A practical total synthesis of both enantiomers of epoxyquinols A and B

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Abstract—A practical total synthesis of both enantiomers of epoxyquinols A and B has been developed. Key reactions are the chromatography-free preparation of an iodolactone by using acryloyl chloride as dienophile in the Diels–Alder reaction of furan, the lipase-mediated kinetic resolution of a cyclohexenol derivative, and a modified procedure for α-iodonation of a cyclohexenone.

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Epoxyquinols A (1) and B (2), recently discovered anti-angiogenic natural products, have complex, highly-oxygenated, heptacyclic structures.1 These structures are quite distinct from those of known angiogenesis inhibitors,2 making their mechanism of action a matter of considerable interest. To facilitate elucidation of this mechanism, methods for the multi-gram synthesis, and derivatization of epoxyquinols A (1) and B (2) are highly desirable. We have completed the first asymmetric total synthesis of these molecules,3 determining their absolute stereochemistry, in which an HfCl4-mediated Diels–Alder reaction of furan with Corey’s chiral auxiliary,4 and a biomimetic, oxidative dimerization were developed as key reactions (Scheme 1). Porco et al. also have accomplished the total synthesis of epoxyquinols A (1) and B (2) just recently.5 Though our HfCl4-mediated, highly diastereoselective Diels–Alder reaction of a chiral auxiliary is suitable for the construction of opti-

Scheme 1. Total synthesis of epoxyquinols (+)-A (1) and (+)-B (2) via diastereoselective Diels–Alder reaction.

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cally-active, cyclohexanol derivatives, an equimolar amount of the auxiliary is necessary. To circumvent this problem, we have developed a more efficient and practical synthetic route to epoxyquinols A (1) and B (2), which is disclosed in this letter.

We chose as the key reaction of our new strategy kinetic resolution of racemic cyclohexenol (±)-6 using lipase, as such reactions are known to be easily scaleable. However, preparation of this intermediate itself proved to be difficult, as while the Diels–Alder reaction of furan and acrylate derivatives is a powerful means of synthesizing this class of compounds, no method suitable for large-scale applications has yet been described. Establishing such a route was our first goal. Acryloyl chloride, a reactive dienophile, is known to react with furan in the presence of a hydrogen chloride scavenger, propylene oxide, over 48 h providing the Diels–Alder adducts in 76.5% overall yield after conversion of the adduct to the corresponding ester. Under these conditions the thermodynamically-stable, exo-isomer predominates (endo:exo = 3:7). After some experimentation, we developed an efficient, chromatography-free procedure for the synthesis of iodolactone (±)-5 via hydrolysis and iodolactonization of the kinetically-favored, endo-Diels–Alder adduct (Scheme 2). Thus, the Diels–Alder reaction of acryloyl chloride and furan (8 equiv.) proceeds in 5 h at 23°C, providing the endo- and exo-cycloadducts in 54% and 25% yield, respectively (1H NMR yield). Hydrolysis of the acid chloride to the sodium salt of the acid was carried out by treatment with aq. 1.5 M NaOH. On addition of I₂ and CH₂Cl₂ to the aqueous phase, iodolactonization proceeded efficiently, providing (±)-5 in 42% yield as a white solid, which is pure enough to be used in the next experiment. Unreacted acryloyl chloride, and the exo-Diels–Alder adduct could be easily separated from iodolactone (±)-5 because the former two remain in the aqueous phase as the sodium salt of the corresponding acid. Though the yield is moderate, the reaction could easily be scaled up to 60 g.

After conversion of the iodolactone (±)-5 to the substituted cyclohexenol (±)-6 using the previously reported procedures, the kinetic resolution by lipase was examined. After screening various lipases, it was found that the *Pseudomonas stutzeri* lipase (Meito TL) was most efficient. When racemic (±)-6 was treated with a catalytic amount of this lipase (10 wt%) in vinyl acetate at room temperature for 40 h, acetate (–)-7 was obtained in 48% yield with 96% ee, while the desired alcohol (+)-6 was recovered in 49% yield with 99% ee, indicating a very high selectivity (k_fast/k_slow = 211). Activity of recovered lipase dose not decrease, and it works as efficiently as fresh batches. The absolute configuration of (+)-6 was determined by comparison of its optical rotation with that of previously synthesized (+)-6, as well as by using the advanced Mosher’s MTPA.
method. As acetate (−)-7 was easily converted to alcohol (−)-6 on treatment with K₂CO₃ in MeOH, providing (−)-6 in 97% yield, both enantiomers of alcohol 6 could be synthesized in large quantity and with high optical purity. This kinetic resolution is suitable for producing chiral cyclohexenol 6 on a gram-scale, not only because high selectivity is achieved, but also because only a catalytic amount of lipase is necessary and this can be recycled.

We went on to prepare monomer (+)-4 using the procedures developed during our previous synthesis, with the exception of the conversion of cyclohexenone (+)-8 to 2-iodocyclohexenone (+)-9. There was a problem with the reproducibility of this step, in which I₂, PhI(OOCOC₅H₄)₂ and pyridine were used. We observed that iodonation proceeded only after a certain induction period, and that once generated (+)-9 began to decompose after a further induction period. Based on our speculation that the side reaction was radical in nature, we carried out the reaction in the dark in the presence of 2,6-di-tert-butyl-4-methylphenol (BHT) as a radical scavenger, conditions which gave reproducible results, providing (+)-9 in 67% yield.

We also synthesized the enantiomer, monomer (−)-4, by the same route from resolved monomer (−)-6.

Epoxquinols A (1) and B (2), were synthesized from (+)-4, and their enantiomers from (−)-4, by the biomimetic oxidative 6n-electrocyclization, followed by Diels–Alder reaction procedure we have previously established. In summary we have developed a practical synthetic route to epoxquinols A (1) and B (2), which is suitable for their multi-gram synthesis. Key reactions are the chromatography-free preparation of iodolactone (±)-5 by using acryloyl chloride as a dienophile, the P. stutzeri lipase-mediated kinetic resolution of a key intermediate (±)-6, and a modified procedure for α-iodination of cyclohexene 8. The efficiency of the present method was successfully demonstrated by the simple synthesis of both enantiomers of epoxquinols A (1) and B (2).

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References

10. Experimental procedure for the synthesis of (±)-5: A mixture of acryloyl chloride (45 mL, 0.56 mol) and furan (338 mL, 4.62 mol) was stirred at room temperature, while the progress of the reaction was monitored by 1H NMR. After 5 h, a 1.5 M NaOH solution (336 mL, 0.51 mol) was added and the reaction mixture was stirred for a further 2 h. The water phase was separated and CH₂Cl₂ (520 mL) and I₂ (70.2 g, 0.27 mol) were added to it. The mixture was stirred vigorously for 2 h. Sat. Na₂S₂O₃ solution was added until the color of iodine disappeared. After the organic solvent had been removed under reduced pressure, a white solid precipitated which was collected and dried to afford 62 g (0.23 mol) of iodolactone (±)-5 (42%).
11. To a solution of vinyl acetate (150 mL) of racemic cyclohexenol derivative (±)-6 (14.0 g, 82.5 mmol) was added P. stutzeri lipase (Meito TL) (1.40 g), and the reaction mixture was stirred vigorously for 40 h at room temperature. After filtration of the lipase, the volatile
organic compounds were removed under reduced pressure and the remaining materials were purified by flash column chromatography (ethyl acetate:hexane = 1:3–1:1) to afford (+)-6 (6.75 g, 49%, 99% ee) and (−)-7 (8.25 g, 48%, 96% ee).

12. HPLC conditions: Chiralcel OD-H column (Daicel Chemical Ind.), 2-propanol:hexane = 1:20, 1.5 mL/min, retention times, 5.6 min (major), 6.0 min (minor).

13. HPLC conditions: Chiralcel OD-H column (Daicel Chemical Ind.), 2-propanol:hexane = 1:20, 1.5 mL/min, retention times, 28.7 min (major), 11.1 min (minor).


16. Detailed biological study of both enantiomers of epoxyquinols A (1) and B (2) is underway, the results of which will be reported in due course.