Enantioselective Desymmetrization of *meso*-Decalin Diallylic Alcohols by a New Zr-Based Sharpless AE Process: A Novel Approach to the Asymmetric Synthesis of Polyhydroxylated *Celastraceae* Sesquiterpene Cores**

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Crude plant extracts of the *Celastraceae* have been valued since antiquity for their stimulant, appetite suppressive, antiarthritic, antibacterial, insect repellent, and memory-restorative properties.¹ Pervasive among the secondary metabolites isolated from this class of plants is a large family of polyhydroxylated sesquiterpene esters having a dihydro-β-agarofuran skeleton.² Many members of this family, particularly esters of three polyhydroxylated agarofurans: euonyminol, 4/3-hydroxyalatol, and 14-deoxyalatol, exhibit significant biological activity. These include: triptolides A-1/A-6[⁴] and cellhin A[⁵] (antitumor), willortrine[⁶] (immunosuppressive), willorine[⁷] (insecticidal), and celangulin[⁸] and cathedulins E-3/E-4/E-5[⁹] (insect antifeedant). Additionally, hypoglaunine B and related macrocyclic lactone derivatives of euonyminol have recently been shown to display significant anti-HIV activity[⁷] (Scheme 1).

One striking feature of the three core structures common to these natural products is a symmetric array of hydroxyl groups on the top face of their “northern” periphery. We were intrigued by the possibility of exploiting this symmetry to facilitate their synthesis. In particular, we identified epoxide B as a pivotal intermediate for the preparation of all the core structures and we envisaged that a two-directional synthesis of *meso*-diallylic alcohol A followed by epoxidative enantioselective desymmetrization[⁶] would provide an efficient route to this intermediate (Scheme 1). Here we describe how the successful implementation of this plan required the development of a Zr-based Sharpless asymmetric epoxidation (AE) process for tertiary diallylic alcohols.

At the outset of our work, only one *trans*-decalinic diallylic alcohol had been reported[¹⁰] in view of this limited precedent, and the potentially labile nature of the structure, we opted to evaluate the feasibility of our strategy on simple model system 5 (Scheme 2). Epoxide I was prepared from naphthalene by Birch reduction (Na/NH₃; 74 % yield) then epoxidation (CH₃CO₂H; 87 % yield).[¹⁰] Ring opening with Et₂AlCN[¹¹] followed by completely diastereoselective epoxidation and trans-diaxial ring opening with Me₃Al gave triol 4. Selective mesylation then *anti* elimination in neat DBU furnished the requisite diallylic alcohol 5. This alcohol was prone to partial [1,3]-allylic rearrangement to give the corresponding conjugated dienyl alcohol on silica, but could be obtained pure after chromatography on grade 1 basic alumina.

Sharpless AE[¹²] with either catalytic[¹³] or stoichiometric[¹³] amounts of Ti(OiPr)₄/(-)-(−)-diisopropyl tartrate (DIPT) pro-

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**Scheme 1. Desymmetrization strategy. R = protecting group, Ac = acetyl.**
ceeded without detectable [1,3]-allylic rearrangement and afforded epoxy alcohol (−)-6 in yields up to 70 %, but despite extensive experimentation the ee value was reproducibly in the range of 10–20 % (Scheme 3). Known variations employing other tartrate/tartramide ligands[14] and/or CaH2/silica[15]

Enantioselective desymmetrization of diallylic alcohol 12 by the Zr-modified Sharpless AE (Zr(OiPr)4, iPrOH (3 equiv), d-(-)-DIPT (3.3 equiv), BuOOH (3.4 equiv), CH2Cl2, −20 °C, 3 d) afforded epoxy alcohol (+)-13 in 44 % yield (55 % accounting for recovered 12) and >95 % ee[24] (Scheme 5).

Scheme 4. Synthesis of diallylic alcohol 12. a) BnBr, NaH, nBu4NI, NMP, 50 °C (83 %); b) Ph3PBr2, CH2Cl2, RT (87 %); c) TBSOTf, 2,6-lutidine, CH2Cl2, RT (98 %); d) DBU, 50 °C (98 %); e) OsO4, NMO, acetone:H2O (5:1), RT (79 %); f) MeO(OiPr)2, TsOH, CH2Cl2, RT (95 %); g) K2- OsO4(OH), K2Fe(CN)6, K2CO3, MeSO2NH2, quinuclidine, BuOH:H2O (1:1), RT (74 %); h) MeO(OiPr)2, TsOH, CH2Cl2, RT (98 %); i) Na/NH3, THF, −78 °C, then TBAF, THF, RT (91 %); j) MsCl, Et3N, CH2Cl2, RT (99 %); k) DBN, toluene, 110 °C (67 %). Bn = benzyl, NMO = N-methyl-2-pyrrolidinone, TBS = tert-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, NMO = 4-methylmorpholine-N-oxide, Ts = tosyl = toluene-4-sulfonyl, TBAF = tetrabutylammonium fluoride, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

Enantioselective desymmetrization of diallylic alcohol 12 by the Zr-modified Sharpless AE (Zr(OiPr)4, iPrOH (3 equiv), d-(-)-DIPT (3.3 equiv), BuOOH (3.4 equiv), CH2Cl2, −20 °C, 3 d) afforded epoxy alcohol (+)-13 in 44 % yield (55 % accounting for recovered 12) and >95 % ee[24] (Scheme 5).

Scheme 5. Epoxidation of diallylic alcohol 12.

An analogous reaction with l-(-)-DIPT afforded (−)-13 in 59 % yield (74 % accounting for recovered 12) and >95 % ee. A control reaction under standard Sharpless AE conditions (that is, stoichiometric Ti(OiPr)4, l-(-)-DIPT)[23] afforded (+)-13 in 40 % yield and just 14 % ee, which confirms the crucial importance of employing Zr in place of Ti for this type of substrate.

To conclude, we have shown that epoxidative enantioselective desymmetrization of meso-decalin diallylic alcohols can be achieved in good yields and with high ee values through a Zr-based Sharpless AE process. The utility of the process has been exemplified by its employment for a potentially expedient synthesis of core structures of bioactive Celastraceae natural products in which eight contiguous chiral centers are established with >95 % ee in a single step.

Experimental Section

Procedure for the epoxidative desymmetrization of diallylic alcohol 12: d-(-)-Diisopropyl tartrate (0.066 mL, 0.31 mmol) was added to a solution of

Scheme 6. Synthesis of benzylideneacetal 14. a) NBS, CH2Cl2, reflux (82 %); b) OsO4, NMO, acetone:H2O (5:1), RT (66 %); c) MeO(OiPr)2, TsOH, CH2Cl2, RT (92 %); d) Me3Al, MeCN, RT (92 %).

Scheme 7. Synthesis of benzylideneacetal 14. a) NBS, CH2Cl2, reflux (82 %); b) OsO4, NMO, acetone:H2O (5:1), RT (66 %); c) MeO(OiPr)2, TsOH, CH2Cl2, RT (92 %); d) Me3Al, MeCN, RT (92 %).
**The First Crystalline Calcium Porphyrin and Tetrakis(t-Butylphenyl)porphyrinato Calcium(II): Its Synthesis, Structure, and Binding Properties Towards Alkali and Alkaline Earth Metal Salts**

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The study of alkaline earth metals and particularly of calcium in porphyrin systems is of great importance because of their relationship to the role of magnesium and iron porphyrin derivatives in naturally occurring systems. This notwithstanding, information available on the synthesis, structure, and spectroscopic properties of calcium porphyrin is practically nonexistent,[1] with only UV/Vis data being available.[2] The field of alkali metal porphyrin and porphyrin analogues has burgeoned in recent years,[3] with a significant example being that of calcium porphyrinogen chemistry. [3] The iso-

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