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Stereoselective synthesis of (–)-cytoxazone†

A. Madhan, A. Ravi Kumar and B. Venkateswara Rao*

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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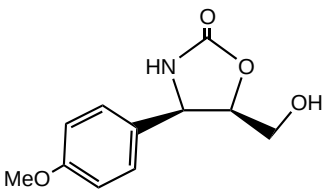
Abstract—A novel stereoselective synthesis of (–)-cytoxazone **1** was achieved via addition of *p*-methoxyphenylmagnesium bromide to the benzylimine derived from (*S*)-2,3-*O*-isopropylidene glyceraldehyde followed by one-step regioselective cyclization of *N*-Boc amino diol **7**. © 2001 Published by Elsevier Science Ltd.

1. Introduction



(-)-Cytoxazone 1

Cytoxazone **1**, a novel 4,5-disubstituted-2-oxazolidinone compound isolated[1] from *Streptomyces* species, has shown cytokine modulating activity.[2] It interferes with cytokine IL4, IL10 and IgG production by selective inhibition of the signalling pathway of Th2 cells, but not Th1 cells.

Inhibitors of Th2-dependent cytokine production have potential as potent chemotherapeutic agents in the field of immunotherapy. Cytoxazone **1** is different from known immunomodulators such as FK 506 and rapamycin in respect of structure and biological activity. As such, **1** should be a useful tool for understanding signalling pathways in Th2 cells. Therefore, the synthesis of cytoxazone is of interest for the development of new cytokine modulators. Nakata et al.[3] established the absolute configuration of the molecule by its total synthesis. Two more syntheses[4] of **1** were also published. Herein, we report a stereoselective synthesis of **1** via stereoselective Grignard addition of *p*-methoxyphenylmagnesium bromide to *N*-benzylimine derived from (*S*)-2,3-*O*-isopropylidene glyceraldehyde **2**, based on an efficient and highly diastereoselective approach developed by Cativiela et al.,[5b] followed by a single step regioselective conversion of the *N*-BOC amino diol **7** to afford the oxazolidinone (Scheme 1).[6]

2. Results and discussion

In the approach of Cativiela et al., the benzylimine derived from (*R*)-2,3-*O*-isopropylidine glyceraldehyde was treated with PhMgBr to give a benzylamine derivative having *erythro* configuration (*anti* product) with high diastereoselectivity.[5b] Based on this protocol, treatment of (*S*)-2,3-*O*-isopropylidine glyceraldehyde **2**[7] with benzylamine in ether gave imine **3**, which on addition to *p*-methoxyphenylmagnesium bromide solution gave **4**. The amine functionality in **4** was protected as its *N*-Boc derivative to give **5** (the overall yield starting from (*S*)-2,3-*O*-isopropylidine glyceraldehyde is 20%). Hydrolysis of the isopropylidine moiety yielded **6**, which on hydrogenation resulted in the formation of **7**. The next step in the sequence is the formation of oxazolidinone. The *N*-Boc protective group was advantageously utilised for the formation of the oxazolidinone ring, which avoided the protection and deprotection of the primary hydroxyl group unlike other syntheses.[3,4b] Thus, compound **7** on exposure to NaH/THF cyclised regioselectively to cytoxazone **1**, whose NMR spectral data was in agreement with reported values.[3,4]

* Corresponding author. Fax: +91-40-7170512; e-mail: venky@iict.ap.nic.in

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3. Conclusion

In conclusion, we have developed a short and efficient synthesis of (−)-cytoxazone **1** which involves the stereoselective addition of *p*-methoxyphenylmagnesium bromide to the benzylimine of (*S*)-2,3-*O*-isopropylidine glyceraldehyde **2** and the subsequent regioselective cyclization of *N*-Boc amino diol **7** to give the oxazolidinone unit of **1**.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F_{254} plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixtures as eluents. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. In the case of syrups and liquids, IR spectra were recorded by adding a drop of solution of compound in chloroform on a KBr pellet. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on Varian Gemini-200 MHz spectrometer. Optical rotations were measured with a Jasco-Dip-360 digital polarimeter. The mass spectra were recorded on a VG MICROMASS-7070H at 70 eV using a direct inlet system. FABMS were recorded on a VG AUTOSPEC at 70 eV using a direct inlet system.

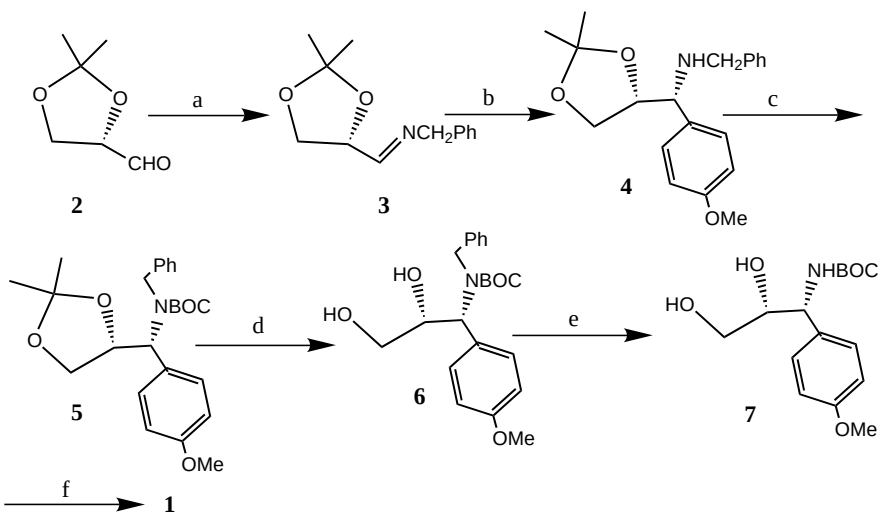
4.1. (2*R*,3*R*)-3-Benzylamino-1,2-*O*-isopropylidene-3-(4-methoxyphenyl)-1,2-propanediol 4

To a solution of benzylamine (1.8 mL, 16.4 mmol) in dry ether (10 mL) was added (*S*)-2,3-*O*-isopropylidene glyceraldehyde **2** (1.4 g, 10.7 mmol) in dry ether (10 mL) at 0°C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was carried to the next step without further purification.

To a suspension of magnesium (0.78 g, 32.1 mmol) in dry ether (25 mL) was added dibromoethane (0.1 mL) followed by slow addition of *p*-bromoanisole (1.8 mL, 14.4 mmol) at 0°C and stirred for 45 min. To the reaction mixture was added slowly the imine **3** in dry ether and stirred at room temperature overnight. The mixture was poured into a saturated ammonium chloride solution and extracted with ether (80 mL). The combined organic layers were dried (Na_2SO_4), concentrated in the rotavapor and the residue was passed through a silica gel column using 3% ethyl acetate in hexane to give **4** as a thick syrup (1 g).[8] $[\alpha]_D^{25} = -42.4$ ($c = 1$, $CHCl_3$); IR: 2984, 1611, 1511, 1455, 1370, 1246, 1177, 1036 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.38 (s, 3H), 3.50 (d, 1H, $J = 14$ Hz), 3.72–3.78 (m, 2H), 3.80 (s, 3H), 3.85 (d, 1H, $J = 4$ Hz), 4.00 (dd, 1H, $J = 8$ Hz), 4.15–4.25 (m, 1H), 6.85 (d, 2H, $J = 8$ Hz), 7.15–7.35 (m, 7H); FABMS (m/z): 328 $(M+H)^+$, 270, 240, 226; FAB-HRMS: calcd for $(M^+ + 1)$ $C_{20}H_{26}O_3N$: 328.191269, found: 328.192409.

4.2. (2*R*,3*R*)-3-Benzylamino-*N*-*tert*-butoxycarbonyl-1,2-*O*-isopropylidene-3-(4-methoxyphenyl)-1,2-propanediol 5

To a solution of compound **4** (0.6 g, 1.8 mmol) in ethanol (20 mL) were added di-*tert*-butyl dicarbonate (1.20 g, 5.5 mmol) and triethylamine (0.76 mL, 3.0 mmol) and the mixture was stirred for 24 h. The reaction mixture was concentrated on a rotavapor and purified by silica gel chromatography using ethyl acetate and hexane (2:98) to give **5** as a syrup (0.55 g,



a) $PhCH_2NH_2$, dry ether, 0°C, b) MeO–⟨⟩–MgBr, dry ether, c) $(BOC)_2O$,Et_3N, dry ethanol

d) PTSA (cat), methanol, e) Pd/C (cat), conc.HCl (a drop), ethanol, f) NaH, dry THF

Scheme 1.

overall yield for three steps 20.1%). $[\alpha]_D^{25}=-37.1$ ($c=1$, $CHCl_3$); IR: 1693, 1613, 1513, 1397, 1370, 1267, 1219, 1155, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.22–1.28 (2s, 6H), 1.45 (br s, 9H), 3.45–3.78 (br m, 2H), 3.80 (s, 3H), 4.0 (br d, 1H, $J=14$ Hz), 4.20–4.60 (br m, 2H), 4.85–5.18 (br s, 1H), 6.85 (d, 2H, $J=8$ Hz), 7.0–7.40 (m, 7H); FABMS (m/z): 428 (M^++1); FAB-HRMS: calcd for (M^++1) $C_{25}H_{34}O_5N$: 428.243699, found: 428.243568.

4.3. (2*R*,3*R*)-3-Benzylamino-*N*-*tert*-butoxycarbonyl-3-(4-methoxyphenyl)-1,2-propanediol 6

To a solution of compound **5** (0.45 g, 1.05 mmol) in methanol (10 mL) was added *p*-toluenesulphonic acid (0.016 g, 0.08 mmol), and the mixture was stirred for 3 h at room temperature. The reaction mixture was concentrated and purified through column chromatography using ethyl acetate:hexane (1:1) to give **6** as a colorless oil (0.33 g, 81%). $[\alpha]_D^{25}=-29.3$ ($c=1$, $CHCl_3$); IR: 3390, 2976, 2933, 1682, 1612, 1514, 1455, 1407, 1366, 1251, 1163, 1035; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.70 (br s, 1H), 3.22 (br s, 1H), 3.4–3.6 (br m, 2H), 3.8 (s, 3H), 3.82–4.0 (m, 2H), 4.30 (br d, 1H, $J=14$ Hz), 5.0 (br d, 1H, $J=7$ Hz), 6.82 (d, 2H, $J=8$ Hz), 7.0 (m, 2H), 7.18–7.38 (m, 5H); FABMS (m/z); 388 (M+H) FAB-HRMS: calcd for (M^++1) $C_{22}O_5H_{30}N$: 388.212398, found: 388.212324.

4.4. (2*R*,3*R*)-3-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)-1,2-propanediol 7

To a solution of compound **6** (0.150 g, 0.38 mmol) in ethanol (5 mL) was added 10% Pd/C (0.028 g) and conc. HCl (one drop) and hydrogenated at room temperature under stirring. After 15 h the reaction mixture was concentrated and purified by column chromatography using ethyl acetate:hexane (6:4) to give **7** as a white solid (0.073 g, 63%); mp: 118°C; $[\alpha]_D^{25}=-51.2$ ($c=1$ in $CHCl_3$); IR (KBr): 3384, 2927, 1689, 1511, 1366, 1247, 1169, 1033, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.42 (s, 9H), 2.38 (br s, 1H), 2.95 (br s, 1H), 3.62–3.7 (br m, 2H), 3.70–3.8 (m, 1H), 3.80 (s, 3H), 4.60 (dd, 1H, $J=7$ Hz), 5.02 (br d, 1H, $J=7$ Hz), 6.88 (d, 2H, $J=8$ Hz), 7.22 (d, 2H, $J=8$ Hz); FABMS (m/z): 320 $(M+Na)^+$.

4.5. (4*R*,5*R*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-2-oxazolidinone 1

To a solution of **7** (0.061 g, 0.2 mmol) in dry THF (8 mL) was added sodium hydride (0.009 g (60% w/w in wax), 2.4 mmol) at room temperature and the mixture was stirred under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated, dichloromethane was added, washed with NH_4Cl (saturated), the organic layer was separated, concentrated and purified through column chromatography using ethyl acetate:hexane (6:4) to give **1** as a white solid (0.043 g, 94%); mp 118–120°C (lit.[1] mp 118–121°C); $[\alpha]_D^{25}=-69.7$ ($c=0.5$ in MeOH); lit.[2] $[\alpha]_D^{23}$ −71.0 ($c=0.1$, MeOH); IR (KBr): 3228, 1711, 1394, 1236, 1041, 766, 450 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.78 (m, 1H), 4.84 (t, 1H, $J=5$ Hz), 4.90 (d, 1H, $J=8$ Hz), 6.93 (d, 2H, $J=8.6$ Hz), 7.15 (d, 2H, $J=8.6$ Hz), 8.03 (br s, 1H); ^{13}C NMR (acetone-d_6+acetone, 50 MHz): δ 160.27, 159.22, 129.86, 128.62, 114.23, 81.11, 62.17, 57.48, 55.19; EIMS (m/z): 223 $(M)^+$; FAB-HRMS: calcd for (M^++1) $C_{11}O_4H_{14}N$: 224.092283, found: 224.091146.

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7. Compound **2** was prepared by sodium periodate cleavage of 1,2-*O*-isopropylidene-1,2,3,4-tetrol, which in turn was prepared from ascorbic acid. See the following references and references cited therein: (a) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc*. **1980**, *102*, 6304; (b) Abushnab, E.; Venishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D.C.-J.; Saibaba, R.; Panzica, P. *J. Org. Chem*. **1988**, *53*, 2598.
8. TLC indicated a minor impurity having a very close R_f value to the desired product. Therefore a small portion of the product was purified by preparative TLC for clear spectral analysis and the product was used in the next step 'as is'.