Tetrahedron Letters 53 (2012) 5936–5938

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Temporary thio-derivatization in the synthesis of (+)-4-acetylbromoxone

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ARTICLE INFO

Article history:
Received 14 June 2012
Revised 13 August 2012
Accepted 24 August 2012
Available online 1 September 2012

Keywords:
Epoxyquinol
NFκB
Lipase
Kinetic resolution

ABSTRACT

A stereocontrolled synthesis of the marine natural products (+)-bromoxone (**1**) and (+)-4-acetylbromoxone (**2**) is reported. The sequence features the enzymatic kinetic resolution of 4-hydroxycyclohexenone (**6**) via its *S*-benzyl adduct. Thereafter, a base-mediated elimination–silylation generated an optically active (−)-4*S*-4-*tert*-butyldimethylsilyoxycyclohexenone (**5**), which then underwent diastereoselective epoxidation. Saegusa–Ito oxidation enabled formation of the corresponding α,β-unsaturated ketone **13**. Bromination–elimination and subsequent removal of the silicon protecting group afforded (+)-bromoxone (**1**) which was converted into (+)-(4*S*,5*R*,6*R*)-4-acetoxy-2-bromo-5,6-epoxycyclohex-2-enone (**2**) [(+)-4-acetylbromoxone]. Using a luciferase gene reporter assay ED_{50} for NFκB inhibition of 9 μM was determined.

Epoxyquinols represent a class of natural products that have received interest based on both their chemical structures and biological activities (Fig. 1).[1] (+)-Bromoxone (**1**), a representative member of this family, was first discovered in 1987 from a marine acorn worm found off the coast of Hawaii.[2] It was isolated along with its more abundant 4-acetyl congener **2** and several structurally related brominated cyclohexenyl compounds. 4-Acetylbromoxone (**2**) was shown to be active against P388 leukaemia cells at a dose of 10 ng/mL.[2] Since its first synthesis in 1994, bromoxone (**1**) has proven a popular synthetic target.[3] In part, this is because the 2-bromo substituent represents an ideal handle for further functionalization enabling additional members of this epoxyquinol family to be prepared, perhaps most notably panepophenanthrin and hexacyclinol.[4] In contrast, however, only the direct preparation of unnatural, (−)-2,[5] has been detailed, although in the original isolation work it was stated that the standard acetylation of natural **1** gave **2**.[2] We have been involved in a project aimed at the synthesis of optically active cyclohexenone derivatives in relation to their inhibition of the transcription factor, nuclear factor kappa B (NFκB). To this end we have developed a means of resolving 4-hydroxycyclohexenone (**6**) via its *S*-benzyl adduct.[6] This method enables the synthesis of both 4*R*- and 4*S*-4-*tert*-butyldimethyl-silyloxycyclohexenone (**5**) (95% to 99% enantiomeric excess) which have proven utility for the synthesis of various target compounds.[7] In this communication we report a synthesis of (+)-1 and the first total synthesis of (+)-2 using our method for the preparation of (−)-4*S*-*tert*-butyldimethylsilyloxycyclohexenone (**5**).

The route began with the four-step conversion of anisole into racemic 4-hydroxycyclohexenone (**6**).[8] Compound **6** is not a practical substrate for enzyme-mediated resolution, presumably since the sp^2 and sp^3 hybridized carbon atoms flanking the stereogenic centre are sterically too similar.[9] In contrast, after a *cis*-diastereoselective conjugate addition using benzyl mercaptan (which seems to occur due to a thiolate–alcohol directed delivery) an efficient enzymatic kinetic resolution (EKR) of the racemic adduct **8** takes place using a commercially available resin supported form of *Candida antarctica* lipase B (CAL-B).[6] Hence acetylated (−)-**10** can be readily separated from unreacted (+)-**8**, which was isolated in 95% ee [Chiralpak® IC; isocratic heptane/EtOH; 4:1 (1.0 mL/min); R_t (−)-**8** = 21.1 min; R_t (+)-**8** = 22.9 min]. In relation to this

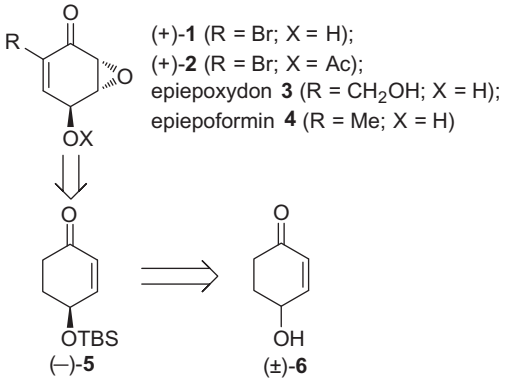

Figure 1. 2-Functionalized epoxyquinol natural products and their proposed synthesis from 4-hydroxycyclohexenone (**6**).

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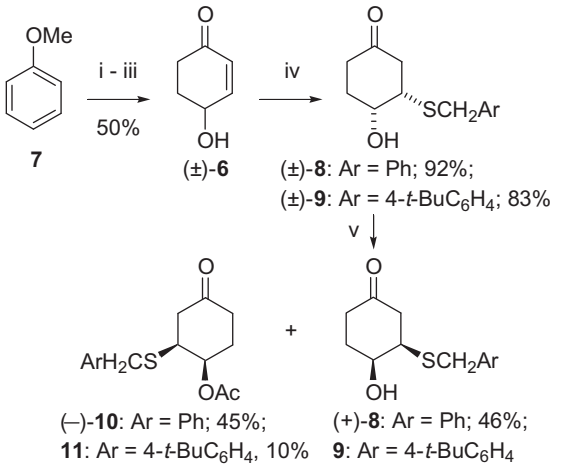
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.101

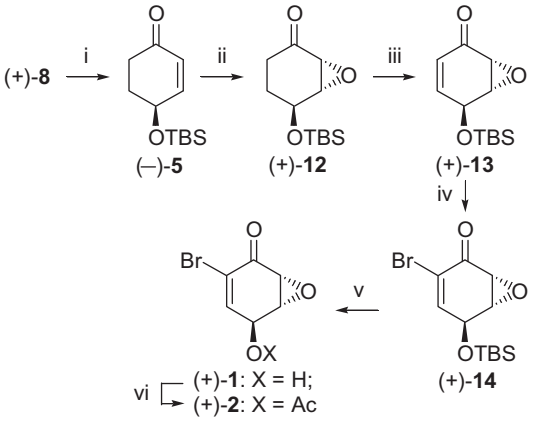
sequence the persistent malodour associated with the use of benzyl mercaptan has been addressed by Node et al.[10] They have shown that the introduction of substituents, particularly a 4-*tert*-butyl group, onto the aromatic ring serves to reduce its odour. However, following the synthesis of the *tert*-butyl substituted adduct *cis*-**9**, inefficient resolution was observed using CAL-B, an unexpected finding explained presumably by an unfavourable interaction between the *tert*-butyl group and the lipase (Scheme 1).

Treatment of (+)-**8** with TBSCl under basic conditions served to introduce both the silyloxy unit and to remove the steric buttress, thus, generating (−)-**5** in reasonable yield (Scheme 2). Analysis of this material by chiral GC [Supelco AlphaDex 120; gradient 60–180 °C; R_t (−)-**5** = 21.5 min; R_t (+)-**5** = 21.7 min] indicated that no erosion of optical purity had taken place during this step. With a supply of optically active **5** in hand its epoxidation was next considered. Use of aqueous hydrogen peroxide with either sodium hydroxide or benzyltrimethylammonium hydroxide (Triton B)[3d,11] gave good conversion. However, mixtures of the major *trans*-epoxide **12** and its minor *cis*-epoxide diastereoisomer (ca. 5:1) were encountered. In contrast *tert*-butyl hydroperoxide (TBHP) gave *trans*-epoxide (+)-**12** as the sole isolable product in good yield (87%). The next task was introduction of the enone. The use of IBX at elevated temperature led to decomposition whereas a combination of IBX and NMO at room temperature led to poor conversion (**12**:**13**; 80:20).[12] Epoxide **12**, however, was found to cleanly undergo trimethylsilylenol ether formation at −78 °C[3d] and this material was directly treated with stoichiometric amounts of $Pd(OAc)_2$.[13] Although this Saegusa–Ito reaction gave clean samples of (+)-**13**, the yield for this process was modest which may be attributed to the formation of acetic acid during the reaction. Nevertheless, (+)-**13** could then be converted into vinyl bromide (+)-**14** on bromination followed by direct base-mediated elimination.[14]

Removal of the *tert*-butyldimethylsilyloxy protecting group from this type of compound has been routinely performed using HF.[15] In our hands, aqueous HF in acetonitrile[15,16] led to a sluggish reaction during which decomposition proved to be an issue. Using Evans' protocol, a HF·pyridine solution in THF buffered with pyridine[17] led to a more controlled and efficient deprotection and (+)-**1** could be isolated. Finally, (+)-**1** underwent rapid acetylation with acetic anhydride and pyridine in the presence of DMAP to give



Scheme 1. Synthesis and resolution of racemic alcohol **8**.



Scheme 2. Synthesis of (−)-**5** and its use in the synthesis of (+)-**1** and **2**.

(+)-**2**. Purification was performed by standard flash chromatography on silica which gave a sample of (+)-**2** in 56% yield from (+)-**14** whose data[18] were consistent with those reported.[2,5] In relation to the purification of (+)-**2** it should be noted that this compound does undergo gradual decomposition on silica over time.

The ability of **2** to inhibit the transcription factor NFκB was determined with a gene reporter cell-based assay.[19] It was found that at 9 μM, phorbol challenged NFκB activation was halved (ED_{50} = 9 μM). However, an alamar blue® cell viability assay demonstrated that at 100 μM significant toxicity became evident (LD_{50} = 100 μM).

In summary, (+)-**2** was prepared in 9% overall yield from enantioenriched (+)-**8** in a sequence requiring five chromatographic purification operations. Based on the optical purity of (−)-**5** this material is 95% ee.

Acknowledgments

We would like to thank UCD for financial support including an Ad Astra scholarship (A.O'B.). Membership (P.E.) of COST action CM0804 is acknowledged.

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18. Data for (+)-**2**: $[\alpha]_D^{22}$ +212 (*c* = 0.2, $CHCl_3$) {Lit. (+)-**2**: $[\alpha]_D^{19}$ +265 (*c* = 0.12, $CHCl_3$) Ref. 2; (−)-**2** $[\alpha]_D$ −278.2 (*c* = 2.55, $CHCl_3$) Ref. 5}; δ_H (600 MHz, $CDCl_3$) 2.15 (3H, s, CH_3), 3.69 (1H, dd, *J* = 1.0, 3.5 Hz, CH), 3.76–3.78 (1H, m, CH), 5.75 (1H, d, *J* = 5.5 Hz, CH), 7.06 (1H, dd, *J* = 2.5, 5.5 Hz, CH); δ_C (150 MHz, $CDCl_3$) 20.6, 53.0, 55.0, 65.4, 125.6, 139.6, 169.5, 185.9; *m*/*z* (ES^-) found 246.9427 ($M\text{-}H^+$), $C_8H_6O_4Br^{81}$ requires 246.9429 (−0.8 ppm).
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