Dynamic Kinetic Asymmetric Transformations of Conduritol B Tetracarboxylates: An Asymmetric Synthesis of D-*myo*-Inositol 1,4,5-Trisphosphate

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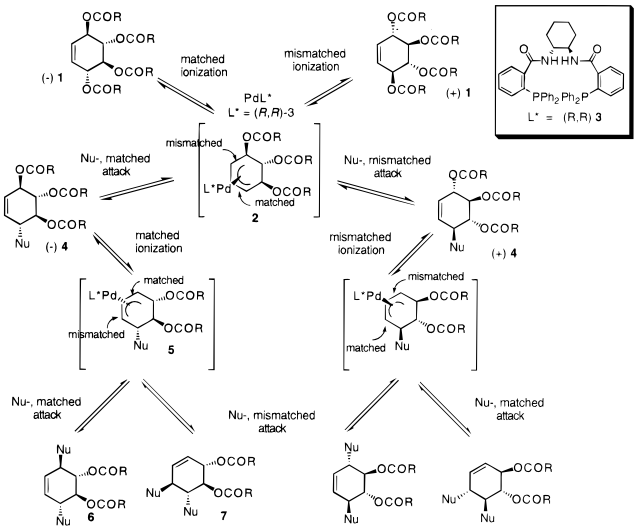
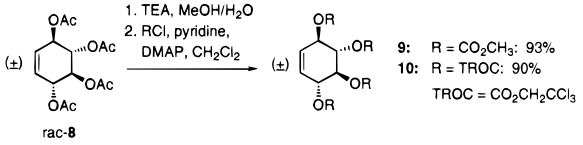
The importance of the cyclohexene tetraol conduritol B and its derivatives as synthetic building blocks is amply demonstrated by its extensive use in natural product synthesis.[1−7] The synthesis of derivatives of conduritol B in enantiomerically enriched form has proven difficult, requiring resolutions[8−10] or synthesis from chiral pool starting materials.[11−17] The enantioselective palladium-catalyzed allylic alkylation[18] of conduritol B derivatives **1** is somewhat complex due to their C_2-axis of symmetry (see Scheme 1). The ionization of either enantiomer of **1** leads to the same meso π-allylpalladium complex **2**, however, at different rates with chiral catalysts (matched vs mismatched ionization). In the presence of the chiral ligand (*R,R*) **3**, matched attack of a nucleophile at one of the enantiotopic termini of the π-allyl **2** gives the monosubstitution product (−)-**4**. Mismatched attack would lead to the opposite enantiomer (+) **4**. Furthermore, the monoalkylated product **4** can be a substrate for a second allylic alkylation. Ionization of (−)-**4** would lead to π-allylpalladium complex **5**, which can go on to the 1,4 disubstituted product **6** since both processes involve matched events, or, less likely, to the 1,2 disubstituted product **7** via a mismatched nucleophilic attack. On the other hand, both formation and further reactions of (+)-**4** should be disfavored (i.e., mismatched) under these conditions.

Since the initial ionization of racemic **1** involves both a matched and mismatched ionization, a kinetic resolution of conduritol B tetracarboxylate should be possible and was demonstrated with oxygen nucleophiles.[19] On the other hand, it is more desirable to perform a dynamic kinetic asymmetric transformation (henceforth abbreviated DYKAT) on the conduritol B system to provide complete conversion of the racemic starting material to enantiomerically enriched product. To achieve this goal, the chiral palladium−ligand complex must be able to ionize both enantiomers of the starting material **1**, and then convert the resulting meso π-allyl into a single enantiopure product. This goal is complicated by the fact that, because the ionization of (−)-**4** is a matched event, its ionization leading to polysubstitution may be competitive or even faster than the mismatched ionization of (+)-**1**—a circumstance that can lead to mixtures of mono- and disubstituted products. We wish to report that synthetically useful DYKAT reactions leading selectively to either mono- or disubstitution can be accomplished. Further, the latter has been applied to a short asymmetric synthesis of the cellular signal transducer D-*myo*-inositol-1,4,5-trisphosphate, and formal syntheses of the 1,2,4,5-tetrakisphosphate and cyclophellitol, an inhibitor of HIV.

Scheme 1. Dynamic Kinetic Asymmetric Transformation of Conduritol B



Racemic conduritol B tetraacetate **8** was synthesized in three steps from benzoquinone by a simple modification of the method of Guo.[20] When **8** was used as a substrate for the palladium-catalyzed allylic alkylation, a kinetic resolution was observed with oxygen nucleophiles, and no reaction was observed with carbon and nitrogen nucleophiles. In hopes of increasing the reactivity, tetraacetate **8** was converted into the tetramethyl carbonate **9** or the tetratrichloroethyl carbonate (TROC) **10** by a two-step, one-pot procedure. While low conversion was still observed in the reactions of tetracarbonate **9** with carbon nucleophiles (such as Meldrum's acid), switching to the more reactive tetratrichloroethyl carbonate **10** led to 95% yield of monosubstituted product **11b** with an enantiomeric excess of 96%.[21] Acetoxy Meldrum's acid behaved similarly whereby **11c** was obtained in 89% yield and 89% ee (99% after one recrystallization). The fact that complete conversion is observed indicates that a DYKAT has been achieved, that is, both enantiomers of starting material are being ionized and converted to the same product. None of the disubstituted product was observed in alkylations using carbon nucleophiles. Surprisingly, when the steric bulk of the carbon nucleophile was increased by using methyl Meldrum's acid, the



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(21) The enantiomeric excess of **11b** was determined by conversion to the corresponding dimethyl ester, and chiral HPLC analysis of this ester (see Supporting Information). The enantiomeric excess of the recovered starting material **10** was determined by conversion to the tertaacetate **8** and chiral HPLC on **8**.

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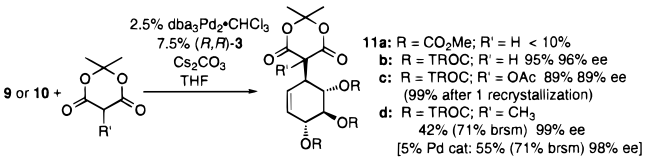
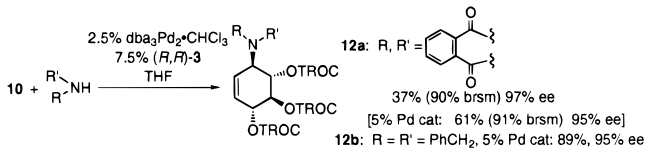


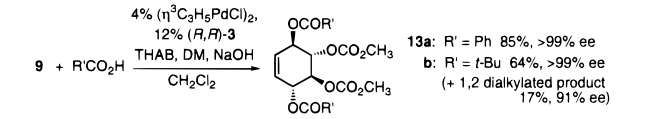
reaction became mainly a simple kinetic resolution giving **11d** of 99% ee in 42% (71% brsm) yield. Increasing the palladium loading to 10% increased the yield to 55% (99% ee) which demonstrates the beginning of the DYKAT.

When phthalimide was used in the substitution reaction of **10**, the result paralleled those with methyl Meldrum's acid. Using 2.5 mol % of $(dba)_3Pd_2{\cdot}CHCl_3$, the monosubstituted product **12b** was obtained in 37% yield (maximum 50% yield) and 97% enantiomeric excess in a kinetic resolution. When the catalyst

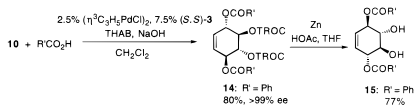


loading was increased to 5 mol %, the reaction proceeded to give a 61% yield (95% ee) in a process that is, at least in part, a DYKAT. When dibenzylamine was used, a DYKAT was observed since complete conversion to **12b** in 89% yield (95% ee) could be achieved.

While only the monosubstituted products were observed in the asymmetric alkylation of conduritol B tetracarbonates with carbon and nitrogen nucleophiles, disubstitution was the major process when carboxylate nucleophiles were employed under conditions for DYKAT reactions. Treatment of **9** with π-allylpalladium chloride dimer and either enantiomer of ligand **3** led to nearly complete conversion to the 1,4-disubstituted product **13a** in >99% enantiomeric excess. Pivalate also was an effective nucleophile,

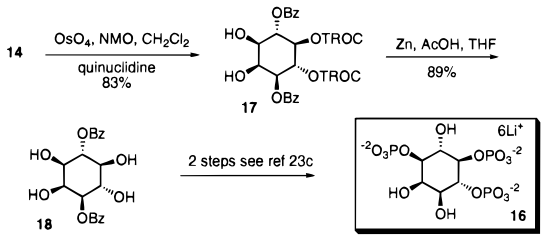


giving a good yield 64% (>99% ee) of the 1,4-disubstituted product **13b**, along with a significant amount (17%, 91% ee) of the 1,2-disubstituted product, presumably because of the steric bulk of the pivalate and how it interacts with the walls of the chiral pocket. The enantiomeric series is easily accessed simply by switching the chirality of the ligand. Thus, dicarbonate **10** gave the mirror image product **14** in 80% yield and >99% ee with the *S*,*S* enantiomer of ligand **3**. With oxygen nucleophiles, therefore,



a DYKAT can be achieved, and racemic starting material can be selectively converted into chiral enantiomerically pure disubstituted products. This reaction constitutes a deracemization of racemic conduritol B tetracarboxylate with the added benefit of differentiation of the esters. For example, treatment of **14** with zinc in THF containing acetic acid gave a 77% yield of diol dibenzoate **15**.

The efficiency of the deracemization induced us to consider a synthesis of D-*myo*-inositol-1,4,5-trisphosphate (1,4,5-IP_3) from achiral starting materials and requiring no resolution. (1,4,5-IP_3) **16** has been recognized as a second messenger to mobilize intracellular calcium ions.[22] When cell surface receptors are activated, 1,4,5-IP_3 is released inside the cell and binds to receptors on the endoplasmic reticulum, stimulating the release of calcium ions from the non-mitochondrial intracellular store. Because of its importance in signal transduction in animal cells and low availibility from natural sources, 1,4,5-IP_3 has been the focus of synthetic interest.[23] To date there are no syntheses of 1,4,5-IP_3 that generate chirality using a catalytic asymmetric transformation. Dibenzoate **14**, available in >99% enantiomeric excess as described above, is dihydroxylated with osmium tetroxide/NMO at 0 °C (temperature important) to give the desired diol **16** in 83% yield as a single diastereomer. Because of the slow rate of



the dihydroxylation, however, a 5% loading of osmium was required to ensure a reasonable reaction time.

Chemoselective removal of the TROC groups with zinc dust in THF containing acetic acid gave an 88% yield of the tetraol **18**. Completion of the synthesis in two steps from tetraol **18** as reported by Meek et al.[24] gave pure 1,4,5-IP_3 ($-24.4°$ (*c* 0.2, H_2O, pH adjusted to ~10 with cyclohexylamine), lit[25] $-25.2°$ (*c* 1.03, H_2O, pH adjusted to 10.5 with cyclohexylamine) whose spectral and physical properties fully agree with the natural product. The synthesis of intermediate **18** also represents a formal asymmetric synthesis of D-*myo*-1,2,4,5-tetrakisphosphate which has shown activity as a phosphatase inhibitor.[26]

DYKAT reactions of conduritol B tetracarboxylates provide ready access to a variety of enantiomerically pure conduritol B derivatives. Chemoselective mono- and disubstitution may be achieved, depending upon the steric demands of the nucleophile. This strategy allows access to either enantiomer of the product, depending only on the choice of chiral ligand. The utility of these intermediates becomes immediately apparent in that the previously reported racemic synthesis of cyclophellitol from the triacetate analogue of **11b** now becomes an asymmetric one.[27] Herein, an efficient synthesis of the natural product D-*myo*-inositol-1,4,5-trisphosphate in five steps from racemic conduritol B tetratrichloroethyl carbonate is reported.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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