Synthesis of a key intermediate for corossolin using hydrolytic kinetic resolution of epoxides

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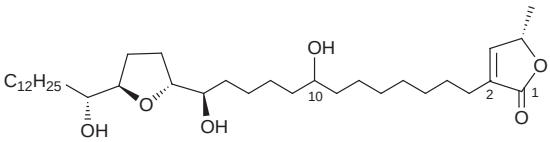
A convergent synthesis of the key intermediate for corossolin has been achieved using hydrolytic resolution of epoxides as the key step, which extends the scope of the applicable substrates for hydrolytic kinetic resolution to cover multifunctionalized large molecules.

Annonaceous acetogenins (AAs) are a relatively new class of natural products, which have been isolated from the tropical and subtropical plants of the *Annonaceae* family. They are characterized by one or more tetrahydrofuran rings, together with a terminal α,β-unsaturated γ-lactone on a 35- or 37-carbon chain. A majority of these compounds exhibit[1] high cytotoxicity and immunomodulating activities, which make these compounds potential parasiticidal, insecticidal, and above all, powerful tumoricidal agents.

As part of our research on the synthesis[2] of annonaceous acetogenins, we performed first a total synthesis[2c] of the



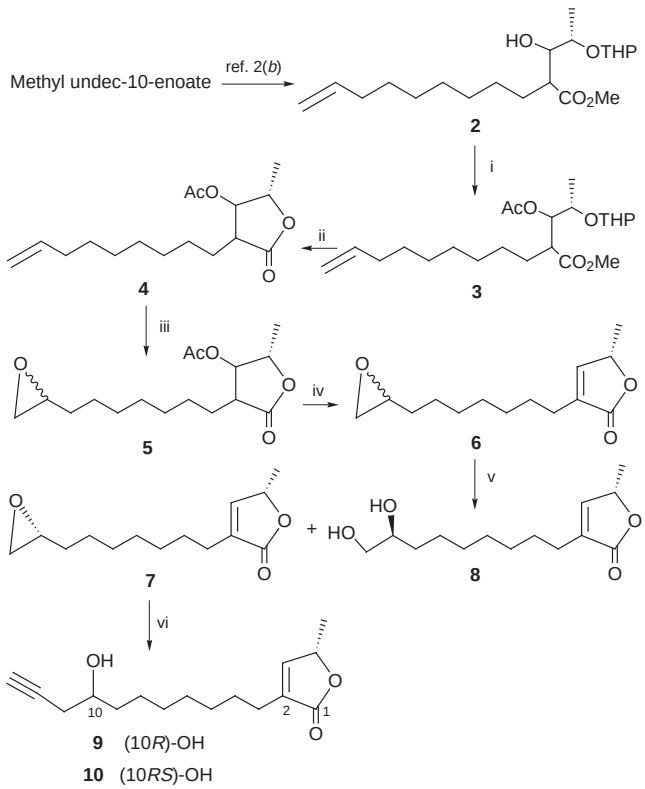
(10*RS*)-epimer mixture of corossolin **1**,[3] and later of both[4] 10-epimers, in an effort to establish the configuration at C-10 of natural corossolin, which was not given in the original structural determination. In our latter work, both epimers of the epoxide fragment were constructed through the chiron approach. Herein we report a more convenient synthesis of the (10*R*)-epoxide **7**, the key intermediate of natural (10*R*)-corossolin, using Jacobsen's hydrolytic kinetic resolution (HKR)[5] to resolve the terminal epoxides as the key step.

The HKR method uses readily accessible cobalt-based chiral salen complexes as catalyst and water as the only reagent to afford chiral epoxides and diols of high ee in excellent yields. These advantages have made it a very attractive asymmetric synthetic tool. However, up to now HRK has *only* been applied to the resolution of simple[6] epoxides of small molecular weight such as styrene oxide, or monofunctional unbranched alkyl-substituted[7] epoxides. In the present work, we pushed the limits further, extending the scope of the applicable substrates to cover multifunctionalized large molecules when developing a facile access to the key intermediate[4] in our previous synthesis of AA.

The substrate for the HKR, the 'racemic' epoxide, was prepared as shown in Scheme 1. Starting from the commercially available methyl undec-10-enoate, the alcohol **2** was prepared in 80% yield by aldol condensation with the aldehyde derived from ethyl L-lactate employing our previous[2b,c] procedure. Conversion of **2** to the acetate ester **3** was achieved in 91% yield. Treatment of **3** with 10% aq. H_2SO_4 in THF removed the THP protecting group and the newly unmasked hydroxy group underwent an intramolecular ester exchange reaction to give lactone **4** in 83% yield. Subsequent epoxidation of **4** with MCPBA gave **5**, which on β-elimination using DBU gave the unsaturated lactone **6** in high yield. The two diastereomers of **6** could not be differentiated on silica gel, presumably due to the large distance between the two stereogenic centers.

The HKR was performed with (*R*,*R*)-salen–Co(OAc) complex (0.5 mol%) and H_2O (0.55 equiv.) to yield epoxide **7** (46%) and diol **8** (38%). The diol **8** could be recycled[4] to **7** in 52% yield, or to the diastereoisomer of **7** in 82% yield. Due to the difficulty in separating chiral epoxide **7** from the salen catalyst, the measurement of its diastereoisomeric excess was performed on **9** and **10**, which were derived in 78% and 85% yields from **7** and **6**, respectively, by reaction with lithium trimethylsilylacetylide. The diastereoisomeric purity of **9** was 99.0% as shown by HPLC (OJ column, 95:5 of hexane–Pr^{i}OH) with the C-10 epimer mixture compound **10** as reference. This is in excellent agreement with the result of optical rotation measurements (+15.1 and +15.3 for **9** and the authentic[4] sample from the chiron approach, respectively). The diastereoisomer of **7** can also be prepared from the (*S*, *S*)-salen–Co(OAc) complex using HKR of **6**.

In conclusion, with HKR of terminal epoxides as the key step, we have developed a short and efficient synthesis (six steps from methyl undec-10-enoate with the overall yield > 24.3%



Scheme 1 *Regents and conditions*: i, Ac_2O, Py, (91%); ii, 10% H_2SO_4, THF, (83%); iii, MCPBA, CH_2Cl_2, (91%); iv, DBU, THF, 2 h, (96%); v, (*R*,*R*)-salen–Co(OAc) (0.5 mol%), dist. H_2O, 40 h, (46% for **7**, 38% for **8**); vi, Bu^{n}Li, trimethylsilylacetylene, $BF_3{\cdot}OEt_2$, −78 °C, (78% and 85%, respectively, 99.0% de).

without taking into consideration the recycled **7** from **8**) of a key intermediate of (10*R*)-corossolin. The present approach is simpler than and therefore superior to the chiral pool method, in which the starting materials are (2*R*)-2,3-*O*-isopropylideneglyceral and azelic acid monoethyl ester (requiring a total of nine steps with 13.4% overall yield[4]), or (2*S*)-1,2-*O*-isopropylidenebutane-1,2,4-triol [derived[5] from (*S*)-malic acid] and a substituted γ-lactone prepared by White's method[9] (in eight steps[8] with 15.1% overall yield for a similar compound). It should be noted that the present approach also provides a facile access to other[10] annonaceous acetogenins with a C-10 hydroxy group.

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