Pergamon

Tetrahedron Letters 41 (2000) 5553–5556

TETRAHEDRON LETTERS

Synthetic applications of the cyclic iminocarbonate rearrangement: enantioselective syntheses of chloramphenicol and 4-*epi*-cytoxazone

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Received 15 March 2000; revised 22 May 2000; accepted 26 May 2000

Abstract

Chloramphenicol and 4-*epi*-cytoxazone have been enantioselectively synthesized using the asymmetric dihydroxylation and the cyclic iminocarbonate rearrangement as key steps. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: enantioselective synthesis; cyclic iminocarbonate rearrangement; regioselection; chloramphenicol; 4-*epi*-cytoxazone.

Amino alcohol functional groups are often found in many bioactive compounds and their stereoselective synthesis is of interest.[1] Of the enantioselective synthetic strategies for this important class of compounds, particularly effective are those employing powerful catalytic asymmetric oxidation processes such as asymmetric epoxidation (AE),[2] dihydroxylation (AD)[3] and aminohydroxylation (AA).[4]

Each of these strategies has its respective issues to resolve when applied to stereoselective synthesis of amino alcohols. For example, the AA-based strategy, while certainly most straightforward, generally gives access to only one type of regio (β-amino-α-hydroxy) and diastereo (*syn*) isomers.[5] On the other hand, the AE- and AD-based ones need to address an issue of regiocontrol.[6,7] The AD strategy is also more convenient for the synthesis of *anti*-diastereomers than for that of *syn*-isomers, which requires an extra step of stereoinversion.[8]

Our interest in the amino alcohol compounds prompted us to search for a versatile synthetic route to this biologically important functionality, employing the AD process as a key step. In particular, we sought to address the limitations of the current synthetic methods as noted above. As a result, we developed a cyclic iminocarbonate rearrangement process as an efficient means to

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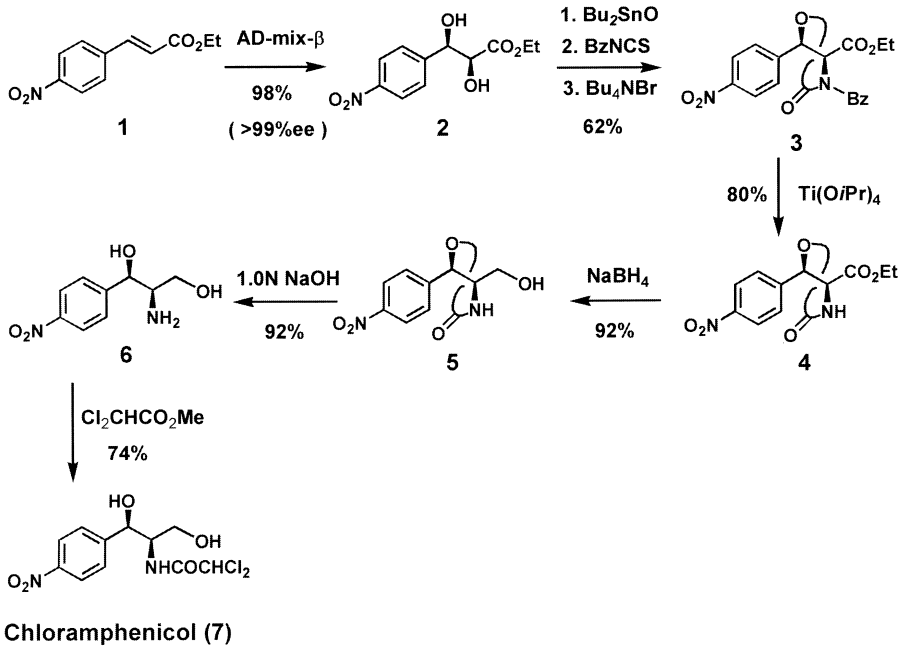
PII: S0040-4039(00)00878-9

converting *syn*-diols to protected *syn*-amino alcohols.[9a] More recently, we reported a new rearrangement protocol, which allows a divergent regiochemical control with cinnamate diol substrates.[9b] Described herein are enantioselective syntheses of chloramphenicol and *epi*-cytoxazone. Each of the two synthetic targets represents a regioisomeric *syn*-β-amino alcohol, and taken together, the two synthetic applications demonstrate a flexibility in regioselection in our cyclic iminocarbonate rearrangement methodology.

Chloramphenicol (**7**), isolated from *Streptomyces venezuela*, was one of the first orally active antibacterial agents and is still in wide use topically.[10] Its structure, containing a *syn*-vicinal amino alcohol functionality with the nitrogen at C-2, is particularly amenable to the original protocol of our cyclic iminocarbonate rearrangement process (Scheme 1).

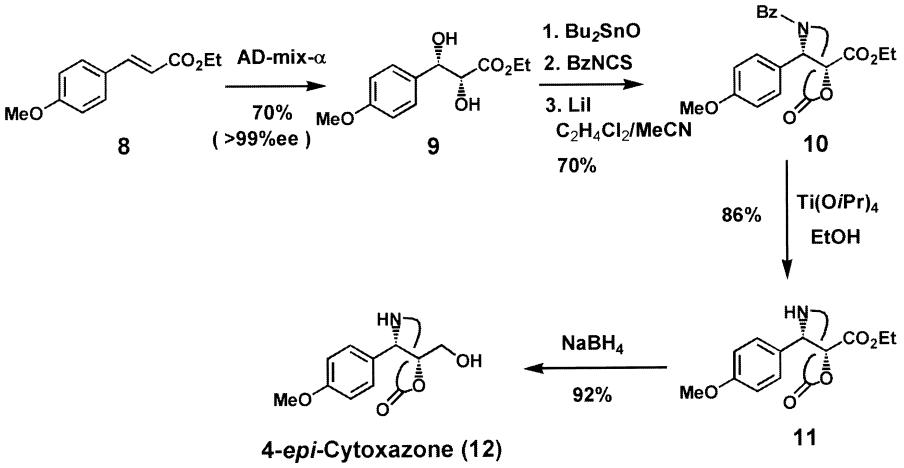


Scheme 1.

Thus, following an AD reaction of the *p*-nitrocinnamate ester (**1**) (AD-mix-β, 98% yield, >99% ee),[8] a $C_2H_4Cl_2$ solution of the resulting (2*S*,3*R*)-diol (**2**) was treated successively with Bu_2SnO (reflux for 24 h with a Dean–Stark removal of water), BzNCS (reflux for 6 h) and finally with Bu_4NBr (10 equiv., reflux for 6 h). This sequence of reactions converts *syn*-diols to protected *syn*-amino alcohols (via cyclic iminocarbonate intermediate) in a one-pot operation, with net retention of configuration at both carbinol carbons. With unsubstituted cinnamate diol substrate, this standard protocol results in a substitution of nitrogen preferentially at the C-2 (2.7:1 regioselectivity).[9a] In the present case, the presence of the electron-withdrawing *p*-nitro group rendered the regiocontrol more strongly for the C-2-nitrogen substitution (8:1 regioselectivity) to give the desired oxazolidinone (**3**) in 62% yield. The remaining functional group transformations were straightforward: debenzoylation under transesterification conditions ($Ti(OiPr)_4$ in ethanol, 80%); ester group reduction ($NaBH_4$, 92%); hydrolysis (1.0N NaOH, 92%); and amidation (Cl_2CHCO_2Me, 74%). Chloramphenicol (**7**) was thus obtained from ethyl *p*-nitrocinnamate in six steps and overall 30% yield (>99% ee).[11]

epi-Cytoxazone (**12**), the diastereomer of the novel cytokine-modulating cytoxazone, has, like chloramphenicol, a *syn*(*threo*)-vicinal-amino alcohol functionality.[12] Unlike the previous synthetic target, however, this compound has a nitrogen function at C-3, which calls for a reversal of the regioselection during the cyclic iminocarbonate rearrangement process.

The (2*R*,3*S*)-diol (**9**) was prepared from *p*-methoxycinnamate ethyl ester (**8**) using AD-mix-α (70%, >99% ee)[11] (Scheme 2). Following the standard protocol of the cyclic iminocarbonate rearrangement (Bu_2SnO; BzNCS; Bu_4NBr), a slight preference for the C-2-nitrogen regioisomer has generally been observed with cinnamate diol substrates.[9a] Replacing Bu_4NBr with LiI and performing the reaction in acetonitrile/$C_2H_4Cl_2$, on the other hand, a reversal of the regioselection has been noted.[9b] In the present case, the electron-donating *p*-methoxy-group in substrate **9** effected a slight preference for the C-3-nitrogen regioisomer (1.7:1 regioselectivity) under the Bu_4NBr reaction conditions. When the diol **9** was subjected to the LiI/MeCN/$C_2H_4Cl_2$ protocol [Bu_2SnO in $C_2H_4Cl_2$, reflux under Dean–Stark for 4 h; BzNCS, reflux for 2 h; LiI (0.2 equiv.) in dry MeCN (total solvent MeCN:$C_2H_4Cl_2$ 1:1 v/v), reflux for 2 h], a complete regioselection resulted for the desired C-3-nitrogen isomer (**10**, 70%). The remaining functional group transformations proceeded eventlessly (debenzoylation with Ti(O*i*Pr)$_4$ in ethanol, 86%; ester group reduction with $NaBH_4$, 92%). 4-*epi*-Cytoxazone (**12**) was thus prepared from ethyl *p*-methoxycinnamate in four steps and overall 39% yield (>98% ee).[11]



Scheme 2.

The two syntheses reported herein represent an efficient and versatile synthetic route for amino alcohol compounds and demonstrate the synthetic utility of the cyclic iminocarbonate rearrangement process. In particular, the two issues in the current AD-based synthetic applications, namely regio- and diastereo-control, have been deftly dealt with.

Acknowledgements

This work was supported by the MOST through the National R&D Program for Women's Universities (Project No. 99-N6-01-01-A-08), and by the KOSEF (1999-2-122-002-4). J.N.P. is grateful to the Brain Korea 21 project for a graduate fellowship.

References

1. (a) *Enantioselective Synthesis of β-amino Acids*; Ojima, I., Ed.; VCD Publishers: New York, 1996, and references cited therein. (b) Cole, D. C. *Tetrahedron* **199**4, *50*, 9517. (c) Juraristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (d) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev*. **1996**, *25*, 117.
2. For a review, see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. Catalytic asymmetric epoxidation of allylic alcohols. VCD Publishers: New York, 1993; pp. 103–158.
3. For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.
4. For a review, see: O'Brien, P. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 326.
5. *cf*. A reversal of regioselection in the AA process has been reported. See: (a) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett*. **1998**, *39*, 2507. (b) Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett*. **1999**, *1*, 1949.
6. The diastereocontrol is achieved in the AE-based strategy by using *cis*/*trans*-epoxy alcohol substrates; the regiocontrol requires a C-2/C-3 regioselective ring-opening of the epoxy alcohols with a nitrogen nucleophile.
7. In 2,3-*syn*-dihydroxy esters, the α-hydroxyl group is selectively converted to a leaving group (sulfonate), which allows an introduction of a nitrogen functionality there (at C-2). See Ref. 3 and: Fleming, P. R.; Sharpless, K. B. *J. Org. Chem*. **1991**, *56*, 2869.
8. *anti*-Diols, potentially more straightforward diol precursors for *syn*-amino alcohols, are not directly accessible via AD as (*Z*)-disubstituted alkenes are generally poor substrates in this process. *cf*. Ko, S. Y.; Malik, M.; Dickinson, A. F. *J. Org. Chem*. **1994**, *59*, 2570.
9. (a) Cho, G. Y.; Ko, S. Y. *J. Org. Chem*. **1999**, *64*, 8745. (b) Cho, G. Y.; Park, J. N.; Ko, S. Y. *Tetrahedron Lett*. **2000**, *41*, 1789.
10. Lednicer, D. *Strategies for Organic Drug Synthesis and Design*; John Wiley & Sons, 1998.
11. The optical purity was determined using chiral HPLC (Pirkle or Chiralcel OD column).
12. (a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot*. **1998**, *51*, 1126. (b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.-i.; Kobayashi, K.; Osada, H. *J. Org. Chem*. **1999**, *64*, 1052. (c) Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. *Tetrahedron Lett*. **1999**, *40*, 4203. (d) Miyata, O.; Asai, H.; Naito, T. *Synlett* **1999**, *12*, 1915.