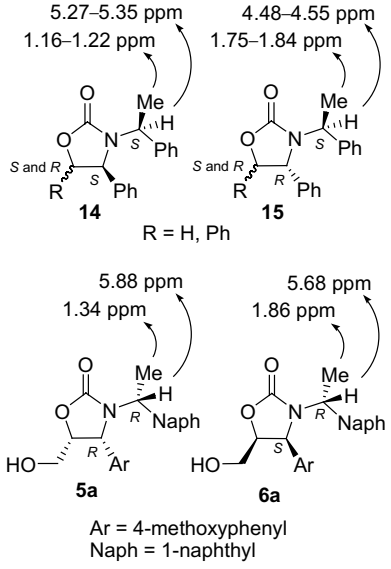


Figure 3. Relationships of shift values on ^{1}H NMR (in $CDCl_3$).

The respective 1-naphthylethyl groups in **5a** and **6a** were removed with MsOH and anisole[7,8] in nitromethane to afford (−)-cytoxazone (−)-**1** and (+)-cytoxazone (+)-**1** in good yield (Scheme 3). We used here nitromethane as a solvent because nitromethane is a good solvent for cationic reactions.[14] The absolute stereochemistry was determined by a comparison of the reported specific rotation.[1]

3. Conclusions

In conclusion, the synthesis of (−)- and (+)-cytoxazones, (−)- and (+)-**1**, respectively, has been conveniently achieved using a five-step synthesis via the Petasis reaction to give a mixture of **8** and **9**, separation of the diastereomers **5a** and **6a** using silica gel column chromatography and the acidic removal of 1-naphthylethyl groups. The diastereomers of **5a** and **6a** have been synthesized from **8** and **9** by a stepwise procedure (**5a**, 39%; **6a**, 17%) or by a one-pot procedure (**5a**, 29%; **6a**, 16%). The overall yields of (−)-**1** and (+)-**1** by the one-pot procedure from the starting material, 4-methoxyphenylboronic acid **3**, were 13% and 6.9%, respectively. Considering the one-pot procedure, this is the shortest route to (−)-**1** from commercially available starting materials. Some phenylboronic acid derivatives, including *m*-methoxy-, *p*-fluoro-, *p*-bromo- and *p*-vinylphenylboronic acids, as well as other heterocyclic boronic acids, are applied for the Petasis reaction.[15] Therefore, various cytoxazone derivatives can be prepared using this procedure.

4. Experimental

All commercially available materials were used without further purification. Melting points were measured with Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were obtained with JEOL JNM-GSX400 (^{1}H NMR: 400 MHz and ^{13}C NMR: 100 MHz) and JEOL JMS-DX302 (^{1}H NMR: 300 MHz, for a mixture of **8** and **9**) spectrometers using tetramethylsilane as an internal standard. MS and high-resolution MS (HR-MS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck). Determination of the enantiomeric purities were performed using CHIRALCEL OD (250 × 4.6 mm) in hexane/2-propanol (3:1) for (−)-**1** and (+)-**1**, flow rate 0.5 mL/min (retention time, (−)-**1**: 27.5 min, (+)-**1**: 40.7 min).

4.1. The Petasis reaction giving 8 and 9

DL-Glyceraldehyde dimer (652 mg, 3.62 mmol) was dissolved in ethanol (16.5 mL), and (*R*)-1-(1-naphthyl)ethylamine **7** (1.24 g, 7.24 mmol) and 4-methoxy-phenylboronic acid **3** (1.00 g, 6.58 mmol) were added to this solution. The mixture was refluxed vigorously for three days (bath temperature: 100 °C). After being cooled to room temperature, the dark brown reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, and the mixture washed with saturated aqueous sodium hydrogen carbonate. The aqueous layer was then extracted twice with ethyl acetate. The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (chloroform) to give a mixture of (2*R*,3*R*)- and (2*S*,3*S*)-3-(4-methoxyphenyl)-3-[(*R*)-1-(1-naphthyl)ethylamino]propane-1,2-diols, **8** and **9**, respectively (1.16 g, 50%, diastereomeric ratio: major/minor, 53:47). R_f = 0.35 ($CHCl_3$/MeOH, 9:1). This

mixture was used in the next reaction without further separation. Characteristic signals of ^{1}H NMR spectrum (300 MHz, $CDCl_3$) δ (major): 1.52 (3H, d, $J = 6.6$ Hz, Me), δ (minor): 1.43 (3H, d, $J = 6.6$ Hz, Me).

4.2. One-pot silylation, cyclization and desilylation giving 5a and 6a from 8 and 9

tert-Butyldimethylchlorosilane (115 mg, 0.76 mmol) was added to a mixture of **8** and **9** (223 mg, 0.64 mmol), triethylamine (96 mg, 0.95 mmol) and DMAP (7.3 mg, 60 μmol) in dichloromethane (6.4 mL). After the mixture was stirred at room temperature for 30 h, 1,1-carbonyl bis-1*H*-imidazole (CDI) (208 mg, 1.28 mmol) was added portionwise to the mixture. After being stirred for four days at room temperature, dichloromethane (15 mL) and 6 M hydrochloric acid (20 mL) were added to the mixture, and the resulting mixture stirred for 23 h at room temperature. The reaction mixture was then extracted three times with dichloromethane. The extracts were combined, dried over magnesium sulfate and concentrated in vacuo. The residue (257 mg) was chromatographed on silica gel (hexane/ethyl acetate, 4:1) to give **5a** (70.0 mg, 29%) and **6a** (38.5 mg, 16%).

4.2.1. (4*R*,5*R*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-3-[(*R*)-1-(1-naphthyl)ethyl]oxazolidin-2-one 5a. $R_f = 0.20$ (hexane/ethyl acetate, 1:1). Colorless needles, mp 169–170 °C. $[\alpha]_D^{30} = -104.9$ (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, d, $J = 8.1$ Hz, Ar), 7.88 (1H, d, $J = 7.8$ Hz, Ar), 7.84 (1H, d, $J = 8.1$ Hz, Ar), 7.49–7.57 (2H, m, Ar), 7.38 (1H, t, $J = 7.6$ Hz, Ar), 7.30 (1H, br s, Ar), 7.14 (1H, d, $J = 6.8$ Hz, Ar), 6.65–7.00 (2H, br m, Ar), 6.40–6.65 (1H, br s, Ar), 5.88 (1H, q, $J = 6.8$ Hz, ArC*H*), 4.27–4.32 (1H, m, OC*H*CH_2OH), 3.81 (3H, s, OMe), 3.77 (1H, d, $J = 8.4$ Hz, C*H*Ar), 3.36 (1H, dd, $J = 11.9$, 8.0 Hz, HOC*H*H), 3.00 (1H, dd, $J = 11.9$, 4.4 Hz, HOCH*H*), 1.34 (3H, d, $J = 6.8$ Hz, Me). ^{13}C NMR ($CDCl_3$) δ: 159.7, 157.1, 133.7, 133.6, 131.3, 128.9, 128.8, 127.7, 127.0, 125.9, 124.5, 124.4, 122,6, 113.9, 82.4, 78.7, 61.5, 59.0, 55.2, 49.2, 18.4. IR ($CHCl_3$) cm^{-1}: 1770, 1610, 1550, 1400, 1250, 1030. MS (FAB) (glycerol) *m*/*z*: 378 [$(M+1)^+$]. HRMS (FAB) (glycerol) calcd for $C_{23}H_{24}NO_4$ (M+1): 378.1705. Found: 378.1702.

4.2.2. (4*S*,5*S*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-3-[(*R*)-1-(1-naphthyl)ethyl]oxazolidin-2-one 6a. $R_f = 0.12$ (hexane/ethyl acetate, 1:1). Colorless amorphous solid. $[\alpha]_D^{31} = +7.6$ (*c* 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 8.07 (1H, d, $J = 8.4$ Hz, Ar), 7.67 (1H, d, $J = 8.0$ Hz, Ar), 7.54 (1H, d, $J = 8.4$ Hz, Ar), 7.36–7.48 (3H, m, Ar), 7.17–7.21 (1H, m, Ar), 6.54 (2H, br d, $J = 7.2$ Hz, Ar), 6.30 (2H, br s, Ar), 5.68 (1H, q, $J = 6.8$ Hz, ArC*H*), 4.66 (2H, m, OC*H*CH_2OH and NC*H*Ar), 3.62 (3H, s, OMe), 3.32–3.37 (1H, m, HOC*H*H), 3.05–3.09 (1H, m, HOCH*H*), 1.86 (3H, d, $J = 7.2$ Hz, Me). ^{13}C NMR ($CDCl_3$) δ: 158.8, 157.3, 134.8, 133.3, 131.3, 128.3, 126.2, 125.7, 125.4, 124.6, 124.1, 123.1, 112.9, 78.2, 61.9, 59.4, 55.1, 49.0, 17.9. IR ($CHCl_3$) cm^{-1}: 1740, 1610, 1260, 1030. MS (FAB) (glycerol) *m*/*z*: 378 [$(M+1)^+$]. HRMS (FAB) (glycerol) calcd for $C_{23}H_{24}NO_4$ (M+1): 378.1705. Found: 378.1708.

4.3. Removal of the 1-(1-naphthyl)ethyl groups

Methanesulfonic acid (257 mg, 2.30 mmol) and anisole (129 mg, 1.15 mmol) were added to a stirred solution of **5a** (86.2 mg, 0.23 mmol) in nitromethane (2.3 mL), and the mixture stirred for 6 h at 50 °C. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted twice with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, and concentrated in vacuo. The residue (139 mg) was purified with silica gel column chromatography (chloroform) to give a pure (−)-**1** (46.0 mg, 90%, >98% ee) as colorless needles.

4.3.1. (−)-Cytoxazone, (4*R*,5*R*)-hydroxymethyl-(4-methoxyphenyl)oxazolidin-2-one (−)-1. Mp 115–116 °C. $[\alpha]_D^{26} = -70.9$ (*c* 0.87, MeOH) {Ref. 1 $[\alpha]_D^{23} = -71$ (*c* 0.100, MeOH)}. ^{1}H NMR (DMSO-d_6) δ: 8.00 (1H, s, NH), 7.14 (2H, d, $J = 8.4$ Hz, Ar), 6.92 (2H, d, $J = 8.8$ Hz, Ar), 4.89 (1H, d, $J = 8.4$ Hz, NC*H*Ar), 4.80 (1H, t, $J = 3.2$ Hz, OH), 4.66–4.71 (1H, m, OC*H*CH_2OH), 3.74 (3H, s, OMe), 2.94–2.97 (2H, m, $COCH_2$). ^{13}C NMR (DMSO-d_6) δ: 158.7 (C=O), 158.4 (Ar, C), 129.0 (Ar, C), 127.7 (Ar, CH × 2), 113.4 (Ar, CH × 2), 79.9 (OCH), 61.0 (CH_2), 56.1 (NHCH), 55.0 (OMe). MS (FAB) (glycerol) *m*/*z*: 224 [$(M+1)^+$]. HRMS (FAB) (glycerol) calcd for $C_{11}H_{14}NO_4$ (M+1): 224.0923. Found: 224.0915.

4.3.2. (+)-Cytoxazone, (4*S*,5*S*)-hydroxymethyl-(4-methoxyphenyl)oxazolidin-2-one (+)-1. According to the method described above, (+)-**1** (35.4 mg, 86%, >98% ee) was synthesized from **6a** (69.4 mg, 0.18 mmol). $[\alpha]_D^{26} = +70.9$ (*c* 0.7, CH_3OH). ^{1}H NMR spectrum was in good agreement with that of (−)-**1**.

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