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Chemoenzymatic formal synthesis of (−)-balanol. Provision of optical data for an often-reported intermediate

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ABSTRACT

Formal total synthesis of (−)-balanol was accomplished from bromobenzene in 13 steps via the bis-benzyl derivative **3**, whose optical rotation data have been provided.

Balanol (**1**) is a fungal metabolite from *Verticillium balanoides* whose isolation and structural elucidation was accomplished by Sphinx Pharmaceticals in 1993.[1] The first total synthesis was accomplished by Nicolaou in 1994.[2a] The compound has become a popular target of synthetic efforts in part because of its potent inhibitory activity against protein kinase C[3] and in part because of the uniquely functionalized hexahydroazepine core. The focused effort resulted in 10 total[2] and 21 formal[4] syntheses of balanol in both enantiomeric series. The formal syntheses usually target the hexahydroazepine core either as the free amino alcohol **2**[4n] or as its partially protected forms such as the *N*-Cbz,[4i,j] *N*-Boc,[4l,o] or *N*-benzyl[2f,4f,p] derivative of **3**, Figure 1.

Several syntheses of the latter compound were reported[2f,4p,f] in recent years including our own approach published in early 2008.[4u] We prepared the bis-benzyl-protected derivative **3** from vinyl oxirane **4** by the action of the chiral version of the Burgess reagent, namely **5**, as shown in abbreviated form in Scheme 1. We were surprised to find no reference in the literature to the optical rotation or optical purity of compound **3** in spite of several reported asymmetric syntheses of this material. Our own synthesis produced alcohol **3** in approximately 95% enantiomeric excess as evaluated by the Mosher ester method and ^{19}F NMR. The less than absolute enantiomeric purity resulted from an incomplete separation of benzoate **6b** from its diastereomer **6a**. Thus, after the removal of the menthyl auxiliary group, the minor diastereomer led to the opposite enantiomer of the final product, contributing to its lower optical purity.

As we failed to locate accurate optical reference data we decided to prepare **3** in a manner that would provide unambiguously the desired enantiomer with absolute optical purity. We chose as the starting material the *cis*-bromo cyclohexadiene **7**, Figure 2, whose absolute stereochemistry as well as absolute enantiomeric constitution is well established.[5]

The strategy of conversion of **7** to balanol intermediate **3**, shown in Figure 2, is based on the recognition that the vinyl bromide functionality is easily saturated, and that the diol is a suitable precursor for the dialdehyde required for reductive amination to the hexahydroazepine core. The *cis* olefin can be converted to an aziridine, which would serve as the means of introduction of the *trans*-amino alcohol moiety.

To this end diol **7** available in multigram quantities from the whole-cell fermentation of bromobenzene[6] with *E. coli* JM109

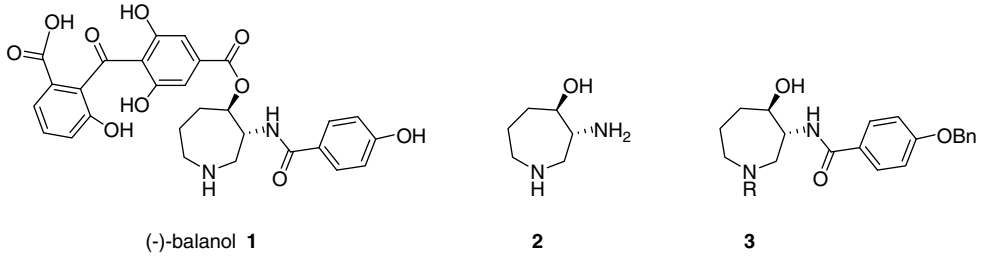

Figure 1. Balanol and intermediates frequently employed in formal syntheses.

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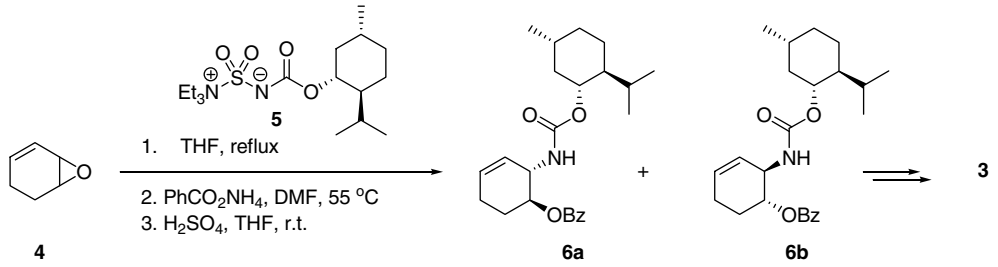
(pDTG601)[7] was protected as its acetonide and converted to the syn aziridine **8** by adaptation of Corey's protocol[8] as shown in Scheme 2. Opening of the acetyl aziridine with acetate provided the protected *trans* amino alcohol **9b** as a 4:1 mixture with the cis product **9a**. Column chromatography followed by crystallization yielded only the trans product (GC–MS analysis), which was



Scheme 1. Formal synthesis of (−)-balanol.[4u]

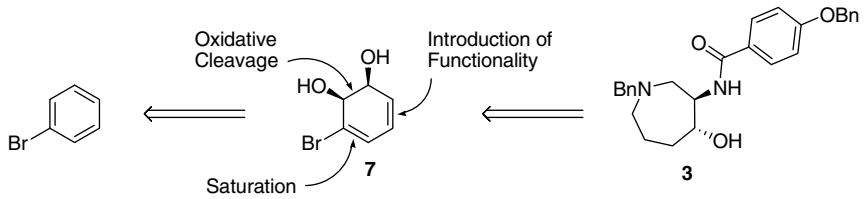
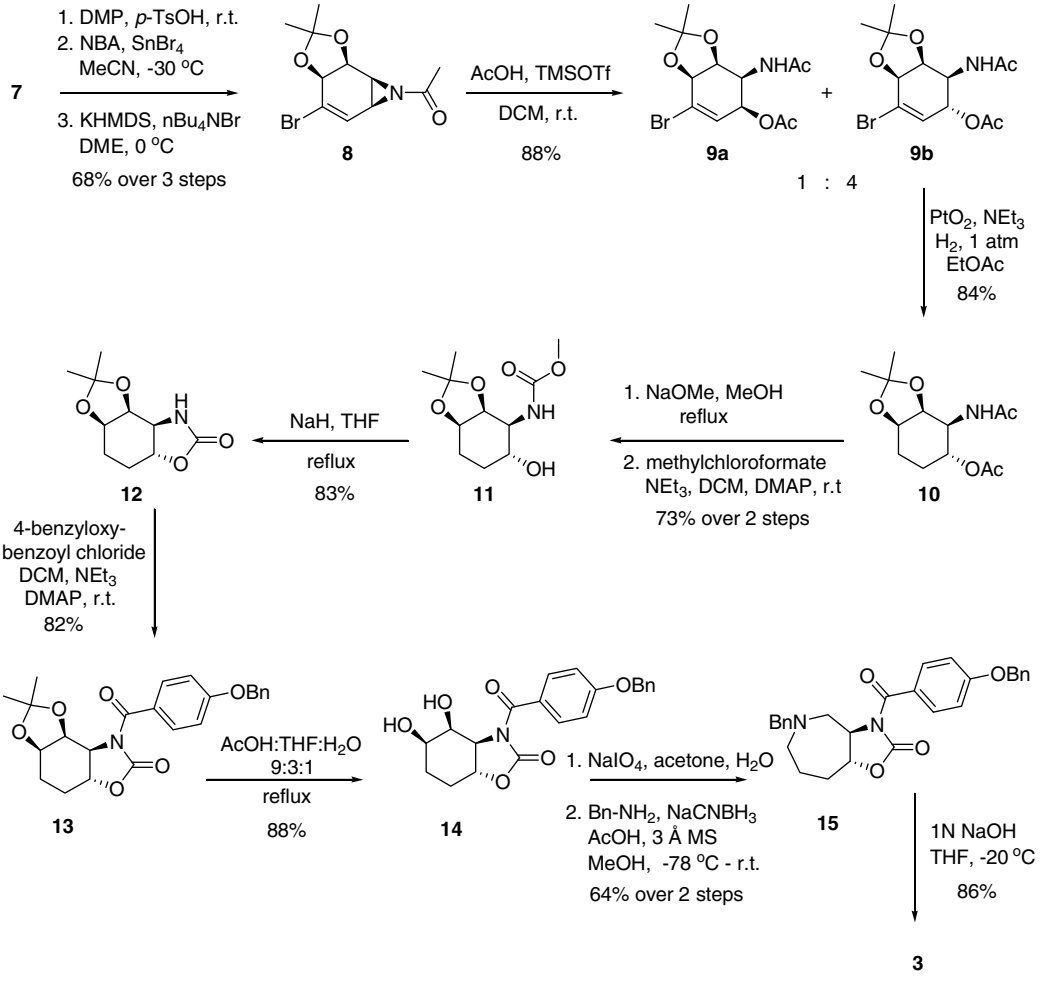


Figure 2. Design of hexahydroazepine **3** from bromobenzene.



Scheme 2. Chemoenzymatic formal synthesis of (−)-balanol.

hydrogenated in the presence of PtO_2 to **10** and converted further to the cyclic carbamate **12** by basic hydrolysis, treatment with methyl chloroformate, and sodium-hydride-mediated cyclization of carbamate **11**. The carbamate was acylated with *p*-benzyloxy benzoyl chloride to yield **13** whose hydrolysis furnished diol **14**. Oxidative cleavage generated a dialdehyde species (not shown) that was immediately subjected to reductive amination conditions in the presence of benzylamine.[9] Mild hydrolysis of the cyclic carbamate **15** furnished the *N*-benzyl derivative **3**[10] exhibiting optical rotation of $[\alpha]_D^{23}$ −5.6 (*c* 0.2, $CHCl_3$).

In summary, the synthesis of (−)-**3** (R = Bn) was accomplished in 12 steps from diol **7** in order to provide accurate optical rotation data. The synthesis of the corresponding (+)-**3** (R = Bn) may be envisioned from the α-isomer of aziridine **8**. Full details of the enantiodivergent synthesis of **3** from bromobenzene will be reported in due course.

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10. *Analytical data for (−)-**3**-yellow oil*: R_f 0.31 (3:2 ethyl acetate–hexanes); $[\alpha]_D^{23}$ −5.6 (*c* 0.2, $CHCl_3$); Standard deviation for (−)-menthol standard: $[\alpha]_D^{23}$ −48.65 ± 0.068 (*c* 10, EtOH); Literature value for (−)-menthol: $[\alpha]_D^{22}$ −50 (*c* 10, EtOH).[11] Optical purity of the Mosher ester of (−)-3 >95% [Within the detection limits of ^{19}F NMR of the (*S*)-(+)-Mosher ester of (−)-3: δ −71.26; (±)-3: δ −71.26 and −71.58.]. IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55–1.99 (m, 4H), 2.50 (m, 1H), 2.73 (dd, *J* = 1.9, 14.3 Hz, 1H), 2.93 (dd, *J* = 2.0, 14.2 Hz, 1H), 3.00 (m, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.74–3.78 (m, 2H), 3.88 (m, 1H), 5.15 (s, 2H), 6.54 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 2H), 7.22–7.50 (m, 12H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.7, 31.5, 54.4, 58.0, 59.9, 64.2, 70.1, 77.5, 114.5, 126.4, 127.4, 127.5 (2 × C), 128.2, 128.7 (2 × C), 128.9 (2 × C), 129.0, 129.5 (2 × C), 136.4, 161.4, 167.8 ppm; MS (FAB) *m*/*z* (%) 431 ($M+H^+$); 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{27}H_{31}N_2O_3$ 431.2310, found 431.2312.
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