of low volatility should be comparable to material of much higher volatility, it appears safe to conclude that redistribution is insignificant. This material was purified by column chromatography (silica gel, Davidson grade 62, 60–200 mesh, 50 g) and eluted with a mixture of hexane/EE (98:2). Yield: 2.37 g (10.4 mmol, 70%). This material is pure by capillary GC (methylsilicone, 50 m, 200 °C). ^{13}C NMR ($CDCl_3$): δ 74.14, 49.60, 41.91, 32.14, 30.62, 29.88, 29.53, 27.34, 26.75, 26.11, 24.83, 24.14, 22.84, 14.28. Mass spectrum (chemical ionization, isobutene) m/z: 225 ($M^+ + H - H_2$, <1), 209 ($M^+ + H - H_2O$, 100). Mass spectrum (electron impact) m/z: 211 ($M^+ + CH_3$, 2), 157 (M^+ – cyclopentyl, 49), 113 ($C_8H_{17}^+$, 100). IR: ν_{max} (neat) cm^{-1} 3457.

Preparation of (±)-2-(*trans*-2-Phenylcyclopentyl)-4-methylheptan-2-ol. This compound was prepared in the same proportions as described above, except that after the addition of phenylcyclopentene (2.38 g, 16.5 mmol), the reaction was stirred at 0 °C for 2 h, then 2-methyl-1-pentene was added (1.85 mL, 15 mmol), and the stirring was continued for an additional hour. Yield (crude): 3.82 g. The product was purified by column chromatography on silica gel as above and eluted with a mixture of hexane/EE (90:10) to give two diastereomeric fractions. Yield: 3.2 g (11.6 mmol, 77%). The fractions were analyzed by capillary GC (methylsilicone, 50 m, 200 °C). Each fraction consisted of a mixture of three diastereomeric alcohols in the ratio of 1:2.1:3.1 and 8.6:2.9:1, respectively, which exhibited identical mass spectra. See above example for a statement on purity and distillation. Mass spectra (chemical ionization, isobutene) m/z: 257 ($M^+ + H - H_2O$, 100). IR: ν_{max} cm^{-1} (neat) 3475 (O–H).

Preparation of 1-(2-Isopinocampheyl)-1-cyclohexylethanol. This compound was prepared as described above in the typical procedure, except that α-pinene (2.4 mL, 15 mmol) was used, followed by cyclohexene (1.62 mL, 15 mmol). The reaction was stirred for 40 min at 0 °C after the second addition. Yield (crude): 3.48 g. The compound was purified on silica gel (hexane/EE, 98:2) to yield 2.97 g (11.25 mmol, 75%). Analysis by capillary GC (methylsilicone, 50 m, 190 °C) showed this to be a 1:2 mixture of diastereomers, which gave identical mass spectra. Mass spectrum (chemical ionization, isobutene) m/z: 263 ($M^+ + H - H_2$ <1), 247 ($M^+ + H - H_2O$, 67), 137 ($C_{10}H_{17}^+$, 100). Mass spectrum (electron impact) m/z: 246 ($M^+ - H_2O$, <1), 181 ($M^+ - C_6H_{11}$, 14), 127 ($M^+ - C_{10}H_{17}$, 100), 83 ($C_6H_{11}^+$, 63), 55 ($C_4H_7^+$, 52), 43 ($C_3H_7^+$, 64). IR: ν_{max} cm^{-1} (neat) 3474 (O–H).

General Procedure for the Determination of Regioselectivity in the Hydroboration of Representative Alkenes by $MeBH_2$ in Molar Ratios of 1:1 and 1:2. The hydroboration in a 1:1 molar ratio was conducted as described under "Reaction of Alkenes with ...", except that an internal standard was added prior to the addition of the alcohol. To the borinic ester was added sodium hydroxide (4.5 mL, 7.5 mmol), and the reaction was cooled to 0 °C and 30% H_2O_2 (1.7 mL) was slowly added. The reaction mixture was heated at 50–60 °C for at least 2 h, potassium carbonate was added to the aqueous phase to near saturation, and the ether layer was separated and dried over $MgSO_4$. This was analyzed for alcohols by capillary GC (methylsilicone, 50 m). For determination of the regioselectivity in a molar ratio of 1:2, the hydroboration–oxidation procedure was identical, except that in the hydroboration step, 2 equiv of alkene was utilized. The results are summarized in Table II. In all cases, the combined alcohols for each run were obtained in >95% yield based on the internal standard.

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Asymmetric Hetero-Diels–Alder Reaction of α-Alkoxy Aldehydes with Activated Dienes. The Scope of Lewis Acid Chelation-Controlled Cycloadditions

M. Mark Midland* and Roger W. Koops

Department of Chemistry, University of California, Riverside, Riverside, California 92521

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The cycloaddition reactions of various α-alkoxy aldehydes with 1,3-dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (Brassard's diene, **2**) were performed under the Lewis acid catalysis of $Eu(hfc)_3$, magnesium dibromide, or diethylaluminum chloride. Moderate to high diastereoselectivities were observed with $Eu(hfc)_3$ and magnesium dibromide. Evidence from reactions of $Eu(hfc)_3$ and magnesium dibromide catalysis indicated a possible "chelation-control" pathway. Lewis acid catalysis from diethylaluminum chloride provided products with moderate to high diastereoselectivity. The mechanistic pathway with catalysis by diethylaluminum chloride was less clear. A possible mechanism based upon a "Cram" addition is considered.

Introduction

The utility of the Diels–Alder reaction has been greatly expanded and the synthesis of heterocycles and complex natural products facilitated by the incorporation of hetero atoms in both the diene and dienophile. The applications of the hetero-Diels–Alder reaction has been recently reviewed.[1]

The use of carbonyl groups as the π group in the dienophile has been successfully employed with highly reactive carbonyl compounds[2] and by employing high pressure techniques.[3] Danishefsky found that aldehydes would undergo cycloaddition reactions with activated dienes under the influence of Lewis acid catalysts.[4] The reactions were performed by using activated dienes such as 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene, Figure 1). The potential for stereocontrol in

(1) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

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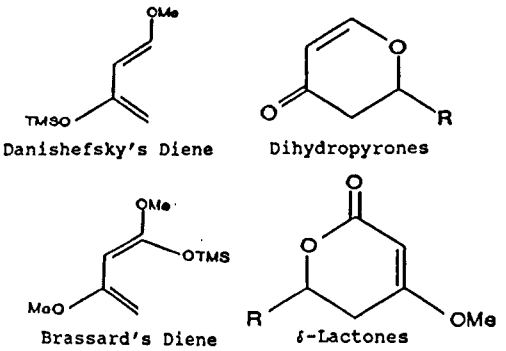


Figure 1.

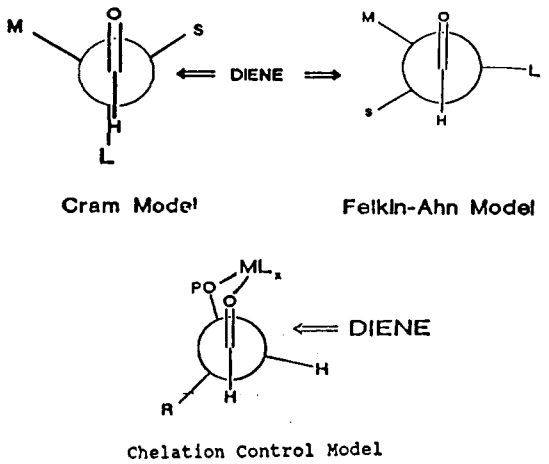


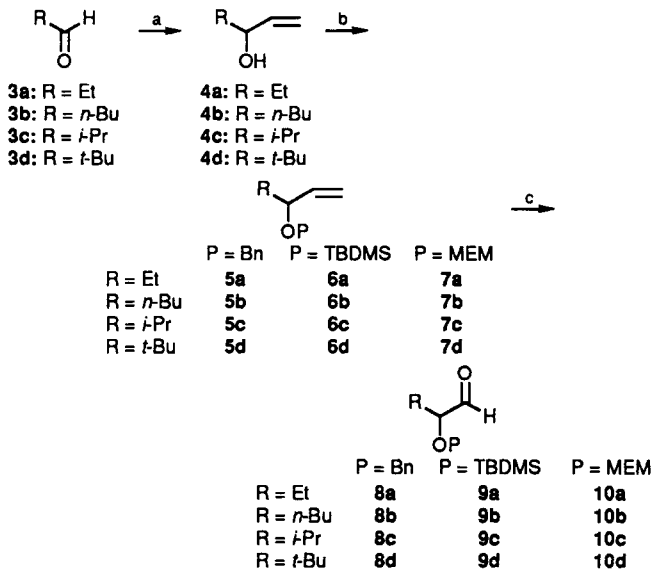
Figure 2.

a reaction utilizing achiral reagents was demonstrated and could be rationalized through a Cram addition model (Figure 2).[4b] In addition, the potential for using aldehydes as heterodienophiles in an asymmetric Diels–Alder synthesis was demonstrated. These cycloadditions provide dihydropyrones that are highly useful intermediates for further transformations (Figure 1).[4c]

When α-alkoxy aldehydes were reacted with activated dienes under Lewis acid conditions, high diastereoselectivity was observed.[5] The resulting relative configurations of the major diastereomers appeared to arise from a chelated intermediate. In addition, the diastereoselectivity appeared to be dependent on the Lewis acid catalyst. Danishefsky observed a high degree of selectivity when using magnesium dibromide as the Lewis acid.[5a,d,e] Other Lewis acids such as $Yb(fod)_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, and $TiCl_4$ appeared to be less selective.

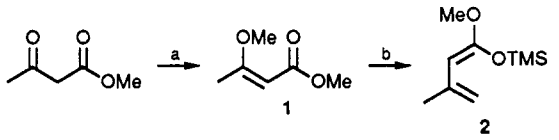
In contrast to Danishefsky's results, the chiral lanthanide shift reagent tris [[(3-heptafluoropropyl)-hydroxymethylene]-(+)-camphorato]europium(III) ($Eu(hfc)_3$) promoted cycloaddition of 1,3-dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (**2**, Brassard's diene,[6] Figure 1) with α-alkoxy aldehydes resulted in a high degree of diastereoselectivity.[5b,c,7] Magnesium dibromide provide

Scheme I[a]



[a] (a) Vinylmagnesium bromide/THF; (b) NaH/THF/benzyl chloride or TBDMSCl/DMF/imidazole or *n*-BuLi/THF/MEMCl; (c) $O_3/CH_2Cl_2/Me_2S$.

Scheme II[a]



[a] (a) $HC(OMe)_3$, H^+; (b) LDA/THF/−78 °C/TMSCl.

less selective.[8] The major product could be explained by invoking the chelation control model.[9]

If the metal does not form a good bidentate chelate, then the direction of attack may be predicted by a Cram[10] or Felkin–Ahn model (Figure 2). Approach of the diene would lead to a cycloaddition product with the opposite relative stereochemistry (*erythro*) as compared to a chelation control mechanism (*threo* relative configuration).

Preliminary results from our laboratories indicated that a chelation control approach model provides a possible explanation to the stereochemical outcome of the cycloaddition of an α-alkoxy aldehyde with Brassard's diene.[5b,7] The scope of this reaction remained to be investigated. The role of the Lewis acid and its relation to the steric environment of the dienophile was not fully understood. The results of such an investigation are reported herein.

Results and Discussion

The necessary substituted α-alkoxy aldehydes were synthesized in three simple steps starting from commer-

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(7) This is in contrast to results that were reported for the cycloaddition reaction of simple aldehydes with activated dienes catalyzed by $Eu(hfc)_3$. The enantioselectivities were only moderate. Danishefsky, S.; Bednarski, M.; Maring, C. *Tetrahedron Lett.* **1983**, *24*, 3451. Danishefsky, S.; Bednarski, M. *J. Am. Chem. Soc.* **1983**, *105*, 6968.

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Table I. Cycloadditions of α-Alkoxy Aldehydes with 2

aldehyde (lactones)	threo:erythro[a] (% yield[b])		
	$Eu(hfc)_3$	Et_2AlCl	$MgBr_2$
8a (11a,b)	85:15 (75)	22:78 (70)	90:10 (45)
8b (14a,b)	90:10 (70)	12:88 (65)	90:10 (50)
8c (17a,b)	73:27 (80)	96:4 (72)	99:1 (45)
8d (19a,b)	50:50 (85)	*c*	*c*
9a (12a,b)	60:40 (70)	18:82 (68)	70:30 (50)
9b (15a,b)	60:40 (70)[d]	25:75 (72)	65:35 (40)
9c (18a,b)	60:40 (65)	75:25 (78)	60:40 (45)
9d	*c*	*c*	*c*
10a (13a,b)	90:10 (60)	*e*	*c*
10b (16a,b)	94:6 (75)	*e*	[65:35 (60)][d,f]
10c	*c*	*c*	*c*
10d	*c*	*c*	*c*

[a] Determined by capillary GC. [b] Isolated yields, not optimized. [c] No cycloadducts recovered. Starting materials recovered. [d] Reference 7. [e] No cycloaddition, some decomposition of starting materials observed. [f] No reaction when repeated.

cially available aldehydes. Preparation of the substituted allylic alcohols was performed via addition of vinyl grignard (Scheme I) to the aldehydes. Protection of the alcohol was performed under standard conditions for each of the protecting groups utilized in this investigation; benzyl (Bn), *tert*-butyldimethylsilyl (TBDMS), and 2-methoxyethoxy)methyl (MEM). The choice of protecting group was based upon the ability of the protecting group to provide chelation. Benzyl and MEM had previously been employed as protecting groups and provided cycloadducts with a high degree of diastereoselectivity.[8] The TBDMS protecting group was chosen as it represented a protecting group best suited for potentially preventing bidentate chelation.[11]

Following protection of the allylic alcohol, ozonolysis afforded the desired α-alkoxy aldehyde in high yield and purity. Since the interest was in investigating the diastereoselectivity, or relative configurations, racemic α-alkoxy aldehydes were employed. Optically pure materials are available via an alternate synthetic route.[5b,12]

Scheme II illustrates the steps leading to 1,3-dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (Brassard's diene, **2**). The stereochemistry of the diene has been determined via NOE experiments.[13] The diene is stable under anhydrous conditions and inert atmosphere when stored at 5 °C for several months. Under Lewis acid conditions, however, the stability appears to be limited and decomposition and polymerization can be observed in 24–48 h.

The cycloaddition reactions were performed by using three different Lewis acid catalysts: a lanthanide shift reagent ($Eu(hfc)_3$), diethylaluminum chloride, and magnesium dibromide etherate. The results of these cycloadditions are depicted in Table I.

The cycloadditions with $Eu(hfc)_3$ catalyst were employed under very mild conditions and true catalytic conditions (typically 5 mol %). Isolated yield of the cycloadducts were generally very high.

The size of the alkyl side chain played an important role in determining the diastereoselectivity of the cycloaddition reactions. The straight-chain alkyl groups, ethyl (**8a**, **10a**) and *n*-butyl (**8b**, **10b**), provided the greatest degree of diastereoselection. The predominant stereoisomer contained the *threo* relative configuration in all cases. This result supports a chelation control mechanism. The increase in steric requirements from ethyl to *n*-butyl had a slight but not dramatic effect in increasing the diastereoselectivity. This trend was consistent for both the benzyl- and MEM-protected compounds. The MEM-protected compound gave higher diastereoselectivity during cycloaddition than did the benzyl, although this difference was not exceptional. As expected via a chelation control mechanism, the use of hindered protecting group (TBDMS, **9a**,**b**), which prevents full chelation and stabilizes the dipolar conformation,[11,14] produced cycloaddition products with little or no diastereoselectivity.

An interesting result occurred when the steric requirements of the alkyl side chain were increased [isopropyl (**8c**) and *tert*-butyl (**8d**)]. Increasing the size of the side chain decreased the diastereoselection of the product cycloadducts. In the *tert*-butyl case, little diastereoselection was observed. The steric environment of the side chain appeared to be of importance in effecting the ability of the europium complex to form a bidentate chelate. Preliminary NMR evidence from lanthanide-induced shift studies (LIS) on the various substrates (**8b**,**c**,**d**) indicates that chelation occurs but the position of the equilibrium between the chelated complex and a monocomplexed aldehyde species is dependent on the nature of the alkyl side chain.[15] As steric bulk is increased, the equilibrium shifts from chelated to monocomplexed species, thus lowering *threo* selectivity.

When bulky aldehydes protected as the MEM ethers were used as substrates (**10c**, **10d**), no products were obtained from cycloaddition. It is known that polyglycolic ethers, such as are found in the MEM group, complex rapidly and very strongly to europium shift reagents.[16] If the steric environment around the α-alkoxy group is demanding, then the ability to form a chelate may decrease. Complexation with the ether oxygens of the MEM group may become competitive and thus no cycloaddition reaction can occur. Proton NMR studies of aldehyde **10** with $Eu(hfc)_3$ indicated that strong complexation was occurring at the MEM group. Some downfield shifting was also observed in the aldehydic proton, although to a lesser extent.

In the situation where the shift reagent is able to complex to the carbonyl of the aldehyde, the resulting complex may be too sterically hindered for the approach of the diene to occur. This may be the case for the TBDMS-protected compound **9d**. Cycloaddition was observed with the isopropyl side chain (TBDMS-protected) although there was no appreciable diastereoselection.

As explanation for the behavior of the europium reagent may be based upon its Lewis acidity and its steric environment. As a more sterically encumberred and soft Lewis acid, the steric environment of the Lewis base may indicate

(11) Keck has performed ^{119}Sn NMR experiments on β-alkoxy aldehydes and $SnCl_4$ and has observed that substrate structure can influence the degree of chelation at low temperature. The protecting group TBDMS can prevent chelation at low temperature; see (d) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136.

(12) Optically active allylic alcohols are available from propargyl ketones via asymmetric reduction: Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J.-S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.

(13) Bell, S. H.; Cameron, D. W.; Feutrill, G. I.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **1985**, *26*, 6519.

(14) (a) For effects of protecting groups on chelation control, see: Keck, G. E.; Hehre, W. J.; Kahn, S. D. *Tetrahedron Lett.* **1987**, *28*, 279. (b) For NMR studies of chelates of magnesium dibromide with β-alkoxy aldehydes, see: Keck, G. E.; Castelmlino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480. Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (c) For NMR studies of Lewis acids and aldehydes, see: Denmark, S. E.; Wilson, T.; Wilson, T. M. *J. am. Chem. Soc.* **1988**, *110*, 984.

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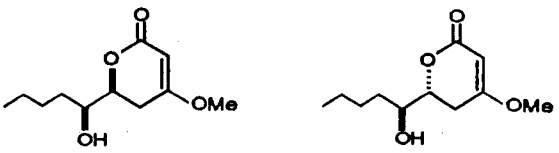

Figure 3.

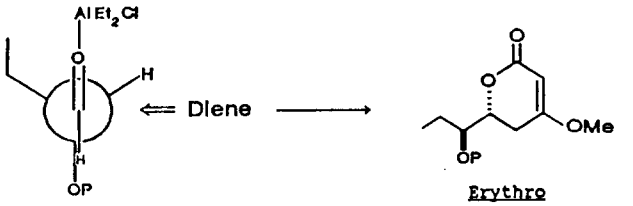

Figure 4.

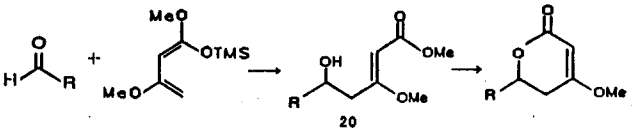

Figure 5. Mukaiyama aldol pathway.

the ability of the complex/chelate to form, thus controlling the extent of both cycloaddition and the extent of diastereoselection. It would appear that the europium catalyst promotes cycloaddition via chelation control with a high degree of diastereoselectivity when the steric environment is not demanding. As the steric environment is increased, however, the ability of chelation to occur is reduced with a corresponding reduction in diastereoselectivity. This behavior makes $Eu(hfc)_3$ an excellent catalyst for smaller α-alkoxy aldehydes and highly substituted dienes.

The second Lewis acid of choice was diethylaluminum chloride. This strong Lewis acid was not previously reported to promote cycloadditions of carbonyl dienophiles to dienes.[17] It has been employed successfully, however, in cycloadditions of imines with activated dienes.[18] Initially, attempts to use this Lewis acid under the conditions employed in the imine examples (addition as a neat liquid at low temperature with rapid warming to room temperature) provided only products in which the ethyl group had added to the carbonyl of the aldehyde. The cycloaddition was successfully performed when a solution of diethylaluminum chloride in hexane was added at low temperature and then the mixture was slowly warmed to room temperature.[19] This procedure eliminated the competing addition reaction. We have subsequently employed this catalyst in other synthetic problems involving cycloadditions in our laboratories.[20] It should also be noted that although the results reported in this paper utilized a stoichiometric amount of catalyst, we have observed identical results under catalyst conditions.

Diethylaluminum chloride produced excellent results when utilized with side chains of moderate bulk (**8c**, **9c**). The diastereoselectivity was improved (over $Eu(hfc)_3$) when diethylaluminum chloride catalyzed the cycloaddition reactions of α-alkoxy aldehydes with the isopropyl side chain. The *threo* (or chelation) stereoisomer was predominant when either benzyl or TBDMS protecting groups were employed.

When straight-chain aldehydes were employed in the cycloaddition reactions, *erythro* cycloadducts were obtained as the major products. The diastereoselection was approximately 4:1 in all cases. This result would be expected if a nonchelation pathway for the cycloaddition was occurring.

Diethylaluminum chloride appeared to be incompatible with the MEM protecting group, and no cycloaddition products were isolated from these reactions. Deprotection of the MEM group appeared to be a significant side reaction.

The results of these cycloadditions provide no clear mechanism for the reaction. The results may be reflecting a simple "Cram" addition pathway (Figure 2). If the alkyl group is assumed to be the large group in the Cram model (or a Felkin–Ahn model), the mode of attack of the diene would predict products with relative stereochemistry of *threo*, the same as chelation control (such as in **8c** and **9c**). If the α-alkoxy group is the larger group, the "Cram" mode of addition would lead to products that would have the *erythro* selectivity (such as in **8a,b** and **9a,b**). A dipolar model that would place the alkoxy groups anti to the carbonyl would predict *erythro* products (Figure 4).[10]

The use of diethylaluminum chloride with the *tert*-butyl side-chain examples (**8d**, **9d**, **10d**) did not lead to cycloaddition. The reaction yielded products that were not cycloaddition products, although some starting materials were recovered. There was no single product of significance, hence characterization was not performed.

The third Lewis acid employed was magnesium dibromide. This Lewis acid was observed to be highly efficient in promoting cycloadditions with high diastereoselectivity in the examples of Danishefsky.[5a,d,e] Our preliminary results (ref 5b) indicated that it was not as efficient when Brassard's diene was used as the diene.

Products of a chelation control process appear to be preferred for magnesium dibromide.[14] The best results were obtained with benzyl as protecting group (**8a–c**), although in all cases yields were not high and starting materials were recovered. As the steric demands of the side chain increased, a corresponding increase in diastereoselectivity was observed. It is interesting to note that in the example of the isopropyl side chain, the benzyl-protected compound provided the open-chain methyl ester (Figure 5, **20**). The product appeared to be a single diastereomer. It is not known if the open-chain compound was obtained via the workup procedure or by a Mukaiyama aldol pathway[22] (Figure 5). Such high diastereoselectivity is not usually encountered in a Mukaiyama mechanism.

The corresponding TBDMS-protected compound was obtained as the desired lactone (in low selectivity). This may indicate that the compound **20** was obtained through workup procedures.

The cycloadditions of α-alkoxy aldehydes using magnesium dibromide provided *threo* (or chelation) products in all examples when benzyl was the protecting group. Use of a TBDMS-protecting group significantly lowered the selectivity in each example. These results seem to indicate that a chelation-controlled pathway may be governing the cycloadditions catalyzed by magnesium dibromide.

(17) Ethylaluminum dichloride has been used in hetero-Diels–Alder reactions of dienes with formaldehyde: Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett.* **1981**, *22*, 2059.

(18) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.* **1988**, *29*, 4653.

(19) Cycloadditions can also be performed by using neat diethylaluminum chloride, maintaining low-temperature conditions.

(20) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368.

(21) Afonso, M. M. Private Communication.

(22) Mukaiyama, T.; Banno, K.; Narasaka, K. J. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

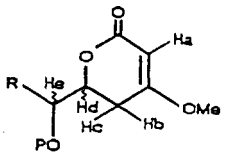

Figure 6. Proton assignments of δ-lactones.

No cycloaddition products were observed in the *tert*-butyl examples when magnesium dibromide was used as catalyst. As was the case with diethylaluminum chloride, the strong Lewis acidity of magnesium dibromide may be responsible for decomposition of some of the starting materials.

The diastereoselectivity of the cycloaddition reaction was determined by capillary gas chromatography (GC) and ^1H and ^{13}C NMR spectroscopy. Determination of relative configuration was performed by direct comparison to spectroscopic and analytical data previously reported for the natural product pestalotin and epipestalotin (Figure 3).[23]

Spectral data have been known for the two diastereomeric compounds of pestalotin.[8b] Analysis of the diastereomeric mixture was performed by capillary GC and NMR spectroscopy. In most cases, the *threo* diastereomer displayed a longer retention time on GC analysis (TBDMS compounds gave retention times that were inverted in order). This method also provided the diastereomeric ratios reported in Table I.

Establishment of relative configuration was also performed by NMR spectroscopy. The relative configurations are known for compounds **11–16** from previous work.[8] The only compound that was obtained that required determination of relative configuration was **17** (compound **18** was obtained in virtually equal amounts of *threo* and *erythro*). Only a 1:1 mixture was obtained for compound **19**. Compound **17** was determined via proton and carbon NMR spectroscopy. Trends in the proton and carbon NMR spectral data for each respective diastereomer are distinctive. Figure 6 displays each labeled proton and carbon in the cycloadducts. The vinyl proton Ha in the *threo* isomer has a resonance slighly upfield of that observed in the *erythro* isomer. The lactone ring methylene group, Hb and Hc, has upfield resonances in the *threo* isomer as opposed to the *erythro*. The ring carbinol proton, Hd, is observed to be slightly upfield in the *threo* isomer. This effect is more pronounced in the side-chain carbinol proton, He, which produces a signal markedly upfield in the *threo* isomer as compared to the *erythro* isomer. Changes in the methoxy was not observable in many cases. When the protecting group was benzyl, the benzyl protons of the *threo* isomer gave either a singlet or an AB doublet pattern with very small chemical shift differences ($\Delta\delta_{AB}$). In the *erythro* isomer, however, AB doublets with large $\Delta\delta_{AB}$ values were observed. Finally, occasionally the R-group resonance would exhibit minor differences. Typically, the R group would be more downfield in the *threo* isomer compared to the *erythro* isomer.

For the proton Hd, the coupling to proton He (J_{de}) was also definitive for *threo* or *erythro*. It has been observed that the coupling constant J_{de} for the *threo* isomer is larger than the J_{de} for the *erythro* isomer. This trend provided an additional piece of evidence toward relative configuration determination.

The ^{13}C NMR resonances of the corresponding carbons for the relative protons described above exhibited similar shifts. For the *threo* isomers, upfield shifts of the carbons associated with protons Hb and Hc, Hd, and He were observed in comparison to the *erythro* isomers.

Summary

The Lewis acid mediated cycloaddition of α-alkoxy aldehydes with Brassard's diene produces products that may be predicted by a chelation-controlled mechanism (magnesium dibromide and Eu(hfc)$_3$) or by a "Cram" addition (diethylaluminum chloride). The degree of diastereoselectivity appears to be dependent upon the steric nature of the dienophile. The Lewis acid used to catalyze the reaction plays an important role in the determination of stereoselectivity.

Cycloadditions performed with diethylaluminum chloride as catalyst produce products that may be predicted through a "Cram" addition model. The determining factor appears to be the relative steric bulk of the alkoxy group versus the alkyl side chain. If the alkyl side chain is larger than the alkoxy group, products with *threo* relative stereochemistry are obtained. Conversely, if the alkoxy group is larger than the side chain, products with *erythro* relative stereochemistry predominate.

Experimental Section

General Methods. Proton and ^{13}C NMR spectra were obtained at 199.5 and 50.10 Mhz, respectively. Capillary gas chromatography (GC) was performed on a 30-m methylsilicone stationary phase using a flame ionization detector (FID). Purity of compounds was determined by capillary GC (unless otherwise stated) and was greater than 90% unless otherwise noted. High performance liquid chromatography was performed with a Macro Silica column, using a refractive index detector. Silica gel was obtained from Fluka, Inc., and was 70–230 mesh unless otherwise stated. Thin-layer chromatography was performed on Merck aluminum backed precoated TLC plates using silica gel 60, F-254. Diethylaluminum chloride, magnesium dibromide etherate, and (+)-Eu(hfc)$_3$[24] were obtained from Aldrich Chemical Company. Tetrahydrofuran (THF) was distilled over potassium. Dichloromethane was distilled over calcium hydride. Triethylamine was distilled over potassium hydroxide pellets. All air- and moisture-sensitive reactions were carried out in flame-dried glassware under an inert atmosphere.

General Procedure for the Preparation of Allylic Alcohols. A solution of vinylmagnesium bromide (1.0 M in THF, 1.5 equiv) was cooled to 0 °C, and aldehyde (1.0 equiv, typical scale of 0.1 mol) was added via syringe. The solution was stirred for 15 min and then quenched at 0 °C by slow addition of 1 HCl (aq). The solution was extracted by using diethyl ether (3×) followed by washing the organic extracts with brine. Upon drying ($MgSO_4$) and filtering, the solution was distilled through a Vigreoux column (1 atm) to yield the clear oil product (typical yield 80–90% yield). Capillary GC indicated a purity of >95% for all compounds.

General Procedure for Preparation of Benzyl-Protected Allylic Alcohols. Sodium hydride (as 60% dispersion in mineral oil, 1.25–1.5 equiv) and anhydrous THF (to make a 1 M solution) were cooled to 0 °C, and allylic alcohol (1.0 equiv, typical scale was 50–100 mmol) was added dropwise. The suspension was stirred for 1 h at 0 °C. Benzyl chloride (1.3–1.6 equiv) was added to the suspension, and the suspension was warmed slowly to reflux. Following reflux (typically 12–20 h), the suspension was cooled to 0 °C and quenched with water. The suspension was diluted with 3 N HCl and was extracted with diethyl ether (3×). The combined organic layer were extracted with saturated sodium bicarbonate (aq) and brine. The solution was dried ($MgSO_4$),

(23) Ellestad, G. A.; McGahren, W. J.; Kunstmann, M. P. *J. Org. Chem.* **1972**, *37*, 2045. Syntheses: Carlson, R. M.; Oyler, A. R. *Tetrahedron Lett.* **1974**, 2615. Makaiyama, T.; Toshio, I. *Chem. Lett.* **1978**, 409. Masaki, Y.; Nagata, K.; Serizawa, Y.; Kaji, K. *Tetrahedron. Lett.* **1984**, *25*, 95. Spectra data: Kimura, Y.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1980**, *44*, 451.

(24) The Eu(hfc)$_3$ was utilized directly from the commercial source. Purification via sublimation was performed but the cycloaddition results remained identical with unpurified material.

filtered, and concentrated to yield the desired crude benzyl-protected allylic alcohol. Vacuum distillation (0.100 mmHg) yielded the desired pure product in good yields (typically 60–80%). Capillary GC analysis indicated a purity >93% in all compounds.

General Procedure for the Preparation of *tert*-Butyldimethylsilyl-Protected Allylic Alcohols.[25] To a solution of allylic alcohol (1 equiv, typical scale was 50 mmol) and dimethylformamide (to make a 1 M solution) was added imidazole (3 equiv), followed by cooling to 0 °C. To the suspension was added *tert*-butyldimethylsilyl chloride (3 equiv), and the solution was stirred at room temperature for 24 h. Upon dilution with diethyl ether, the solution was extracted with 1 N HCl (aq) (2×), 1 N NaOH (aq) (1×), and brine (1×). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified via distillation (0.100 mmHg); Typical yield (50–85%). Capillary GC analysis indicated a purity of >90% for all compounds.

3-[(*tert*-Butyldimethylsilyl)oxy]-1-pentene (6a):[26] ^1H NMR ($CDCl_3$) δ 5.78 (m, 1-H), 5.10 (m, 2 -H), 4.00 (m, 1-H), 1.50 (m, 2-H), 0.92 (s, 9-H), 0.90 (t (overlap), 3-H), 0.10 (s, 6-H).

3-[(*tert*-Butyldimethylsilyl)oxy]-1-heptene (6b): see ref 8.

3-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-1-pentene (6c):[26] ^1H NMR ($CDCl_3$) δ 5.75 (ddd, J = 6.4, 10.4, 17.4 Hz, 1-H), 5.10 (m, 2-H), 3.82 (t, J = 6.4 Hz, 1-H), 1.65 (m, 1-H), 0.85–0.95 (m, 15-H), 0.04 (d, 6-H); ^{13}C NMR ($CDCl_3$) δ 140.15, 114.56, 78.80, 34.43, 25.87, 18.23, 17.80, -4.8, -5.1.

3-[(*tert*-Butyldimethylsilyl)oxy]-4,4-dimethyl-1-pentene (6d): ^1H NMR ($CDCl_3$) δ 5.75 (ddd, J = 7.4, 9.8, 17.6 Hz, 1-H), 5.10 (m, 2-H), 3.65 (d, J = 7.4 Hz, 1-H), 0.88 (s, 18-H), 0.03 (s, 6-H); ^{13}C NMR ($CDCl_3$) δ 139.0, 115.6, 25.7, -2.88.

General Preparation for (2-Methoxyethoxy)methyl-Protected Allylic Alcohols. A solution of allylic alcohol (1 equiv, typical scale was 50 mmol) and anhydrous THF (to make a 2 M solution) was cooled to 0 °C, and *n*-butyllithium (1.6 M in hexane, 1.2–1.3 equiv) was added dropwise. The suspension was stirred for 30 min at 0 °C followed by slow addition of (2-methoxyethoxy)methyl chloride (1.5 equiv). The solution was warmed to room temperature and stirred for 24 h. The reaction was quenched by slow addition of water at 0 °C. The mixture was diluted with diethyl ether and was washed with 1 N HCl (aq) followed by washing with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by silica gel chromatography (ethyl acetate/hexanes, 25/75) to yield the desired product; typical yield 60–75%. Capillary GC analysis indicated purities as follows: **7a**, 89%; **7b**, 89%; **7c**, 85%; **7d**, 80%.

3-[(2-Methoxyethoxy)methoxy]-1-pentene (7a): ^1H NMR ($CDCl_3$) δ 5.66 (ddd, J = 7.3, 10.3, 17.1 Hz, 1-H), 5.20 (m, 2-H), 4.77 (d, J = 6.8 Hz, 1-H), 4.66 (d, J = 6.8 Hz, 1-H), 3.95 (q, 1-H), 3.53–3.85 (m, 4-H), 3.39 (s, 3-H), 1.60 (m, 2-H), 0.90 (t, 3-H); ^{13}C NMR ($CDCl_3$) δ 138.20, 117.14, 92.81, 78.75, 71.79, 66.88, 58.95, 28.20, 9.72.

3-[(2-Methoxyethoxy)methoxy]-1-heptene (7b): ^1H NMR ($CDCl_3$) δ 5.65 (ddd, J = 7.8, 10.3, 17.6 Hz, 1 H), 5.20 (m, 2 H), 4.77 (d, J = 6.8 Hz, 1 H), 4.64 (d, J = 6.8 Hz, 1 H), 4.00 (q, 1 H), 3.53–3.84 (m, 4 H), 3.39 (s, 3-H), 1.25–1.75 (m, 6-H), 0.85 (t, 3-H); ^{13}C NMR ($CDCl_3$) δ 138.49, 116.94, 92.76, 77.39, 71.79, 66.88, 58.95, 35.06, 27.47, 22.56, 13.95.

3-[(2-Methoxyethoxy)methoxy]-4-methyl-1-pentene (7c): ^1H NMR ($CDCl_3$) δ 5.65 (ddd, J = 7.8, 10.4, 17.2 Hz, 1-H), 5.22 (m, 2-H), 4.76 (d, J = 6.8 Hz, 1-H), 4.64 (d, J = 6.8 Hz, 1-H), 3.5–3.85 (m, 5-H), 3.39 (s, 3-H), 1.75 (m, 1-H), 0.94 (d, 3-H), 0.88 (d, 3-H); ^{13}C NMR ($CDCl_3$) 136.6, 118.2, 92.81, 82.59, 71.79, 66.93, 58.95, 32.44, 18.4, 18.33.

4,4-Dimethyl-3-[(2-methoxyethoxy)methoxy]-1-pentene (7d): ^1H NMR ($CDCl_3$) δ 5.70 (ddd, J = 8.4, 10.2, 17.2 Hz, 1-H), 5.20 (m, 2-H), 4.74 (d, J = 6.8 Hz, 1-H), 4.60 (d, J = 6.8 Hz, 1-H), 3.81 (m, 1-H), 3.60–3.65 (m, 4-H), 3.34 (s, 3-H), 0.90 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 135.33, 118.99, 92.91, 85.27, 71.79, 67.03, 58.95, 34.24, 26.06.

General Procedure for Preparation of α-Alkoxy Aldehydes via Ozonolysis. A solution of the protected allylic alcohol (**5a–d**, **6a–d**, or **7a–d**, 1 equiv; typical scale was 10 mmol) and dichloromethane (to make a 0.1 M solution). The solution was purged with nitrogen for 10 min, while being cooled to -78 °C. Ozone (Welsbach Ozone Apparatus, 75 V, 5.2 psi O_2, 1.0 slpm O_3/O_2) was bubbled through the solution until a blue color presisted. The solution was stirred for an additional 5 min without ozone flow. If the blue color presisted, the solution was purged with nitrogen for 15 min until clear. Dimethyl sulfide (6–8 equiv) was added slowly to the solution at -78 °C. The solution was slowly warmed to room temperature for a period of 2-3 h and stirred for 12 h at room temperature. Following concentration (75 mmHg, 30°C), the crude oil was diluted with water and extracted with diethyl ester (3×). The organic layer was washed with brine (1×) and dried ($MgSO_4$). Concentration in vacuo yielded the desired aldehyde in high purity. When necessary, additional purification was performed via column chromatography (silica gel, ethyl acetate/hexane, 10/90); typical yield 75–95%. Purity was determined by thin layer chromatography and NMR spectroscopy. Aldehydes were homogeneous spots on TLC. Spectroscopic purity was 90% or greater.

2-(Benzyloxy)-3-methylbutanal (8c):[27] ^1H NMR ($CDCl_3$) δ 9.60 (d, J = 2.4 Hz, 1-H), 7.30 (s, 5-H), 4.67 (d, J = 11.8 Hz, 1-H), 4.44 (d, J = 11.8 Hz, 1-H), 3.43 (dd, J = 2.4, 5.8 Hz, 1-H), 2.03 (m, 1-H), 0.94 (dd, 6-H); ^{13}C NMR ($CDCl_3$) δ 204.4, 128.3, 127.8, 127.7, 127.5, 88.0, 72.7, 29.9, 18.3, 17.5; IR (neat, NaCl) cm^{-1} 3000–3100, 2880–3000, 1740, 1605, 1595, 1500, 1455, 1375.

2-(Benzyloxy)-3,3-dimethylbutanal (8d): ^1H NMR ($CDCl_3$) δ 9.68 (d, J = 3.6 Hz, 1-H), 7.31 (s, 5-H), 4.60 (d, J = 11.6 Hz, 1-H), 4.38 (d, J = 11.6 Hz, 1-H), 3.24 (d, J = 3.6 Hz, 1-H), 0.97 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 204.95, 128.32, 127.84, 90.44, 72.87, 35.29, 26.04; IR (neat, NaCl) cm^{-1} 3000–3100, 2880–3000, 1735, 1605, 1595, 1505, 1460.

2-[(*tert*-Butyldimethylsily)oxy]butanal (9a): ^1H NMR ($CDCl_3$) δ 9.59 (d, J = 1.8 Hz, 1-H), 3.90 (t, J = 1.8 Hz, 1-H), 1.65 (m, 2-H), 0.90 (ms, 12-H), 0.10 (s, 6-H); ^{13}C NMR ($CDCl_3$) δ 204.5, 78.76, 25.86, 25.614, 9.08, -2.96, -3.57; IR (neat, NaCl) cm^{-1} 2945, 2925, 2875, 1740, 1470, 1255, 835, 775.

2-[(*tert*-Butyldimethylsilyl)oxy]hexanal (9b): see ref 8.

2-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutanal (9c): ^1H NMR ($CDCl_3$) δ 9.54 (d, J = 2.0 Hz, 1-H), 3.68 (dd, J = 2.0, 5.4 Hz, 1-H), 2.00 (m, 1-H), 0.85 (ms, 15-H), 0.05 (d, 6-H); ^{13}C NMR ($CDCl_3$) δ 204.7, 81.93, 31.39, 25.61, 18.56, 16.68, -4.5, -5.1; IR (neat, NaCl) cm^{-1} 2940, 2915, 2845, 1740, 1255, 1065, 835.

2-[(*tert*-Butyldimethylsilyl)oxy]-3,3-dimethylbutanal (9d): ^1H NMR ($CDCl_3$) δ 9.58 (d, J = 2.9 Hz, 1-H), 3.46 (d, J = 2.9 Hz, 1-H), 0.90–0.95 (ms, 18-H), 0.05 (d, 6-H); ^{13}C NMR ($CDCl_3$) δ 204.7, 84.24, 35.5, 35.0, 25.86, 25.74, -5.15, -5.34; IR (neat, NaCl) cm^{-1} 2945, 1735, 1460.

2-[(1-Methoxyethoxy)methoxy]butanal (10a):[5e] ^1H NMR ($CDCl_3$) δ 9.58 (d, J = 1.76 Hz, 1-H), 4.78 (d, J = 9.4 Hz, 1-H), 4.68 (d, J = 9.4 Hz, 1-H), 3.85 (m, 1-H), 3.65 (m, 2-H), 3.54 (m, 2-H), 3.35 (s, 3-H), 2.10 (m, 2-H), 0.94 (t, 3-H); ^{13}C NMR ($CDCl_3$) δ 202.76, 95.43, 83.20, 71.65, 67.45, 58.82, 23.12, 9.08; IR (neat, NaCl) cm^{-1} 2940, 2890, 1735, 1465, 1120, 1100, 1040, 850.

2-[(2-Methoxyethoxy)methoxy]hexanal (10b):[5b,8] ^1H NMR ($CDCl_3$) δ 9.62 (d, J = 2.35 Hz, 1-H), 4.79 (q, 2-H), 3.95 (t, 1-H), 3.75 (m, 2-H), 3.55 (m, 2-H), 3.37 (s, 3-H), 1.75 (m, 2-H), 1.35 (m, 4-H), 0.90 (t, 3-H).

2-[(2-Methoxyethoxy)methoxy]-3-methylbutanal (10c): ^1H NMR ($CDCl_3$) δ 9.63 (d, J = 2.4 Hz, 1-H), 4.78 (q, J = 7.4 Hz, 2-H), 3.74 (m, 3-H), 3.55 (m, 2-H), 3.37 (s, 3-H), 2.01 (m, 1-H), 0.95 (t, 6-H); ^{13}C NMR ($CDCl_3$) δ 203.3, 95.85, 86.67, 71.59, 67.51, 58.94, 29.87, 18.50, 17.29; IR (neat, NaCl) cm^{-1} 2950, 2900, 1765, 1145, 1075.

3,3-Dimethyl-2-[(2-methoxyethoxy)methoxy]butanal (10d): ^1H NMR ($CDCl_3$) δ 9.64 (d, J = 2.94 Hz, 1-H), 4.72, (q, 2-H), 3.72 (m, 2-H), 3.50 (m, 3-H), 3.33 (s, 3-H), 0.97 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 203.61, 95.91, 89.16, 71.47, 67.51, 58.88, 35.10, 25.98; IR (neat, NaCl) cm^{-1} 2970, 2890, 1740, 1475, 1375, 1175, 1120, 1050.

Methyl 3-Methoxy-2-butenoate (1).[6] A solution of methyl acetoacetate (16.01 g, 0.138 mol) and trimethyl orthoformate (14.63 g, 0.138 mol) was cooled to 0 °C, and concentrated sulfuric acid (0.250 mL) was added dropwise. The solution was stirred at room temperature for 24 h, filtered through potassium carbonate, and

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(26) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3830. See also: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. Compound **4a** is also available from Aldrich Chemical Co.

distilled by Kugelrohr (100 °C, 80 mmHg) to yield 17.0 g (95%) of clear oil: ^{1}H NMR ($CDCl_3$) δ 5.02 (s, 1-H), 3.68 (s, 3-H), 3.62 (s, 3-H), 2.29 (s, 3-H).

Preparation of 1,3-Dimethoxy-1-[(trimethylsilyl)oxy]-1,3-butadiene (2, Brassard's Diene).[6] A solution of anhydrous THF (50 mL) and diisopropylamine (5.97 g, 59.1 mmol) was cooled to −5 °C via a salt–ice bath, and *n*-butyllithium (1.6 M in hexane, 35 mL, 56 mmol, 1.25 equiv) was added dropwise via syringe over 10 min. The light yellow solution was stirred at −5 °C for 45 min and then cooled to −78 °C and stirred for an additional 1 h. Methyl 3-methoxy-2-butenoate (5.85 g, 45.0 mmol, 1.00 equiv) was added slowly to the LDA solution. The solution was stirred for 30 min at −78 °C following complete addition. Chlorotrimethylsilane (10.0 mL, 8.45 g., 78 mmol) was slowly added to the solution at −78 °C, and the solution was stirred for 10 min and then allowed to warm to room temperature over 1 h. The solution was diluted with pentane (50 mL) and filtered (repeated three times or until no precipitates observed on dilution). Following the last filtration, the solution was concentrated in vacuo (80 mmHg, 30 °C). The crude oil was distilled by Kugelrohr (0.100 mmHg, 65 °C) to yield 6.4 g (70%) of diene (stored under nitrogen in cold). Purity was determined to be greater than 90% by NMR spectroscopy: ^{1}H NMR ($CDCl_3$) δ 4.32 (d, J = 1 Hz, 1-H), 4.00 (dd, 2-H), 3.53 (d, 6-H), 0.28 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 157.9, 89.60, 77.83, 74.91, 54.09, 53.11, −0.55.

General Procedure for Cycloaddition Reactions of α-Alkoxy Aldehydes with Brassard's Diene Using Eu(hfc)$_3$ or $MgBr_2$·OEt_2 as Lewis Acid Catalyst. To a solution or suspension of Lewis acid [Eu(hfc)$_3$ or $MgBr_2$·OEt_2] (0.05 equiv or 1.1 equiv, respectively) and dry dichloromethane (to make a 0.5 M solution) was added α-alkoxy aldehyde (1.0 equiv, typical scale was 0.5 mmol). To solution or suspension was cooled to 0 °C and stirred for 5 min. Brassard's diene (1.2–1.3 equiv) was added dropwise, and the solution or suspension was allowed to warm to room temperature.[28] After being stirred for 18–24 h at room temperature, the reaction was quenched by addition of water and extracted with ethyl acetate. The combined organic extracts was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by flash chromatography (silica gel, 70–230 mesh, typically ethyl acetate/hexane 50/50). Capillary gas chromatography was used to determine the diastereomeric ratios. High resolution mass spectrometry was performed on the mixture of diastereomers. The mixture of diastereomers were separated by normal-phase HPLC. Each isomer was identified and relative configuration were assigned by spectroscopic methods followed by capillary gas chromatography for absolute identification (and purity determination).

General Procedure for Lewis Acid Cycloaddition Reactions of α-Alkoxy Aldehydes with Brassard's Diene Using Diethylaluminum Chloride as Catalyst. A solution of dry dichloromethane (volume = 1.5 × mmol aldehyde) and α-alkoxy aldehyde (1.0 equiv, typical scale was 0.5 mmol) was cooled to −78 °C while under a nitrogen atmosphere and diethylaluminum chloride (as 2.1 M in hexane, 1.1 equiv) was added dropwise. The solution was stirred for 5 min followed by addition of Brassard's diene (1.2–1.3 equiv). The solution was stirred for 12 h at −78 °C and then was slowly warmed to −30 °C over 8–10 h. The reaction was quenched with methanol (2 equiv), and the solution was allowed to warm to room temperature. The reaction was slowly diluted with water and extracted with ethyl acetate (3×). The combined organic layers were washed with brine (1×) and dried ($MgSO_4$). The crude solution was subject to purification as described above.

6-[1-(Benzyloxy)propyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (11a, *threo*): mass calcd. for $C_{16}H_{20}O_4$, 277.1440 (M + 1) exact mass (CI, M + 1) 277.1433; MS (NH_3/CI) 187, 127, 105, 91, 77; ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5-H), 5.14 (d, J = 1.4 Hz, 1-H), 4.65 (s, 2-H), 4.55 (dt, J = 4, 13 Hz, 1-H), 3.74 (s, 3-H), 3.50 (dt, J = 4.8 Hz, 1-H), 270 (ddd, J = 1.4, 13, 18 Hz, 1-H), 2.25 (dd, J = 4, 18 Hz, 1-H), 1.65 (m, 2-H), 0.99 (t, J = 7 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 173, 166, 129, 128, 127, 127, 95, 90, 80, 76, 73, 55, 28, 23, 10. Capillary GC analysis (intial temperature 200 °C, initial time 1 min, temperature program 10 °C per min to 250 °C with a 20-min hold) indicated 100% purity.

6-[1-(Benzyloxy)propyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (11b, *erythro*): ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5-H), 5.14 (d, J = 1.6 Hz, 1-H), 4.75 (d, J = 11.2 Hz, 1-H), 4.65 (d, J = 11.2 Hz, 1 H), 4.40 (dt, J = 4.4, 11.8 Hz, 1-H), 3.74 (s, 3-H), 3.69 (m, 1-H) 2.80 (ddd, J = 1.6, 12, 17.4 Hz, 1-H), 2.40 (dd, J = 4.4, 17.4 Hz, 1-H), 1.65 (m, 2-H), 1.00 (t, J = 7 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 173, 128.4, 127.8, 127.7, 90.1, 80.3, 73.2, 56.0, 28.2, 23.7, 9.53. Capillary GC analysis (same conditions as described for **11a**) indicated 100% purity.

6-[1-[(*tert*-Butyldimethylsilyl)oxy]propyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (12a, *thero*): mass calcd for $C_{15}H_{28}O_4Si$ (M + 1), 301.1835; exact mass (CI, M + 1) 301.1840; MS (NH_3/CI) 275, 243, 187, 125, 58; ^{1}H NMR ($CDCl_3$) δ 5.13 (d, J = 1.95 Hz, 1-H), 4.35 (dt, J = 3.91, 12.7 Hz, 1-H), 3.76 (m overlap), 1-H), 3.75 (s, 3-H), 2.63 (ddd, J = 1.95, 12.7, 17.1 Hz, 1-H), 2.27 (dd, J = 3.91, 17.1 Hz, 1-H), 1.4–1.8 (m, 2-H), 0.95 (t, J = 7 Hz, 3-H), 0.89 (s, 9-H), 0.12 (s, 6-H); ^{13}C NMR ($CDCl_3$) δ 175.8, 166.9, 90.32, 73.90, 56.02, 36.08, 27.93, 25.86, 10.23, −4.4. Capillary GC analysis (as described for **11a**) indicated 99% purity.

6-[1-[(*tert*-Butyldimethylsilyl)oxy]propyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (12b, *erythro*): ^{1}H NMR ($CDCl_3$) δ 5.127 (d, J = 1.47 Hz, 1-H), 4.31 (dt, J = 3.9, 12.21 Hz, 1-H), 3.91 (q, J = 5.1 Hz, 1-H), 3.75 (s, 3-H), 2.75 (ddd, J = 1.47, 12.21, 17.1 Hz, 1-H), 2.23 (dd, J = 3.9, 17.1 Hz, 1-H), 1.4–1.65 (m, 2-H), 0.94 (t (partial overlap), 3-H), 0.900 (s, 9-H), 0.11 (s, 6-H); ^{13}C NMR ($CDCl_3$) δ 167.25, 123.70, 90.136, 87.70, 84.88, 55.98, 26.40, 25.92, 21.98, 9.10, −4.24. Capillary GC analysis (as described for **11a**) indicated 98% purity.

6-[1-[(2-Methoxyethoxy)methoxy]oxy]propyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (13a, *threo*): mass calcd for $C_{13}H_{22}O_6$ (M + 1), 275.1480; exact mass (CI, M + 1), 275.1495; MS 199, 127, 89; ^{1}H NMR ($CDCl_3$) δ 5.14 (d, J = 1.95 Hz, 1-H), 4.82 (s, 2-H), 4.57 (dt, J = 3.91, 13.2 Hz, 1-H), 3.75 (s, 3-H), 3.70 (m, 3-H), 3.55 (t, 2-H), 3.38 (s, 3-H), 2.72 (ddd, J = 1.95, 13.2, 17.1 Hz, 1-H), 2.28 (dd, J = 3.91, 17.2 Hz, 1-H), 1.5–1.9 (m, 2-H), 0.99 (t, J = 7 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 173.08, 95.85, 90.32, 79.37, 76.21, 71.77, 67.57, 59.00, 56.08, 38.91, 28.66, 22.76, 9.87. Capillary GC analysis (as described for **11a**) indicated 98% purity.

6-[1-[(2-Methoxyethoxy)methoxy]propyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (13b, *erythro*): ^{1}H NMR ($CDCl_3$) δ 5.15 (d, J = 1.90 Hz, 1-H), 4.80 (s, 2-H), 4.60 (dt, J = 4.0, 12.6 Hz, 1-H), 3.75 (s, 3-H), 3.71 (m, 3-H), 3.65 (t, 2-H), 3.39 (s, 3-H), 2.84 (dd, J = 1.90, 12.6, 17.6 Hz, 1-H), 2.38 (dd, J = 4.0, 17.6 Hz, 1-H), 1.7 (m, 2-H), 0.99 (t, J = 7 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 173.80, 95.91, 90.35, 79.72, 76.30, 71.78, 67.91, 59.92, 56.12, 38.94, 28.82, 22.90, 9.89. Capillary GC analysis (as described for **11a**) indicated 98% purity.

6-[1-(Benzyloxy)hexyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (14a,b): see refs 5b and 8 (99% pure by capillary GC analysis).

6-[1-[(*tert*-Butyldimethylsilyl)oxy]hexyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (15a,b): see refs 5b and 8 (98% pure by capillary GC analysis).

6-[1-[(2-Methoxyethoxy)methoxy]hexyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (16a,b): see refs 5b and 8 (98% pure by capillary GC analysis).

6-[1-(Benzyloxy)-2-methylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (17a, *threo*): mass calcd for $C_{17}H_{22}O_4$, 290.1518; exact mass (EI) 290.1515; MS (EI) 184, 163, 127, 91; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 5.14 (d, J = 1.4 Hz, 1-H), 4.81 (d, J = 11.2 Hz, 1-H), 4.65 (d, J = 11.2 Hz, 1-H), 4.58 (ddd, J = 4, 5.4, 12.8 Hz, 1-H), 3.74 (s, 3-H), 3.30 (t, J = 5.4 Hz, 1-H), 2.68 (ddd, J = 1.4, 12.8, 17.2 Hz, 1-H), 2.25 (dd, J = 4, 17.2 Hz, 1-H), 2.04 (m, 1-H), 1.02 (t, J = 6.8 Hz, 6-H); ^{13}C NMR ($CDCl_3$ δ 172.8, 138.4, 128.3, 127.8, 127.6, 90.32, 84.42, 77.43, 74.45, 56.02, 29.69, 29.08, 19.90, 17.59. Capillary GC analysis (as described for **11a**) indicated a purity of 100%.

6-[1-(Benzyloxy)-2-methylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (17b, *erythro*): ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 5.14 (d, J = 1.6 Hz, 1-H), 4.80 (d, J = 11.2 Hz, 1-H), 4.61 (d, J = 11.2 Hz, 1-H), 4.59 (dt, J = 4, 12.2 Hz, 1-H), 3.75 (s, 3-H), 3.50 (dd, J = 3.8, 6.8 Hz, 1-H), 2.85 (ddd, J = 1.6, 12.2, 17.2

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Hz, 1-H), 2.30 (dd, J = 3.8, 17.2 Hz, 1-H), 1.88 (m, 1-H), 1.03 (d, J = 6.8 Hz, 3-H), 0.99 (d, J = 6.8 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 173.47, 166.96, 138.40, 128.33, 127.79, 127.60, 90.04, 84.64, 77.24, 75.00, 55.98, 29.91, 28.01, 19.40, 18.57. Capillary GC analysis indicated a purity of 99%.

6-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (18a, *threo*): ^{1}H NMR ($CDCl_3$) δ 5.14 (d, J = 2.0 Hz, 1-H), 4.30 (ddd, J = 3.8, 5.8, 12.7 Hz, 1-H), 3.75 (s, 3-H), 3.63 (m, J = 3.8, 5.8 Hz, 1-H), 2.55 (ddd, J = 2.0, 12.7, 17 Hz, 1-H), 2.23 (dd, J = 3.8, 17 Hz, 1-H), 1.82 (m, 1-H), 1.02 (d, J = 6.8 Hz, 3-H), 0.92 (s, 9-H), 0.89 (d (partial overlap), 3-H), 0.14 (s, 3-H), 0.1 (s, 3-H); ^{13}C NMR ($CDCl_3$) δ 172.70, 139.66, 90.48, 78.51, 77.54, 68.82, 56.03, 29.96, 29.32, 26.11, 16.53, −3.76. Capillary GC analysis indicated a purity of 98%.

6-[1-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (18b, *erythro*): mass calcd for $C_{16}H_{30}O_4Si$ (M + 1), 315.1991; exact mass (CI, M + 1) 315.1995; MS (NH_3/CI) 257, 157, 139, 74, 58; ^{1}H NMR ($CDCl_3$) δ 5.12 (d, J = 1.6 Hz, 1-H), 4.41 (dt, J = 3.4, 12.2 Hz, 1-H), 3.75 (s, 3-H), 3.67 (dd, J = 3.4, 6.8 Hz, 1-H), 2.81 (ddd, J = 1.6, 12.2, 17 Hz, 1-H), 2.20 (dd, J = 3.4, 17 Hz, 1-H), 1.72 (m, 1-H), 0.97 (d, J = 6.8 Hz, 3-H), 0.91 (d (partial overlap), 3-H), 0.90 (s, 9-H), 0.11 (s, 6-H); ^{13}C NMR ($CDCl_3$) δ 178.8, 173.3, 90.01, 77.85, 77.24, 55.96, 31.27, 27.44, 26.10, 19.17, 18.99, −3.69, −4.3. Capillary GC analysis indicated a purity of 97%.

Methyl 6-(benzyloxy)-3-methoxy-7-methyl-5-hydroxy-2-octenoate (20): ^{1}H NMR ($CDCl_3$) δ 7.30–7.50 (m, 5-H), 5.14 (s, 1-H), 4.69 (s, 2-H), 4.05 (m, 1-H), 3.68 (s, 3-H), 3.66 (s, 3-H), 3.25 (dd, J = 9.5, 13.5 Hz, 1-H), 3.09 (dd, J = 3.4, 6.35 Hz, 1-H), 2.83 (s, 1-H), 2.79 (dd, J = 3.9, 9.5 Hz, 1-H), 2.05 (m, 1-H), 1.02 (d, 6-H). Capillary GC indicated a purity of 98%.

6-[1-(Benzyloxy)-2,2-dimethylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (19a, *threo*): mass calcd for $C_{18}H_{24}O_4$ (M + 1), 305.1753; exact mass (CI, M + 1) 305.1745; MS (NH_3/CI) 177, 157, 127, 91, 83, 49; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5-H), 5.10 (d, J = 1.47 Hz, 1-H), 4.61–4.71 (m, 3-H), 3.69 (s, 3-H), 3.09 (d, J = 2.44 Hz, 1-H), 2.83 (ddd, J = 1.46, 11.7, 16.6 Hz, 1-H), 2.23 (dd, J = 3.9, 16.6 Hz, 1-H), 1.11 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 172.8, 167, 138.3, 128.5, 128.3, 127.6, 127.3, 90.2, 87.7, 76.1, 55.9, 36.4, 31.1, 27.5. Capillary GC analysis indicated a purity of 100%.

6-[1-(Benzyloxy)-2,2-dimethylpropyl]-5,6-dihydro-4-methoxy-2*H*-pyran-2-one (19b, *erythro*): ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5-H), 5.14 (d, J = 1.46 Hz, 1-H), 4.88 (d, J = 11.7 Hz, 1-H), 4.62 (d (overlap), J = 11.7 Hz, 1-H), 4.61–4.63 (ddd (overlap), J = 1.95, 3.91, 12.2 Hz, 1-H), 3.74 (s, 3-H), 3.53 (d, J = 1.96 Hz, 1-H), 2.95 (ddd, J = 1.47, 12.21, 17.6 Hz, 1-H), 2.30 (dd, J = 3.91, 17.6 Hz, 1-H), 1.01 (s, 9-H); ^{13}C NMR ($CDCl_3$) δ 173.9, 138.54, 128.3, 127.4, 89.89, 87.58, 75.30, 56.02, 35.16, 29.20, 26.95. Capillary GC analysis indicated a purity of 100%.

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Supplementary Material Available: NMR (^{1}H and ^{13}C) spectral data for compounds 4a,[26] 4b, 4c,[26,29], 4d,[26] 5a–d, 8a,[5e] 8b,[5b,8] 11–13, and 17–19 (11 pages). Ordering information is given on any current masthead page.

Asymmetric Diels–Alder Reactions with γ-Functionalized α,β-Unsaturated Chiral *N*-Acyloxazolidinones: Synthesis of (+)-S-145

Michael J. Martinelli

Process Research & Development Division, Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

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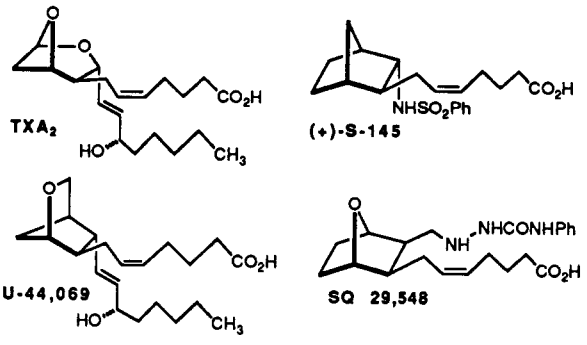
An extension of the asymmetric Diels–Alder cycloaddition with chiral γ-substituted, α,β-unsaturated imides is described. The application of these results to the synthesis of the potent TxA_2 receptor antagonist (+)-S-145 was successfully achieved in a practical manner.

Thromboxane A2 (TxA_2) receptor antagonists are an important class of pharmacological tools and are being studied clinically for the treatment of diseases such as asthma, angina pectoris, thrombosis, and other circulatory disorders.[1] A number of reports that discuss TxA_2 receptor antagonists have appeared recently.[1,2] In most cases, replacement of one or both of the ring substituted oxygen atoms of TxA_2, while maintaining the bicyclic steric nature of the ring system, has resulted in the discovery of very potent compounds with higher stability than TxA_2 itself (below). Moreover, modification of the α and ω side chains has also been shown to modulate the potency and intrinsic efficacy of these compounds at the TxA_2 receptor. The norbornyl nucleus has served as a pivotal framework on which to append various α and/or ω moieties, and S-145 is a potent norbornyl-derived TxA_2 receptor antagonist.[1a] We desired access to an optically active, substituted norbornyl ring which would allow flexibility for functionalization of the side chains in order to obtain the desired biological activity. As part of a collaboration with chemists at Shionogi and Company, we were interested in developing synthetic methodology for the preparation of highly substituted, optically active norbornane derivatives.



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