A Novel Example for Optical Resolution of Racemic Ketones Originating from Batrachotoxin Synthesis

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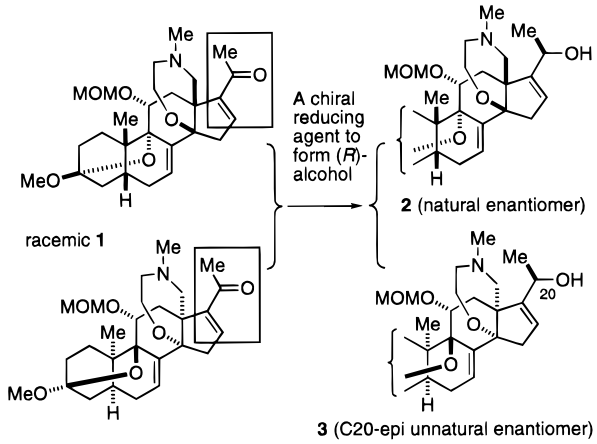
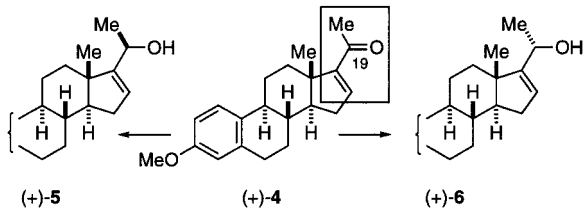
In a recent paper,[1] we reported a total synthesis of (±)-batrachotoxinin A from (±)-Wieland−Miescher diketone. Since both (+)- and (−)-Wieland−Miescher diketones are available through proline-based asymmetric cyclization,[2] the total synthesis reported could provide batrachotoxinin A and batrachotoxin in both natural and unnatural enantiomeric forms. We recognized, however, the intriguing possibility that an optical resolution of racemic methyl ketone **1** could be achieved via asymmetric reduction. Provided with a chiral reducing agent that recognizes the boxed portion of the molecule perfectly but ignores the remaining portion completely, one would expect asymmetic reduction of **1** to yield a 1:1 mixture of optically pure **2** and **3**.



To test the feasibility of this approach, we first studied the oxazaborolidine-catalyzed reduction (widely known as the CBS reduction)[3] of optically active ketone **4**[4] derived from commercially available (+)-estrone. Treatment of (+)-**4** with BH_3·SMe_2 in the presence of an equimolar amount of (*S*)-*B*-Me CBS (purchased from Strem Chemical) at −45 °C for 30 min furnished (*R*)-alcohol (+)-**5** in 95% yield without contamination of its C19 diastereomer (Scheme 1). After acetylation, the C19 stereochemistry was established by X-ray crystallographic analysis.[5] In contrast, the reduction of (+)-**4** with (*R*)-*B*-Me CBS (purchased from Strem Chemical) provided (*S*)-alcohol (+)-**6** in greater than 99% de. It is worth noting that (+)-**6** was cleanly converted into (+)-**5** via a Mitsunobu reaction (DEAD/Ph_3P/*m*-ClPhCO_2H/PhH/rt)[6]

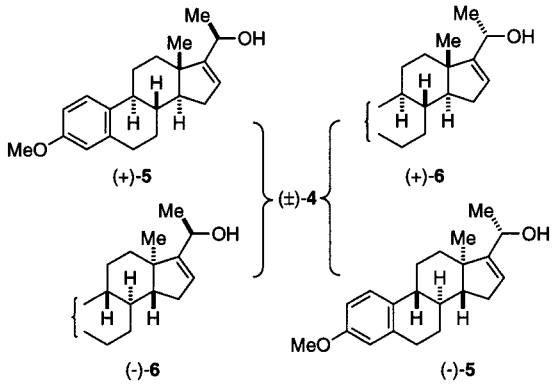
Scheme 1



followed by NaOMe/MeOH treatment or Dess−Martin oxidation[7] followed by CBS reduction.

These two asymmetric reductions have unambiguously demonstrated the feasibility of this approach. To demonstrate its practicality experimentally, we synthesized racemic **4**[4,8] and examined its CBS reduction (Scheme 2). As expected, the CBS reduction with (*S*)-oxazaborolidine gave a 1:1 diastereomeric mixture of (+)-**5** and (−)-**6**, which was subjected to acetylation and then to chromatographic separation to furnish the acetates of (+)-**5** and (−)-**6**, with each having an enantiomeric excess of >99%[9] in 95% combined yield. Similarly, the CBS reduction of (±)-**4** with (*R*)-oxazaborolidine provided (+)-**6** and (−)-**5**, each having an enantiomeric excess of >99%.[9]

Scheme 2



These experiments have demonstrated that the CBS reagent is practically perfect in recognizing the boxed portion of **4** (Scheme 1), but it has not been established how absolutely it ignores the remaining portion of **4**. In this connection, we noticed a small but significant difference in the reaction rates between the reduction of (+)-**4** with (*S*)- and (*R*)-oxazaborolidines at −45 °C.[10] When the reduction was conducted at −78 °C, the difference in the rates became very distinct. A time-course experiment has established that the reduction proceeds with approximately $S = 27$[11] at −78 °C, suggesting the possibility of kinetic resolution of (±)-**4**. Indeed, when the reduction of (±)-**4** with (*S*)-oxazaborolidine at −78 °C was quenched at approximately 60% completion, (−)-**4** was isolated in 40% yield with greater than 93% ee,[12] along with a 5:1 mixture of (+)-**5** and (−)-**6**, each with >99% ee.[9,13]

(1) Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627.

(2) Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 167; *Organic Synthesis*; Wiley: New York, 1990; Collect. Vol. VII, p 368.

(3) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(4) (+)-**4** was prepared from (+)-estrone by adopting the method reported by: Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(5) The C19 configuration introduced in this reduction matches the one predicted by the Corey transition-state model: Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429. Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 2880.

(6) For a review on the Mitsunobu reaction, see: Mitsunobu, O. *Synthesis* **1981**, 1.

(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(8) For the synthesis of (±)-estrone, see: Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *23*, 1553.

(9) Optical purity was determined by ^{1}H NMR and ^{19}F NMR analyses of the corresponding (*S*)-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester.

(10) A concept of kinetic resolution of racemic ketones is well recognized. For a recent work on this subject, see: Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 88.

(11) The stereoselective factor, $S = K_R/K_S$, was calculated by the equation $S = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$; C = conversion.

(12) Enantiomeric excess was determined from the optical rotation in reference to that of the optically pure authentic sample.

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Both methods reported allow us to convert (±)-**4** into (+)-**5** and (−)-**5**, but the former method is superior in terms of practicality and simplicity. As noted, this study was initiated with the specific application to the batrachotoxin case, and the CBS reduction of (±)-**1** indeed proceeded in a completely analogous manner to the case of (±)-**4**.[14] These experiments demonstrate the usefulness of achieving the optical resolution and stereospecific reduction of a polyfunctional racemic substrate simultaneously at a very late stage of a synthesis, thereby providing both enantiomers of a target molecule in one synthesis.[15]

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Supporting Information Available: The experimental details and the X-ray structure of the acetate of (+)-**5** (6 pages).

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(13) The kinetic resolution of (±)-Wieland−Miescher diketone was also tested with 0.6 equiv of (*R*)-Me-B·BH_3 (at −78 °C for 30 min) to give (+)-unsaturated keto alcohol as a single diastereomer with 99% ee, along with the recovered (−)-diketone with 90% ee. For the details, see the Supporting Information.

(14) The details of this experiment shall be reported in the full acount of batrachotoxin synthesis.

(15) When using an optically active starting material or applying an asymmetric process at an early stage of a synthesis, one needs to carry out two syntheses to obtain both enantiomers of a target molecule.