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Influence of Diene Substituent Position on the Stereochemical Outcome in IMDA Reaction of Decatrienones. An Asymmetric Synthesis of C_{10}-*epi*-Dihydro-*epi*-deoxy Arteannuin B

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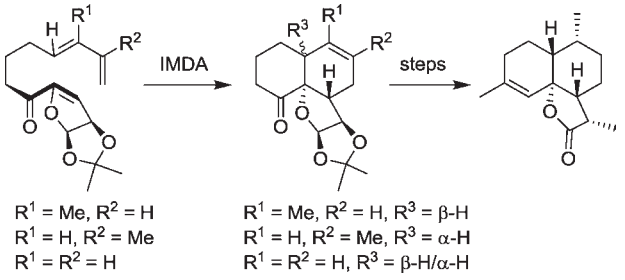
ABSTRACT



An asymmetric synthesis of C_{10}-*epi*-dihydro-*epi*-deoxy arteannuin B is reported employing an IMDA reaction of sugar embedded decatrienone. During this investigation it has been demonstrated that changing the position of the methyl group on the diene moiety changes the stereochemical outcome leading to access to either *cis*- or *trans*-decalin derivatives exclusively.

Artemisinin or Qinghaosu **1**,[1] a sesquiterpene endoperoxide natural product isolated from *Artemisia annua L.*,[2] has been the subject of synthetic, mechanistic, and pharmacological studies due to its efficacy in the battle against malaria (Figure 1). It is the active principle of the herbal medicine known as Qinghao that has been in use in China and other parts of South East Asia for thousands of years. In addition to its antimalarial activity, artemisinin exhibits selective cytotoxicity against iron-rich cancer cells and is considered to be a lead compound in cancer research.[3] Arteannuin B **4**[4] and dihydro-*epi*-deoxy arteannuin B **6**[5] are two other important compounds that have been isolated from *A. annua*. Although both compounds lack antimalarial activity, Nowak and Lansbury[6] have demonstrated that arteannuin B **4** can chemically be transformed to artemisinin through dihydro-*epi*-deoxy areteannuin B **6** manifesting **4** as the biosynthetic precursor of artemisinin.

The challenge associated with the synthesis of artemisinin having an endoperoxide bridge combined with its pharmacological activities has elicited considerable synthetic interest. A number of syntheses of artemisinin[7] and its analogues[8] have been developed. Synthesis of some

(1) (a) Klayman, D. L. *Science* **1985**, *228*, 1049–1055. (b) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73–79.
(2) Liu, J.-M.; Ni, M.-Y.; Fan, Y.-F.; Tu, Y.-Y.; Wu, Z.-H.; Wu, Y.-L.; Zhou, W. S. *Huaxue Xuebao* **1979**, *37*, 129.
(3) Lai, H.; Nakase, I.; Lacoste, E.; Singh, N. P.; Sasaki, T. *Anticancer Res.* **2009**, *29*, 3807–3810 and the references cited therein.
(4) Jeremic, D.; Jokic, A.; Behbude, A. *Tetrahedron Lett.* **1973**, 3039–3042.
(5) Brown, G. D. *J. Nat. Prod.* **1992**, *55*, 1756–1760.
(6) Nowak, D. M.; Lansbury, P. T. *Tetrahedron* **1998**, *54*, 319–336.
(7) Hao, H.-D.; Li, Y.; Han, W.-B.; Wu, Y. *Org. Lett.* **2011**, *13*, 4212–4215 and the references cited therein.
(8) (a) Zhou, W. S. *Pure Appl. Chem.* **1986**, *58*, 817–824. (b) Posner, G. H.; Paik, I.-H.; Chang, W.; Borstnik, K.; Sinishtaj, S.; Rosenthal, A. S.; Shapiro, T. A. *J. Med. Chem.* **2007**, *50*, 2516–2519. (c) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397–404.
(9) Avery, M. A.; Jennings-white, C.; Chang, W. K.M . *J. Org. Chem.* **1989**, *54*, 1792–1795.

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artemisinin analogues relies on the transformation of arteannuin B analogues. For example, Avery et al.[9] have synthesized $C_{10,11}$-didesmethyl artemisinin **2** which shows significant antimalarial activity against strains of *Plasmodium falciparum*. To synthesize the artimisinin analogue **3**, Schwaebe and Little[10] have synthesized C_{10}-desmethyl arteannuin B **5**. These investigations reveal that the presence or absence of a Me group on the B ring influences the antimalarial activity of artemisinin significantly.

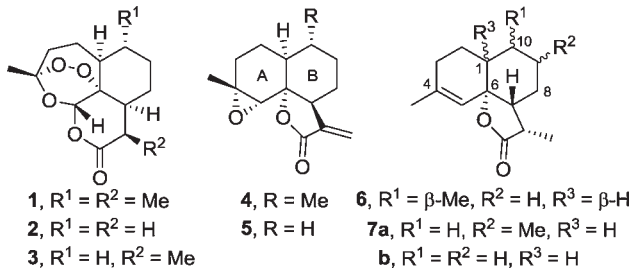


Figure 1. (−)-Artemisinin (**1**), (−)-arteannuin B (**4**), etc.

The only route reported in the literature[11] for the synthesis of **6**, the precursor of artemisinin, lacks generality for incorporation of substituents on its nucleus. Thus the main focus of the present investigation is to develop a general methodology for the synthesis of dihydro-*epi*-deoxy arteannuin B **6** and its analogues **7a** and **b**. Compounds **7a** and **b** can then be converted to the corresponding artemisinin analogues employing the method of Nowak and Lansbury.

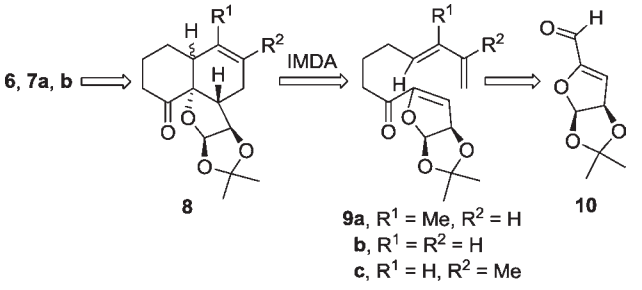
Our synthetic protocol relies on an intramolecular Diels−Alder (IMDA) reaction[12] of the trienone **9** which was anticipated to lead to a functionalized decalin **8**, the furanose ring of which could be employed to construct the γ-butyrolactone unit present in **6** and **7** (Scheme 1). The trienone **9** would be available from the aldehyde **10**.[13]

The stereochemical outcome in a Diels−Alder reaction to form decalins is dependent on a number of factors including conformation, steric, and electronic effects of the substituents in the transition state. We became interested to see whether substituents at various locations on the diene moiety could enable the cycloaddition to be stereoselective to give exclusively either the *cis*- or *trans*-fused decalins. This will then lead to access to the structures related to arteannuin B as well as dihydro-*epi*-deoxy arteannuin B.

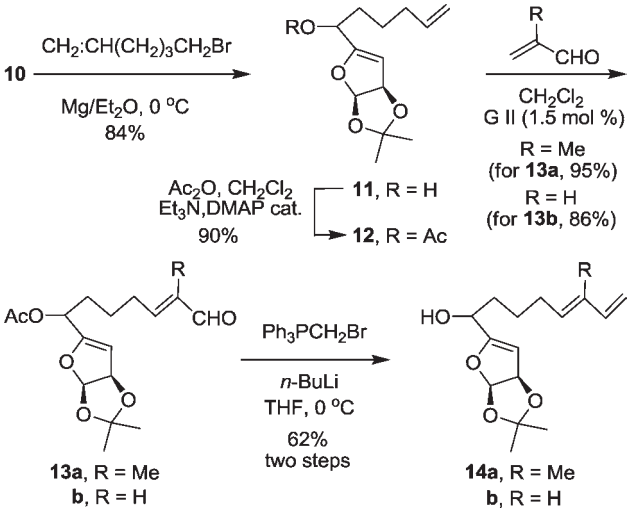
The synthesis of the IMDA precursors was achieved in the following way. Addition of a Grignard reagent prepared from 5-bromo-1-pentene to the aldehyde **10** gave the hydroxy compound **11** as a single diastereoisomer in 84% yield (Scheme 2). The acetate **12** derived from **11** was subjected to cross metathesis with methacrolein in the presence of Grubbs' second generation catalyst (G II) to provide the aldehyde **13a** in excellent yield. Wittig olefination of the aldehyde **13a** with the ylide generated from methyltriphenylphosphonium bromide provided, with concomitant deacetylation, the trienol **14a** in 62% yield. In a similar fashion cross metathesis of **12** with acrolein gave the aldehyde **13b** in 86% yield. Wittig olefination of **13b** using the above protocol gave the trienol **14b**.

The synthesis of the trienol **20** was achieved as delineated in Scheme 3. Addition of the Grignard reagent prepared

Scheme 1. Retrosynthesis



Scheme 2. Synthesis of IMDA Precursors **14a,b**

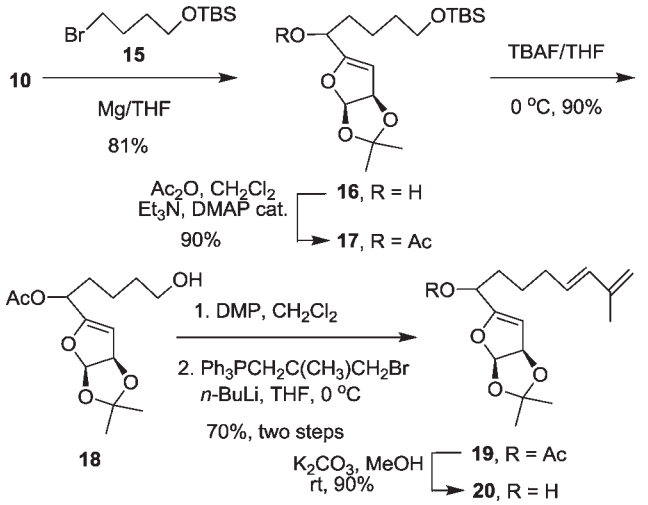


from the bromide **15**[14] afforded the hydroxy compound **16**. The acetate **17** obtained from **16** was desilylated, and the resulting alcohol **18** was oxidized to give an aldehyde. Wittig olefination of this aldehyde with the ylide generated from methallyltriphenyl phosphonium bromide followed by basic hydrolysis of the resulting acetate **19** provided in excellent yield the trienol **20** along with its *Z*-isomer (2:1) as evidenced by *J*-values of the olefinic protons in the central alkene unit.

(10) Schwaebe, M.; Little, R. D. *J. Org. Chem.* **1996**, *61*, 3240–3244.
(11) Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007**, *9*, 2839–2842.
(12) For reviews, see: (a) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183–234. (b) Singh, V.; Iyer, S. R.; Pal, S. *Tetrahedron* **2005**, *61*, 9197–9231.
(13) Sun, K. M.; Fraser-Reid, B. *Synthesis* **1982**, 28–29.
(14) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142.

With the trienols ready in hand they were subjected to oxidation with Dess–Martin periodinane (DMP) and subsequently to an IMDA reaction (Scheme 4). Treatment of the trienol **14a** with DMP at 0 °C to rt resulted in oxidation with concomitant cycloaddition of the resulting enone **9a** to produce the *trans*-decalin derivative **21** exclusively in 85% yield. The trans ring fusion in **21** followed from the single-crystal X-ray structure of the compound **39** prepared from **21** (Scheme 6). The unstable trienone **9c** obtained by DMP oxidation of the trienol **20**, without purification and characterization, was subjected to IMDA reaction by heating its toluene solution in a sealed tube at

Scheme 3. Synthesis of IMDA Precursor **20**

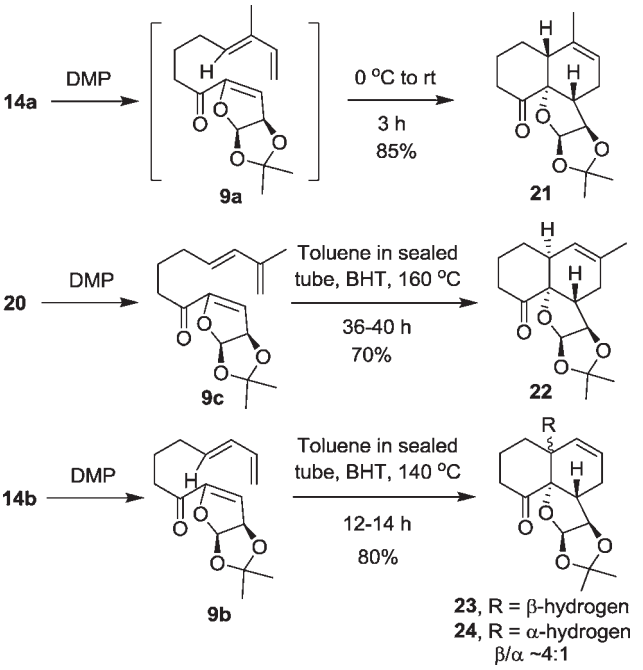


160 °C for nearly 40 h to produce the *cis*-decalin derivative **22**, mp 108–109 °C in 70% yield. The structure of this adduct was established through X-ray (Figure 2).[15] In contrast to the above observation, IMDA reaction of the unstable trienone **9b** obtained from the trienol **14b** was achieved on heating its toluene solution in a sealed tube at 140 °C for 12 h to produce **23** and **24** in 64% and 16% yields respectively. The stereochemical assignment to the adducts **23** and **24** were based on comparison of the chemical shifts of the acetonide methyl protons of **21** and **22**. It may be noted that the difference in chemical shifts of the acetonide methyls in ^{1}H NMR spectrum for the *trans*-adduct **21** is 0.98 while that for the *cis*-fused product is 0.17. In the major isomer obtained from IMDA reaction of **9b** the chemical shift difference between the two acetonide methyls was found to be 0.95, and accordingly this adduct was assigned the *trans*-decalin structure **23** while the minor isomer for which this value is 0.163 was assigned the *cis*-decalin structure **24**.

It is interesting to note that the stereochemical outcome in an IMDA reaction of the decatrienones **9a**–**c** is strongly

(15) Crystallographic data for compounds **22** and **39** have been deposited with the Cambridge Crystallographic Data Center as supplimentary publication numbers CCDC 844476 and 844475, respectively. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ, U.K. Fax: +44-1233-336033. Email: deposit@ccdc.cam.ac.uk.

Scheme 4. IMDA of **9a**–**c**



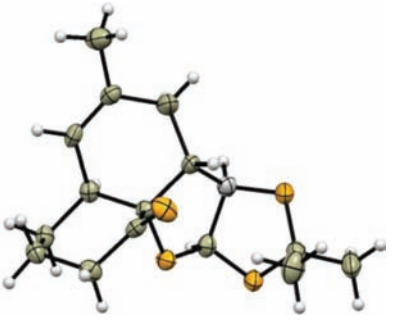
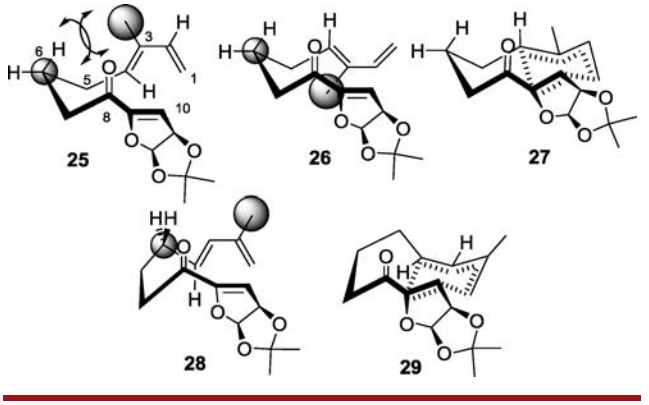
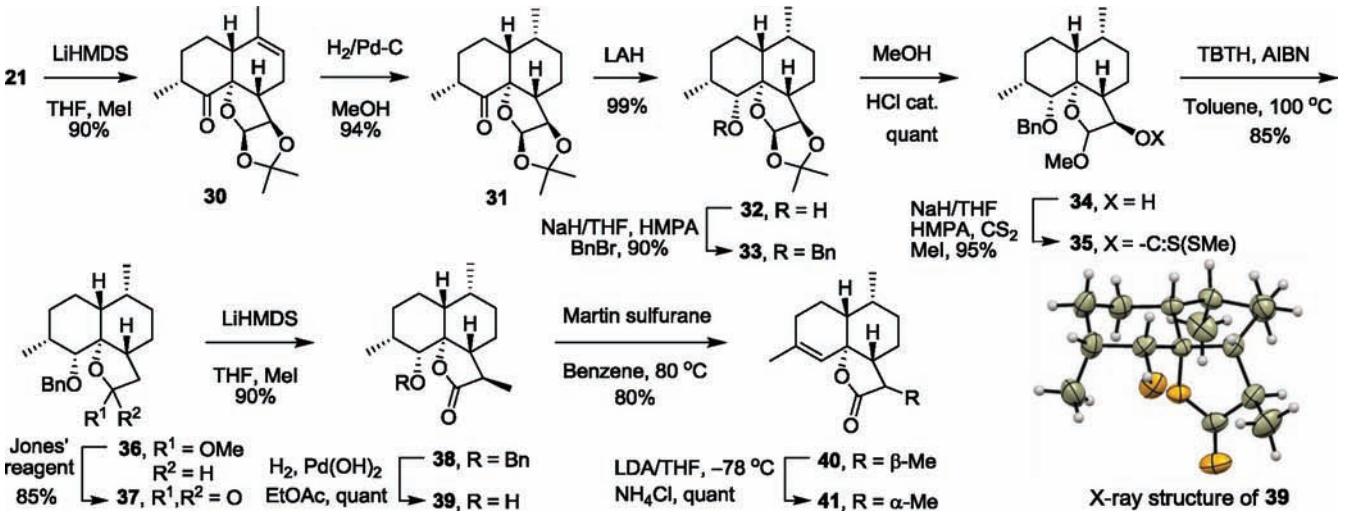


Figure 2. X-ray structure of **22**.

Scheme 5. TS for IMDA Reaction of **9a,c**



Scheme 6. Synthesis C_{10}-*epi*-Deoxy-*epi* Arteannuin B



dependent on the position of the Me substituent on the diene moiety. The observed results may be attributed to the steric interaction in the transition states (Scheme 5). A Diels–Alder reaction of the decatrienone **9a** may proceed through either the endo mode **25** or the exo mode **26**. Endo oriented structure **25** is strained due to steric interaction between C_6-methylene hydrogens and the C_3-methyl substituent. This steric interaction is absent in exo mode **26**. Thus cycloaddition proceeds through the chair, chair transition state (TS) **27** to give rise to thermodynamically more stable *trans*-decalin **21**. In contrast, the endo orientation **28** of the trienone **9c** is devoid of this sort of interaction. Thus reaction proceeds through the boat, chair TS **29** to produce the *cis*-decalin **22**. IMDA reaction of the trienone **9b**, devoid of any Me group on the diene moiety, proceeds through a chair, chair TS to produce the thermodynamically more stable *trans*-decalin as the major product. It is probably the relief of steric strain that makes **9a** more reactive than the trienones **9b** and **c** which are free of this strain.

After successfully finding methodology for synthesizing exclusively the *trans*- or *cis*-decalin, we focused our attention toward the synthesis of dihydro-*epi*-deoxy arteannuin B in which a *trans*-decalin system is present. The tricyclic ketone **21** was methylated on treating its lithium enolate with MeI, resulting exclusively in the ketone **30** in 90% yield (Scheme 6). Catalytic hydrogenation of **30** gave exclusively the saturated compound **31** in 94% yield. The stereochemistry of the C_{10}-methyl in **31** was found to be epimeric with that in the natural isomer **6**. LAH reduction of the ketone **31** produced the alcohol **32**, the hydroxyl group of which was then protected to provide the benzyl ether **33** in an overall excellent yield. The stereochemical assignment to these compounds was based on an X-ray structure of the lactone **39**.

Conversion of the furanose residue in **33** to the γ-butyrolactone unit was initiated with acid catalyzed opening of the acetonide moiety in methanol to produce the acetal **34** in quantitative yield. Deoxygenation of the hydroxyl group in **34** was effected through TBTH reduction of its xanthate derivative **35** to afford the acetal **36** in high overall yield. The cyclic acetal **36** when subjected to treatment with Jones' reagent furnished directly the lactone **37** in 85% yield. Hydrogenolysis of the benzyl ether in **38** was carried out with $Pd(OH)_2$ cat. to provide the hydroxy-lactone **39** as a crystalline solid, mp 142–143 °C in quantitative yield. The structure of the hydroxy-lactone **39** was unambiguously established through X-ray. With the establishment of the structure of the lactone **39**, the structures of the compounds **21** and **30**–**38** were also established. Finally, a Martin sulfurane mediated dehydration[16] of the hydroxy compound **39** led to the formation of the olefin **40** in 80% yield. Kinetic protonation of the lithium enolate of the lactone **40** led to complete epimerization to afford the lactone **41**, the C_{10}-epimer of dihydro-*epi*-deoxy arteannuin B in quantitative yield. The C_{10}-epimer **41** should in principle be converted to C_{10}-*epi*-artemisinin by the procedure of Nowak and Lansbury.

In conclusion, we have demonstrated that an IMDA reaction of decatrienones **9a**–**c** may lead to either *cis*- or *trans*-decalin exclusively by changing the position of the substituent on the diene moiety, leading to the synthesis of a C_{10}-epimer of dihydro-*epi*- deoxy arteannuin B and offering an opportunity to access its analogues with or without a Me group on the B ring.

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Supporting Information Available. Experimental procedure and spectroscopic data for all the new compounds and crystallographic data for **22** and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Spangler, J. E.; Carson, C. A.; Sorensen, E. J. *Chem. Sci.* **2010**, *1*, 202–205.