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The first enantiocontrolled synthesis of naturally occurring polyoxygenated cyclohexenylmethanol dibenzoates (–)-zeylenol, (–)-uvarigranol G, (–)-tonkinenin A and (+)-pipoxide

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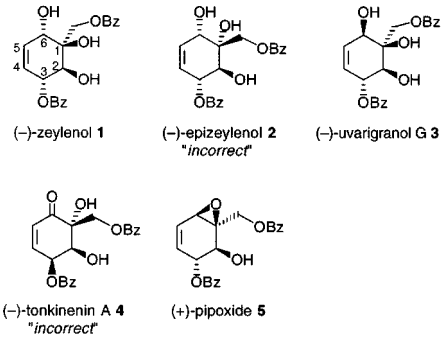
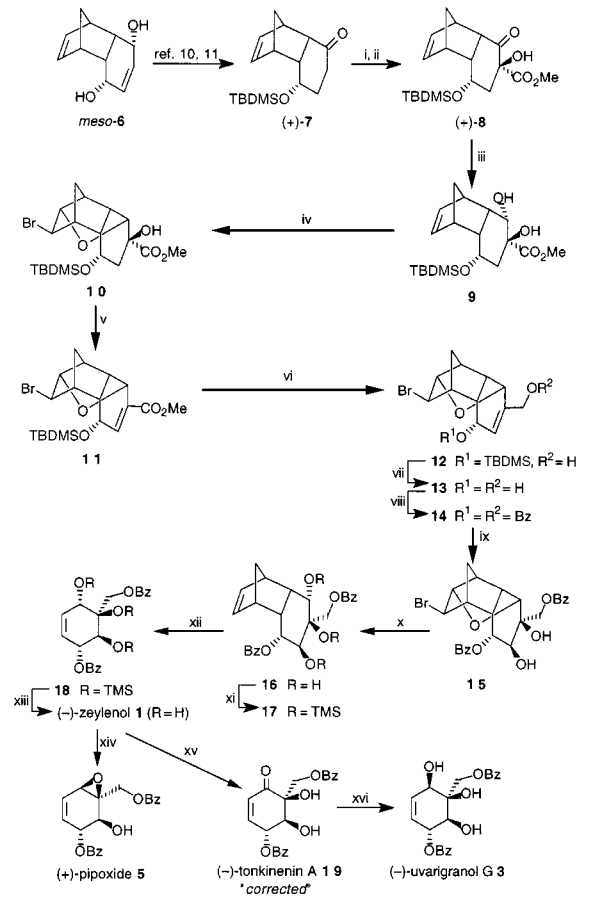
The first enanticontrolled synthesis of five naturally occurring polyoxygenated cyclohexenylmethanol dibenzoates has been achieved to confirm three [(–)-zeylenol, (–)-uvarigranol G, (+)-pipoxide], revise one [(–)-tonkinenin A] and disprove one [(–)-epizeylenol] of the proposed structures.

The isolation has been reported[1] of five polyoxygenated cyclohexenylmethanol dibenzoates, (–)-zeylenol[2,3] **1**, (–)-epizeylenol[2,4] **2**, (–)-uvarigranol G[5] **3**, (–)-tonkinenin A[6] **4** and (+)-pipoxide[2,7] **5**, from plants of the genus *Uvaria* which are

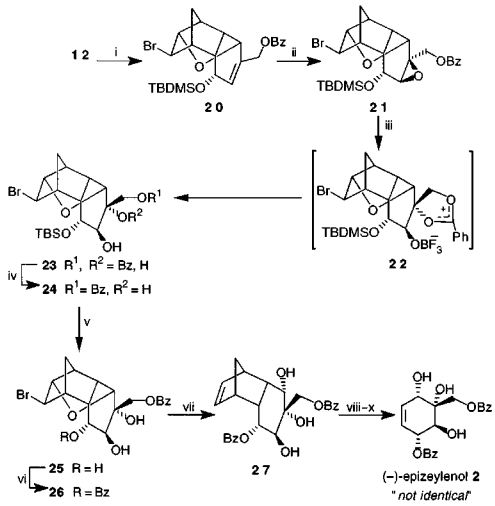


widely distributed across Asia, Africa, and Australia and are used in Chinese traditional medicine to treat digestive disorders. Although the structures of two, **1** and **5**, have been determined unambiguously on the basis of chemical correlation[8] and the racemic synthesis of the latter as well as X-ray analysis[7] of the racemate, the structures of the other three were proposed only on the basis of spectroscopic measurements. Since the diastereo- and enantio-controlled synthesis of these natural products has so far not been reported, we were interested in the construction of these natural products utilizing the chiral cyclohexanoid building block[9] **7** prepared from the *meso*-enediol **6** by either a catalytic[10] or an enzymatic[11] asymmetric desymmetrization procedure. We report here our study leading to the first diastereo- and enantio-controlled synthesis of all of these five compounds which concluded the validity of the proposed structures of three, (–)-zeylenol **1**, (–)-uvarigranol G **3** and (+)-pipoxide **5**, and the invalidity of two, (–)-epizeylenol **2** and (–)-tonkinenin A **4**. The present work has determined the structure of (–)-tonkinenin A not as **4** but as **19**, unambiguously, although the structure of (–)-epizeylenol still remains to be ascertained.

Besides diastereo- and enantio-controlled introduction of their oxygen functionalities, one difficulty which had to be resolved in the construction of these polyoxygenated molecules was regioselective introduction of two benzoyl groups on appropriate oxygen functionalities. To this end, we first transformed the (+)-siloxy ketone[10,11] **7** into the β-hydroxyketo ester† **8**, mp 110 °C, $[\alpha]_D^{29}$ +60.1 (*c* 0.95, $CHCl_3$), by sequential α-methoxycarbonylation and convex-face selective α-hydroxylation as we have carried out in the synthesis of its enantiomer (Scheme 1).[12] Reduction of **8** with $NaBH_4$ occurred diastereoselectively from the convex-face to give the single *trans*-1,2-diol **9**. To block the cyclopentene olefin, **9** was exposed to NBS to give the bromo ether **10**, $[\alpha]_D^{29}$ −22.6 (*c* 2.65, $CHCl_3$). Dehydration of **10**, followed by reduction of the resulting α,β-unsaturated ester **11**, mp 155–156 °C, $[\alpha]_D^{29}$ −8.4 (*c* 1.45, $CHCl_3$), gave the primary alcohol **12** which, on desilylation, afforded the diol **13** having an appropriate structure for dibenzoylation and diastereoselective dihydroxylation. Thus, **13** was benzoylated to give the dibenzoate **14**, mp 134–135 °C, $[\alpha]_D^{28}$ −36.1 (*c* 1.31, $CHCl_3$), whose dihydroxylation using a catalytic amount of OsO_4 and NMO occurred stereoselectively from the convex-face to give the single diol **15**. At this stage, the cyclopentene olefin was regenerated by treating the bromo ether



Scheme 1 *Reagents and conditions*: i, NaH, $(MeO)_2CO$, THF, room temp. (89%); ii, O_2, KF, $(EtO)_3P$, DMSO, ~30 °C (82%); iii, $NaBH_4$, MeOH–THF, −15 °C; iv, NBS, CH_2Cl_2, −15 °C (96%, 2 steps); v, $POCl_3$, pyridine, 50 °C (84%); vi, DIBAL-H, toluene, −78 °C; vii, Bu_4NF, THF, room temp. viii, BzCl, pyridine, DMAP (cat.) (97%, 3 steps); ix, OsO_4 (cat.), NMO, aq. THF, room temp. x, Zn, NH_4Cl, aq. THF, reflux (96%, 2 steps); xi, TMSCN, DMF, 80 °C; xii, Ph_2O, reflux, 15 min; xiii, HF; MeCN (83%, 3 steps); xiv, DEAD, PPh_3, THF (62%); xv, MnO_2, CH_2Cl_2–AcOEt (5:1) (100%); xvi, $NaBH_4/CeCl_3 \cdot 7H_2O$, MeOH, −70 °C (100%).



Scheme 2 *Reagents and conditions*: i, BzCl, pyridine, DMAP (cat.) (90%); ii, *M*CPBA, CH_2Cl_2, room temp. (91%); iii, $BF_3{\cdot}OEt_2$, toluene, –20 °C; iv, TsOH, $CHCl_3$, ~30 °C; v, HF, MeCN, THF, ~30 °C (83%, 3 steps); vi, BzCl (1 equiv.), pyridine, DMAP (cat.) (52%); vii, Zn, NH_4Cl, aq. THF, reflux (77%); viii, TMSCN, DMF, 80 °C; ix, Ph_2O, reflux, 25 min; x, HF, MeCN, ~30 °C (76%, 3 steps).

15 with zinc in aqueous THF containing NH_4Cl to give the triol **16**, mp 166–168 °C, $[\alpha]_D^{29}$ −55.4 (*c* 0.66, $CHCl_3$), having four contiguous oxygen functionalities on the cyclohexane moiety.

Having introduced the requisite functionalities, the triol **16** was pertrimethylsilylated using TMSCl[13] in DMF to give the silyl ether **17** which was heated in refluxing Ph_2O for 15 min to give (–)-zeylenol **1**, mp 129–130 °C, $[\alpha]_D^{23}$ −140.5 (*c* 1.02, $CHCl_3$) [lit.,[3] mp 144–145 °C, $[\alpha]_D^{25}$ −116.3 (*c* 0.915, $CHCl_3$)], after desilylation of the crude product.

(+)-Pipoxide **5** was obtained from (–)-zeylenol **1** under Mitsunobu conditions.[14] Thus, on treatment with DEAD and PPh_3 in THF, **1** afforded (+)-pipoxide **5**, mp 129 °C, $[\alpha]_D^{28}$ +55.2 (*c* 0.78, $CHCl_3$) [lit.,[7] mp 152 °C, $[\alpha]_D^{23}$ +53 (*c* 0.02, $CHCl_3$)], stereoselectively.

In order to obtain (–)-uvarigranol G **3**, which was proposed as the C-6 epimer of (–)-zeylenol **1**, we attempted its synthesis from **1** by sequential allylic oxidation and stereoselective reduction. Thus, we first treated **1** with MnO_2 in a mixture of CH_2Cl_2 and EtOAc to give the enone **19**. To our surprise, the physical and spectroscopic data of the enone **19**, mp 158–160 °C, $[\alpha]_D^{27}$ −26.0 (*c* 0.89, MeOH), obtained quantitatively, were found to be identical with those of (–)-tonkinenin A, mp 158–159 °C,[6] $[\alpha]_D^{24}$ −21.6 (*c* 1.71, MeOH),[6] which was proposed as **4**.[6] Thus, we were able to accomplish the first synthesis of this natural product unexpectedly and have revised its structure as **19**. As expected, reduction of **19** with $NaBH_4$/$CeCl_3$[15] allowed diastereoselective reduction of the enone carbonyl to give (–)-uvarigranol G **3**, mp 62–64 °C, $[\alpha]_D^{29}$ −45.8 (*c* 0.73, $CHCl_3$) [lit.,[5]: mp 67–69 °C, $[\alpha]_D^{16}$ −44 (*c* 0.08, $CHCl_3$)].

To obtain (–)-epizeylenol **2**, which was proposed as the C-1 epimer of (–)-zeylenol **1**, the primary alcohol **12** was benzoylated to give **20**, which was converted into the epoxide **21**, diastereoselectively, from the convex-face (Scheme 2). On exposure to $BF_3{\cdot}OEt_2$[16] in toluene, **21** afforded a mixture of the secondary and the primary monobenzoates **23** and **24** after hydrolytic work-up, presumably through the 1,3-dioxolenium intermediate **22**. The mixture without separation was then stirred in $CHCl_3$ containing TsOH to converge to the single primary monobenzoate **24**, which was desilylated to give the triol **25**, mp 208–209, $[\alpha]_D^{30}$ –70.3 (*c* 0.92, THF). Benzoylation of **25** using 1 equiv. of BzCl allowed regioselective monoacylation at the desired position to give the single dibenzoate **26**, mp 254–256 °C, $[\alpha]_D^{31}$ −94.4 (*c* 0.59, THF), along with a minor amount of the separable regioisomer. The observed preferential generation of **26** may be due to the steric hindrance of the primary benzoate functionality, which shields the *exo*-hydroxy functionality considerably. The bromo ether linkage of **26** was then cleaved reductively to yield the triol **27**, mp 169–170 °C, $[\alpha]_D^{28}$ –64.5 (*c* 0.54, $CHCl_3$). As above, on sequential per-*O*-silylation, thermolysis and desilylation, **27** afforded the cyclohexene dibenzoate having the structure **2** which was proposed as (–)-epizeylenol, mp 154–155 °C, $[\alpha]_D^{27}$ −139.1 (*c* 0.22, $CHCl_3$), but its physical and spectroscopic data were not identical with those reported for the natural product, mp 206–207 °C.[4] It was also confirmed that the secondary benzoyl functionality of **2** was not rearranged during these transformation reactions as it afforded the corresponding 6-keto derivative, mp 230–232 °C, $[\alpha]_D^{29}$ −220.5 (*c* 0.12, $CHCl_3$). Thus, the proposed structures of (−)-epizeylenol **2** and (−)-tonkinenin A **4** were both found to be erroneous.

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Notes and references

† Satisfactory analytical (combustion and/or high resolution mass) and spectroscopic (IR, ^1H and ^{13}C NMR, MS) data was obtained for isolable new compounds.

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