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# Recent chemoenzymatic total syntheses of natural and unnatural products: Codeine, balanol, pancratistatin, and oseltamivir*

Tomas Hudlický‡

*Department of Chemistry and Centre for Biotechnology, Brock University, 500 Glenridge Avenue, St. Catharines, ON L2S 3A1, Canada*

*Abstract*: Presented here is a short summary of the recent accomplishments in total synthesis in our laboratories. In particular, recent generations of the syntheses of pancratistatin derivatives, codeine, balanol, and oseltamivir (Tamiflu) are described in relation to their common chemoenzymatic origin in toluene-dioxygenase-mediated dioxygenation of aromatic substrates. Perspectives and projections are discussed in the conclusion.

*Keywords*: balanol; chemoenzymatic synthesis; codeine; oseltamivir; pancratistatin; Tamiflu; toluene-dioxygenase.

## INTRODUCTION

The combination of biological methods with the traditional techniques of organic synthesis has been shown to lead to greater efficiency in the manufacturing of compounds of interest. The targets **1–4** discussed here originate from homochiral metabolites obtained via the whole-cell fermentation of a particular aromatic substrate with *Escherichia coli* JM109(pDTG601), a recombinant organism that overexpresses the enzyme toluene dioxygenase. The four targets are shown in Fig. 1 along with the arene *cis*-dihydrodiol metabolites of enzymatic hydroxylation chosen as starting materials.

Each synthesis discussed here represents the latest accomplishments resulting from multigenerational approaches to these targets. The syntheses of 7-deoxypancratistatin (**1**) and its unnatural C-1 derivatives from *cis*-dihydrodiol **5** constitute the eighth-generation approach to these alkaloids. The enantiodivergent syntheses of (+)- and (–)-codeine from metabolite **6** are fourth- and fifth-generation efforts, respectively. The *cis*-dihydrodiol derived from bromobenzene served a convenient starting material for the enantiodivergent synthesis of the hexahydroazepine core of balanol, leading to a formal total synthesis. Finally, an efficient formal total synthesis of oseltamivir was attained from **7**, the metabolite from ethyl benzoate.

These relatively short (fewer than 14 steps) syntheses are designed with the practicality of process chemistry in mind. The preparation of oseltamivir in particular features several one-pot operations. We anticipate that the efficiency in the next-generation synthesis will approach a level useful for process production of the drug.

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‡E-mail: thudlicky@brocku.ca

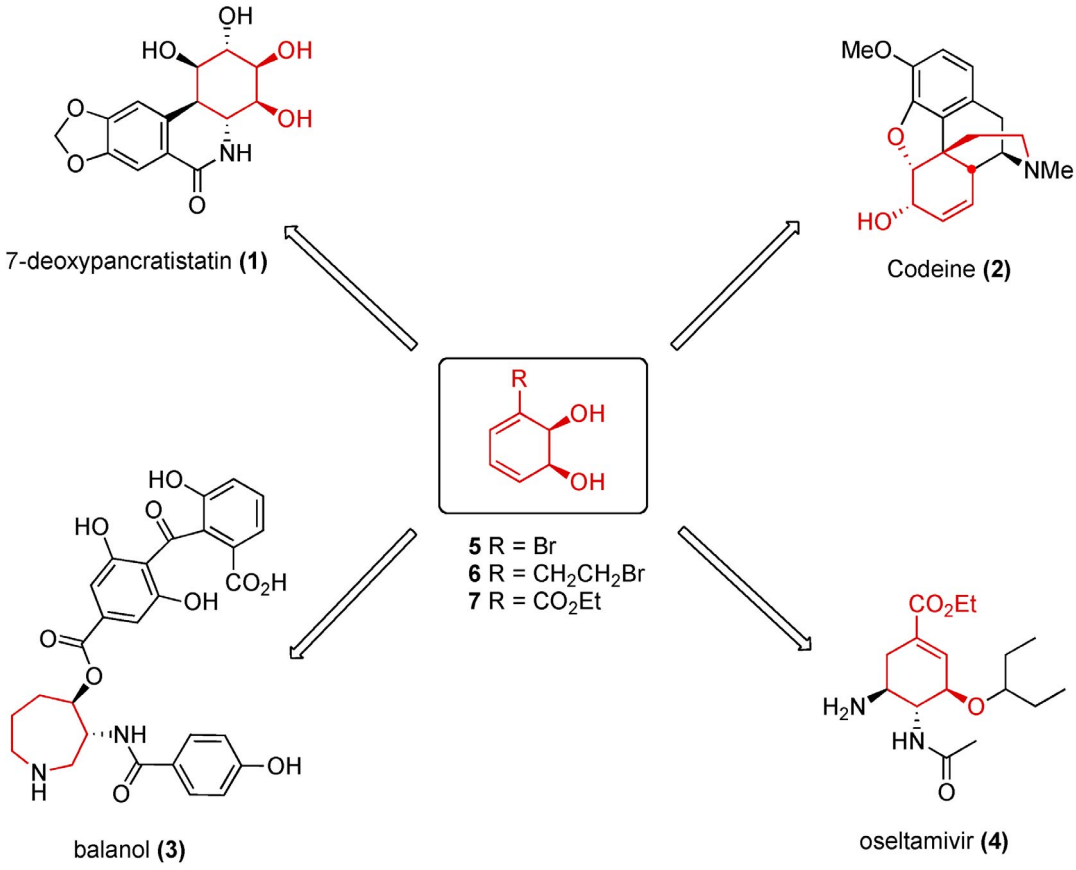



**Fig. 1** Chemoenzymatic strategies toward 7-deoxypancratistatin (**1**), (+)- and (–)-codeine (2), (+)- and (–)-balanol (**3**), and oseltamivir (Tamiflu) (**4**).

## RESULTS AND DISCUSSION

The mainstay of our program in chemoenzymatic synthesis is the whole-cell fermentation of aromatic compounds with recombinant strains of *E. coli* that over-express toluene dioxygenase. The organisms, such as *E. coli* JM109(pDTG601) developed by Gibson [1], enjoy widespread use in the provision of many enantiopure diol metabolites such as **5**, **6**, and **7**, Fig. 2. The latest compilation of these metabolites by Johnson lists more than 400 such structures [2], only a few of which have been exploited in total synthesis [3]. Given the diverse functionality in the substrates that the enzyme tolerated, this large number of enantiopure metabolites provides an almost limitless opportunity for applications to asymmetric synthesis of natural products. This paper provides an overview of the latest results from our laboratory.

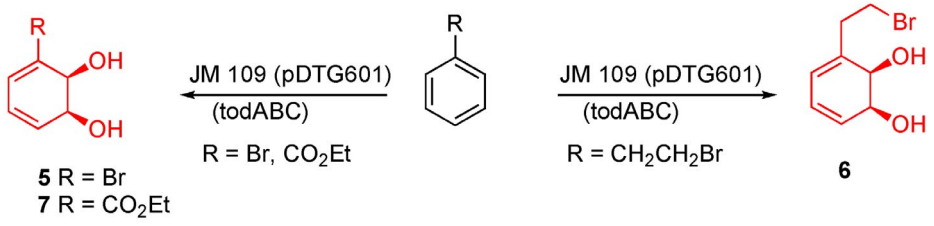
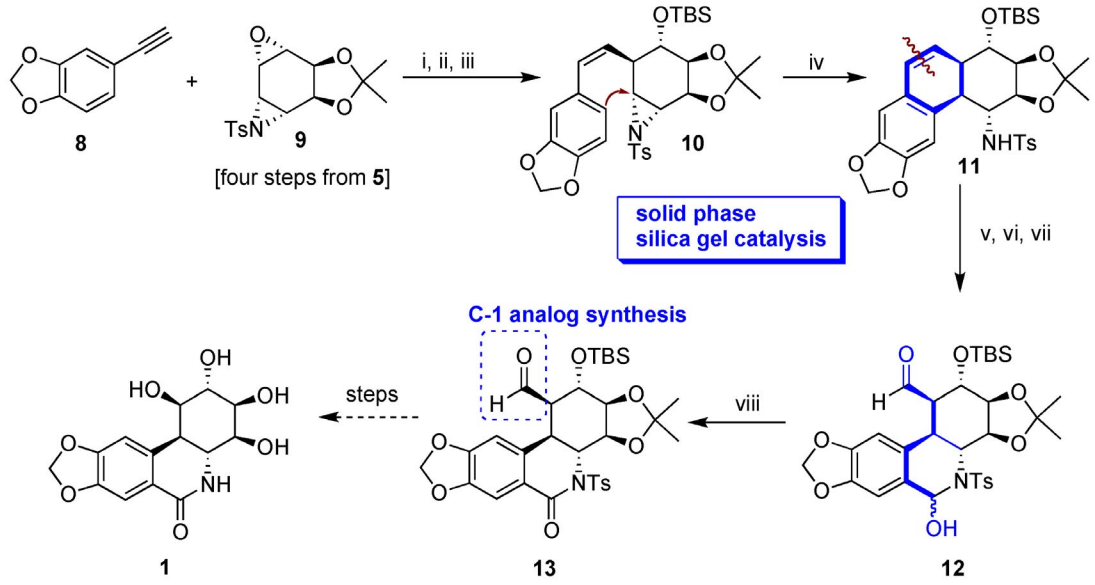



**Fig. 2** Enantiopure *cis*-dihydrodiols derived from single-ring aromatic substrates.

## Amaryllidaceae constituents

Our latest approach to pancratistatin, 7-deoxypancratistatin and its unnatural C-1 derivatives, featured a number of intriguing strategic events. In 2004, we reported the synthesis of various pancratistatin mimics [4] via a solid-phase silica-gel-catalyzed opening of aziridines with weak carbon nucleophiles [5]. This technique was applied to a new approach to pancratistatin via the construction of the phenanthrene core and its oxidative cleavage to generate the full phenanthridone skeleton of the target, as shown in Scheme 1. Thus, the epoxy aziridine **9**, obtained in four steps from diol **5**, was reacted with the aluminum salt of aryl acetylene **8** to provide regioselectively the *cis*-olefin **10** after partial saturation. The silica-gel-catalyzed intramolecular aziridine opening furnished the phenanthrene nucleus **11**, whose oxidative cleavage led to the immediate recyclization to phenanthridol **12**, Scheme 1. Oxidation with *o*-iodoxybenzoic acid (IBX) then provided the C-1 carboxaldehyde **13** and the corresponding C-1 carboxylic acid, accomplished in an efficient manner in 13 steps from bromobenzene [6a]. The C-1 aldehyde provides an opportunity for generation of new derivatives for biological screening, as it was demonstrated that alterations at C-1 do not diminish activity in these compounds [7]. Aldehyde **13** may also be converted to 7-deoxypancratistatin (**1**) through additional steps [6b].

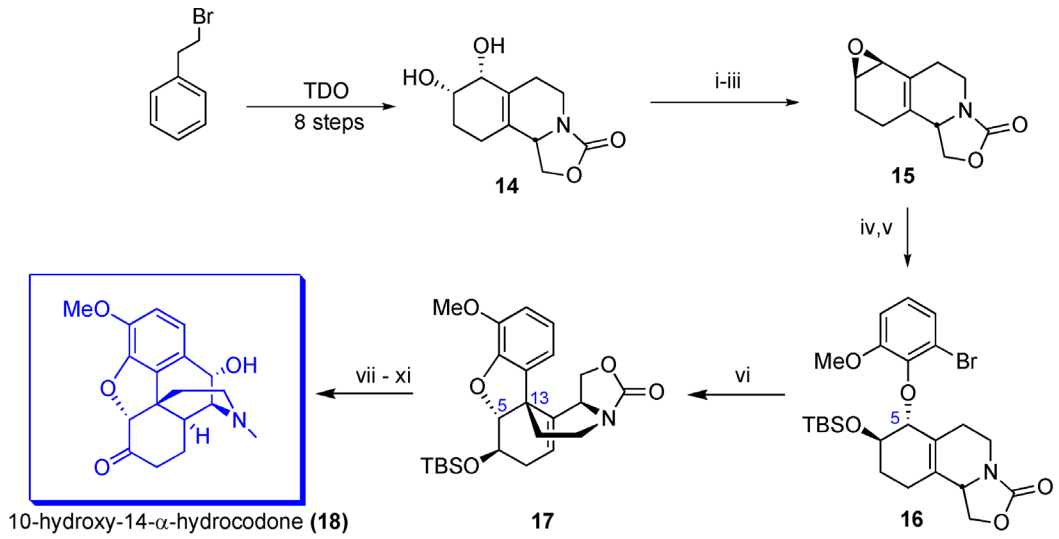



Reaction Conditions: i) n-BuLi, $Me_2AlCl$, Toluene, -78 °C; ii) TBDMSOTf, $Et_3N$ , $CH_2Cl_2$, -78 °C; iii) $BH_3$/THF, cyclohexene, 0 °C; iv) Silica gel, heat; v) $OsO_4$, NMO, $CH_2Cl_2$; vi) $NaBH_4$, dioxane/EtOH; vii) $NaIO_4$, dioxane/$H_2O$; viii) IBX, DMF.

**Scheme 1** Synthesis of C-1 derivatives of 7-pancratistatin.

## Morphine alkaloids

The synthesis of codeine and morphine has been pursued in our group through several generations. The latest ones involved the use of the Heck reaction [8] to establish the C-13 stereogenic center. One such approach provided the 10-hydroxymorphinan derivative **18**, which was synthesized from the *cis*-dihydrodiol **6**, derived from β-bromoethylbenzene, via octahydroquinoline intermediates **14** and **15**, Scheme 2. A regioselective epoxide opening led to aryl ether **16**, whose Heck cyclization provided the pentacyclic precursor to **18** [9]. We realized during this particular synthesis that the configuration of the




Reaction conditions: i)TsCl/Py; ii) BzOH/$nBu_3P$/DEAD; iii)MeONa/MeOH/THF; iv) potassium 2-bromo-6-methoxyphenoxide/DME/18-crown-6; v) TBSOTf/$(iPr)_2NEt/CH_2Cl_2$; vi) $Pd(PPh_3)_4$/Proton SpongeTM/$PhCH_3$/D; vii) TBAF/THF; viii) $H_2/PtO_2$/AcOH; ix) DIBAL-H; x) Swern [ox]; xi) TFA

**Scheme 2** Synthesis of 10-hydroxymorphinan via intermolecular Heck cyclization.

ether linkage at C-5 determines the outcome of all subsequent stereochemical events pursued in the assembly of the morphine skeleton.

With this recognition, we devised an enantiodivergent approach to codeine from the Boc-protected amine **19**, obtained in a few steps from diol **6**. A single Mitsunobu inversion with bromoisovanillin at C-5 would provide the aryl ether **20** whose Heck cyclization and further transformations would lead to *ent*-codeine (**2**) as shown in Fig. 3.

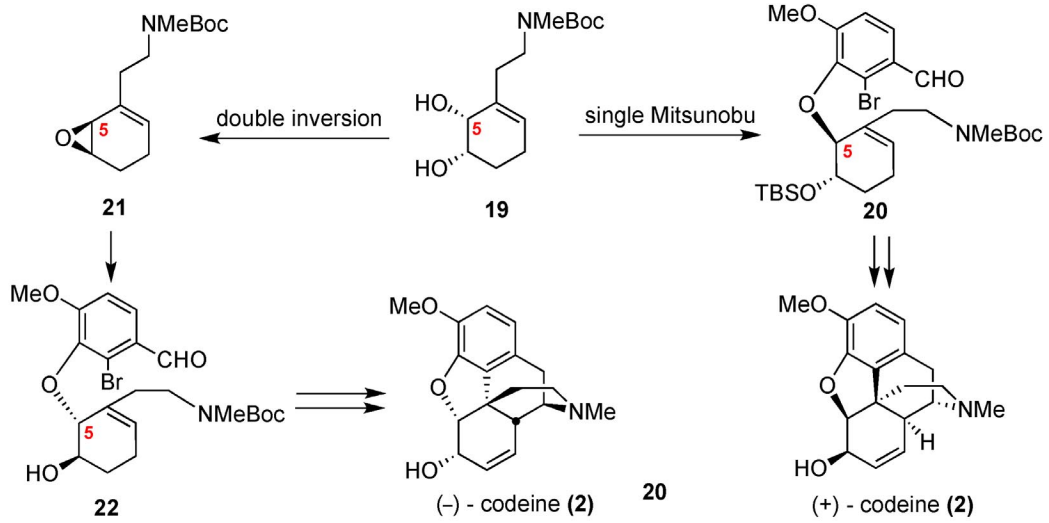
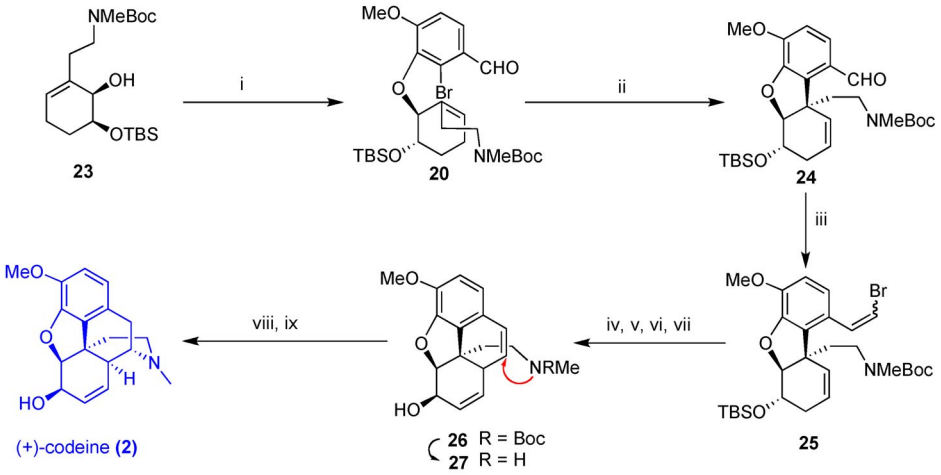



**Fig. 3** Enantiodivergent approach to codeine from a single enantiomer of **19**.

On the other hand, we experienced difficulties in some of our past approaches in executing a second Mitsunobu inversion in order to set up the C-5 center for the natural series [10]. A solution to the problem was envisioned in generating the allylic epoxide **21** and attaching the required aryl residue by the regioselective opening of the epoxide at C-5 (morphine numbering). This maneuver would lead to ether **22** and hence to natural codeine by further manipulation.

The approaches described above were reduced to practice commencing with the synthesis of (+)-codeine, as depicted in Scheme 3. Diol **6**, available from β-bromoethylbenzene by fermentation in yields of ca. 20 g/l, was reduced with potassium azodicarboxylate (PAD) and converted to the protected amine derivative **19**, whose distal hydroxyl was then protected as its *tert*-butyldimethylsilyl (TBS) ether, **23**. The C-5 center was conveniently set by the Mitsunobu reaction with bromoisovanillin to produce aryl ether **20**, whose Heck cyclization yielded the tricyclic system **24** in excellent yield.



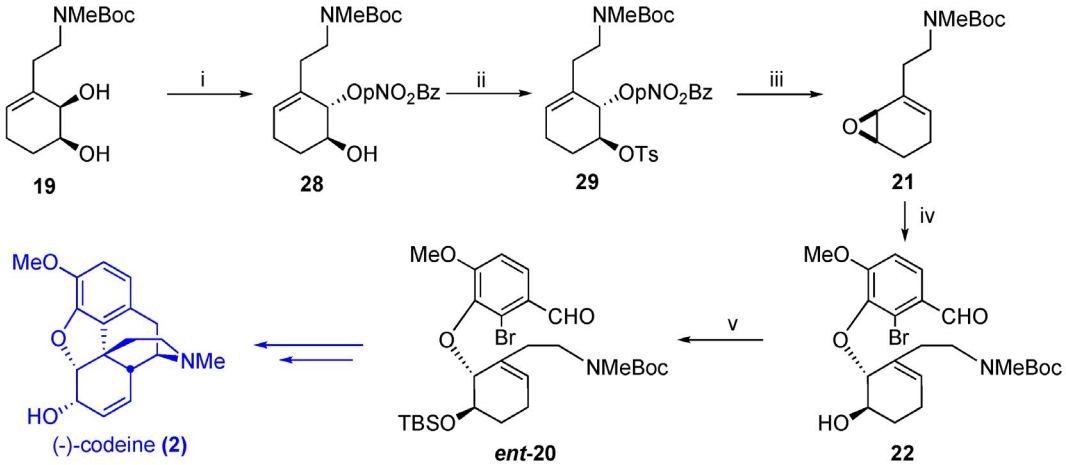

Reaction conditions: i)bromoisovanillin, *n*-$Bu_3P$, DIAD, THF, 0 ¡C to rt; ii) $Pd(OAC)_2$, $Ag_2CO_3$, dppf, Toluene, 110 °C; iii) $PPh_3CH_2Br_2$, *t*-BuOK, THF, -30°C; iv) $Pd(OAC)_2$, $Ag_2CO_3$,dppp, Toluene, 92 °C; v) TBAF, THF; vi) IBX, DMF; vii) Luche reduction; viii) LDA, tungsten lamp (150 W) -78 °C - r.t., 6h or $Hg(OAc)_2$, TEA, THF, r.t. 24h; ix) LAH, r.t. 2h

**Scheme 3** Synthesis of (+)-codeine via Heck cyclization.

From this point in the synthesis we focused on previously demonstrated strategies, namely, those of Trost and Parker, respectively. Trost [11] used the Heck cyclization of a vinyl bromide similar to **25** to establish the C-14 stereogenic center, whereas Parker [12] employed a reductive detosylation with concomitant hydroamination for late-stage construction of C-9. Conversion of the aldehyde in **24** to the vinyl bromide did not proceed in our hands with either the stereoselectivity or the yields reported by Trost. The mixture of vinyl bromides **25** resulted in moderate yields from the Wittig reaction. The second Heck cyclization provided the tetracycle, which was then subjected to the known oxidation-reduction sequence to adjust the C-6 stereochemistry, as shown in **26**. Deprotection gave **27**, the crucial secondary amine needed for hydroamination. We attempted to repeat Trost's procedure for photochemical hydroamination of the lithium amide derived from **27**; however, we observed no evidence of ring closure, despite having received detailed advice from Prof. Tang, who worked on the project while in the Trost group. To solve this tactical issue, we resorted to mercury(II)-catalyzed amination followed by reduction. We completed the synthesis of *ent*-codeine in 9 steps from carbamates **23** or 13 steps from diol **6** [13].

The synthesis of the natural enantiomer of codeine from diol **19** described above required a double Mitsunobu reaction at C-5. As discussed above, we found this protocol to be inefficient and low-yielding. To solve the problem, we transformed **19** to the allylic epoxides **21** via inversion of C-5 to produce nitrobenzoate ester **28**, and in the next step the distal hydroxyl was converted to tosylate **29**. Hydrolysis of the nitrobenzoate allowed the intramolecular displacement of the tosylate and led to the allylic epoxide in excellent yields, Scheme 4. Regioselective opening of the epoxide at C-5 with bromoisovanillin led to the aryl ether **22**, and protection of the C-6 hydroxyl as its TBS ether furnished the enantiomer of **20**. The synthesis of (–)-codeine was completed in essentially the same way as that of *ent*-codeine, except for some minor problems encountered during the adjustment of C-6 stereochemistry [14].




Reagents and Conditions: i) p-nitrobenzoic acid, $Ph_3P$, DIAD, toluene, 0 °C to rt (71%); ii) TsCl, $NEt_3$, DCM, DMAP, 0 °C to rt (73%); iii) MeONa, MeOH, THF, 0 °C to rt (88%); iv) potassium salt of isobromovanilin, 18-crown-6, DMF, DME, sealed tube, 100 °C (78%); v) TBSCl, imidazole, DCM, DMF, - 78 °C to rt (61%).

**Scheme 4** Synthesis of (–)-codeine via epoxide **21**.

## Balanol—the Burgess reagent route

Our interest in balanol arose from the investigation of a general method of synthesis for all *cis*- and *trans*-isomers of 1,2-amino alcohols in both enantiomeric series, a project for which we developed a chiral auxiliary version of the Burgess reagent, **30**. It reacted with oxiranes to produce a diastereomeric pair of cyclic *cis*-fused sulfamidates such as **32a** and **32b**, Fig. 4.

Separation of these compounds followed by hydrolysis provided enantiomerically pure *cis*-1,2-amino alcohols **33a** and **33b**. Cyclic sulfamidates resemble cyclic sulfates in their reactive tendencies toward nucleophilic opening, so reaction of **32a** and **32b** with ammonium benzoate produced cleanly the *trans*-amino alcohol derivatives **34a** and **34b** [15]. It is important to note that the enantiomeric purity of the final product depends on the efficiency of separation of the diastereomeric sulfamidates.

We applied this methodology to the formal synthesis of balanol via the often-used hexahydroazepine intermediate **35**. The design of the published synthesis is shown in Fig. 5.

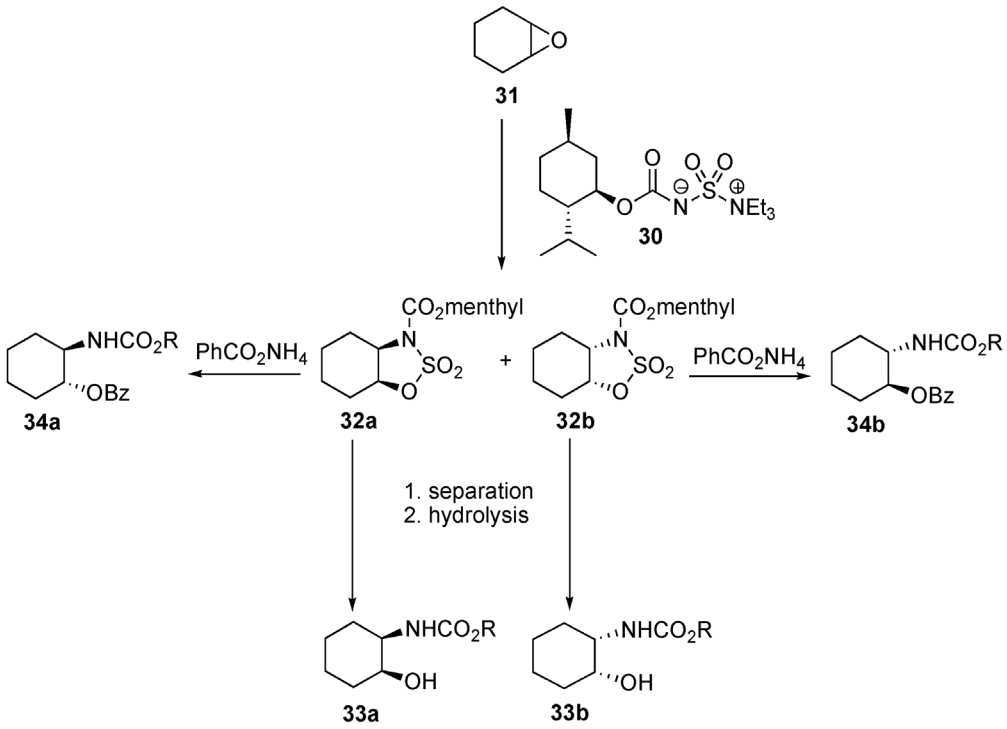



**Fig. 4** Design of enantiodivergent synthesis of amino alcohols via a chiral auxiliary version of the Burgess reagent and its reaction with oxiranes.

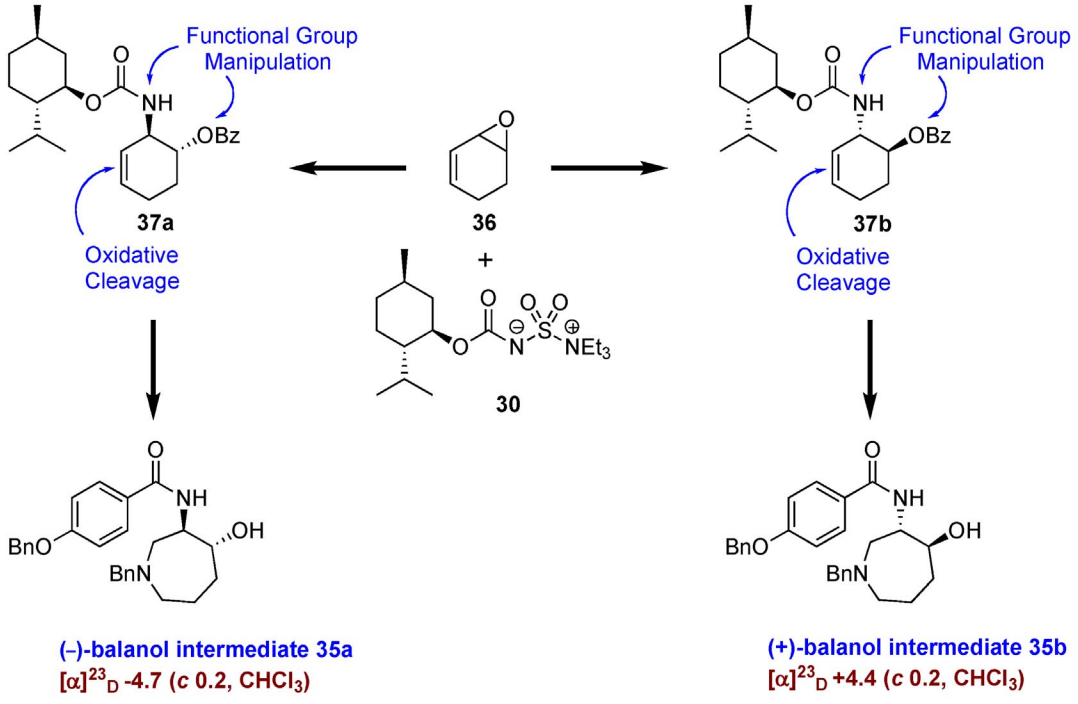



**Fig. 5** Burgess reagent route to the enantiodivergent synthesis of balanol.

Thus, the reaction of the menthyl chiral auxiliary version of the Burgess reagent with vinyl oxiranes **36** produced cleanly the *cis*-fused sulfamidates whose cleavage with ammonium benzoate gave the diastereomers **37a** and **37b**. Adjustment of the functionalities on the nitrogen and oxygen atoms followed by the oxidative cleavage of the olefin and reductive amination furnished the known balanol intermediates **35a** and **35b**, thus completing a formal enantiodivergent synthesis of balanol [16].

We evaluated the optical purity of the intermediates by the Mosher ester method and found both enantiomers to be approximately 95 % optically pure. The less-than-absolute optical purity is, as mentioned above, due to incomplete separation of the initially formed diastereomers, whose impurities are then reflected in the final enantiomeric composition following removal of the chiral auxiliary. We were surprised to find that no optical rotation data were available in the literature for either of the two enantiomers of **35** in several published syntheses of these compounds. To supply this data, we decided to embark on a synthesis of the intermediates **35a** and **35b** in a manner that would guarantee the final optical purity of the products. We designed a synthesis beginning with diol **5**, whose optical purity is absolute.

## Balanol—the chemoenzymatic route

We chose to convert diol **5** to its acetonide and then to two stereochemically distinct vinyl aziridines by employing different aziridination protocols. In one case, the use of the Yamada–Evans–Jacobsen protocol [17] led to the *anti*-isomer **39**, a compound that we have used in several approaches to Amaryllidaceae alkaloids [18]. In the other case, the *syn*-isomer **38** becomes available via Corey's aziridination protocol [19] employing $SnBr_4$ and *N*-bromoacetamide, as shown in Fig. 6.

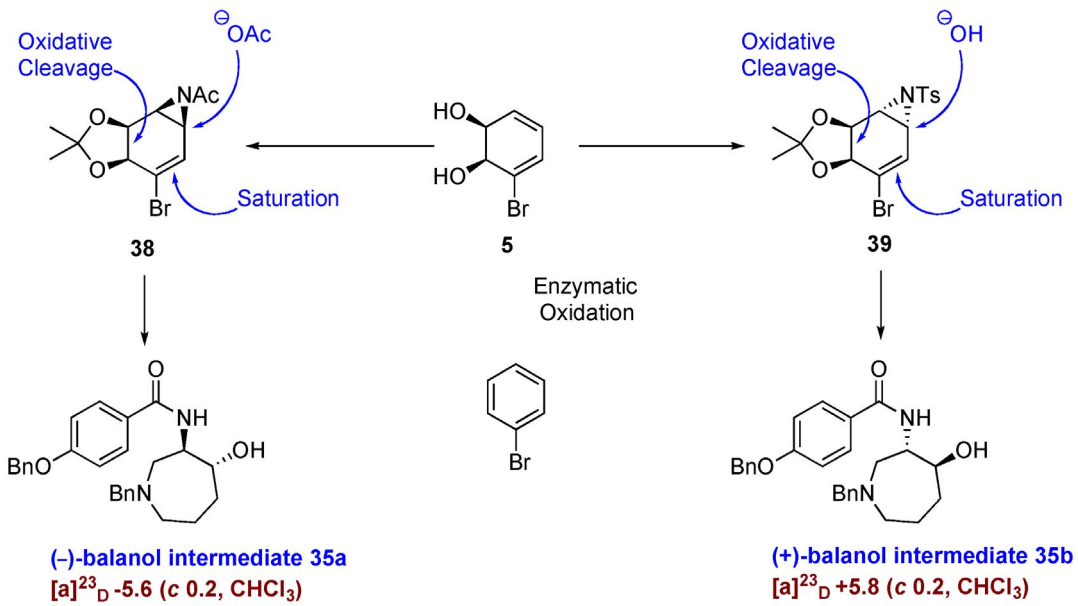



**Fig. 6** Chemoenzymatic enantiodivergent route to balanol via *cis*-dihydrodiol **5**.

The *trans*-diaxial opening of these aziridines provided the corresponding *trans*-amino alcohol derivatives that were in both cases easily purified and rendered free of any diastereomeric impurities. In both instances, the remaining steps consisted of saturation of the vinyl bromide moiety, replacement of tosyl and acetyl groups with the correct acyl functionality for balanol, and oxidative cleavage of the *cis*-diol followed by reductive amination with benzyl amine. Thus, in this approach the enzymatically

installed diol is used for chirality transfer within the synthetic intermediates and is removed once its function and purpose has been served. We noted a 15–20 % relative difference in the values of optical rotations obtained for both enantiomers of **35** as obtained via the Burgess and chemoenzymatic routes, respectively. As expected, the chemoenzymatic protocol provided essentially absolute optical purity in **35**, and led to additional enantiodivergent formal synthesis of balanol [20].

## Oseltamivir (Tamiflu)

In our continuing investigations of new metabolites derived from aromatic compounds, we examined a series of benzoate esters as substrates [21] and were able to produce diol **7** from ethyl benzoate in preparatively useful amounts. We have designed a second-generation approach to oseltamivir from this diol. Our earlier synthesis from diol **5** necessitated a palladium-catalyzed carboethoxylation protocol to install the ethyl ester midway through the synthesis. We recognized the latent symmetry in the depiction of oseltamivir structure, as shown in Fig. 7. In the route originating in diol **5**, the position of the double bond in the final product remains as it was in the starting material, whereas in the approach utilizing diol **7**, it is "reflected" across the latent plane of symmetry. This allows great flexibility in the order of introduction of nitrogen and oxygen functionalities, leaving the setting of the acrylate moiety for late-stage synthesis.

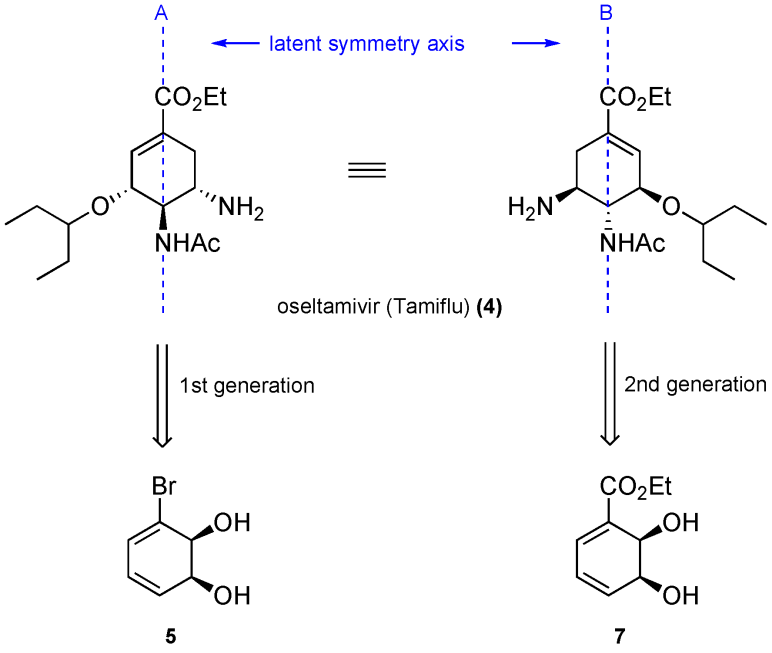
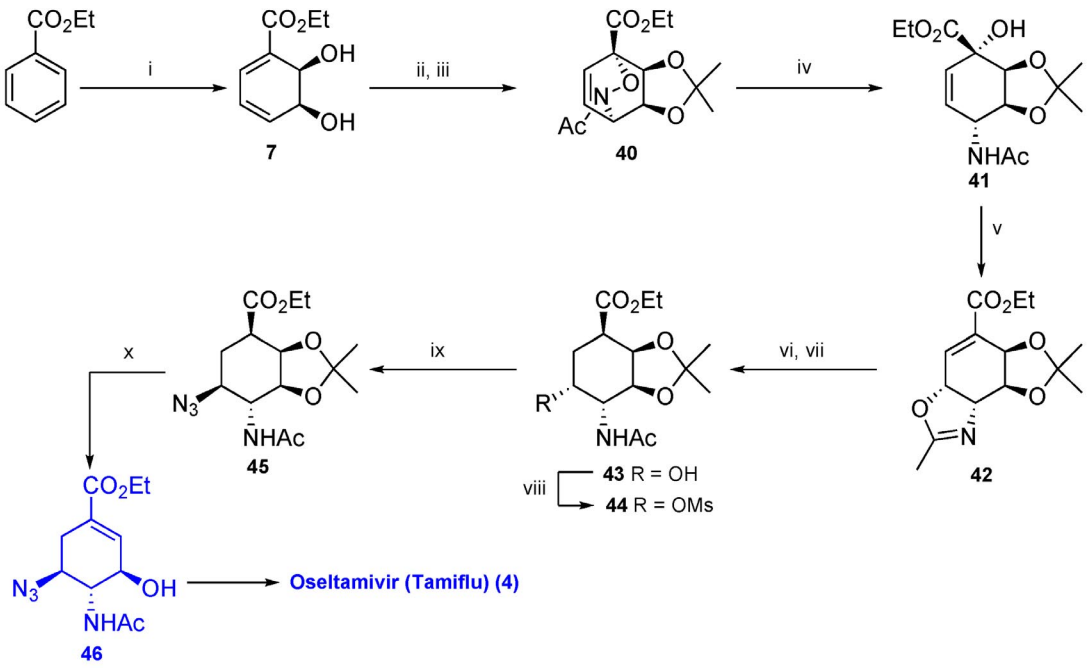



**Fig. 7** Symmetry-based design for oseltamivir from *cis*-dihydrodiols **5** and **7**.

As shown in Scheme 5, this design was reduced to practice by converting diol **7** to its acetonide and allowing it to undergo hetero-Diels–Alder cycloadditions to produce oxazine **40** in excellent yield and with absolute regio- and stereoselectivity. Reduction of the oxazine provided the allylic alcohol **41**, which was transformed to oxazoline **42** upon exposure to methanesulfonyl chloride. Hydrolysis of the oxazoline was effected in aqueous ethanol and in the presence of calcium carbonate followed by hydrogenation to give the fully saturated alcohol **43**, which was converted to its mesylate (**44**). Displacement of the mesylate with azide led to **45**, whose base-catalyzed elimination provided Fang's




Reaction conditions: i) *E. coli* JM109 (pDTG601A); ii) DMP, TsOH, rt; iii)$CH_3CONHOH$, $NaIO_4$, MeOH, rt; iv) $Mo(CO)_6$, MeCN:$H_2O$ (15:1), Δ; v) MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt; vi) $CaCO_3$, EtOH:$H_2O$ (1:1), Δ; vii) 5% $Rh/Al_2O_3$, 60 psi $H_2$, 85% EtOH; viii) $Ms_2O$, $Et_3N$, $CH_2Cl_2$, rt; ix) $NaN_3$, acetone, $H_2O$, rt; x) DBU, $CH_2Cl_2$, rt.

**Scheme 5** Chemoenzymatic synthesis of oseltamivir from ethyl benzoate.

intermediate (**46**) via the collapse of the acetonide functionality. This maneuver represents the "symmetry switch" of the acrylate olefin, as portrayed in Fig. 7. Thus, a formal synthesis of oseltamivir was completed from ethyl benzoate, a commodity chemical, in 10 steps to attain azide **46** in only 7 operations [22a]. In the most recent generation of oseltamivir synthesis the target was attained in 10 steps and 5 operations without the use of azide [22b].

## CONCLUSION

We have demonstrated the effectiveness of the combination of biological methods with traditional synthetic techniques in the multigenerational design of four complex molecules. In each case, the starting material was generated from an achiral precursor by an enzymatic reaction. Biocatalysis offers advantages over traditional methods in that it provides enantiopure starting materials in an environmentally benign manner. In the case of *cis*-dihydrodiols, it produces additional complexity in the functional groups that are generated by oxidative dearomatization. The generation of downstream complexity is an important parameter of efficiency on organic synthesis. It has been shown on numerous examples that biocatalytic steps performed early in a synthetic pathway greatly contribute to complexity generation in the products [23]. Our future endeavors in the area are focused on further refinements of the approaches to the targets presented in this paper as well as on the discovery and implementation of new metabolites for asymmetric synthesis of complex natural and unnatural products.

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