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Short asymmetric syntheses of bioactive β-aryl ethanolamine derivatives via the highly diastereoselective delta lactol oxy-Michael addition

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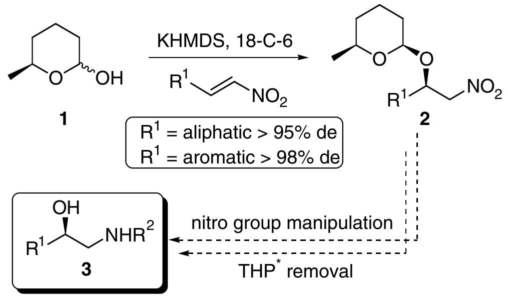
Abstract—Short, stereoselective and efficient total syntheses of the bioactive β-aryl ethanolamine derivatives (*R*)-tembamide, (*R*)-aegeline and (*R*)-pronethalol have been achieved using the highly diastereoselective oxy-Michael addition of 'naked' delta lactol anions to nitro olefins as the key step.

The enantiopure β-aryl ethanolamine structural motif occurs frequently in nature and has been exploited by pharmaceutical companies in the development of compounds for combating high blood pressure, hypertension, arrhythmia, asthma and angina.[1] Recent studies have demonstrated that in most β-aryl ethanolamine drug substances the (*R*)-enantiomer gives rise to more desirable biological activity than its antipode.[1d,2] These facts coupled with the general utility of enantiomerically pure amino alcohol products as building blocks in asymmetric synthesis have stimulated us to develop methodology that can be rapidly applied to their synthesis.

Owing to its technical simplicity we have pursued the diastereoselective oxy-Michael addition approach of anionic chiral alcohols to nitro olefin acceptors.[3] Recently, we have found that (*S*)-6-methyl delta lactol **1** undergoes highly diastereoselective oxy-Michael additions to β-substituted nitro olefin acceptors when reacted as their 'naked' anions.[4] The reaction constitutes an attractive key step in the stereoselective synthesis of 1,2-amino alcohol derivatives **3** because the source of chirality becomes a readily removable tetrahydropyranyl (THP*) ether group in the *O*-protected Henry products **2**[5,6] (Scheme 1).



Scheme 1. The highly diastereoselective oxy-Michael addition of 'naked' delta lactol anions to nitro olefins and its potential in the synthesis of bioactive β-aryl ethanolamine derivatives.

Herein we report a simple but effective application of this work to the total syntheses of some important bioactive β-aryl ethanolamine derivatives—(*R*)-tembamide **4**,[7] (*R*)-aegeline **5** and (*R*)-pronethalol **6**[8]—to highlight our new methodology (Fig. 1).

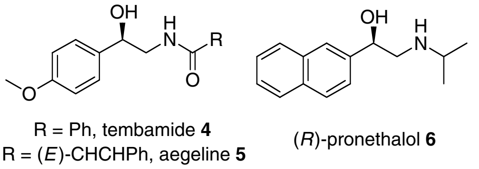


Figure 1. Bioactive β-aryl ethanolamine derivatives.

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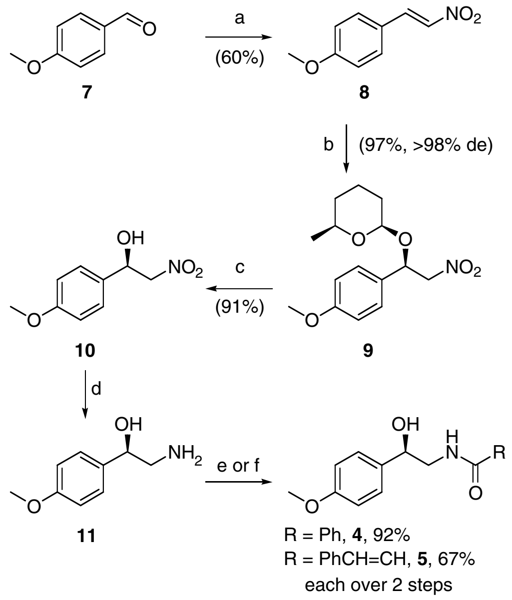
Tembamide and aegeline are naturally occurring β-aryl ethanolamine derivatives isolated from various members of the family Rutaceae.[9] These compounds are reported to have adrenaline-like and insecticidal activity.[10] Furthermore, extracts of *Aegle marmelos* Corr., which contain tembamide, show hypoglycaemic activities and have been used in traditional Indian medicines.[11] Pronethalol was the first clinically available β-blocker and was effective not only in the treatment of angina but also controlled certain kinds of cardiac arrhythmia and reduced elevated blood pressure.

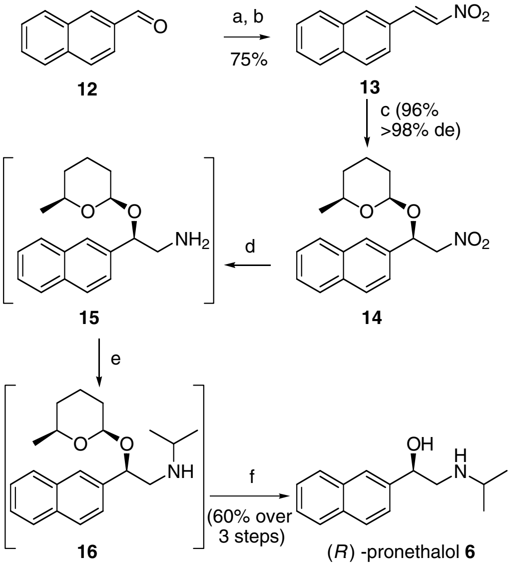
The total syntheses of aegeline and tembamide began from *para*-anisaldehyde **7**. Condensation with nitromethane following the method of Feng et al. afforded (*E*)-*para*-methoxy β-nitrostyrene **8** in acceptable yield (60%)[12] (Scheme 2).



Scheme 2. Highly stereoselective total syntheses of (*R*)-tembamide **4** and (*R*)-aegeline **5**. Reagents and conditions: (a) NH_4OAc, $MeNO_2$; (b) **1**, KHMDS, THF, −78 °C, 18-crown-6, then **8**; (c) MP–TsOH, MeOH; (d) Pd/C, H_2 (50 bar), MeOH; (e) PhCOCl, NaOH, H_2O/DCM; (f) (*E*)-PhCHCHCOCl, NaOH, H_2O/DCM.

Deprotonation of lactol **1**[13] with KHMDS in THF at −78 °C followed by addition of 18-crown-6 (1.0 equiv) and nitro olefin acceptor **8**, gave on protic work-up, the oxy-Michael addition product **9** in >98% de[14] and in 97% yield. Interestingly, when the oxy-Michael reaction is performed in the absence of crown ether, the dr at the β-centre for the *syn*-THP* isomers is ~1:1. Simple acidic methanolysis using polymer supported sulfonic acid resin[15] gave the Henry product **10** in 91% yield after purification by column chromatography. Conversion of **10** to tembamide and aegeline was then possible in two consecutive steps. First the material was reduced to the crude 1,2-amino alcohol **11** using Pd/C in methanol under an atmosphere of hydrogen at 50 bar. Under Schotten–Baumen conditions this crude material was then treated with benzoyl chloride and also cinnamoyl chloride to give tembamide **4** and aegeline **5**, respectively, in 92% and 67% yields over the two steps. In both cases all physical and spectroscopic data as well as the specific rotation were in good agreement with the reported data. The enantiomeric excesses of both **4** and **5** were both >98% as determined by derivatisation as their Mosher's esters.

The synthesis of (*R*)-pronethalol **6** followed a similar strategy. Thus 2-naphthaldehyde **12** was condensed with nitromethane in the presence of potassium *tert*-butoxide (10%) to give the Henry product, which was subsequently eliminated to the nitro olefin acceptor **13** using acetic anhydride (2.6 equiv) and DMAP (cat) in 75% yield over the two steps. Subjection of this material to the 'naked' lactol anion following the usual procedure led to the desired oxy-Michael adduct **14** in 96% yield and >98% de[14] (Scheme 3).



Scheme 3. Stereoselective synthesis of (*R*)-pronethalol **6**. Reagents and conditions: (a) $MeNO_2$, KO^{t}Bu, THF, ^{t}BuOH; (b) Ac_2O, DMAP, CH_2Cl_2; (c) **1**, THF, KHMDS, −78 °C 18-crown-6, then **13**; (d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C; (e) PtO_2, AcMe, H_2, EtOAc; (f) MP–TsOH (2 equiv), MeOH.

From **14**, (*R*)-pronethalol could be accessed in three steps. First, a nickel boride reduction of the nitro group gave the crude primary amine **14**, which was then subjected to a reductive amination using acetone and platinum oxide under an atmosphere of hydrogen to give isopropyl amine **16**. Dissolution in methanol and addition of an excess of polymer supported sulfonic acid resin[15] effected smooth THP* removal to afford (*R*)-pronethalol **6** in 60% yield over the three steps. The spectroscopic and physical data for the synthetic material were in excellent agreement with those reported previously. The enantiomeric excess of **6** was determined as >98% using 2,2,2-trifluoro-1-(9-anthryl)-ethanol chiral shift reagent.

In conclusion, the highly diastereoselective oxy-Michael addition of the 'naked' lactol anion of 6-methyl tetrahydropyranol **1** to β-aryl nitro olefins has been exploited as the key step in the stereoselective synthesis of a range of bioactive β-aryl ethanolamine derivatives. Further investigations into the origins of stereocontrol and applications of the stereoselective oxy-Michael reaction are underway.

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