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A Concise Diels−Alder Strategy for the Asymmetric Synthesis of (+)-Albicanol, (+)-Albicanyl Acetate, (+)-Dihydrodrimenin, and (−)-Dihydroisodrimeninol

Jeff R. Henderson, Masood Parvez, and Brian A. Keay*

Department of Chemistry, University of Calgary, Calgary, AB, Canada, T2N 1N4

keay@ucalgary.ca

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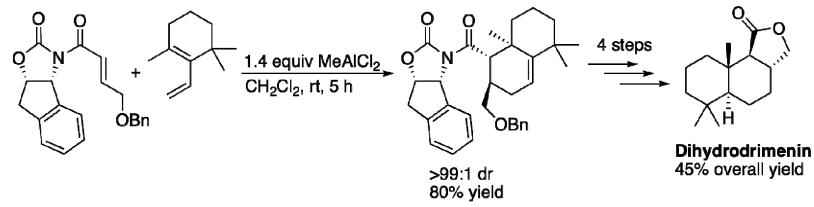
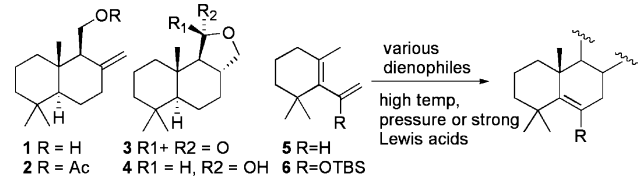
ABSTRACT



A short, mild, highly diastereo-, regio-, and stereoselective Diels−Alder strategy has been developed for the asymmetric synthesis of (+)-albicanol, (+)-albicanyl acetate, (+)-dihydrodrimenin, and (−)-dihydroisodrimeninol.

The drimane class of natural products is ubiquitous in nature (Scheme 1)[1] with many of them exhibiting a wide range of biological activity.[2] For example, (+)-albicanol **1**[3a,b] and (+)-albicanyl acetate **2**[3b] have exhibited potent piscicidal effects, while (+)-dihydrodrimenin **3**[3c] shows antimicrobial activity against *Photobacterium leiognathi* and moderate inhibition of Na^+/K^+-ATPase.[3d] While **3** and **4** have not been synthesized to date, synthetic strategies toward albicanol **1** and albicanyl acetate **2** have been reported. Initial syntheses of **1** and **2** were racemic,[4,5] while more recent endeavors have involved asymmetric approaches involving (a) kinetic resolutions of suitable synthetic precursors with enzymes[6] or *N*-Boc-L-proline,[7] (b) starting the synthesis with ready available natural products (+)-sclareolide[8] and (+)-manool,[9] and (c) using enantiopure Wieland−Miescher ketone as the starting material.[10] A simple, short, asymmetric route to the drimane skeleton is still needed.

Scheme 1



(1) (a) Jansen, B. J. M.; de Groot, A. *J. Nat. Prod.* **1991**, *8*, 319. (b) Jansen, B. J. M.; de Groot, A. *J. Nat. Prod.* **1991**, *8*, 309.

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(3) (a) Ohta, Y.; Andersen, N. H.; Liu, C.-B. *Tetrahedron* **1977**, *33*, 617. (b) Hellou, J.; Andersen, R. J. *Tetrahedron* **1982**, *38*, 1875. (c) Paul, V. J.; seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Bergquist, P. R. *J. Nat. Prod.* **1997**, *60*, 1115. (d) To our knowledge, (−)-dihydro-isodrimeninol **4** has not been tested for biological activity: Montagnac, A.; Martin, M.-T.; Debitus, C.; Pais, M. *J. Nat. Prod.* **1996**, *59*, 866.

(4) Armstrong, R. J.; Harris, F. L.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 1002.

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(6) (a) Akita, H.; Nozawa, M.; Mitsuda, A.; Ohsawa, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1375. (b) Anilkumar, A. T.; Sudhir, U.; Joly, S.; Nair, M. S. *Tetrahedron* **2000**, *56*, 1899.

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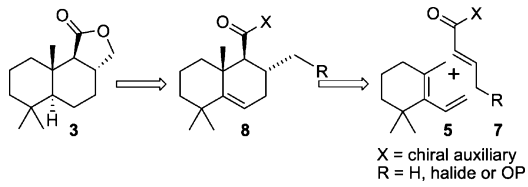
The nonasymmetric Diels−Alder (DA) reaction approaches to **1** using diene **5** (Scheme 1) with various dienophiles involved in the use of harsh conditions. For example, high pressures and/or strong Lewis acids,[11] high temperatures,[12] or dienophiles containing two electron-withdrawing groups have been found necessary to effect a successful DA reaction.[11,12] Mayelvaganan et al. reported the use of $AlCl_3$ in nonasymmetric Lewis acid catalyzed DA reactions of diene **5** with *cis*-substituted dienophiles; however, no other milder aluminum Lewis acids were mentioned in the paper.[13]

Asymmetric variants of the DA reaction involving diene **5** have been limited to the use of high pressures (12−15 kbar) with either quinones containing substrate-bound chiral auxiliaries[14] or chiral Lewis acids.[15]

More recently, the use of allenic dienophiles with **6** resulted in [2 + 2] cycloadditions with the silyl enol ether in **6** after heating a neat mixture of diene and dienophile at 110 °C for 14 days.[16] Subsequent thermolysis of the formed cyclobutene gave products expected from a [4 + 2] cycloaddition. While these DA reactions are noteworthy, there is still a need for an asymmetric variant of this reaction that proceeds under mild reaction conditions and with high regio-, stereo-, and diastereoselective control. We herein report a mild yet highly selective DA reaction of this type that provides a convenient, high-yielding route to drimanes **1**−**4**.

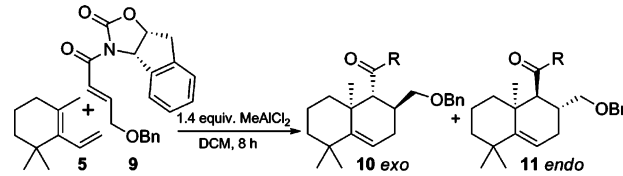
Our previous work with DA reactions catalyzed by BCl_3[17] and milder Lewis acids like $MeAlCl_2$[18] led us to investigate the synthetic strategy outlined in Scheme 2 toward the drimane family of natural products. If the regio-, endo/exo-, and facial selectivity were controlled during the DA reaction with a *trans*-disubstituted dienophile like **7**, then this strategy could provide a facile route to (+)-dihydrodrimenin (**3**) via **8**. Subsequently, (+)-dihydrodrimenin (**3**) could be used further as an intermediate to other natural products within the drimane class.

Scheme 2



Given that chiral 1,3-oxazolidin-2-ones act as excellent auxiliaries in asymmetric DA reactions,[19] we began our investigation with the *trans*-substituted dienophile **9** that contained (*S*-3a-*cis*)-(−)-3,3a,8,8a-tetrahydro-2*H*-indeno-[1,2-d]oxazolidin-2-one as the chiral entity. Treatment of a mixture of **5**[20] and **9** with 1.4 equiv of $MeAlCl_2$ at −25 °C for 8 h provided a 2:1 mixture of two compounds (Table 1, entry 1) in which the major compound **10** crystallized from hexanes. The X-ray crystal structure of **10**[21] (Figure 1) indicated the major product from the DA reaction with **9** was the *exo* isomer. It had the regiochemistry in which the oxazolidinone ring was adjacent to the ring-fused methyl

Table 1. Initial Diels−Alder Results with *Trans*-Substituted Dienophile **6**



entry	temp (°C)	conversion[a]	*exo*:*endo*[b]
1	−25	10%	2:1
2	0	55%	10:1
3	23	75%	15:1 [99:1][c]

[a] % conversion determined by ^{1}H NMR. [b] Determined by 400 MHz ^{1}H NMR. [c] Recrystallized from hexanes to give >99:1. R = (*S*-3a-*cis*)-(−)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-d]-oxazolidin-2-one.

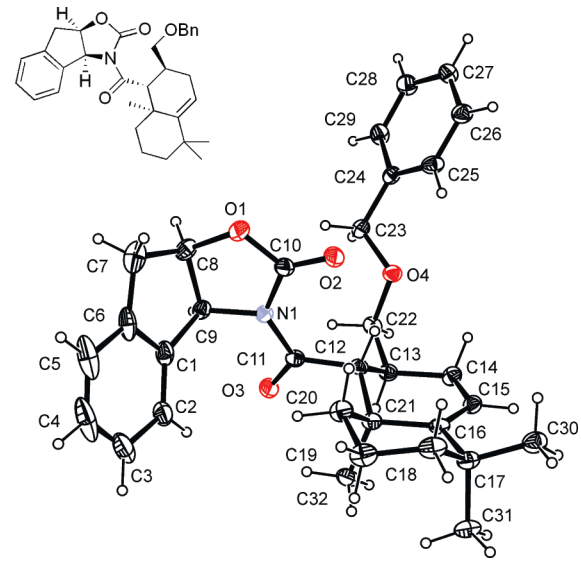


Figure 1. X-ray crystal structure of **10**.

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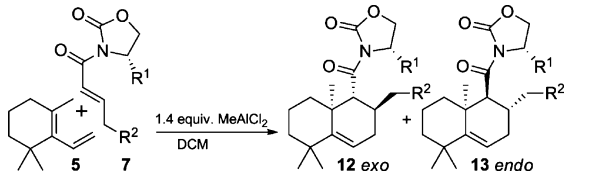
(10) (a) Shishido, K.; Tokunaga, Y.; Omachi, N.; Hiroya, K.; Fukumoto, K.; Kametani, T. *Chem. Commun.* **1989**, 1093. (b) Shishido, K.; Tokunaga, Y.; Omachi, N.; Hiroya, K.; Fukumoto, K.; Kametani, T. J. *Chem. Soc., Perkin Trans.1* **1990**, 2481.
(11) (a) Engler, T. A.; Sampath, U.; Velde, D. V.; Takusagawa, F. *Tetrahedron* **1992**, *48*, 9399. (b) Engler, T. A.; Naganathan, S. *Tetrahedron Lett.* **1986**, *27*, 1015.
(12) Howell, S. C.; Ley, S. V.; Mahon, M.; Wothington, P. A. *Chem. Commun.* **1981**, 507.
(13) For examples using olefin dienophiles with $AlCl_3$, see: Mayelvaganan, T.; Hadimani, S. B.; Bhat, S. V. *Tetrahedron* **1997**, *53*, 2185.

group, but the absolute stereochemistry of the decalin ring was opposite to that required for the synthesis of the drimane skeleton.

This single result indicated that the DA reaction between *trans*-disubstituted dienophile **9** and **5** was possible under very mild conditions (mild LA at −25 °C), which is in stark contrast to the severe reaction conditions previously reported in DA reactions with **5** (Scheme 1). In addition, the DA reaction proceeded with very high regio- and facial selectivity.[22] To optimize the *exo*:*endo* ratio and increase the % conversion, the DA reaction was repeated at different temperatures. We were extremely pleased to find that performing the reaction at 0 °C for 8 h provided a 10:1 *exo*:*endo* ratio and that this ratio was increased to 15:1 when the reaction was performed at 23 °C over the same length of time. One recrystallization of the *exo*:*endo* mixtures from hexanes gave **10** as a pure compound.

To probe the scope and limitations of this reaction and to attempt to improve the *exo*:*endo* ratio further, a variety of dienophiles and 1,3-oxazolidin-2-ones were used in the DA reaction with **5** (Table 2). The first set of DA reactions

Table 2. Diels−Alder Results of Diene **5** with Various Dienophiles and 1,3-Oxazolidin-2-ones



	compd	R^1	R^2	temp (°C)	time (h)	% yield[a]	*exo*:*endo*[b]
1	**7a**	Bn	H	23	5	87	1:1
2	**7a**	Bn	H	23	24	75	1.5:1
3	**7b**	Bn	Br	23	5	40	1:1
4	**7c**	Bn	OTBS	23	5	nr	na
5	**7d**	Bn	OBn	0	12	62	10:1
6	**7d**	Bn	OBn	23	5	65	12:1
7	**7e**	Ph	OBn	0	12	52	3:1
8	**7e**	Ph	OBn	23	5	52	3:1
9	**7f**	iPr	OBn	0	12	60	12:1
10	**7f**	iPr	OBn	23	5	60	20:1

[a] Isolated yields. [b] Determined by 400 MHz NMR.

involved using several Bn-substituted 1,3-oxazolidin-2-ones (**7a**−**d**). Treatment of a mixture of **5** and crotonate **7a**[23] with 1.4 equiv of $MeAlCl_2$ at 23 °C for 5 h provided a 1:1 *exo*-**12** to *endo*-**13** mixture (Table 2, entry 1) that could be slightly improved to a 1.5:1 ratio after stirring the reaction mixture for 24 h (entry 2). Allylic bromination of **7a** afforded **7b**[24] that when subjected to the same DA reaction conditions with **5** provided a complex mixture of products in which the major constituents were a 1:1 mixture of *exo* and *endo* adducts albeit in lower yield due to decomposition of the DA products (entry 3). While the −OTBS-substituted dienophile **7c** did not react with **5** (entry 4), −OBn-substituted olefin **7d** provided a 10:1 mixture of *exo*:*endo* adducts in 62% yield at 0 °C after 12 h (entry 5) that improved to a 12:1 ratio at 23 °C after only 5 h.

While these results were encouraging, the *exo*:*endo* ratio was still lower than that with **9** (Table 1, entry 3). Changing the Bn group on the oxazolidinone to a phenyl group while using the −OBn-substituted crotonate dienophile **7e** provided a 3:1 ratio of isomers at 0 °C that did not change upon warming to 23 °C (entries 7 and 8). Finally, dienophile **7f** with an iPr-substituted oxazolidinone gave the best *exo*:*endo* ratio of 20:1 (entry 10) when the reaction was stirred at 23 °C after only 5 h. This ratio improved from a 12:1 ratio when the reaction mixture was stirred at 0 °C for 12 h (entry 9).

A few points are noteworthy from the results presented in Tables 1 and 2. First, changing the substituents on both the oxazolidinone and allylic carbon atom within the dienophiles (**7a**−**e** and **9**) affects the *exo*:*endo* ratio, with the *exo* isomer predominating in most examples when the reaction is performed at higher temperatures. Second, the best *exo*:*endo* ratios were obtained with the OBn-substituted dienophiles **7d**−**f** and **9**. To understand better the observed changes in the *exo*:*endo* ratio and why the OBn-substituted dienophiles gave the best product ratios, some time studies were performed, and an additional dienophile was studied.

The DA reaction appears to be under thermodynamic control under the reaction conditions since more of the *exo* isomer is formed at higher temperatures. To provide further evidence for this, the reaction between **5** and **9** was stopped after 2 h at −25 °C to give a 1:2 ratio in favor of the *endo* isomer **11**. The *exo*:*endo* mixture was purified from the remaining unreacted starting materials **5** and **9**, dissolved in DCM, and retreated with 1.4 equiv of Me_2AlCl. After 2 h at 23 °C, the ratio changed to 1.5:1 in favor of the *exo* isomer **10** which further equilibrated to give essentially the *exo* isomer after 18 h[25] in addition to a few unidentified compounds. This experiment, in combination

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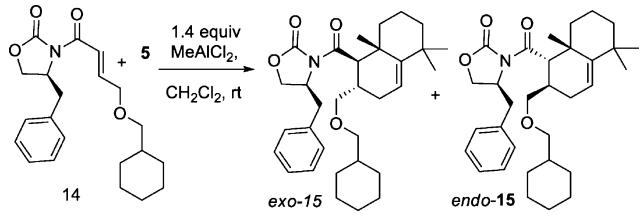
(17) (a) Henderson, J.; Parvez, M.; Keay, B. A. *Org. Lett.* **2007**, *9*, 5167. (b) Lait, S. M.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2003**, *14*, 749. (c) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.
(18) Hunt, I. R.; Rogers, C.; Woo, S.; Rauk, A.; Keay, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 1049, and references therein.
(19) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(20) Diene **5** was easily prepared from β-ionone by oxzonolysis followed by a Peterson olefination. For details, see: (a) Crombie, B. S.; Smith, C.; Varnavas, C. Z.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 206. (b) Howell, S. C.; Ley, S. V.; Mahon, M.; Worthington, P. A. *Chem. Commun.* **1981**, 507.
(21) X-ray crystal data for **10**: monoclinic $P2_1$; a = 9.847(3) Å, b = 25.533(8) Å, c = 10.795(2) Å, α = 90°, β = 91.114(18)°, γ = 90°, V = 2713.6(13) Å^3; Z = 4; R = 0.0474; R_w = 0.0977.
(22) Roush et al. have reported successful DA reactions using $MeAlCl_2$ with acyclic (*Z*)-1,3-dienes using *N*-acryloyl sultam as a chiral auxiliary. (a) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543. Interestingly, a similar reaction with an achiral oxazolidinone did not provide any DA products, see: (b) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402.
(23) The DA reaction of **5** and **7a** did not provide any products when 1.4 equiv of Me_2AlCl, $EtAlCl_2$, Et_2AlCl, or $Sc(OTf)_3$ was used (DCM, 5 h, rt).
(24) Martinelli, M. J. *J. Org. Chem.* **1990**, *55*, 5065.

with the results in Tables 1 and 2, conclusively demonstrates that the DA reaction is under thermodynamic control and that the *exo*:*endo* ratio is governed by both the substituent on the oxazolidinone and on the dienophile. Changes in either can alter the *exo*:*endo* ratio from 1:1 (Table 1, entry 1, crotonate with Bn-substituted 1,3-oxazolidin-2-one) to up to >99:1 (**9** at 23 °C for 18 h).

The best *exo*:*endo* results were provided with the OBn-substituted crotonate dienophiles **7d**−**f** and **9**. To determine if the benzene ring within this substitutent was in any way specifically responsible for the higher *exo*:*endo* product ratios, we prepared **14** that contained a cyclohexyl ring in place of the phenyl ring in **7d** but still retained a Bn -substituted 1,3-oxazolidin-2-one. Treatment of **5** and **14** with 1.4 equiv of Me_2AlCl at 23 °C for 1 h provided a 2:1 *exo*:*endo* ratio that did not change over a 24 h period (Table 3, all entries). It is

Table 3. Diels−Alder Results of Diene **5** with **14**



	time (h)	% conversion[a]	**15** *exo*:*endo*[b]
1	1	82	2:1
2	3	91	2:1
3	6	94	2:1
4	24	100	2:1

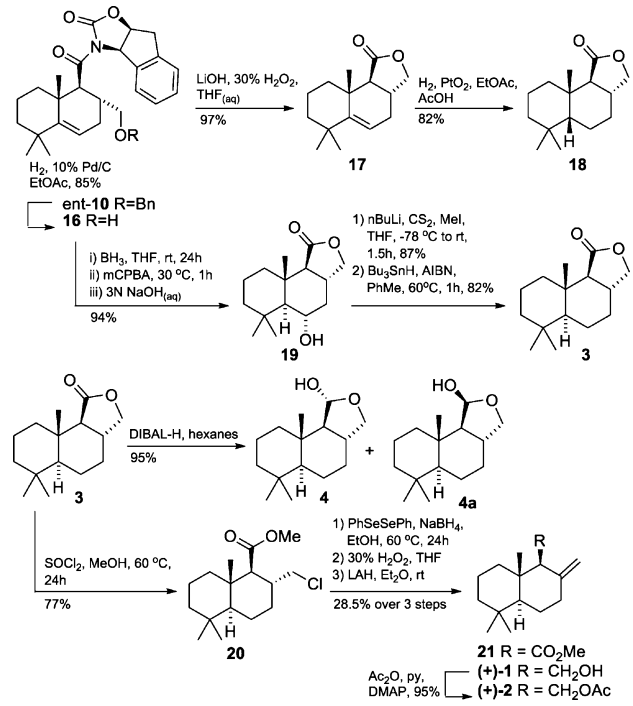
[a] Determined by 400 MHz ^{1}H NMR.

noteworthy that the DA reaction was not finished after one hour, as the % conversion gradually increased from 82 to 100% upon allowing the reaction to stir for 24 h. These results indicate that the DA reaction was already at its thermodynamic equilibrium after 1 h but that the reaction was still progressing to completion. In contrast, OBn-substituted dienophile **7d** provided a 12:1 *exo*:*endo* ratio after 5 h at 23 °C. Unfortunately, we do not have a rationale at this time for why dienophiles with an OBn substituent provide the best *exo*:*endo* ratios but were very satisfied with the knowledge that the DA is under thermodynamic control providing the desired isomer in high yield for the synthesis of some drimane natural products as demonstrated below.

Debenzylation of ent-**10** gave **16** followed by spontaneous lactone formation/chiral auxiliary cleavage which afforded tricycle **17**. Reduction of the olefin in **17** required Adam's catalyst and AcOH, which unfortunately provided *cis*-decalin **18**.[26] Hydroboration−oxidation of ent-**10** afforded *trans*-fused decalin **19** that was subjected to a Barton deoxygenation sequence to provide (+)-dihydrodrimenin (**3**). Reduction of (+)-**3** with DIBAL-H gave a 10:1 ratio of (−)-dihydroisodrimeninol (**4**) and its epimer **4a**.

(+)-Dihydrodrimenin (**3**) was easily converted into (+)-albicanol (**1**) and (+)-albicanol acetate (**2**). Treatment of (+)-**3** with thionyl chloride in methanol at 60 °C for 24 h provided **20**[27] that was easily converted into **21** by treatment with PhSeSePh and $NaBH_4$ followed by a 30% H_2O_2 workup. Reduction of the ester in **21** with LAH gave (+)-**1**. Finally, acetylation of (+)-**1** gave (+)-albicanol acetate (**2**).

Scheme 3



We have shown that the D−A reaction with **5** and *trans*-substituted olefins **7a**−**g** and **9** proceeds with excellent regio-, stereo-, and facial selectivity in the presence of the mild Lewis acid $MeAlCl_2$. The DA adduct **10** was easily converted into four drimane natural products. Work is continuing to apply this method to the synthesis of more elaborate drimanes and labdane natural products.

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Supporting Information Available: Crystallographic data of **10**, **18**, **19**, and **3** and experimental procedures for all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The *exo* isomer was the major product in the ^{1}H NMR spectrum with a few very minor unidentified compounds. After 18 h, the *endo* isomer could not be detected in the NMR spectrum. See the Supporting Information for more details.

(26) The structure of **18** was confirmed by X-ray crystal structure analysis. See the Supporting Information section for more details.

(27) This reaction gave a 5:1 mixture of isomers that were epimeric at the ester in **20**.