Tetrahedron Letters,Vol.30,No.52,pp 7305-7308,1989	0040-4039/89 $3.00 + .00
Printed in Great Britain	Pergamon Press plc

Synthesis and Diels-Alder Reactions of 2-Alkyl-5-methylene-1,3-dioxolan-4-ones and 2-Alkyl-3-acyl-5-methylene-1,3-oxazolidin-4-ones: Highly Exo and Diastereoface Selective Chiral Ketene Equivalents

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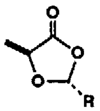
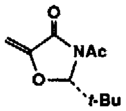
Abstract: *Chiral dienophiles **1-3** undergo highly exo and diastereoface selective Diels-Alder reactions. The Diels-Alder reactions of **3** are also highly exo selective under Lewis acid catalyzed conditions.*

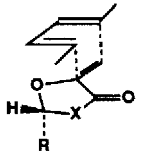
In connection with an ongoing effort in the natural products arena we required a highly diastereoselective chiral ketene equivalent.[3,4] By analogy to the numerous applications of chiral 2-alkyl-1,3-dioxolan-4-ones and 2-alkyl-3-acyl-1,3-oxazolidin-4-ones in asymmetric synthesis,[5] we reasoned that dienophiles such as **1-3** would display a very large diastereofacial bias in both the exo (**4**) and endo (**5**) transition states, with the diene approaching the dienophile from the face opposite the bulky acetal substituent. For these reagents to be maximally useful, however, it is also necessary that they exhibit a significant preference for either exo or endo cycloaddition, since the enantiotopicity of the diene is reversed in the two transition states, **4** and **5**. A recent report describing the Diels-Alder reaction of **1** and cyclopentadiene[6] prompts us to disclose herein some of our results on the synthesis and Diels-Alder reactions of **1-3**. Especially noteworthy is the observation that these dienophiles are exceptionally exo selective in addition to being highly diastereoface selective (c. f., **4**). Thus, the critical criteria necessary for application in asymmetric synthesis have been met.[7]



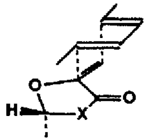
1, R = t-Bu
2, R = C_6H_{11}



3



4, exo



5, endo

Dienophiles **1-3** were synthesized by a route that permits introduction of the exo-methylene unit after establishment of the chiral acetal center. Thus, treatment of hydroxy acid **6**[8] with pivalaldehyde and $BF_3 \cdot Et_2O$ in CH_2Cl_2 at 0 °C provided **8** in 87% yield as a 93 : 7 mixture of cis- and trans-isomers which are separated by recrystallization. A similar procedure was used to prepare **9** (92%), with the exception that the diastereoselectivity was much higher in this case (97 : 3). Oxidation of **8** or **9** with 1 equiv. of MCPBA at -78 °C provided sulfoxides that smoothly eliminated to **1** and **2** when heated in refluxing benzene in the presence of $(EtO)_3P$ as PhSOH

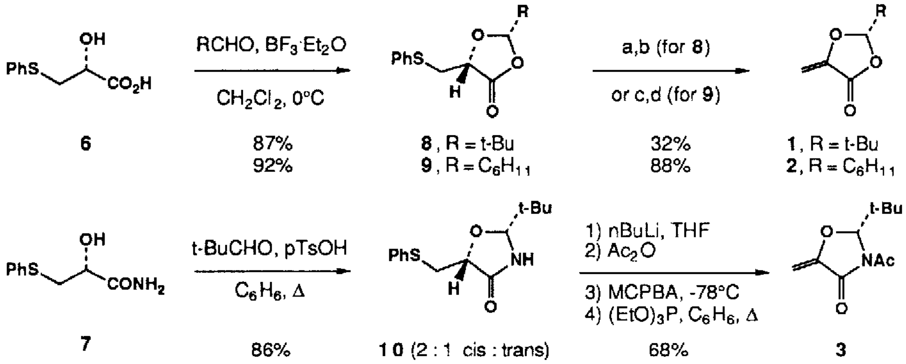


Figure 1. (a) MCPBA (1 equiv), CH_2Cl_2, -78°C (93%); (b) $(EtO)_3P$ (2 equiv), C_6H_6, reflux, (32%) (c) MCPBA (2 equiv), CH_2Cl_2, 23°C (95%); (d) DBU, CH_2Cl_2, 0°C, (93%)

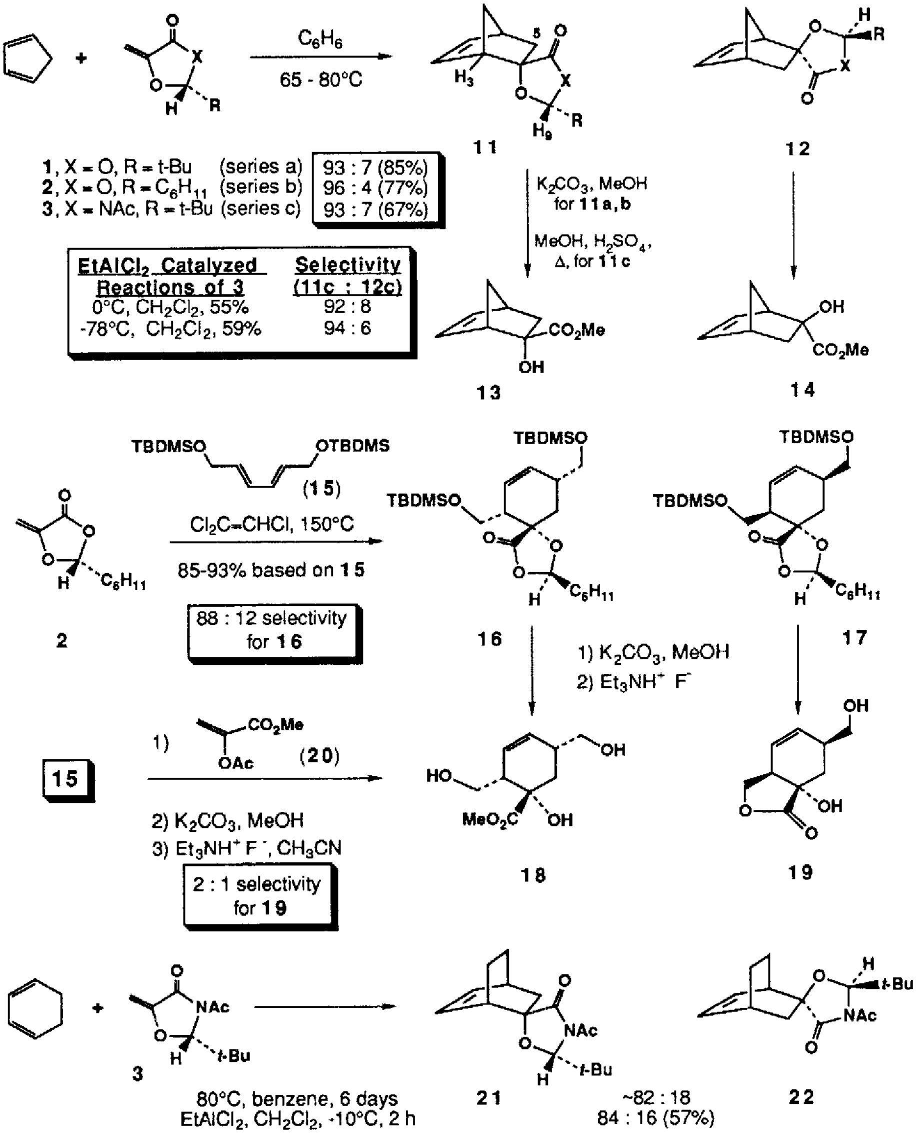
trap. Unfortunately, the volatility of **1** and **2** together with the difficulty of removing sulfur and phosphorus containing materials resulted in low isolated yields of product. A much better method proceeds via the sulfone that undergoes elimination upon treatment with DBU in CH_2Cl_2 (see conversion of **9** to **2**, 88% yield). The synthesis of **3** requires little comment, with the exception that an acylation step was included in the elaboration of **10** since the lactam corresponding to imide **3** displayed very poor Diels-Alder reactivity.[9]

The Diels-Alder reactions of **1-3** and excess cyclopentadiene proceeded smoothly in benzene at 60-80 °C. The reactions of **1** and **3** provided **11** and **12** as the only detected products in a ratio of 93 : 7, while the reaction of cyclopentadiene and **2** provided **11** and **12** in a ratio of 96 : 4. That **11a-c** are exo cycloadducts was established by conversion of each to **13**. An authentic sample of endo diastereomer **14** was prepared by the enolate hydroxylation of methyl norbornene-4-carboxylate [$(NaN(SiMe_3)_2$, 2-(phenylsulfonyl)-3-phenyloxaziridine].[10] The stereochemistry of the acetal center in **11a** and **11c** was assigned on the basis of an NOE enhancement (12%) of H_3, but not of H_{5exo} or H_{5endo}, upon irradiation of the acetal proton H_9. This analysis is in complete agreement with the X-ray structure recently reported for **11a**.[6] The Diels-Alder reaction of **2** and **15** (1 : 1, 1 M in $Cl_2C{=}CHCl$, 150 °C; 85-93% based on recovered diene) is similarly selective for exo cycloadduct **16** (Figure 2). The stereochemical assignments in this series follow logically from the conversion of endo cycloadduct **17** to cis-lactone **19**.

The significant preference for exo cycloaddition of **1-3** is a surprising and unexpected result, especially since most ketene equivalents and other α-oxygenated dienophiles generally display only a modest preference for either cycloadduct.[4,11] For example, the reaction of **15** and α-acetoxy acrylate (**20**) (benzene, 160 °C) provides a 2 : 1 mixture favoring the endo diastereomer. The exceptional diastereofacial selectivity of these reactions of **1-3** is also noteworthy, since as a general rule the most selective asymmetric Diels-Alder reactions require Lewis acid catalysis.[3]

The Diels-Alder reactions of **1-3** with several other dienes and the use of Lewis acid catalysts have also been explored. For example, the thermal reaction of cyclohexadiene and **3**

Figure 2



(80°C, 6 days) provides a ca. 82 : 18 mixture of **21** and **22** (the exo stereochemistry of **21** is assumed by analogy to **11** and **16**). A much cleaner and more rapid reaction occurs, however, with Lewis acid catalysis ($EtAlCl_2$, CH_2Cl_2, -10°C; 84 : 16 mixture of **21** and **22** (57% yield)). Similarly, the $EtAlCl_2$ catalyzed reactions of **3** and cyclopentadiene proceed with excellent, and slightly improved, selectivity for exo cycloadduct **11** (94 : 6 selectivity at -78°C). It is noteworthy that high exo selectivity was observed under these conditions, since the preference for the endo product generally significantly increases with Lewis acid catalysis.[3] These results also differ from those reported by Mattay for **1** and cyclopentadiene, who observed an erosion of diastereoface selectivity in the Lewis acid catalyzed cycloadditions.[6,12] The thermal reaction of **3** and isoprene (110°C, toluene, 6 days) provides a 61 : 39 mixture of regioisomers, but regioselectivity improves dramatically to >95 : 5 when the reaction is catalyzed with $EtAlCl_2$ (CH_2Cl_2, -78°C). Finally, and most impressively, a highly regio- (30 : 1), exo (8-9 : 1) and diastereoface selective thermal Diels-Alder reaction of **2** and an unsymmetrical triene has been performed as the key step in a stereoselective synthesis of the top half fragment of kijanolide. The latter studies are described in the accompanying Letter.[13,14]

Acknowledgement. This research was supported by a grant from the National Institute of General Medical Sciences (GM 26782). We also gratefully acknowledge synthetic studies on the top half of chlorothricolide by Dr. M. Kageyama that stimulated the present investigation.

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1. Address correspondence to this author at Indiana University.
2. Portions of this work, in particular the synthesis and Diels-Alder reactions of **1**, are described in the 1985 Ph.D. Thesis of A. P. Essenfeld, M. I. T., Cambridge, MA 02139.
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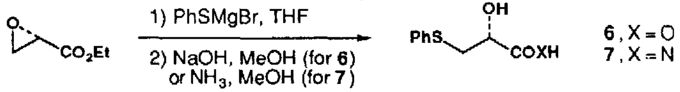
7. The studies described herein were performed with racemic **1**-**3**. Optically active **1** has been prepared by an alternative method (ref. 6; see also Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, 70, 1104) and shown to provide Diels-Alder adducts with enantiomeric purity identical within experimental error to that of **1** and its precursors.
8. Intermediates **6** and **7** were prepared from ethyl glycidate as indicated below.



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12. Our results with **3** suggest that the erosion of diastereofacial selectivity observed by Mattay and coworkers (ref. 6) in the Lewis acid catalyzed reactions of **1** and cyclopentadiene may be due to the instability of cycloadduct **11** to Lewis acids (e.g., post cycloaddition epimerization).
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14. The spectroscopic and physical properties of all new compounds reported herein are in complete agreement with the assigned structures.

(Received in USA 11 September 1989)