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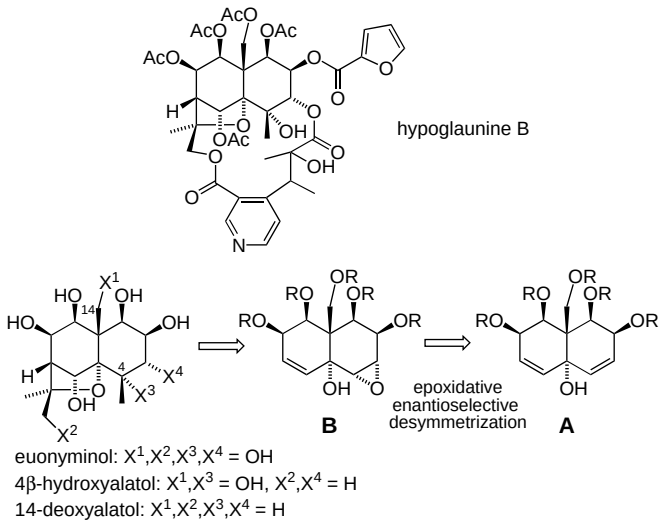
ularly esters of three polyhydroxylated agarofurans: euonyminol, 4β-hydroxyalatol, and 14-deoxyalatol, exhibit significant biological activity. These include: triptogelins A-1/A-6[3a] and celhin A[3b] (antitumor), wilfortrine[4] (immunosuppressive), wilforine[5] (insecticidal), and celangulin[6a] and cathedulins E-3/E-4/E-5[6b] (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).



Scheme 1. Desymmetrization strategy. R = protecting group, Ac = acetyl.

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**

Alan C. Spivey,* Steven J. Woodhead, Matthew Weston, and Benjamin I. Andrews

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, 4β-hydroxyalatol, and 14-deoxyalatol, exhibit significant biological activity. These include: triptogelins A-1/A-6[3a] and celhin A[3b] (antitumor), wilfortrine[4] (immunosuppressive), wilforine[5] (insecticidal), and celangulin[6a] and cathedulins E-3/E-4/E-5[6b] (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[8] 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.[9] 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 **1** was prepared from naphthalene by Birch reduction (Na/NH_3; 74% yield) then epoxidation (CH_3CO_3H; 87% yield).[10] Ring opening with Et_2AlCN,[11] followed by completely diastereoselective epoxidation and *trans*-diaxial ring opening with Me_3Al 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(O*i*Pr)$_4$/D-(−)-diisopropyl tartrate (DIPT) pro-

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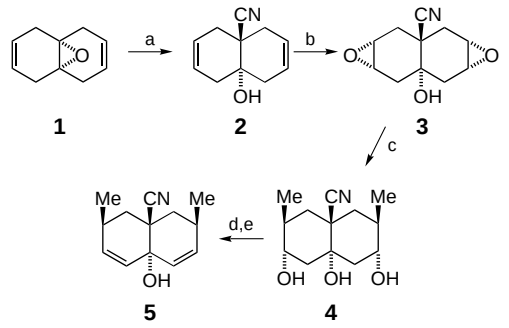
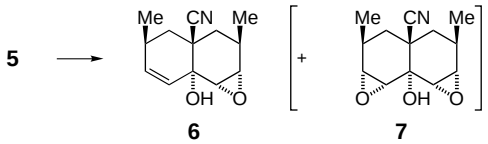
[**] AE = Asymmetric epoxidation. Grateful acknowledgement is made to the EPSRC for a QUOTA studentship (S.J.W.) and to Pfizer (Drs. Alan R. Brown and John P. Mathias) for financial support of this work.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



Scheme 2. Synthesis of diallylic alcohol **5**. a) Et_2AlCN, CH_2Cl_2, RT (98%); b) $[VO(acac)_2]$, *t*BuOOH, CH_2Cl_2, 70°C (87%); c) Me_3Al, CH_2Cl_2, 40°C (88%); d) MsCl, Et_3N, CH_2Cl_2, RT (81%); e) DBU, 100°C (92%). acac = acetylacetonate, Ms = mesyl = methanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

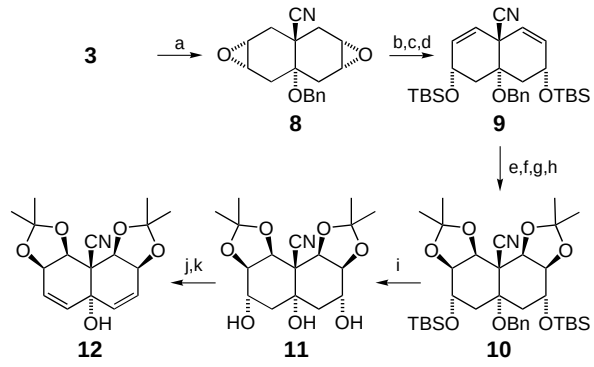
ceeded without detectable [1,3]-allylic rearrangement and afforded epoxy alcohol (−)-**6** in yields up to 70%, but despite extensive experimentation the *ee* value was reproducibly in the range of 10–20% (Scheme 3). Known variations employing other tartrate/tartramide ligands[14] and/or CaH_2/silica[15]



Scheme 3. Epoxidation of diallylic alcohol **5**.

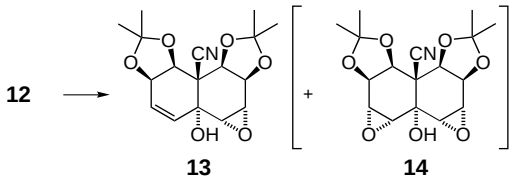
additives failed to improve the situation. Tertiary alcohols are notoriously poor substrates for Sharpless AE because they bind poorly to the tartrate–Ti complex,[12, 16] so we explored the replacement of $Ti(OiPr)_4$ with $Zr(OiPr)_4$, reasoning that complex formation might be facilitated by the increased Zr–O bond length compared to that of Ti–O.[17, 18] To our delight we found that use of commercial $Zr(OiPr)_4 \cdot i$PrOH (1 equiv),[19] D-(−)-DIPT (1.1 equiv), and *t*BuOOH (1.2 equiv) in CH_2Cl_2 at −20°C for 3 days afforded epoxy alcohol (+)-**6**, in 76% yield and 92% *ee*. An analogous reaction with L-(+)-DIPT afforded (−)-**6** in 90% yield and 92% *ee*.[20]

Our efforts then turned to the preparation of a fully functionalized decalin (see **A**, Scheme 1). The synthesis of such a compound, wherein the C-14 hydroxymethyl group (product numbering) is protected as a nitrile, is outlined in Scheme 4. Thus, protection of the tertiary hydroxyl group of bis-epoxide **3** as the benzyl ether allowed for a completely diastereoselective three-step conversion into the corresponding bis-allylic ether **9**. OsO_4-mediated *cis*-dihydroxylation took place from the top face (that is, *anti* to the TBS ether C–O bonds)[21] in sequential oxidation and protection steps to afford bis-acetonide **10** with complete diastereocontrol. The stereochemistry of this compound was confirmed by a single-crystal X-ray structure determination.[23] Benzyl and TBS ether deprotection was effected by Birch-type reduction followed by treatment with TBAF to give triol **11**. Selective mesylation and bis-elimination, this time with DBN in toluene, smoothly furnished the diallylic alcohol **12**.



Scheme 4. Synthesis of diallylic alcohol **12**. a) BnBr, NaH, nBu_4NI, NMP, 50°C (83%); b) Ph_3PBr_2, CH_2Cl_2, RT (87%); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT (98%); d) DBU, 50°C (98%); e) OsO_4, NMO, acetone:H_2O (5:1), RT (79%);[22] f) $Me_2C(OMe)_2$, TsOH, CH_2Cl_2, RT (95%); g) $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, quinuclidine, *t*BuOH:H_2O (1:1), RT (74%); h) $Me_2C(OMe)_2$, TsOH, CH_2Cl_2, RT (98%); i) Na/NH_3, THF, −78°C, then TBAF, THF, RT (91%); j) MsCl, Et_3N, CH_2Cl_2, RT (99%); k) DBN, toluene, 110°C (67%). Bn = benzyl, NMP = *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 ($Zr(OiPr)_4 \cdot i$PrOH (3 equiv), D-(−)-DIPT (3.3 equiv), *t*BuOOH (3.4 equiv), CH_2Cl_2, −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)[13] 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

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$Zr(OiPr)_4$ (109 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) with 4 Å molecular sieves at $-20\,^{\circ}C$ (salt/ice bath), followed by *tert*-butyl hydroperoxide (3.8 M solution in toluene, 0.085 mL, 0.32 mmol). The reaction mixture was stirred at $-20\,^{\circ}C$ for 0.5 h before addition of diallylic alcohol **12** (30 mg, 0.094 mmol) in CH_2Cl_2 (5 mL) which was also cooled to $-20\,^{\circ}C$. The reaction mixture was then stirred for a further 0.5 h before transfer to a freezer at $-20\,^{\circ}C$ for 3 days. H_2O (2.5 mL) and saturated aqueous Na_2SO_3 (2.5 mL) were added to the reaction mixture. The resulting biphasic system was stirred vigorously for 0.5 h at ambient temperature and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered through Celite, and concentrated under vacuum. Flash column chromatography (elution with EtOAc:petroleum ether (1:3)) gave epoxy alcohol (+)-**13** as a colorless oil (14 mg, 44 %). (see Supporting Information for analytical data,).

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[19] Unfortunately, attempts to employ sub-stoichiometric amounts of $Zr(OiPr)_4$ have so far been unsuccessful.

[20] Use of $Ti(OiPr)_4$ with D-(−)-DIPT gives (−)-**6**/**13** and with L-(+)-DIPT gives (+)-**6**/**13**, whereas $Zr(OiPr)_4$ with D-(−)-DIPT gives (+)-**6**/**13** and with L-(+)-DIPT gives (−)-**6**/**13**. This reversal in the sense of induction between the two metals suggests that topologically distinct complexes may be involved. We have yet to establish the absolute configurations of the products but, by analogy with Ti-based AE of other cyclic allylic alcohols, and allowing for the reversal of sense of induction with $Zr(OiPr)_4$, the configurations drawn in Schemes 3 and 5 would correspond to the levorotatory enantiomers. See: a) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237 – 6240; b) J. A. Marshall, K. E. Flynn, *J. Am. Chem. Soc.* **1982**, *104*, 7430 – 7435.

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[22] Base-promoted cyclization of the axial hydroxyl group onto the nitrile moiety to give an imidolactone ensues if this reaction is allowed to proceed too long or if the conditions summarized in step (g) are employed for this step.

[23] Details of this structure determination, full experimental details for all transformations in Schemes 2 and 4, and details of additional studies which led to the selection of this synthetic route will be published in a forthcoming full account of this work.

[24] *meso*-Bis-epoxide **14** is also formed in 21 % yield. After just 24 h the *ee* value of epoxy alcohol (+)-**13** is 82 % and there are just traces of *meso*-bis-epoxide **14**. Enhancement of the *ee* value as a function of conversion is expected in this type of reaction; see: S. L. Schreiber, T. S. Schreiber, D. B. Smith, *J. Am. Chem. Soc.* **1987**, *109*, 1525 – 1529.

The First Crystalline Calcium Porphyrin and Tetrakis(*tert*-butylphenyl)porphyrinato Calcium(II): Its Synthesis, Structure, and Binding Properties Towards Alkali and Alkaline Earth Metal Salts**

Lucia Bonomo, Marie-Line Lehaire, Euro Solari, Rosario Scopelliti, and Carlo Floriani*

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.[1a]

The field of alkali metal porphyrin and porphyrin analogues has burgeoned in recent years,[2] with a significant example being that of calcium porphyrinogen chemistry.[3] The isolation and characterization of alkaline earth metal porphyrin systems have failed so far because of the use of protic conditions in their synthesis.[1] Therefore, we turned our

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