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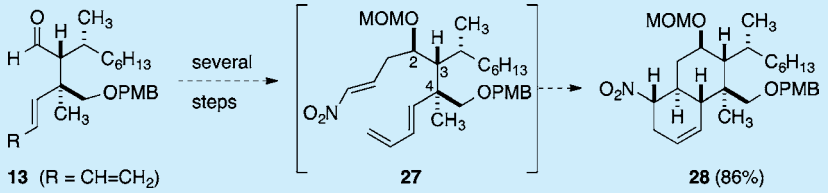
# Intramolecular Diels–Alder (IMDA) Studies toward the Synthesis of Australifungin. Stereocontrol in the Acetate Aldol Reaction of β,β′-Branched Aldehydes

David R. Williams* and J. Cullen Klein

Department of Chemistry, Indiana University, Bloomington, Indiana 47405, United States

Supporting Information




**ABSTRACT:** Studies of australifungin illustrate an enantiocontrolled synthesis of the *trans*-decalin core **28** via an intramolecular [4π + 2π] cycloaddition. This strategy utilizes the nitroalkene dienophile of **27** as a surrogate ketene equivalent. Stereocontrol at C-2 is critically important for an effective intramolecular Diels–Alder (IMDA) process. Our studies report high asymmetric induction using a nonracemic Duthaler titanium enolate in the acetate aldol reaction with β,β′-branched aldehyde **13** to introduce the required C-2 chirality.

The increasing incidence of life-threatening fungal infections is coupled to an emerging resistance to first-line treatment protocols, emphasizing the need for new therapeutic agents with unique modes of action. The isolation and structure determination of australifungin (**1**, Figure 1), a

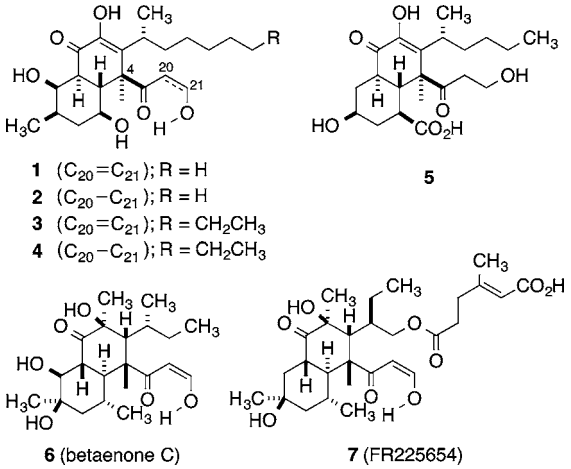



**Figure 1.** Australifungin (**1**) and related metabolites.

potent broad-spectrum antifungal natural product of *Sporomiella australis* (MG5672, ATTC74157), has been described and is accompanied by the closely related australifunginol (**2**).[1] Australifungin is reported as the first nonsphingosine-based inhibitor of sphingolipid biosynthesis.[2] It functions as a selective inhibitor of sphingosine *N*-acyl transferase (ceramide synthase), an enzyme responsible for the production of ceramide via the acylation of the long chain amines, sphingosine, sphinganine, and 4-hydroxysphinganine. Ceramide is the key precursor to sphingomyelin, gangliosides, and glycosphingolipids. Ceramide may also function as an intracellular messenger in a lipid signal transduction pathway[3] implicated in several processes linked to cell differentiation, apoptosis, and cell proliferation.[4] A recent study has identified the natural metabolite NBRI17671 (**3**) and the reduced derivative **4** as novel inhibitors of the interaction of RAGE (receptor for advanced glycation end-product) and amphoterin.[5] Blocking the interaction of RAGE and amphoterin results in an inhibition of tumor growth, motility, and angiogenesis.[6]

Cytosporic acid (**5**) has similar structural features and has been shown to inhibit HIV-1 integrase, an enzyme essential for viral replication.[7] Other members of the family include the betaenones A, B, C (**6**), and D,[8] and FR225654 (**7**),[9] a potent hypoglycemic agent, which is an ester of stemphyloxin.[10] Stereochemical relationships among compounds of this family may require further study. While absolute stereochemistry is undetermined in most cases, positive optical rotations have been recorded for compounds **1**–**5** whereas negative rotations are observed for the betaenones (**6**), as well as FR225654 (**7**). Absolute configuration has been unambiguously assigned solely for **7**.[9]

Herein we communicate our studies toward the enantiocontrolled synthesis of **1**. These findings describe a stereoselective route to provide the *trans*-decalone core of the natural product by utilizing a nitroalkene as a surrogate ketene equivalent for an effective intramolecular Diels–Alder (IMDA) cycloaddition. Features of asymmetry within the tethering linkage have

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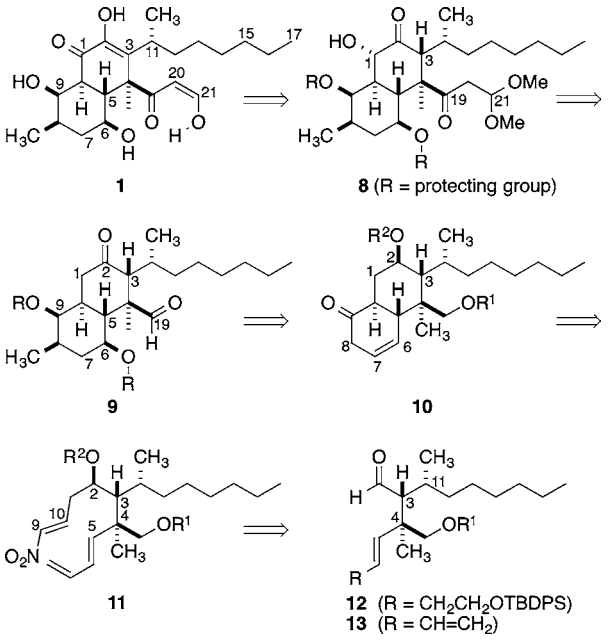
important consequences for cyclization. A stereoselective synthesis of the desired IMDA precursor is described by utilizing a Duthaler acetate aldol reaction. High asymmetric induction is achieved for the reagent-controlled nucleophilic addition with a nonracemic $\beta,\beta'$-branched aldehyde.

Australifungin (**1**) presents a challenging target for synthesis studies because it exhibits a densely functionalized skeleton possessing six contiguous asymmetric carbon centers. Our retrosynthetic hypothesis, diagrammed in Scheme 1, features

**Scheme 1. Retrosynthetic Analysis**



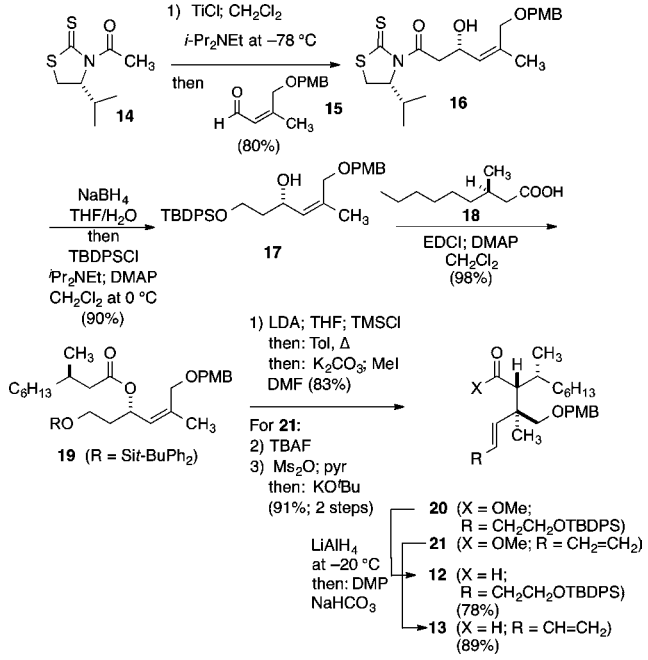

the $\alpha$-hydroxyketone of **8** as the penultimate intermediate for the oxidation and deprotection to yield the natural product. The dimethyl acetal and the $\alpha$-hydroxy ketone of **8** can be sequentially introduced from the C-19 aldehyde and the C-2 ketone of **9**, respectively. Furthermore, a suitably protected $\beta,\gamma$-enone **10** permits the stereocontrolled elaboration of the A-ring substitution, and this ketone is available by the intramolecular Diels–Alder cycloaddition of the nitroalkene **11** followed by application of the Nef oxidation. Finally, nonracemic aldehyde **12** was projected as a key precursor leading to the formation of the desired IMDA substrate **11**.

Our prior studies have generally examined cycloaddition reactions of nitroalkenes, and we have described the relative reactivity and high stereoselectivity of an asynchronous cyclization to afford *trans*-fused decalins.[11] An enantiocontrolled access to the IMDA precursor **11** (Scheme 1) was devised utilizing an Ireland–Claisen strategy to construct the contiguous asymmetry along the carbon backbone at C-3, C-4, and C-11 of the aldehyde **12** for late-stage generation of the diene moiety. These plans also considered advancing the intact diene of aldehyde **13**.

Studies began with investigations of acetate aldol methodology for preparation of an enantioenriched allylic alcohol to be used in the Claisen rearrangement. Initial efforts examined the Fujita–Nagao protocol,[12] in which a solution of *N*-acetylthiazolidine thione **14** and tin(II) triflate was treated with *N*-ethylpiperidine and aldehyde **15**[13] at −78 °C to yield the desired adduct **16** in 78% yield. The use of stoichiometric amounts of tin(II) triflate and the variability of yields and diastereoselectivity (ranging from 10:1 to 6:1 dr) in preparative scale reactions subsequently led us to pursue an alternative procedure as described by Villarasa and co-workers.[14] Treatment of **14** on the multigram scale with titanium tetrachloride and diisopropylethylamine at −78 °C routinely produced an 80% yield of the diastereomer **16** following chromatography of the crude product (86:14 dr). Sodium borohydride reduction and protection of the resulting primary alcohol as the *tert*-butyldiphenylsilyl (TBDPS) ether led to the (*S*)-alcohol **17** as confirmed by a Mosher ester analysis.[15] The esterification of the *Z*-allylic alcohol **17** with (+)-3-methylnonanoic acid (**18**)[16] gave ester **19**, and the conversion of **19** to an intermediate (*E*)-trimethylsilylketene acetal was followed by heating in toluene which led to preparation of the expected methyl ester **20** after esterification.[17] Formation of aldehyde **12** was accomplished by $LiAlH_4$ reduction of **20** at −20 °C followed by Dess–Martin oxidation[18] (78% for 2 steps). Formation of diene **21** from **20** proceeded via TBAF deprotection and subsequent elimination of a homoallylic mesylate (91% over 2 steps). The aldehyde **13** was then obtained by application of the previous reduction and oxidation conditions (91%).

Initially, we devised a preparation of IMDA precursor **11** (Scheme 1) without stereocontrol at C-2. Cycloadditions of a 1:1 mixture of C-2 diastereomers resulted in at least five products and required HPLC separations. Studies indicated that the (*R*)-C-2 isomer **11** cleanly provided an efficient reaction whereas the (*S*)-C-2 epimer led to a mixture of products. Thus, efforts were undertaken to advance diastereoselective reactions of the chiral aldehydes **12** and **13** from Scheme 2. A literature survey did not uncover examples of

**Scheme 2. Preparation of Nonracemic Aldehydes 12 and 13**




stereocontrolled nucleophilic additions to acyclic $\beta,\beta'$-branched aldehydes, and the problematic nature of these reactions is underscored by a compilation of our results in Table 1. For substrate control, the high-yielding addition of allylmagnesium bromide is completely nonselective (entry 1; dr 1:1). However, reagent-controlled reactions of **12** using the boron-mediated Brown Ipc-allylation[19] or the Corey (stien-controller)[20]



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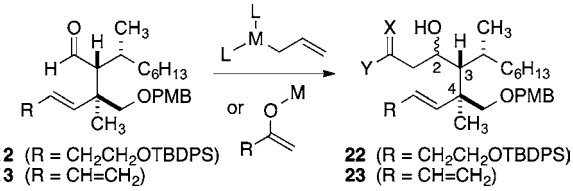
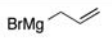
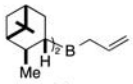
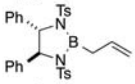
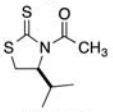
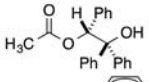
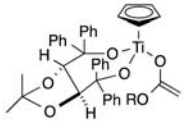
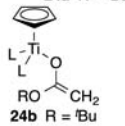
**Table 1. Asymmetric Induction for Reactions with Aldehyde 12 and 13**




| entry | reagents[a] | conditions | product (yield)[b] | dr[c] (β/α) |
|---|---|---|---|---|
| 1 |  | $Et_2O$ −78 °C | **22** (98%) | 50:50 |
| 2 |  | $Et_2O$ −78 °C | **22** (65%) | 60:40 |
| 3 |  | $CH_2Cl_2$ −78 °C | **22** (35%) | 55:45 |
| 4 |  | $Sn(OTf)_2$ *N*-ethylpiperidine $CH_2Cl_2$; −78 C to r.t. | **23** (N.R.)[d] | – |
| 5 |  | LDA; $MgBr_2$•$OEt_2$ THF; −78 °C | **23** (71%) | 60:40 |
| 6 |  **24a** R = $^t$Bu | $Et_2O$; −78 °C | **23** (65%) | 80:20 |
| 7 |  **24b** R = $^t$Bu L = DGDA | $Et_2O$; −78 °C | **23** (86%) | >95:5 |
| 8 | **24c** R = *i*Bu L = DGDA | $Et_2O$; −78 °C | **23** (88%) | 93:7 |
| 9 | **24d** R = Et L = DGDA | $Et_2O$; −78 °C | **23** (68%) | 90:10 |

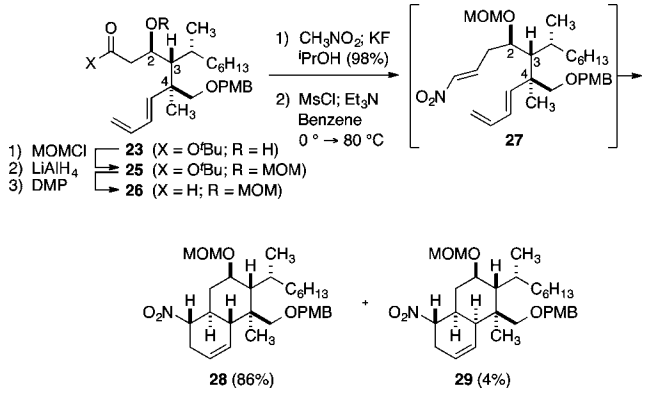
[a]Reagents were prepared according to published procedures. Generally, 2 equiv of reagent were used in each attempted reaction with **12**. Titanium ligand L is derived from precomplexation of $CpTiCl_3$ with D-glucose diacetonide (DGDA). [b]Isolated yield. [c]Diastereomeric ratios [dr] were determined by integration of $^1$H NMR signals in crude product mixtures. [d]No reaction products were observed.

methodology also provided unusually low levels of asymmetric induction (Table 1; entries 2 and 3). No improvement was observed using the Brown allylation under salt-free conditions.[19]

In similar fashion, an efficient, albeit nonselective, condensation of **13** with the lithium enolate of *tert*-butylacetate (>95% yield; dr 1.1:1) led us to explore reagent-controlled aldol reactions. The Nagao procedure[12] using the Sn(II)-enolate (Table 1; entry 4), as well as the Ti-enolate modification of Vilarrasa,[14] delivered traces of aldol adducts, whereas the Braun acetate aldol methodology[21] afforded a facile reaction (71% yield) with modest stereoselectivity (entry 5; dr 60:40). In contrast, the chiral titanium enolates as developed by Riediker and Duthaler offered significant improvement.[22] The use of the (*S*,*S*)-TADDOL titanium enolate **24a** (Table 1, entry 6) produced a 65% yield of adducts with moderate stereocontrol (dr 80:20). Optimal results were achieved using a solution of the ligated titanium complex $CpTiL_2Cl$ which is formed from 2 equiv of D-glucose diacetonide and $CpTiCl_3$. Low temperature exchange with a kinetically generated lithium enolate of *tert*-butylacetate led to *in situ* formation of nonracemic enolate **24b**, and the introduction of aldehyde **13** at −78 °C produced **23** in high yield with excellent diastereoselectivity [dr >95:5] (Table 1; entry 7). The steric bulk of the *tert*-butyl ester also provided an optimization as shown by the isobutyl and ethyl ester enolates **24c** and **24d**, which result in diminishing stereoselectivity (compare entries 7, 8, and 9). Our findings describe the first report of stereocontrol for acetate aldol reactions with particularly challenging acyclic β,β′-disubstituted aldehydes. Mechanistic analysis has suggested that these titanium enolates react via boat-like transition states.[23]

Alcohol **23** was purified by flash chromatography and was immediately protected as MOM ether **25** in 90% yield (Scheme 3). The ester of **25** was transformed into the aldehyde **26** by

**Scheme 3. IMDA Studies**




$LiAlH_4$ reduction and Dess−Martin oxidation (DMP) (75% yield; 3 steps).[18] Submission of **26** to a mild Henry reaction[24] with nitromethane used spray-dried KF as a fine suspension in isopropanol. This technique avoided unwanted elimination of the C-2 OMOM ether and produced a 1:1 mixture of diastereomeric alcohols (98% yield). These alcohols were separated and independently characterized, but led to the same alkene for the IMDA reaction as illustrated in Scheme 3. Treatment of the mixture of alcohols with methanesulfonyl chloride and $Et_3N$ led to the observation of an IMDA reaction that slowly proceeds at room temperature. In practice, the crude *E*-nitroalkene **27** is heated in benzene in the presence of a small amount of BHT (butylated hydroxytoluene) and results in the formation of the desired *trans*-decalin **28** (86% yield) in addition to a small amount of the *cis*-fused **29** (4% yield). The presence of the C-3 alkyl substitution in the triene precursor **27** leads to the observation of a substantial rate acceleration and a preference for the *endo*-transition state leading to *trans*-fused decalin **28**.[11] The stereochemistry of **28** is readily assigned by key NOESY crosspeaks of the 1,3-diaxial hydrogens at C2 and C10 with the C4-methyl substituent. Likewise, NOESY crosspeaks are seen for hydrogens at C1, C3, C5, and C9.

In summary, our studies have described an enantiocontrolled synthesis of the highly substituted *trans*-decalin of australifungin (**1**). Our IMDA strategy incorporates sterically demanding alkyl substitution in the linking carbon tether which accelerates the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[4π + 2π] cyclization using a nitroalkene dienophile as a ketene surrogate. These investigations report an unprecedented acetate aldol reaction to establish asymmetric induction leading to the crucial (*R*)-stereochemistry of the C-2 alcohol. The condensation features a Duthaler chiral titanium enolate for reaction with a nonracemic *β*,*β*′-branched aldehyde.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03463.

Experimental details, $^{1}H$ and $^{13}C$ NMR spectra (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: williamd@indiana.edu.


### Notes

The authors declare no competing financial interest.

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