Total Synthesis of the NF-κB Inhibitor (−)-Cycloepoxydon: Utilization of Tartrate-Mediated Nucleophilic Epoxidation

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Received August 30, 2001
Revised Manuscript Received September 27, 2001

NF-κB is an inducible transcription factor that regulates the expression of various cellular genes involved in immune and inflammatory responses.[1] The epoxyquinoid natural product cycloepoxydon (**1**) (Figure 1) was isolated from fermentations of a deuteromycete strain[2] and shown to inhibit activation of NF-κB. Due to our interest in the synthesis of epoxyquinoid natural products,[3] we have targeted cycloepoxydon for a total synthesis effort. Herein, we report the first total synthesis and absolute stereochemical assignment of (−)-cycloepoxydon utilizing a tartrate-mediated nucleophilic epoxidation to introduce initial stereocenters.

A retrosynthetic analysis for the synthesis of cycloepoxydon is depicted in Figure 1 and is based on a "stereochemically linear" strategy[4] in which initial stereogenic centers associated with the epoxide in conjunction with substrate control are used to establish all remaining stereocenters. Key steps involve pyran formation through *endo*-cyclization of epoxy alcohol precursor **2** and reagent-controlled asymmetric nucleophilic epoxidation[5] of quinone monoketal **3**.

The synthesis was initiated by hypervalent iodine oxidation[6] of **4**[3b] to afford dimethoxyketal **5** (Scheme 1). Transketalization of **5** with 2,2-diethyl-1,3-propanediol afforded 1,3-dioxane **3**, which was found to be an improved substrate for nucleophilic epoxidation relative to **5**. Using **3**, a number of methods for asymmetric nucleophilic epoxidation were evaluated.[5] We obtained promising results using modifications of the tartrate-modified[7] nucleophilic epoxidation system reported by Jackson and co-workers.[8] Although reactions did not proceed using

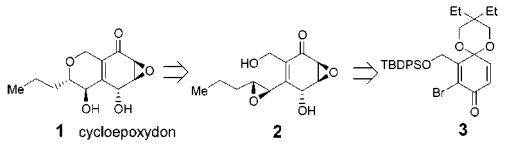
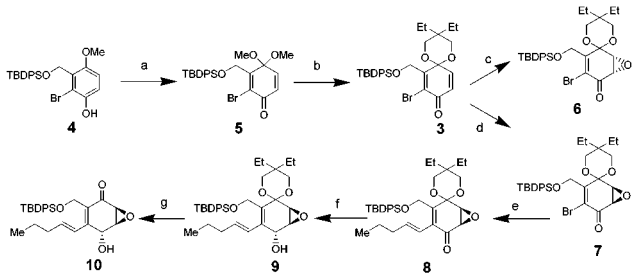


Figure 1.

Scheme 1[a]



[a] *Reagents*: (a) $PhI(OAc)_2$, MeOH, rt, 30 min, 84%; (b) 2,2-diethyl-1,3-propanediol, PPTS, benzene, 70 °C, 80 min, 89%; (c) ^{n}BuLi, L-DIPT, Ph_3COOH, $PhCH_3$, rt, 24 h, 88% conversion (68% ee); (d) NaHMDS, L-DIPT, Ph_3COOH, $PhCH_3$ (20% THF), −50 °C, 30 h, 97%, 96% ee; (e) (*E*)-tributyl-1-pentenyl-stannane, Pd_2dba_3·$CHCl_3$, $ClCH_2CH_2Cl$, 60 °C, 40 h, 81%; (f) DIBAL-H, THF, −78 °C, 15 min, 88%; (g) 48% HF, CH_3CN, 0 °C, 5 min, 92%.

n-BuLi−(L) -diisopropyl tartrate (DIPT) employing ^{t}BuOOH,[9] we found trityl hydroperoxide (Ph_3COOH) to be an effective peroxide source. Optimization of reaction conditions [Ph_3COOH (5 equiv), *n*-BuLi (2.7 equiv), (L)-DIPT (1.0 equiv), toluene, rt] provided monoepoxide **6** (68% ee). Interestingly, using NaHMDS, reactions using (L)-DIPT were found to proceed at −50 °C and to afford the *opposite* enantiomer **7**.[10] Use of KHMDS afforded moderate conversion, but resulted in low ee (=10%). Production of **7** (97% yield, 96% ee) from substrate **3** was optimized using NaHMDS−(L)-DIPT [Ph_3COOH (6.4 equiv), NaHMDS (5.2 equiv), (L)-DIPT (1.6 equiv), 0.1 M in toluene, −50 °C, 30 h]. The absolute stereochemistry of **7** was assigned by correlation with compounds produced by diastereoselective epoxidation of a chiral quinone monoketal (see Supporting Information for details).[3b,11] Stille coupling[12] of **7** with (*E*)-tributyl-1-pentenyl-stannane[13] afforded **8** which was reduced with Dibal-H in THF[11b,14] to afford *anti*-epoxy alcohol **9**. Treatment of **9** with HF−CH_3CN effected acetal hydrolysis[3] to provide epoxyquinol **10**.

A mechanistic proposal for tartate-mediated nucleophilic epoxidations is shown in Figure 2. The asymmetric induction and counterion dependency may be explained by preferential formation of complexes **A** (Li) or **B** (Na) in which 2 equiv of either lithium or sodium tritylperoxide form bowl-shaped chelates with either five- or six-membered ring hydrogen-bonded tartrate conformers.[15] The resulting bowl-shaped complexes may then promote formation of two different epoxide enantiomers by hydrogen-bond activation of the dienone and face-selective conjugate addition of a peroxide anion.[16] In both cases, the substrate binds in an orientation such that the bulky Br and

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10.1021/ja0169769 CCC: $20.00 © 2001 American Chemical Society
Published on Web 10/23/2001

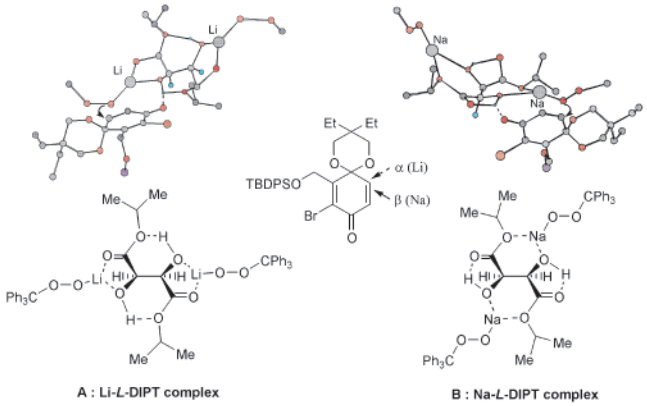
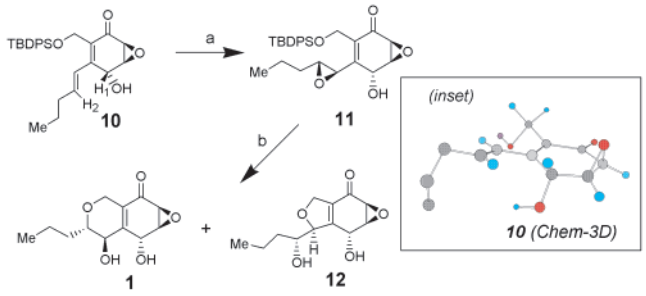


Figure 2.

Scheme 2[a]



[a] Reagents: (a) *m*-CPBA, CH_2Cl_2, rt, 4 h, 85%; (b) 48% HF, CH_3CN, rt, 2 h, **1** (53%), **12** (35%).

protected hydroxymethyl group are positioned in the convex face of the chelated complex. For complex **A**, this positioning of the substrate results in addition of the peroxide anion from the α-face of the dienone, while addition to the *β*-face is observed for **B**.[17] Preferred formation of **B** in the case of the sodium counterion may result from a combination of energetic preference for five-membered ring hydrogen bonding[15] coupled with the increased atomic radius of sodium favoring a six-membered metal chelate.

Completion of the synthesis of cycloepoxydon required regio- and diastereoselective epoxidation of epoxyquinol **10** (Scheme 2). Although electrophilic epoxidations of conjugated dienone substrates generally provide *γ*,*δ*-epoxy enones,[18] the hydroxyl-directing[19] group effects of **10** were unclear at the outset. In the event, treatment of **10** with *m*-CPBA cleanly afforded *γ*,*δ*-epoxy enone **11**. The stereochemistry of **11** was tentatively assigned using conformational analysis[20] which showed minimum energies for *s*-trans conformers of **10** (cf. Scheme 2, inset), indicating that the directed epoxidation should proceed to afford the diastereomer shown. The *s*-trans conformation of **10** was also confirmed using NOE experiments (15% NOE between H_1 and H_2). Final synthesis of (−)-cycloepoxydon was achieved by tandem deprotection and cyclization by treatment of **11** with HF/CH_3CN, which provided *endo*-epoxide opening product (−)-cycloepoxydon **1** and *exo*-epoxide opening product **12** ("*iso*-cycloepoxydon") in 53 and 35% yields, respectively.[21] The relative stereochemistries of **1** and **12** were further confirmed by single X-ray crystal structure analysis.[22] Synthetic **1** was confirmed to be identical to data reported for natural (−)-cycloepoxydon[2a] by ^1H and ^{13}C NMR and $[\alpha]_D$ (−139°, c = 1.0, $CDCl_3$:CD_3OD 95:5).

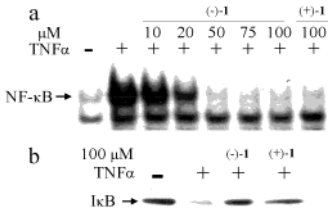


Figure 3.

As shown in Figure 3a, 50 μM (−)-**1** inhibited tumor necrosis factor (TNF)-induced NF-*κ*B DNA binding in mouse 3T3 cells. Furthermore, (−)-**1** blocked degradation of I*κ*Bα, a required upstream event in the activation of NF-*κ*B (Figure 3b). The enantiomer (+)-**1** also inhibited TNF-induced NF-*κ*B DNA binding and degradation of I*κ*Bα (Figure 3, a and b).

In summary, the first total synthesis and absolute stereochemical assignment of the NF-*κ*B inhibitor (−)-cycloepoxydon has been achieved employing a tartrate-mediated asymmetric nucleophilic epoxidation of a quinone monoketal. The enantioselectivity in this epoxidation system has been rationalized by the formation of hydrogen-bonded chelates of tartrate and hydroperoxide anion. Further studies on epoxyquinoids and mechanistic studies regarding the tartrate-mediated epoxidation of electron-deficient olefins are in progress.

Acknowledgment. This research was supported by the American Cancer Society (RSG-01-135-01-CDD, J.A.P, Jr.) and the NIH (grant CA47763, T.D.G). M-C.L. was partially supported by the Ministry of Education, Taiwan. E.A.P. was supported in part by the Boston University Undergraduate Research Opportunities Program. We thank Mr. X. Wang, Mr. D. Kalaitzidis, Professor J. Snyder, and Professor S. E. Schaus for helpful discussions.

Supporting Information Available: Chemical and biological procedures and characterization data for all new compounds, including X-ray structural analyses of **1** and **12** (PDF). X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) See the Supporting Information for further details on X-ray structures and coordinates.