An expedient preparation of chiral building blocks having levoglucosenone chromophore: a new enantiocontrolled route to (−)-β-multistriatin and (+)-*exo*-brevicomin

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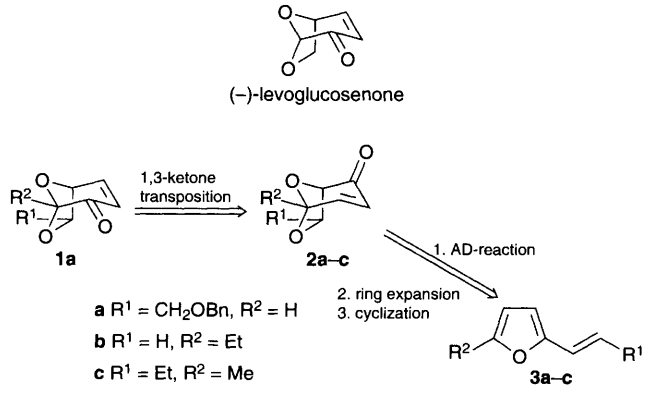
2-Alkenylfurans are transformed enantioselectively into the bicyclic enones having the levoglucosenone chromophore, whose synthetic utility is demonstrated by a stereocontrolled synthesis of two insect pheromones (−)-β-multistriatin and (+)-*exo*-brevicomin.

(−)-Levoglucosenone,[1,2] a cellulose pyrolysis product, is a highly versatile chiral building block[3] owing to its functionality confined in a structurally biased rigid bicyclic framework. However, its practical acquisition is not easy[1,4] and limited to the (−)-enantiomer, although a multi-step synthesis of the (+)-enantiomer from natural galactose has recently been disclosed.[5] For this reason, we investigated the asymmetric synthesis of the chiral building blocks having the levoglucosenone chromophore from readily accessible achiral starting materials, employing Sharpless asymmetric dihydroxylation (AD reaction).[6] The procedure we planned consisted of four stages of conversions, commencing with AD reaction of 2-alkenylfurans **3**, followed by sequential oxidative ring-expansion, acid-catalysed cyclization, and 1,3-ketone *trans*-position to give the bicyclic compounds **1** and **2** having the levoglucosenone chromophore (Scheme 1).

Thus, (*E*)-2-(3-benzyloxyprop-1-enyl)furan **3a**, obtained in 93% overall yield in three steps from furfural, was treated with AD-mix-α† in the presence of methylsulfonamide[6] to give the single diol‡ (−)-**4a**, mp 37.0–38.0 °C, $[\alpha]_D^{25}$ −15.8 (*c* 1.0, $CHCl_3$), in 82% yield with 98% ee.§ Similarly, the same furan **3a** was transformed into the enantiomeric diol (+)-**4a**, mp 37.0–38.0 °C, $[\alpha]_D^{30}$ +15.9 (*c* 1.1, $CHCl_3$), in 72% yield with 99% ee§ by using AD-mix-β.†

The oxidative ring-expansion[7] was best carried out by treating the diol **4a** with *N*-bromosuccinimide (NBS) in aqueous tetrahydrofuran (THF) in the presence of sodium acetate[8] to give the 3-pyrone derivative **5a** as a mixture of epimers. Without separation, the mixture was refluxed azeotropically in benzene in the presence of a catalytic amount of toluene-*p*-sulfonic acid (TsOH) to give the bicyclic ketoacetal **2a** having opposite enone disposition to that of levoglucosenone **1**. Thus,

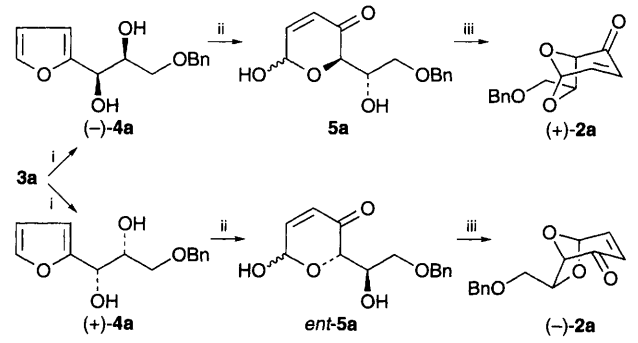


Scheme 1

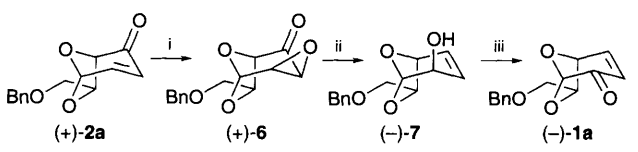
(−)-**4a** afforded (+)-enone (+)-**2a**, mp 55.5–56.5 °C, $[\alpha]_D^{29}$ +185.3 (*c* 1.0, $CHCl_3$), in 51% overall yield and (+)-**4a** afforded enantiomeric (−)-enone (−)-**2a**, mp 56.0–57.0 °C, $[\alpha]_D^{29}$ −183.9 (*c* 1.0, $CHCl_3$), in 53% overall yield, respectively, on the same treatment. Both of the enantiomeric products **2a** were optically purified by single recrystallization (>99% ee§). Although **2a** possesses the opposite enone disposition to that of levoglucosenone, it may be taken as functionally the same from the synthetic viewpoint (Scheme 2).

To adjust the enone disposition to that of levoglucosenone **1**, (+)-**2a** was first transformed into the epoxide **6**, mp 58.5–59.5 °C, $[\alpha]_D^{27}$ +3.2 (*c* 1.0, $CHCl_3$), in 75% yield as a single product. The reaction was presumed to take place selectively from the convex face of the molecule as **6** does not show any coupling between the acetal proton and the adjacent proton on the epoxide carbon (dihedral angle ~90°) in ^1H NMR spectrum. The epoxide **6** was next exposed to hydrazine hydrate in the presence of acetic acid[9] to give the allylic alcohol **7**, $[\alpha]_D^{31}$ −81.3 (*c* 1.0, $CHCl_3$), in 60% yield, which furnished the enone (−)-**1a**, $[\alpha]_D^{29}$ −258.1 (*c* 0.9, $CHCl_3$), having the levoglucosenone framework in 71% yield on oxidation. The enantiomeric enone (+)-**1a**, $[\alpha]_D^{23}$ +260.5 (*c* 0.9, $CHCl_3$), was also obtained from (−)-**2a** in a comparable overall yield on the same treatments (Scheme 3).

To demonstrate the utility of the present procedure, we next examined the enantiocontrolled synthesis of two typical natural compounds having the dioxabicyclo[3.2.1]octane framework.



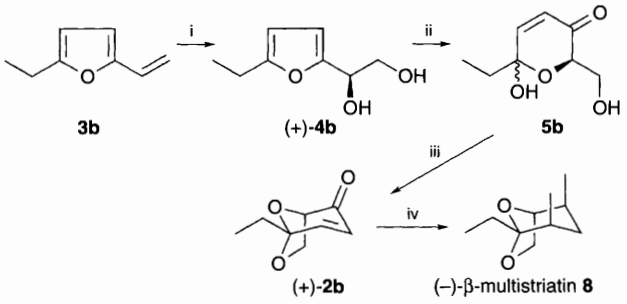
Scheme 2 *Reagents and conditions*: i, AD-mix-α [for (−)-**4a**] or AD-mix-β [for (+)-**4a**] (1 equiv.), $MeSO_2NH_2$ (1 equiv.), aq. Bu^tOH (50%), 0 °C, 12 h, 82% by AD-mix-α, and 72% by AD-mix-β; ii, NBS (1.1 equiv.), NaOAc (1.1 equiv.), aq. THF (20%), 0 °C; iii, *p*-TsOH (cat.), benzene, reflux, 51 and 53% from **4a**



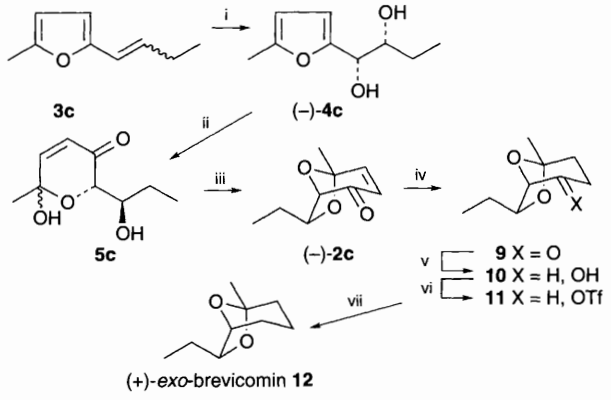
Scheme 3 *Reagents and conditions*: i, 30% H_2O_2 (1.5 equiv.), 0.5 mol dm^{-3} NaOH (0.5 equiv.), THF, 75%; ii, 90% $NH_2NH_2{\cdot}H_2O$ (3 equiv.), AcOH (cat.), MeOH, room temp., 60%; iii, MnO_2, CH_2Cl_2 (71%)

Our first target was the bicyclic enone **2b** which was used as the key intermediate of the first synthesis of (−)-β-multistriatin[10,11] **8** isolated in traces as a component of the pheromone bouquet of the elm bark beetles *Scholytus multistriatus* and *Scholytus scholytus*. Thus, asymmetric dihydroxylation of 5-ethyl-2-vinylfuran **3b**, obtained in 75% from 5-ethyl-2-furfural by Wittig reaction, with AD-mix-α afforded the chiral diol **4b**, $[\alpha]_D^{30}$ +23.2 (*c* 0.9, $CHCl_3$), in 86% yield with 89% ee.§ On oxidative ring-expansion followed by acid-catalysed cyclization as above, **4b** gave the expected bicyclic enone **2b**, $[\alpha]_D^{30}$ +286.0 (*c* 1.0, $CHCl_3$) [lit.,[11] $[\alpha]_D^{20}$ +260.99 (*c* 1.02, $CHCl_3$)], in 49% overall yield *via* **5b**. Transformation of **2b** into the natural product **8** has been carried out in three steps in excellent yield.[11]

Our next target was (+)-*exo*-brevicomin[12] **12**, a pheromone in frass produced by the western pine beetle *Dendroctonus brevicomis*. The starting 5-methyl-2-(but-1-enyl)furan **3c** was prepared from 5-methylfurfural in 76% overall yield as an inseparable *E*/*Z*-mixture (5.6 : 1) by Julia coupling reaction.[13] Fortunately, the AD reaction of **3c** using AD-mix-β proceeded



Scheme 4 *Reagents and conditions*: i, AD-mix-α (1 equiv.), $MeSO_2NH_2$ (1 equiv.), aq. Bu^tOH (50%), 0 °C, 12 h, 86%; ii, NBS (1.1 equiv.), NaOAc (1.1 equiv.), aq. THF (20%), 0 °C; iii, pyridinium toluene-*p*-sulfonate (PPTS) (cat.), benzene, reflux, 49% from **4b**; iv, ref. 11



Scheme 5 *Reagents and conditions*: i, AD-mix-β (1 equiv.), $MeSO_2NH_2$ (1 equiv.), aq. Bu^tOH (50%), 0 °C, 12 h, 70%; ii, NBS (1.1 equiv.), NaOAc (1.1 equiv.), aq. THF (20%), 0 °C; iii, PPTS (cat.), benzene, reflux, 75% from **4c**; iv, H_2, 10% Pd–C, AcOEt; v, $NaBH_4$, MeOH, 98% from **2c**; vi, $(CF_3SO_2)_2O$ (1.1 equiv.), pyridine (1.5 equiv.), CH_2Cl_2, 79%; vii, $NaBH_4$, MeCN, 50%

chemoselectively only with the *E*-alkene component to give the *threo*-diol **4c**, $[\alpha]_D^{27}$ −16.0 (*c* 0.9, $CHCl_3$), in 70% yield with 97% ee§ leaving the *Z*-alkene component intact. Upon the sequential oxidative ring-expansion and acid-catalysed cyclization, the diol **4c** afforded the bicyclic enone **2c**, mp 42–43 °C, $[\alpha]_D^{30}$ −126.9 (*c* 0.9, $CHCl_3$), in 75% yield *via* **5c**. Conversion of **2c** into (+)-*exo*-brevicomin **12** was accomplished in four steps. Thus, on sequential catalytic hydrogenation and sodium borohydride reduction, **2c** afforded the secondary alcohol **10** as a diastereoisomeric mixtures (9 : 1) in 98% yield *via* the ketone **9**, $[\alpha]_D^{27}$ +25.6 (*c* 1.0, $CHCl_3$), in 98% overall yield. Then, trifluoromethanesulfonylation of **10** followed by reduction of the resulting triflate **11** with sodium borohydride in acetonitrile[14] furnished the natural product **12**, $[\alpha]_D^{29}$ +63.4 (*c* 0.7 Et_2O) {lit., $[\alpha]_D^{26}$ + 84.1 (*c* 2.2, Et_2O);[12] $[\alpha]_D^{21}$ + 67.7 (*c* 1.0, Et_2O)[15]}, in 40% overall yield.

Footnotes

† AD-mix-α and AD-mix-β were purchased from Aldrich and used without purification.

‡ Satisfactory spectral (IR, ^1H NMR, MS) and analytical (combustion and/or high resolution MS) data were obtained for all isolable new compounds.

§ Optical purity was determined by HPLC using a chiral column: (+)- and (−)-**4a** (CHIRALCEL OD, elution with Pr^iOH–hexane, 5:95) after conversion to the acetonides; (+)- and (−)-**2a** (CHIRALCEL OD, elution with EtOH–hexane, 10:90); (+)-**4b** and (−)-**4c** (CHIRALCEL OD, elution with Pr^iOH–hexane, 1:99).

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