Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 65–68

# Enantioselective synthesis of (−)-cytoxazone and (+)-*epi*-cytoxazone via Rh-catalyzed diastereoselective oxidative C–H aminations

Srinivasarao V. Narina, Talluri Siva Kumar, Shyla George and Arumugam Sudalai*

*Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India*

Received 10 September 2006; revised 27 October 2006; accepted 2 November 2006
Available online 21 November 2006

**Abstract**—An efficient enantioselective synthesis of (−)-cytoxazone (**1**) and (+)-*epi*-cytoxazone (**2**) using proline-catalyzed asymmetric α-amino-oxylation of aldehydes followed by Rh-catalyzed diastereoselective oxidative C–H amination as the key steps is described. *syn* or *anti* 1,2-aminoalcohols were obtained by Rh-catalyzed intramolecular amidation of the C–H bonds of carbamates or sulfamate esters with good to excellent diastereoselectivity.


(−)-Cytoxazone **1**, containing a novel 4,5-disubstituted-2-oxazolidinone moiety, was isolated[1] from *Streptomyces* sp., and its absolute configuration was unambiguously established by asymmetric synthesis.[2] It exhibits cytokine-modulating activity by inhibiting the signalling pathway of Th2 cells. Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Since Th2 cells play a major role in mediating the immune response to allergens, (−)-cytoxazone **1** could be a useful lead compound for the development of therapeutic agents for atopic dermatitis and asthma. Due to its potential bioactivity and the simple structure, several methods of syntheses of (−)-cytoxazone (**1**) have been accomplished.[3] The synthesis of (+)-*epi*-cytoxazone (**2**) and the stereoisomer of (−)-cytoxazone (**1**) has also been reported.[4] The synthetic precursors of (−)-cytoxazone and (+)-*epi*-cytoxazone are 1,2-aminoalcohols, which have been the subject of thorough synthetic efforts in recent years.[5] Most of the syntheses of cytoxazone described so far have made use of indirect methods to establish the *anti*-amino alcohol functionality. In this letter, we describe an enantioselective synthesis of (−)-cytoxazone (**1**) and (+)-*epi*-cytoxazone (**2**) based on proline-catalyzed asymmetric α-amino-oxylation[6] of aldehydes followed by Rh-catalyzed diastereoselective oxidative C–H amination[7] at the benzylic positions (Fig. 1).

The synthesis of the chiral 1,2-diols **4** and **5**, the key intermediates, in the synthesis of (−)-cytoxazone (**1**) and (+)-*epi*-cytoxazone (**2**), respectively, starts with hydrolytic kinetic resolution (HKR)[8] of the racemic epoxide **3**[9] in the presence of (*R*,*R*)-salen-Co(III)OAc complex to give chiral diol **4** in 44% yield and 98% ee[10] {$[\alpha]_D^{25}$ +12.76 (*c* 2, $CHCl_3$)} and chiral epoxide **6** in 52% yield and 92% ee {$[\alpha]_D^{25}$ +0.74 (*c* 1, $CHCl_3$); lit.[11] $[\alpha]_D^{25}$ +0.8 (*c* 1, $CHCl_3$)}. In order to enhance the optical purity of diol **5**, epoxide **6** (92% ee) was again subjected to hydrolytic kinetic resolution in the presence of (*S*,*S*)-salen-Co(III)OAc complex with 0.95 equiv of water, which resulted in the formation of diol **5** in 92% yield and 98% ee {$[\alpha]_D^{25}$ −12.76 (*c* 2, $CHCl_3$)} (Scheme 1).

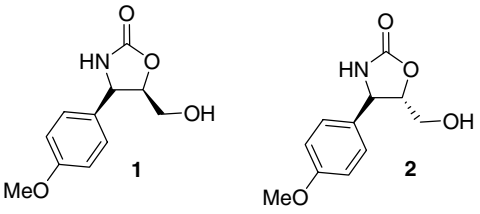
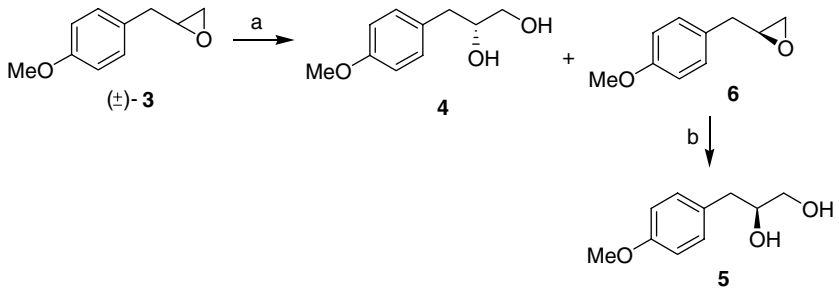



**Figure 1.**

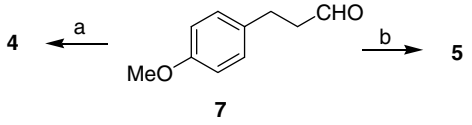
* Corresponding author. Tel.: +91 20 25902174; fax: +91 20 25902676; e-mail: a.sudalai@ncl.res.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.016



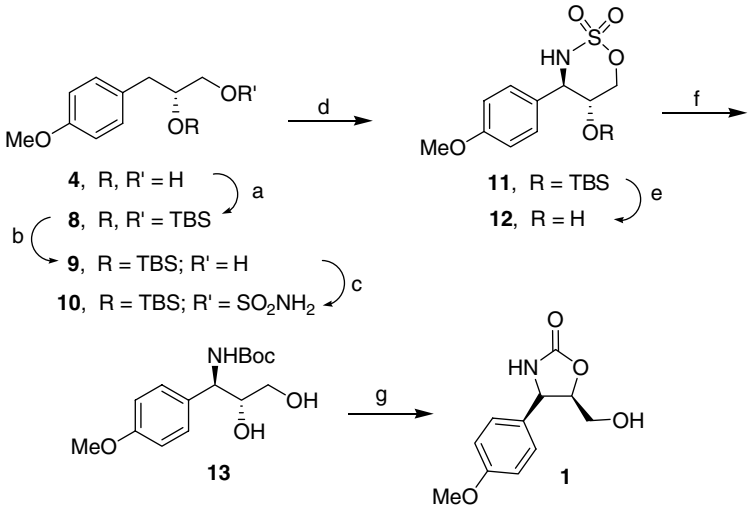

**Scheme 1.** Reagents and conditions: (a) (*R*,*R*)-salen-cobalt(III)OAc (0.5 mol %), THF (0.55 equiv), $H_2O$ (0.45 equiv), 0 °C, 14 h (44%, 98% ee for **4** and 52% and 92% ee for **6**); (b) (*S*,*S*)-salen-cobalt(III)OAc (0.5 mol %), THF (0.95 equiv), $H_2O$ (0.95 equiv), 0 °C, 20 h, 92%, 98% ee.

As HKR generally gives maximum chemical yields up to 50%, we turned our attention to asymmetric α-functionalization[6] of aldehydes by proline, an abundant, inexpensive amino acid available in both enantiomeric forms.[12] Thus, aldehyde **7**[13] was converted into the corresponding chiral diols **4** and **5** by proline-catalyzed asymmetric α-amino-oxylation[6a] in a two-step reaction sequence: (i) the reaction of aldehyde **7** with nitrosobenzene as the oxygen source in the presence of L- or D-proline in $CH_3CN$ at −20 °C, followed by reduction with $NaBH_4$ in MeOH, gave the crude aminoxy alcohol and (ii) subsequent reduction of the crude aminoxy alcohol with 10% Pd/C and $H_2$ (1 atm) gave the chiral diols **4** in 86% yield and 99% ee[10] {$[\alpha]_D^{25}$ +12.90 (*c* 2, $CHCl_3$)} and **5** in 86% yield and 99% ee {$[\alpha]_D^{25}$ −12.90 (*c* 2, $CHCl_3$)}, respectively (Scheme 2).

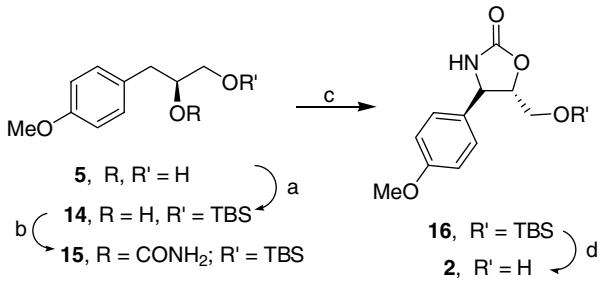



**Scheme 2.** Reagents and conditions: (a) (i) PhNO, L-proline (25 mol %), −20 °C, 24 h, then MeOH, $NaBH_4$; (ii) $H_2$ (1 atm), Pd/C (10%), MeOH, 86% (over two steps); (b) (i) PhNO, D-proline (25 mol %), −20 °C, 24 h, then MeOH, $NaBH_4$; (ii) $H_2$ (1 atm), Pd/C (10%), MeOH, 86% (over two steps).

Having obtained diols **4** and **5** in high enantiomeric purity, the second chiral centre was readily generated by Rh-catalyzed diastereoselective intramolecular C–H amination using either chiral sulfamate or carbamate esters (**10** or **15**) as such methods have proven reliable for the synthesis of amines and amine derivatives.[7] Selectivity for either *syn* or *anti* 1,2-aminoalcohols can be achieved by Rh-catalyzed intramolecular amidation of the C–H bonds of carbamate or sulfamate esters, respectively. Thus, synthesis of (−)-cytoxazone started with bis-TBS-protected silyl ether **8** prepared from **4**. Selective deprotection of the primary OH group in **8** was achieved using camphor sulfonic acid in MeOH[14] to produce alcohol **9** in 95% yield, which was readily converted into sulfamate ester **10** in 76% yield using known conditions ($HCO_2H$, chlorosulfonyl isocyanate, 0 °C).[7b] Sulfamate ester **10** underwent selective γ-C–H insertion in the presence of a catalytic amount of $Rh_2(OAc)_4$ (2 mol %), with $PhI(OAc)_2$ as the oxidant and MgO as the additive in $CH_2Cl_2$ at 40 °C with *anti* (10:1) diastereoselectivity (determined from $^1H$ NMR analysis) to afford the corresponding six-membered ring insertion product **11**[15] in 82% combined yield. The *anti*-diastereomer, oxathiazinane **11**, was readily separated by column chromatography. Deprotection of the TBS group of **11** using camphor sulfonic acid in MeOH furnished alcohol **12** in 97% yield. Carbamoylation[7b]




**Scheme 3.** Reagents and conditions: (a) TBSCl, imidazole, DMF, 25 °C, 4 h, 98%; (b) camphor sulfonic acid, MeOH, 95%; (c) $HCO_2H$, chlorosulfonyl isocyanate, 0 °C, 76%; (d) 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, $CH_2Cl_2$, 40 °C, 82%, *anti*:*syn* (10:1); (e) camphor sulfonic acid, MeOH, 25 °C, 97%; (f) (i) $(Boc)_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, 25 °C; (ii) $CH_3CN$:$H_2O$ (4:3), 60 °C, 84% (over two steps); (g) NaH, THF, 0 °C, 96%.




**Scheme 4.** Reagents and conditions: (a) TBSCl, imidazole, $CH_2Cl_2$, 25 °C, 98%; (b) trichloroacetyl isocyanate, $CH_2Cl_2$, 0–25 °C, 2 h, then $K_2CO_3$, MeOH, $H_2O$, 0–25 °C, 12 h, 92%; (c) 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, $CH_2Cl_2$, 40 °C, 87%, *syn*:*anti* (5.5:1); (d) TBAF, THF, 92%.

of the –NH moiety of oxathiazinane **12** with $Boc_2O$ and $Et_3N$ in $CH_2Cl_2$ followed by ring opening of the crude *N*-Boc protected oxathiazinane[7b] at 60 °C with aq $CH_3CN$ furnished the *anti*-amino alcohol **13** in 84% yield. Finally, regioselective intramolecular cyclization[16] of **13** using NaH in THF at 0 °C furnished (−)-cytoxazone {mp 118–121 °C; $[\alpha]_D^{25}$ −70.3 (*c* 1, MeOH); lit.[1] mp 118–121 °C; $[\alpha]_D^{25}$ −71 (*c* 1, MeOH)} in 96% yield and 99% ee (Scheme 3).

In the case of (+)-*epi*-cytoxazone **2**, protection of the primary alcohol of diol **5** with TBSCl gave the secondary alcohol **14**, which was converted into carbamate **15** in 92% yield using reported conditions (trichloroacetyl isocyanate, $CH_2Cl_2$, then $K_2CO_3$, MeOH, $H_2O$).[7a] Carbamate **15** underwent C–H insertion on treatment with 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$ and MgO in $CH_2Cl_2$ at 40 °C to afford the corresponding oxazolidinone **16**[17] with *syn* diastereoselectivity (5.5:1) (determined from $^1H$ NMR analysis) in 87% combined yield.[7a] The *syn*-diastereomer, oxazolidinone **16**, was readily separated by column chromatography. Finally, deprotection of the TBS group using TBAF in THF furnished (+)-*epi*-cytoxazone {mp 159–160 °C; $[\alpha]_D^{25}$ +28.3 (*c* 1, MeOH); lit.[4c] mp 158–160 °C; $[\alpha]_D^{25}$ +28.6 (*c* 1, MeOH)} in 92% yield and 99% ee (Scheme 4).

In conclusion, the enantioselective syntheses of (−)-cytoxazone **1** and (+)-*epi*-cytoxazone **2** were achieved in fewer steps (36% and 53% overall yields, both 99% ee). The applicability of the two powerful methods, that is, proline catalyzed asymmetric α-amino-oxylation of aldehydes as well as Rh-catalyzed diastereoselective C–H aminations, constitute key steps in the synthesis. The selectivity for *syn*- or *anti*-1,2-aminoalcohol products was achieved by Rh-catalyzed intramolecular amidation of the C–H bonds of carbamates or sulfamate esters with good to excellent diastereoselectivities.

## Acknowledgements

N.V.S., T.S.K. and S.G. thank CSIR, New Delhi, for the award of research fellowships. The authors are thankful to Dr. B. D. Kulkarni, Deputy Director, for his support and encouragement.

## References and notes

1. Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126.
2. (a) Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 4203; (b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.
3. (a) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 5756; (b) Kim, I. S.; Kim, J. D.; Ryu, C. B.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2006**, *62*, 9349; (c) Rozwadowaka, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1749; (d) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4026; (e) Lin, X.; Bentley, P. A.; Xie, H. *Tetrahedron Lett.* **2005**, *46*, 7849; (f) Miyata, O.; Hashimoto, J.; Iba, R.; Naito, T. *Tetrahedron Lett.* **2005**, *46*, 4015; (g) Tokic-Vujosevic, Z.; Petrovic, G.; Rakic, B.; Matovic, R.; Saicic, R. N. *Synth. Commun.* **2005**, *35*, 435; (h) Asano, M.; Nagasawa, C.; Suzuki, M.; Nishiyama, S.; Sugai, T. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 145; (i) Swamy, N. R.; Krishnaiah, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Carbohydr. Chem.* **2004**, *23*, 217; (j) Boruwa, J.; Borah, J. C.; Kalita, B.; Barua, N. C. *Tetrahedron Lett.* **2004**, *45*, 7355; (k) Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893; (l) Sugiyama, S.; Arai, S.; Ishii, K. *Tetrahedron: Asymmetry* **2004**, *15*, 3149; (m) Milicevic, S.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2004**, *45*, 955; (n) Ravi, K. A.; Bhaskar, G.; Madhan, A.; Venkateswara, R. B. *Synth. Commun.* **2003**, *33*, 2907; (o) Carda, M.; Gonzalez, F.; Sanchez, R.; Marco, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1005; (p) Madhan, A.; Kumar, A. R.; Rao, B. V. *Tetrahedron: Asymmetry* **2001**, *12*, 2009; (q) Miyata, O.; Asai, H.; Naito, T. *Synlett* **1999**, 1915.
4. (a) Smitha, G.; Reddy, C. S. *Synth. Commun.* **2006**, *36*, 1795; (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777; (c) Davies, S. G.; Hughes, D. G.; Nicholson, R. L.; Smith, A. D.; Wright, A. J. *Org. Biomol. Chem.* **2004**, *2*, 1549; (d) Carter, P. H.; LaPorte, J. R.; Scherle, P. A.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1237; (e) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett.* **2000**, *41*, 5553.
5. (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561; (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (c) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 243.
6. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673.
7. (a) Bois, J. D.; Espino, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 598; (b) Espino, C. G.; When, P. M.; Chow, J.; Bois, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 6935; (c) Liang, J. L.; Yuan, S. X.; Huang, J. S.; Yu, W. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465; (d) When, P. M.; Lee, J.; Bois, J. D. *Org. Lett.* **2003**, *5*, 4823; (e) He, C.; Cui, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210.
8. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

9. Yli-Kauhaluoma, J. T.; Harwig, C. W.; Wentworth, P., Jr.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 2269.
10. Diol **4** was converted into the corresponding 1,2-benzylidene derivative, which underwent reduction selectively using DIBAL-H to the benzyl protected 1° alcohol, which was converted into the corresponding Mosher's ester.
11. Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1861.
12. For a review of proline-catalyzed asymmetric reactions see: List, B. *Tetrahedron* **2002**, *58*, 5573.
13. Leopold, D.; Fischer, H. *J. Chem. Soc., Perkin Trans. 2* **1992**, 513.
14. Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099.
15. Spectral data for **11**: mp 133–135 °C; $[\alpha]_D^{25}$ +4.0 (*c* 1.1, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.23 (d, 2H, $J = 8.7$ Hz), 6.91 (d, 2H, $J = 8.7$ Hz), 4.62 (d, 1H, $J = 7.6$ Hz), 4.51–4.43 (m, 2H), 4.33 (dd, 1H, $J = 11.3$, 5.3 Hz), 3.97 (m, 1H), 3.81 (s, 3H), 0.07 (s, 9H), −0.12 (s, 3H), −0.53 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 160.1, 137.4, 130.2, 128.9, 128.5, 114.3, 73.4, 67.5, 63.9, 55.4, 25.3, 17.6, −5.1, −5.8; IR ($CHCl_3$) $\nu_{max}$: 3281, 2955, 2931, 2857, 1614, 1518, 1368, 1253, 1193, 1035, 839, 779; elemental analysis: $C_{16}H_{27}NO_5SSi$ requires C, 51.45; H, 7.29; N, 3.75; S, 8.58, found: C, 51.58; H, 7.21; N, 3.67; S, 8.49.
16. Miyata, O.; Asai, H.; Naito, T. *Synlett* **1999**, *12*, 1915.
17. Spectral data for **16**: $[\alpha]_D^{25}$ +19.6 (*c* 0.72, EtOH); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.16 (d, 2H, $J = 8.7$ Hz), 6.81 (d, 2H, $J = 8.7$ Hz), 6.43 (br s, 1H), 5.24 (d, 1H, $J = 4.8$ Hz), 4.60 (m, 1H), 3.78 (s, 3H), 3.08 (dd, 1H, $J = 14.7$, 8.3 Hz), 2.88 (dd, 1H, $J = 14.8$, 5.4 Hz), 0.92 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 159.21, 158.45, 130.12, 128.63, 113.93, 83.02, 78.25, 55.18, 33.68, 25.67, 17.97, −4.36, −4.91; IR ($CHCl_3$) $\nu_{max}$: 780, 838, 1106, 1248, 1514, 1758, 2928, 2954, 3628, 3648; elemental analysis: $C_{17}H_{27}NO_4Si$ requires C, 60.50; H, 8.06; N, 4.15, found: C, 60.59; H, 7.88; N, 4.25.