Intramolecular Diels−Alder Reactions Using α-Methylene Lactones as Dienophile

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Several dienals were prepared and reacted in the presence of zinc metal with ethyl 2-bromomethylacrylate to provide in a Reformatsky-like reaction α-methylene lactones carrying a dienyl side chain. Thermolysis of these compounds (**11**, **21**, **29**, and **37**) gave in an intramolecular Diels−Alder reaction the corresponding tricyclic cycloadducts (**51**, **52**, **53**, and **54**). The cycloadditions took place with good diastereoselectivity and yields. The stereochemistry of the major isomer is in accordance with an endo transition state for cycloadducts **51**, **52**, and **54**. In one instance (compound **58**), the structure was supported by X-ray crystallography. In contrast to the other substrates, the nonatriene **29** cyclized to the exo product **53exo**. The stereochemical situation could also be proven by NOESY NMR. However, the intramolecular Diels−Alder reaction did not work with furan as dienophile (compound **41**) and substrate **50** featuring a densely functionalized tether connecting diene and α-methylene lactone.

Introduction

Among the methods for the creation of polycyclic ring systems, the intramolecular Diels−Alder reaction occupies a dominant role. This has to do with the fact that the number of rings increases by two in the cycloaddition step. In many cases, the reaction is highly stereoselective. Over the years, a large variety of substrates for the intramolecular Diels−Alder reaction have been studied.[1−5] Thus, there might be one or more stereocenters in the chain connecting the diene and dienophile. Furthermore, the diene, part of the diene, or the dienophile might be part of a ring. Then there can be a ring in the connecting chain. Other variables include the attachment of the tether at the diene (type 1 vs type 2) and the inclusion of heteroatoms in the reacting π-bonds. Owing to its synthetic power, the intramolecular Diels−Alder reaction has been a cornerstone in many natural product syntheses.[6] However, this powerful strategy can have its problems. For example, the preparation of the substrate is often a difficult undertaking. Another point is that the stereochemical outcome of an intramolecular Diels−Alder reaction sometimes is difficult to predict without the assistance of molecular modeling.[7−9] For certain substrates, however, some general rules could be deduced.[3] A particular challenge from a synthetic point of view is represented by polycyclic compounds with a quaternary bridgehead center at the fusion point of two rings. If one of the rings is a cyclohexane, a Diels−Alder approach can be envisioned. Figure 1 lists some representative natural products that show this structural feature.

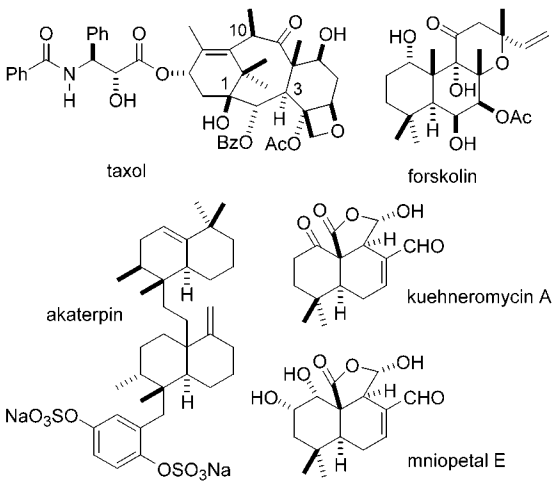

Figure 1. Polycyclic natural products with a quaternary brigdehead center.

These include the antitumor compound Taxol[10] or the labdane diterpene forskolin,[11−14] an activator of adenylate

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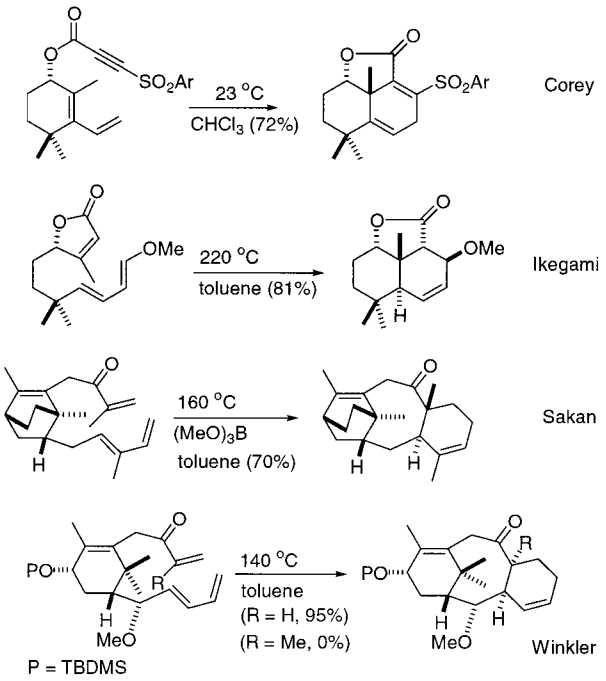
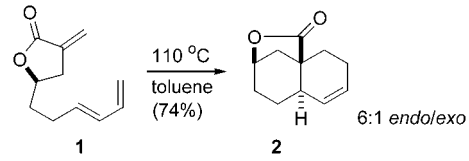


Figure 2. Angular methyl groups by intramolecular Diels–Alder reactions.

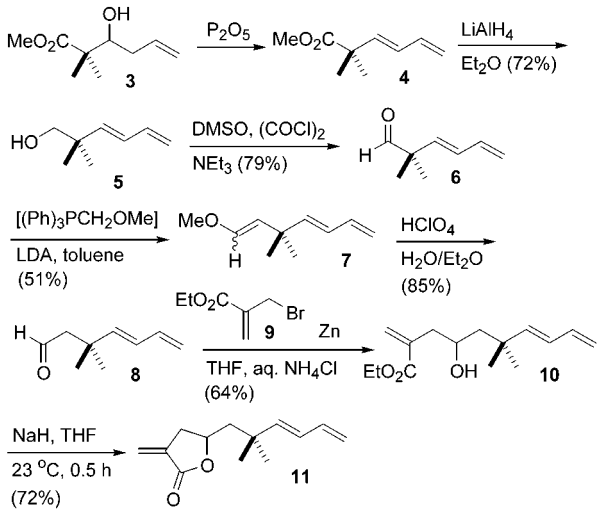
cyclase. Another interesting molecule is akaterpin, which functions as a selective inhibitor of phosphatidylinositol-specific phospholipase C.[15] As has been demonstrated with forskolin, the angular methyl group can be built into the decalin system via an intramolecular Diels–Alder reaction. The methyl group can be attached to either the diene or the dienophile. For example, in the Corey synthesis of forskolin, the methyl group is attached to the diene, whereas Ikegami chose to put it on the dienophile (Figure 2). In the case of Taxol, several intramolecular Diels–Alder have been pursued; however, none of them has ultimately led to the target molecule.[16]

If the angular substituent is a carboxylic group, then the intramolecular Diels–Alder approach is even more obvious. The drimane-type sequiterpenes mniopetal E and kuehneromycin A can be mentioned as examples (Figure 1). The mniopetals were isolated in 1994 by Steglich et al. and found to be inhibitors of reverse transcriptase.[17] A similar activity was reported for kuehneromycin A. Very recently, total syntheses for kuehneromycin A,[18] mniopetal F,[19] and mniopetal E[20] based on intramolecular Diels–Alder strategies were achieved by Jauch and Tadano. In these cases, the dienophile is a butenolide. Alternatively, the angular carboxylic group might be connected to a hydroxyl group at the tether connecting diene and dienophile. In the simplest setting, this corresponds to an intramolecular Diels–Alder reaction of an α-methylene lactone with an attached dienyl residue. We recently communicated an example for such a reaction (Scheme 1).[21] Thus, the thermolysis of **1** led with a selectivity of 6:1 to the cycloadduct **2**.

Scheme 1. Previously Reported Example for an Intramolecular Diels–Alder Reaction of an α-Methylene Lactone



Scheme 2. Synthesis of Substrate 11 Carrying a *gem*-Dimethyl Substituent Next to the Diene



With a view toward delineating the scope of this reaction and its potential application in natural products chemistry, we examined more substrates. The results of this study are presented in this paper.

Results and Discussion

Synthesis of the Triene Substrates. A certain advantage is the fact that α-methylene lactones are easily available from aldehydes by a Reformatsky-type reaction of ethyl 2-bromomethylacrylate[22,23] in the presence of zinc or some other metal.[24,25] It should be noted that this process also can be done in an asymmetric manner. Thus, the synthetic challenge is basically reduced to the synthesis of diene-containing alcohols. Depending on the distance between the alcohol function, the type of substituents at the tether, and the terminal position of the diene, several routes to the advanced substrates were followed. We first targeted some 4-dien-1-ols. Starting from crotonal, a Reformatsky reaction with methyl α-bromoisobutyrate gave the 3-hydroxy ester **3**. Treatment of **3** with phosphorus pentoxide gave the dienoate **4**.[26] Following reduction with lithium aluminum hydride, the dienol **5** was produced (Scheme 2). The synthesis continued with the Swern oxidation[27] of alcohol **5** giving the

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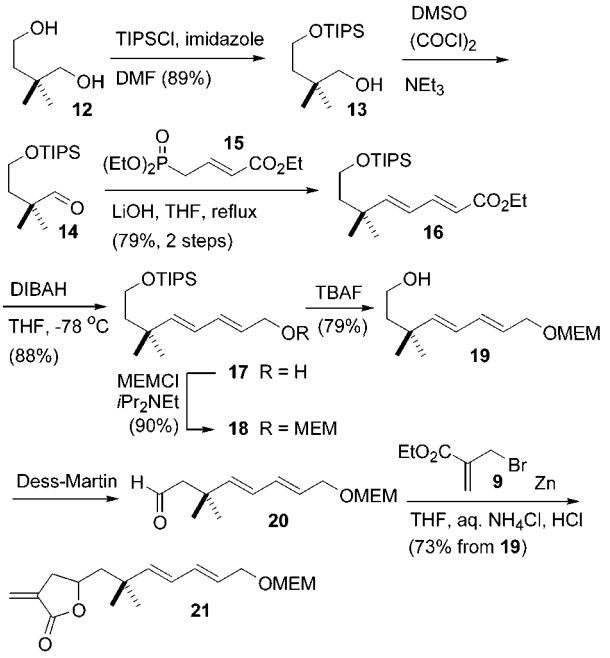
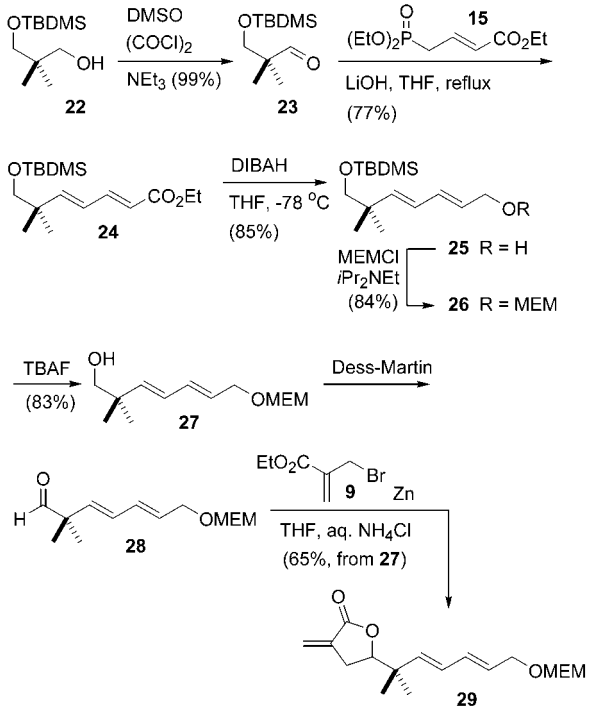
Scheme 3. Synthesis of Substrate 21 Featuring a Disubstituted Diene



Scheme 4. Synthesis of Substrate 29



aldehyde **6**. This aldehyde was subjected to a Wittig reaction with the ylide derived from (methoxymethyl)-triphenylphosphonium chloride. This step resulted in the formation of the separable enol ethers **7Z** and **7E** (ratio = 4:1). However, it proved to be limiting in that the yields were moderate. Hydrolysis of the mixture provided the somewhat labile aldehyde **8**. This was used as such in the subsequent Reformatsky reaction, which delivered the alcohol **10** in reasonable yield. The lactonization of **10** to the α-methylene lactone **11** was performed with a suspension of sodium hydride in THF. The acrylate of type **10** and the α-methylene lactones are prone to polymerization. This could be suppressed by adding hydroquinone to solutions of these compounds. The diastereotopic nature of the methylene and methyl groups in compound **11** is clearly evident from the NMR spectra. For example, the methyl groups are separated by 0.05 ppm and the H-4 protons appear as multiplets at $\delta = 2.51$ and 3.00, respectively.

Due to the biosynthetic pathways, decalin-ontaining terpenes are characterized by the presence of a *gem*-dimethyl group next to a bridgehead atom. Another issue is the substitutent at the terminal position of the diene. In this regard, a hydroxymethyl group is of interest as a precursor for an aldehyde group that is found in the mnipetals and kuehneromycin A. The synthesis of a corresponding diene began with the reduction of 2,2-dimethylsuccinic acid to the diol **12**. A selective mono-protection of the less hindered primary hydroxy group was achieved with triisopropylsilyl chloride in dimethylformamide (Scheme 3). Oxidation of the alcohol **13** provided the aldehyde **14**, which was extended via a Wittig−Horner reaction with ethyl 4-(diethylphosphono)-crotonate[28] to the dienoate **16**. The conditions put forward by Takacs et al.[29] turned out to be advantageous with regard to yield and isomeric purity of the double bonds. The ester **16** was reduced to the alcohol with DIBAH. Protection of the hydroxyl group as a methoxyethoxy-methyl ether furnished the protected diene−diol **18**. Removal of the silyl protecting group of **18** gave the alcohol **19**. Oxidation of **19** with the Dess−Martin periodinane[30,31] provided the aldehyde **20**, which was converted to the α-methylenelactone **21** by a Reformatsky reaction with **9** to give the intermediate hydroxy ester followed by in situ lactonization with hydrochloric acid.

A similar sequence of reactions was used to prepare the α-methylenelactone **29**. In comparison to **21**, the lactone **29** carries a side chain that is shortened by one methylene group (Scheme 4). Thus, monosilylation of 2,2-dimethyl-1,3-propanediol gave the alcohol **22**.[32] Oxidation of **22** under Swern conditions[27] furnished **23**. Chain extension by Wittig−Horner reaction[29] led to the dienoate **24**. Reduction of the ester produced the alcohol **25**, and subsequent protection gave the MEM ether **26**. Again, the remainder of the steps proceeded uneventfully. Removal of the silyl protecting group delivered the alcohol **27** whose oxidation furnished the aldehyde **28**. The formation of the α-methylene lactone was achieved as described previously.

To find out how this intramolecular Diels−Alder reaction performs with a longer tether between diene and dienophile, we targeted the α-methylenelactone **37** (Scheme 5). The synthesis began with a Wittig−Horner reaction of the commercially available aldehyde **30** with the phosphonate **15** yielding the trieneoate **31**. Next, the ester was reduced followed by conversion of the resulting alcohol **32** to the corresponding MEM ether **33** under standard conditions. Treatment of the triene **33** with a slight excess of 9-BBN allowed for a selective hydrobo-

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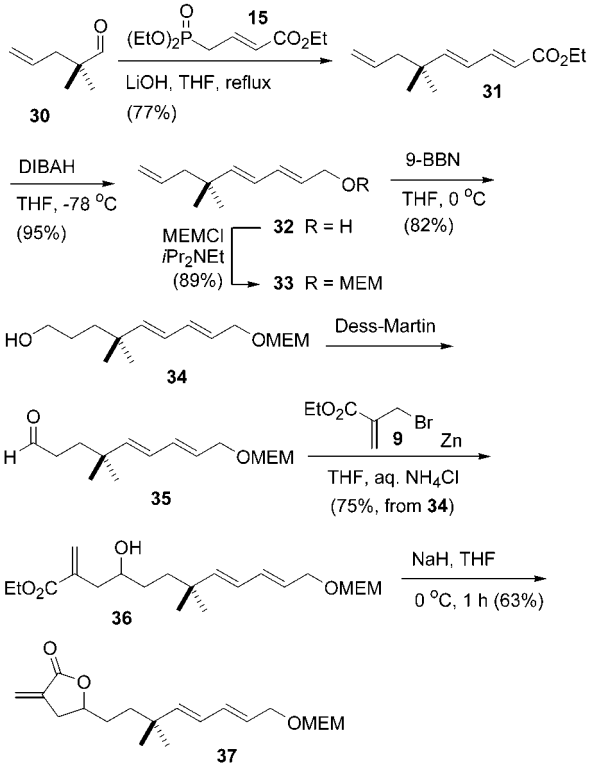
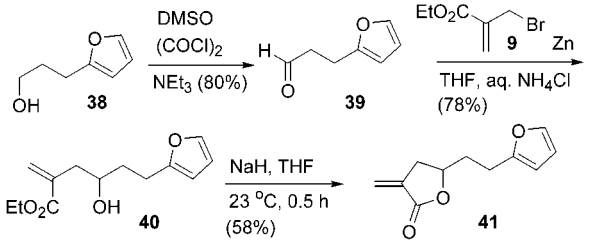
Scheme 5. Synthesis of Substrate 37



Scheme 6. Synthesis of Substrate 41 Featuring a Furan as Diene



ration of the terminal double bond providing the alcohol **34** after oxidative workup. Oxidation of **34** with the Dess−Martin periodinane led to the aldehyde **35** that was extended with the allyl bromide **9** under Reformatsky conditions to yield the hydroxy ester **36**. Subsequent lactonization of **36** under basic conditions furnished the α-methylenelactone **37**. In this case the two-step procedure for the establishment of the lactone moiety gave better yields than the one-pot variant.

To probe the reactivity of the dienophile, we also prepared the furan-containing substrate **41** (Scheme 6).[33,34] This was accessible by Swern oxidation of 3-(2-furyl)propanol (**38**). The aldehyde **39** was converted to the 2-substituted acrylate **40** by the Reformatsky reaction with the allylic bromide **9** in aqueous ammonium chloride. Lactonization to **41** was cleanly achieved by treatment of the 4-hydroxy ester **40** with sodium hydride. Compound **41** proved to be more stable toward polymerization than the other α-methylene lactones. The diastereotopic protons in the lactone ring of **41** appear as two ddd (δ = 2.53, 3.03).

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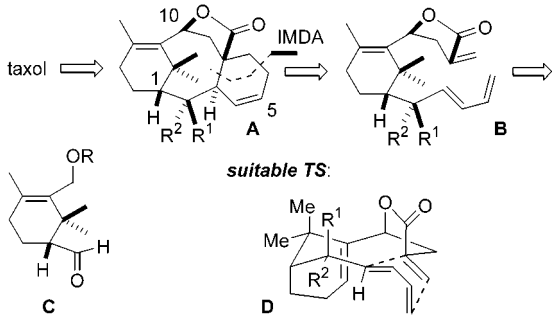
Scheme 7. Retrosynthetic Analysis for Taxol Based on an Intramolecular Diels−Alder Reaction



With the presence of a hydroxy function in position 10, we reasoned that the Taxol skeleton might be accessible by an intramolecular Diels−Alder strategy using an α-methylenelactone as dienophile.[35−39] The corresponding retrosynthetic analysis is shown in Scheme 7. The Taxol-like structure **A** incorporates the α-butyrolactone.[40] Disconnection according to a Diels−Alder reaction leads to the α-methylene lactone **B**. Removal of both the dienophile and dienyl group provides the cyclohexenal **C** as a potential starting material.

This compound itself is easily available by an intermolecular Diels−Alder reaction[41] (Scheme 8). A certain problem is clearly the control of the relative stereochemistry at positions 2 and 10. This study would serve to reveal the scope and limitation of this intramolecular Diels−Alder strategy. The synthesis began with the construction of the A-ring and attachment of a diene or suitable precursor thereof, respectively. As described by Dai et al., the cyclohexenal **43** could be obtained on a large scale by the borontrifluoride etherate (BF_3·Et_2O)-catalyzed cycloaddition between the diene **42**[42] and acrolein. To prevent decomposition, it is best to use the cycloadduct **43** directly after chromatographic purification. With the aldehyde function present, it seemed appropriate to continue the synthesis with the attachment of the dienyl part. Although a dienyl anion can be generated by transmetalation of (*E*)-1,3-(1-tributylstannyl)butadiene, this compound is difficult to obtain.[43,44] We

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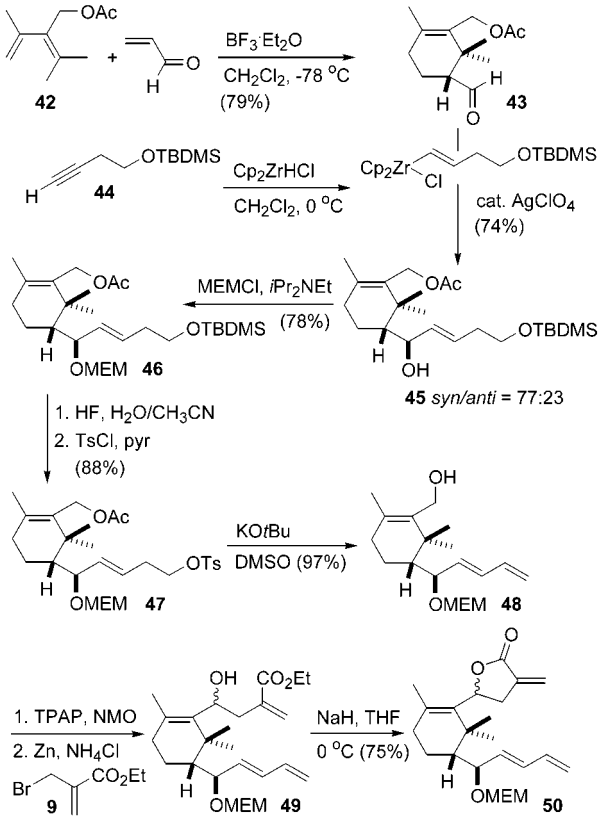
Scheme 8. Synthesis of Substrate 50 Featuring the Taxol A Ring



therefore sought a more practical alternative. This was found with the protected 3-butyn-1-ol **44**.[45] Hydrozirconation with the Schwartz reagent (Cp_2ZrHCl) gave the intermediate vinylzirconocene.[46−48] Addition of the aldehyde and a catalytic amount of silver perchlorate ($AgClO_4$)[49] resulted in the formation of the secondary alcohol **45** in 74% yield. This reaction afforded two diastereomers in a ratio of 77:23. The stereochemical assignment was done in analogy to compounds reported by Fallis.[50] Whereas H-2 of the major diastereomer appears at $\delta = 4.42$, the corresponding signal of the minor isomer is shifted to higher field ($\delta = 4.20$). A similar shift difference, although in the opposite direction is observed for H-1. This proton resonates at $\delta = 1.30-1.37$ in the major isomer and $\delta = 1.52-1.55$ of the minor isomer, respectively. In the next step the secondary alcohol was protected as methoxyethoxymethyl ether **46** using MEMCl and diisopropylamine as base. The long reaction time of 2 d indicates some steric hindrance around the secondary hydroxyl group. The stage was now set for the liberation of the diene. First, the silyl protecting group was removed with HF in aqueous acetonitrile. After workup, the free primary alcohol was directly converted to the corresponding tosylate using pyridine/(dimethylamino)pyridine. Subsequent treatment of the tosylate **47** with three equivalents of potassium *tert*-butoxide induced E2 elimination

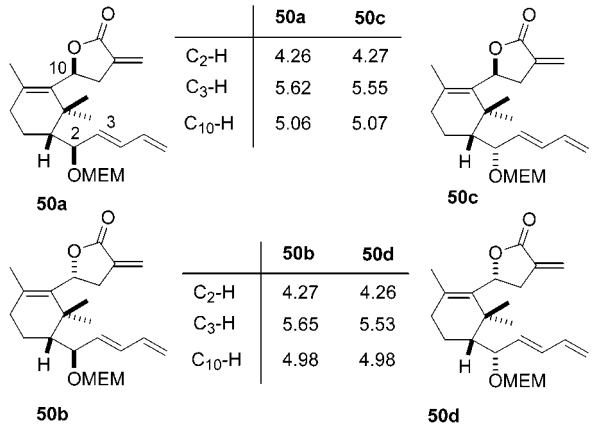


Figure 3. Structures and characteristic chemical shifts for the isomers **50**.

as well as deacylation at position 10 providing compound **48** in almost quantitative yield (Scheme 8). With the lower section completed, we could now concentrate on the introduction of the α-methylene-γ-butyrolactone. This was initiated by the tetrapropylammonium perruthenate mediated oxidation[51] of the alcohol to the corresponding aldehyde. The latter compound was not further characterized. Instead it was directly reacted with ethyl α-bromomethylacrylate (**9**) in the presence of zinc. Lactone formation to the γ-butyrolactone **50** took place smoothly by adding two equivalents of sodium hydride to the hydroxy ester **49** (Scheme 8).

If the diastereomeric mixture of **48** is used, four compounds **50** are produced. There is essentially no diastereoselection in the formation of the asymmetric center at C-10. That means that the ratio of **50a**/**50b**/**50c**/**50d** is about 3:3:1:1. By careful and repeated chromatography the isomers could be separated. Their structures are depicted in Figure 3 together with some characteristic chemical shifts. It is seen that for **50a** and **50b** H-3 appears at lower field than in **50c** and **50d**. In contrast, H-2 has for all isomers about the same chemical shift. On the basis of the similar chemical shift in **50a**, **50c** and **50b**, **50d**, respectively, the stereochemistry at C-10 was assumed to be the same in these pairs. However, the relative assignment also might be exchanged.

Intramolecular Cycloaddition. The intramolecular cycloaddition reactions went smoothly for the substrates **11**, **21**, and **29** (Table 1). Typically, a solution of the triene in toluene was refluxed for 2−3 d. To prevent polymerization, hydroquinone was added. Concentration of the reaction mixture and purification by flash chromatography gave the pure products **51**, **52**, and **53**, respectively. Under the same conditions, the substrate **37** did not give any product. However, changing the solvent to *o*-dichlorobenzene and keeping the solution at reflux temperature for 2 d brought about the desired cycloaddition, yielding a mixture of the endo and exo isomers **54endo** and **54exo** in a ratio of 56:44. The diastereomeric ratios were determined by ^{1}H NMR (**51**, **52**), by GC−MS (**52**, **53**), and by weighing of the fractions (**54**). Unfortunately, thermolysis (110 or 180 °C) of the furan derivative **41** did not give the corresponding cycloadduct. Heating of **41** in DMSO for 18 h at 190 °C gave a black polymer. Lewis

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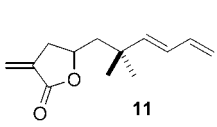
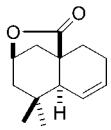
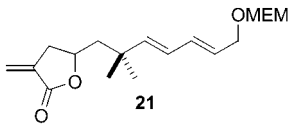
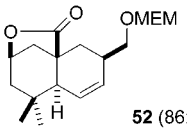
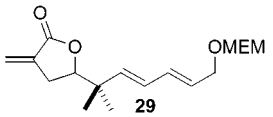
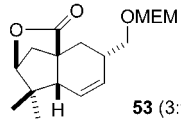
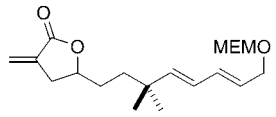
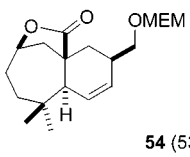
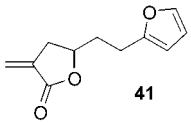
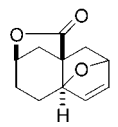
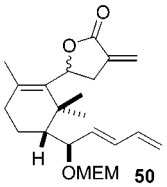
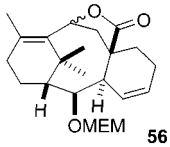
Table 1. Intramolecular Diels−Alder Reactions of Various α-Methylene Lactones

Triene	major Product (endo/exo)	yield (%)
 **11**	 **51** (95:5)	78
 **21**	 **52** (86:14)	61
 **29**	 **53** (3:97)	61
 **37**	 **54** (53:47)	76
 **41**	 **55**	0
 **50**	 **56**	0

acid catalysis (1 equiv of $MeAlCl_2$, CH_2Cl_2, −60−23 °C, 18 h) also left **41** unchanged. It is difficult to explain the failure of the Diels−Alder reaction of **41**. One might speculate that the presence of several rings in the cycloadduct favors the retro-Diels−Alder reaction due to ring strain. For the intramolecular Diels−Alder reaction toward the taxol-like structure **56** each of the four diastereomers **50a**−**d** was heated as a toluene solution in a sealed tube at 160 °C. The presence of catalytic amounts of hydroquinone prevented decomposition. Unfortunately, only starting material was observed even after heating for 48 h. We also attempted the Diels−Alder reaction in the presence of dimethylaluminum chloride (1.2 equiv, CH_2Cl_2, −78 °C). This, however, resulted in the destruction of the tetraene **50**.

Stereochemical Assignment. The structures of the cycloadducts were assigned mainly by 2D NMR spectroscopy. Figure 4 depicts the NOESY spectrum of tricycle **52**. Most revealing are the cross-peaks of the bridgehead proton H-6 with the three axial protons H-2, H-8, and H-12. The relatively strong intensity of the H-6/H-12a cross-peak points to a short distance between these two protons.

Further structural proof for the *trans*-decalin substructure came from the X-ray analysis of the trifluoroacetate **58** (Figure 5). This compound was obtained when the hydroxyester **57**, which was formed from the reaction of the bromomethylacrylate **9** with the aldehyde **20**, was

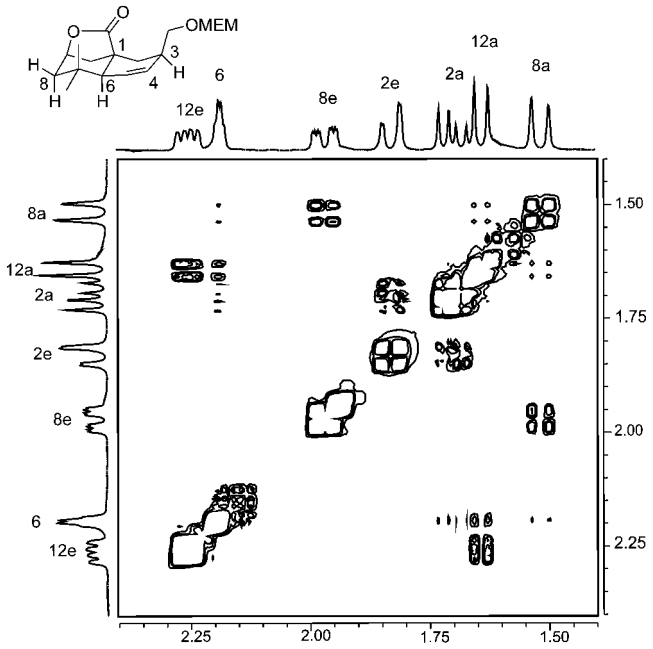


Figure 4. NOESY spectrum of the endo cycloadduct **52**.

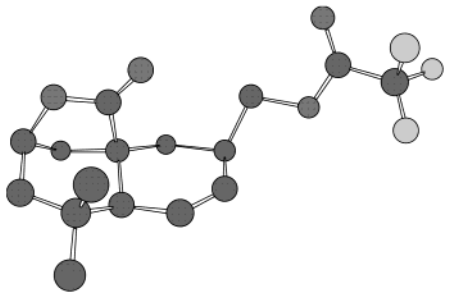
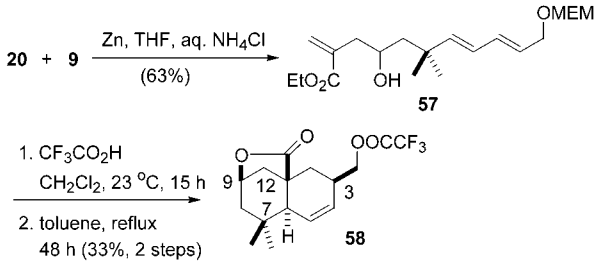


Figure 5. X-ray structure of the cycloadduct **58** (Chem-3D rendering).

Scheme 9. Synthesis of the Cycloadduct 58



cyclized to the corresponding lactone using trifluoroacetic acid. The crude product was then subjected to thermolysis in toluene giving rise to the cycloadduct **58**. Somewhere en route to **58** the MEM protecting group was replaced with a trifluoroacetate. Surprisingly, the OH-free compound was not obtained under these conditions (Scheme 9). However, this transformation was of particular value in that the product formed crystals suitable for X-ray analysis.

The X-ray structure of **58** reveals the *trans*-decalin ring and the pseudoaxial orientation of the hydroxymethyl groups at position 3. The structure **58** is characterized by the following distances: H-6/H-2 262.4 pm, H-6/H-8 272.8 pm, H-6-H/12 231.1 pm. This is in agreement with the trends seen in the NOESY spectrum of **52**. The trifluoromethyl group turned out to be highly disordered.

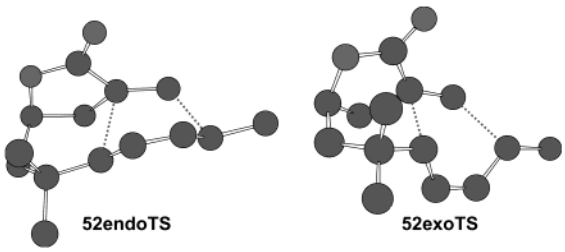


Figure 6. Transition states for **52endoTS** and **52exoTS** as calculated by MacroModel V7.0.

That is, the X-ray structure localized nine fluorine atoms. For clarity, only three are depicted in Figure 5.

By analogy, the cycloadduct **51** was also assigned the endo structure. It should be noted that the ^{1}H NMR spectra of **51** and **52** show striking similarities between 1.0 and 2.5 ppm. The high selectivity in favor of the *trans*-decalin products (endo cycloadduct) can be understood by looking at the two diastereomeric transition states **52endoTS** and **52exoTS** (to simplify matters, the methoxymethyl was replaced with a methyl group). The endo transition state **52endoTS** is clearly favored because of favorable secondary orbital interactions between diene and the dienophile activating group. On the other hand, the exo transition state **52exoTS** is disfavored by the axial position of the butadiene moiety and possibly by steric interactions of H-5 (product numbering) with the axial H-8 and H-12. Transition-state modeling using MacroModel indicates an energy difference in favor of the **52endoTS** of 9.14 kJ mol^{-1} (Figure 6).[52] A substantial asynchronicity in the bond formation is revealed by the calculations. Thus, the peripheral bond of **52endoTS** was calculated to be 209.6 pm, whereas the internal bond is much longer (244.2 pm).

In the case of the nonatriene system **29**, thermolysis led essentially only to the product having cis-annulated carbocyclic rings. The NOESY spectrum of **53** is characterized by cross-peaks of the bridgehead hydrogen H-6 with H-3. In addition, NOE correlations were observed between the olefinic proton H-5 and the axial methyl group at C-7 (C_7-CH_3). The two possible transition states are depicted in Figure 7. It is seen that the endo transition structure **53endoTS** is disfavored because of eclipsing interactions of the two methyl groups with the butadiene. This must even override the usual endo preference. However, the experimental results are not reflected in the force-field calculations. Surprisingly, according to the calculations transition state **53endoTS** is favored by 12.5 kJ mol^{-1}.

The fact that the length of the tether connecting diene and dienophile has a profound influence on the diastereoselectivity of this type of Diels–Alder reaction is evident from the thermolysis of **37**. This triene required heating to 180 °C in order to realize the cycloaddition. The thermolysis produced a 53:47 mixture of the endo and exo isomers **54end**o and **54exo**. Again, the structure of the major isomer was elucidated with the help of a NOESY spectrum. Thus, the bridgehead proton must be in proximity to the axial H-8a, H-2a, and H-13a. The calculated conformations of **54endo** and **54exo** are shown in Figure 8.

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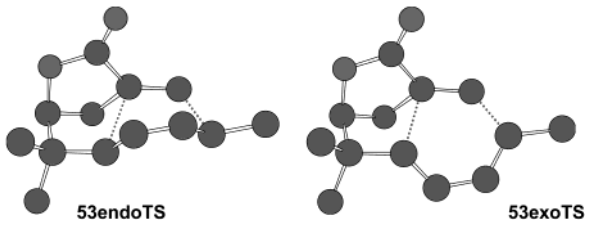

Figure 7. Transition states for **53endoTS** and **53exoTS** as calculated by MacroModel V7.0.

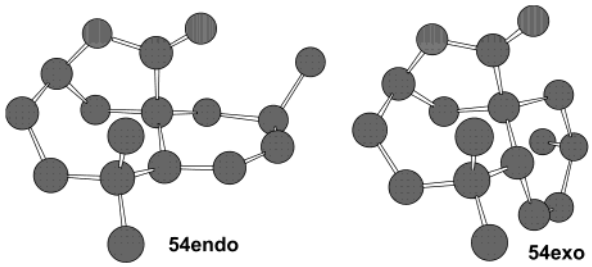

Figure 8. Calculated conformations (MacroModel V7.0) of **54endo** and **54exo**.

Summary

We demonstrated that the intramolecular Diels–Alder reaction of α-methylene lactones represents an efficient approach to tricyclic structures. The cycloadditions are characterized by high diastereoselectivity and reasonable yields. The major isomer is in accordance with an endo transition state. An exception is the cycloaddition of the nonatriene substrate **29**. Another advantage is the fact that the dienophile, the α-methylene lactone, can be very easily installed. However, as it turned out, the intramolecular Diels–Alder reaction did not work with a furan as a dienophile and a densely functionalized tether connecting the diene and the α-methylene lactone. In the course of the synthesis of the triene **50**, we also developed a novel dienyl equivalent.

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Supporting Information Available: Experimental details and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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