Lewis acid-catalyzed Diels-Alder reaction of 2-cyclopentenones with Danishefsky's diene: double bond isomerization of tetrahydro-1*H*-indene-1,5(7a*H*)-diones, and attempts on an asymmetric catalysis

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Dedicated to Prof. Rainer Beckert on the occasion of his 60th birthday

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Abstract

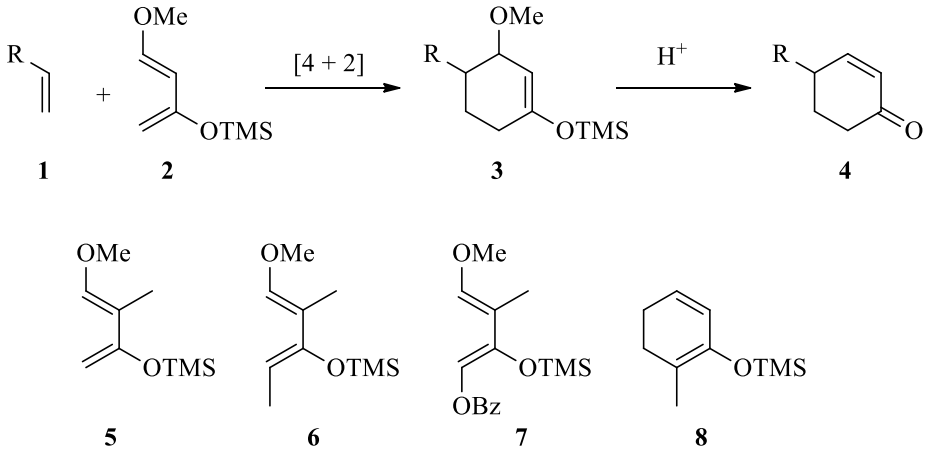
This work describes the investigation of the Diels-Alder reaction of the electron-rich diene *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky′s diene) and the non-activated dienophiles 2-cyclopentenone and 2-methyl-2-cyclopentenone with respect to reactivity, regioselectivity and stereoselectivity. An observed double bond isomerization limits the practicability of 2-cyclopentenone as a dienophile in Diels-Alder reactions. 2-Methyl-2-cylopentenone could be converted quantitatively into one regioisomeric Diels-Alder adduct, however the stereochemical control turned out to be very demanding.

Keywords: Diels-Alder reaction, Danishefsky's diene, cyclic enones, double bond isomerization

Introduction

The use of electron-rich dienes is a common method to improve both reactivity and regioselectivity in Diels-Alder [4+2] cycloadditions. Among the most prominent members of such electron-rich dienes there is Danishefsky's diene, i.e. *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **2** (Scheme 1), which has originally been used to prepare pyrones from aldehyde dienophiles.[1] Later Danishefsky's diene **2** was used extensively for the formation of 6-membered carbo- and heterocycles.[2-4] When diene **2** is treated with alkenes such as **1**, the intermediate cycloadduct **3** can eliminate MeOH very easily so that cyclohexenones **4** become available. Besides Danishefsky's diene **2** a variety of related electron-rich dienes **5**-**8** have been developed.[5] Whereas the use of (-M)-substituted cyclopentenones in Diels-Alder reactions with

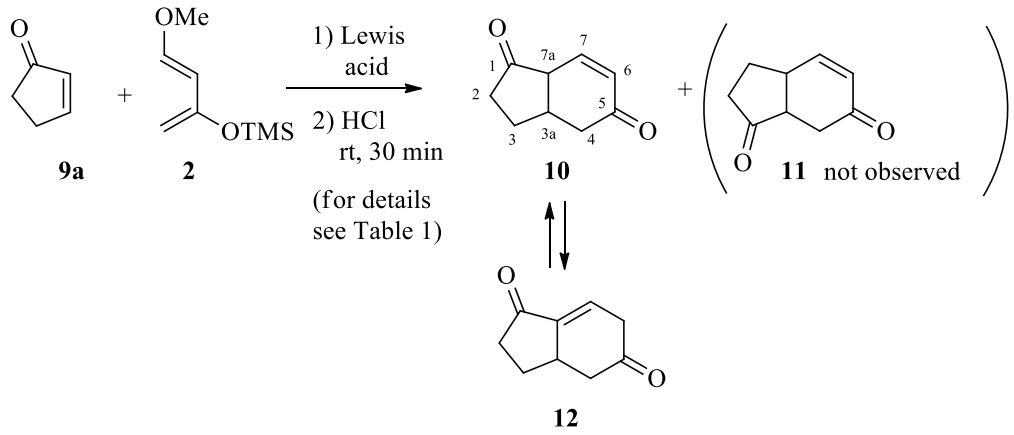
Danishefsky's diene **2** is well explored,[6] only few examples are known, where non-activated cyclopentenones have been employed as starting materials.[7] Thus, we were interested in exploring the scope of [4+2] cycloadditions employing diene **2** and non-activated 2-cyclopentenone **9a** and 2-methyl-2-cyclopentenone **9b** with respect to reactivity, regioselectivity and possibly stereoselectivity. The results towards this goal are reported below.



Scheme 1. Diels-Alder reactions with Danishefsky's diene and related electron-rich dienes.

Results and Discussion

First various conditions were screened for the cycloadditions. The results are summarized in Scheme 2 and Table 1. Following a procedure by Ishikawa,[6a,b] a solution of 2-cyclopentenone **9a** in CH_2Cl_2 was treated with 10 mol% of $ZnCl_2$ for 15 min at room temperature and then cooled to 0 °C. Later 1.2 equiv. of Danishefsky's diene **2** were added and the mixture was hydrolyzed after 2 h with 1 N HCl and submitted to aqueous workup. Although GC of the reaction mixture indicated 99% conversion of the starting material **9a**, only 49% of a 63:37 mixture of two inseparable products with the desired *m/z* 150 (entry 1) was obtained. In order to improve the amount of products, Me_2AlCl in CH_2Cl_2 at -28 °C was tested next, albeit to give only a yield of 18% and a product ratio of 56:44 (entry 5). When $SnCl_4$ in THF at -78 °C was employed, the GC yield improved to 54% but again with an almost equimolar mixture (43:57) of the two products (entry 7). Unfortunately, regardless of the Lewis acid or solvent tested, the product ratio and yield could not be improved very much. The cleanest reaction without accompanying decomposition products was observed for $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C. After 5 min quantitative conversion was achieved with 59% of the two products (43:57), which could be isolated in 20% combined yield.



Scheme 2

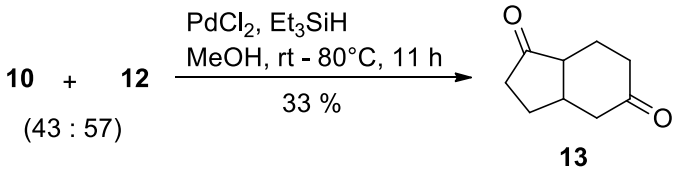
Table 1. Diels-Alder reaction of 2-cyclopentenone **9a** with Danishefsky's diene **2** in the presence of various Lewis acids

Entry	Lewis acid	Solvent	Temperature [°C]	Time	Conv. [%]	GC-Yield [%]	Ratio [%] **10** : **12**	Yield [%]
(1)	$ZnCl_2$	CH_2Cl_2	0	2 h	99	49	63 : 37	
(2)[a]	$ZnCl_2$	CH_2Cl_2	0	1 h	93	39	82 : 18	
(3)	$ZnCl_2$	toluene	40	5 min	100	46	33 : 67	
(4)	$ZnCl_2$	THF	22	7 d	98	13[b]	46 : 54	
(5)	Me_2AlCl	CH_2Cl_2	-28	60 h	100	18	56 : 44	
(6)	Me_2AlCl	THF	0	5 h	94	17	88 : 12	
(7)	$SnCl_4$	THF	-78	3 h	100	54	43 : 57	
(8)	$TiCl_4$	THF	-78	1 h	96	2[c]	50 : 50	
(9)	$BF_3{\cdot}OEt_2$	THF	-78	0.5 h	80	16	56 : 44	
(10)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	5 min	100	59	43 : 57	20

[a]2.4 eqiv. of Danishefsky's diene were used. [b]Besides **10**, **12** 57% of 1,3,5-triacetylbenzene were detected in the GC.[8] [c]58% of 1,3,5-triacetylbenzene was detected.[8]

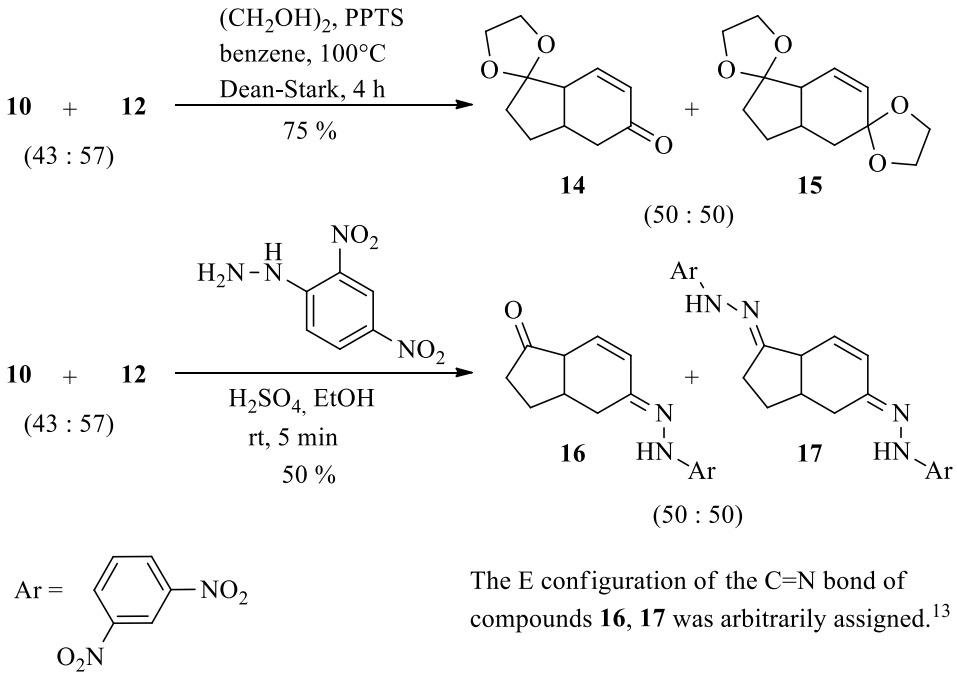
Initially, we surmised that the two peaks in the GC, which referred to *m/z* 150, were the two regioisomers **10**, **11**. However, the presence of almost equimolar mixtures made us suspicious that the two products might not be these regioisomers, because the frontier orbital interactions of the HOMO of Danishefsky's diene **2** with the LUMO of 2-cyclopentenone **9a** and the corresponding orbital coefficients should strongly favor regioisomer **10**, i.e. the "quasi-para" product rather than the "quasi-meta" product **11**.[9,10] A close inspection of the NMR spectra of the mixtures, in particular the 1D ^{1}H-NMR and 2D HSQC and HMBC as well as ^{13}C-NMR DEPT spectra, suggested that the two GC peaks refer to the two C=C bond isomers **10**, **12** rather than the regioisomers **10**, **11**.[11]

In order to prove this assumption, the mixture of **10**, **12** was submitted to reduction of the C=C bond. Following the procedure by Mirza-Aghayan[12] the mixture was treated with 10 mol% of $PdCl_2$ and Et_3SiH in MeOH at 80 °C for 11 h and the resulting product was isolated in 33% (Scheme 3). Indeed, only a single diketone **13** was obtained.



Scheme 3

Any attempts to separate the double bond isomers **10**, **12** by chromatography were unsuccessful and therefore we studied the conversion of **10**, **12** into carbonyl derivatives such as ketals or hydrazones. As shown in Scheme 4, the mixture of **10**, **12** was reacted with 2 equiv. of ethylene glycol in the presence of PPTS in benzene at 100 °C under Dean-Stark conditions. After workup and purification 75% of an inseparable mixture of monoketal **14** and diketal **15** were obtained. Comparison of the NMR spectra with the starting material **10**, **12** revealed that the ketalization took exclusively place with the C6/C7 double bond isomer **10** rather than the C7/C7a isomer **12**.



Scheme 4

Next, we were curious whether the enone **10** with the C6/C7 double bond is indeed the more reactive one. Enones **10**, **12** were treated with 2 equiv. of 2,4-dinitrophenylhydrazine in the presence of H_2SO_4 in EtOH to yield 50% of a 1:1 mixture of mono- and bishydrazone **16**, **17** respectively (Scheme 4). Similarly to the ketalization no trace of the hydrazones derived from the C7/C7a enone **12** was detected. The two products **16**, **17** could be separated by preparative HPLC, but any attempts to remove the hydrazone moiety were unsuccessful.[14]

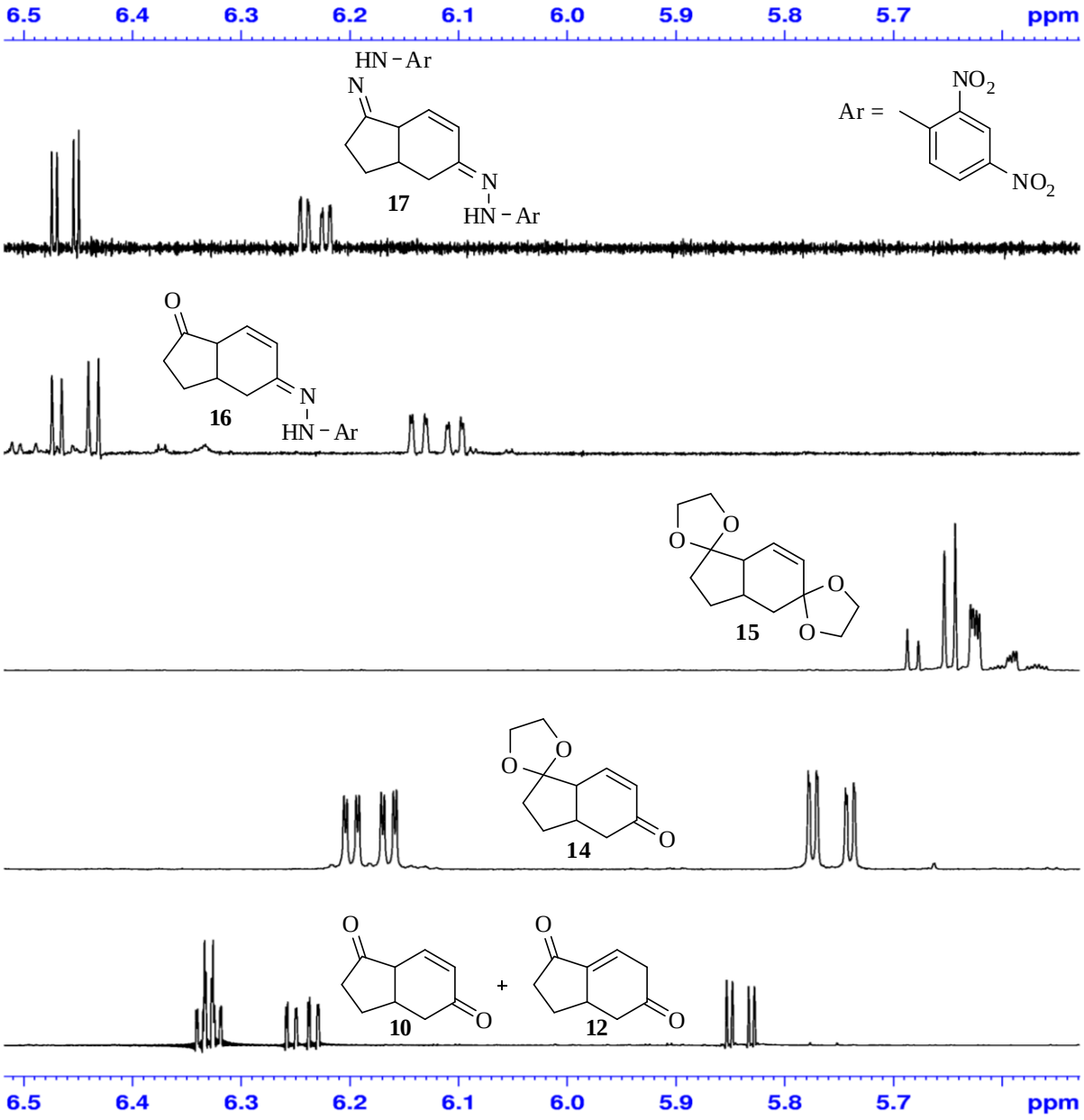
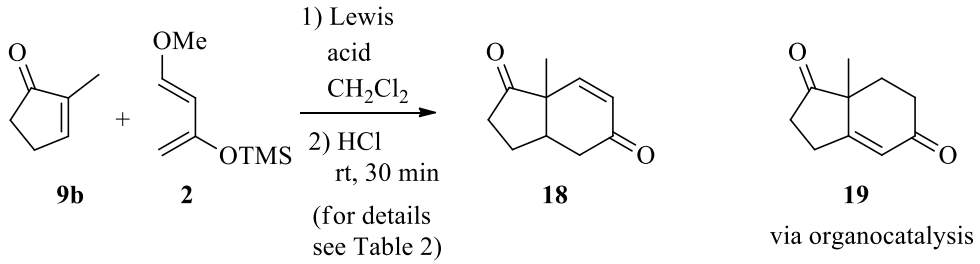


Figure 1. ^{1}H-NMR spectra of the inseparable C=C bond isomers **10** and **12**, the ketals **14** and **15** and the hydrazones **16** and **17** in the range of 5.6 ppm and 6.5 ppm (vinylic domain).[15]

So far we described that C=C bond isomerization severely limits the utility of 2-cyclopentenone **9a** as a dienophile and thus the following experiments were carried out with 2-methyl-2-cyclopentenone **9b**. Thus **9b** was treated with 1.2 equiv. of Danishefsky's diene **2** in CH_2Cl_2 in the presence of 10 mol% $AlCl_3$ at 0 °C for 1h followed by aqueous workup (Scheme 5, Table 2). The GC of the crude product contained 65% of the desired enone **18** together with decomposition products (entry 1). Even the milder Lewis acid $ZnCl_2$ at 0 °C did not improve the yield (entry 2). Although the use of $SnCl_4$ at -78 °C gave an increased yield (81%), product formation was accompanied by decomposition (entry 3). The utilization of BH_3 as Lewis acid did not work at all. No reaction could be detected at room temperature. As in the case of 2-cyclopentenone **9a** again $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C gave the cleanest reaction and the product enone **18** could be isolated in quantitative yield. It should be noted that compound **18** represents a complementary C=C bond isomer to the famous Hajos-Wiechert ketone **19**, which has been prepared by organocatalysis.[16]



Scheme 5

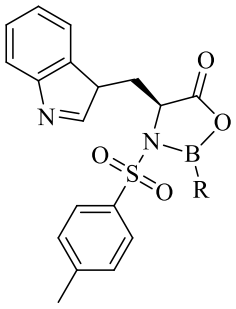
Table 2. Diels-Alder reaction of 2-methyl-2-cyclopentenone **9b** with Danishefsky's diene **2** in the presence of various Lewis acids

Entry	Lewis acid	Temperature [°C]	Time	Conv. [%]	GC-Yield [%]	Yield [%]
(1)	$AlCl_3$	22	2 h	100	65	
(2)	$ZnCl_2$	0	1 h	100	60	
(3)	$SnCl_4$	-78	1 h	100	81	
(4)	BH_3	22	72 h	-	-	
(5)	$ArB(OH)_2$ [a]	0	5 min	100	81	
(6)	$BF_3{\cdot}OEt_2$	0	5 min	100	100	100

[a] $ArB(OH)_2 = 3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$

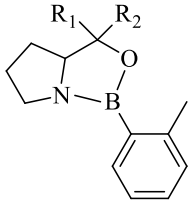
Next, a variety of chiral Lewis acids **20 - 25** were tested (Scheme 6, Table 3). Surprisingly, oxazaborolidinones **20a-c** and oxazaborolidines **21a-d** did not catalyze the Diels-Alder reaction between 2-methyl-2-cyclopentenone **9b** and Danishefsky's diene **2** at all.[17] Their activated counterparts **20a-c**·Lewis acid, or **21a-d**·Lewis acid,[18] titanium BINOL complex **22** (Mikami′s

catalyst),[19,20] or Seebach's titanium TADDOLate complex **23** however enabled the conversion but did not produce any enantioselectivity.[21] Only racemic product **18** was detected. A promising result was obtained, when the boronic ester **24a**[22] was employed, resulting in 81% of the product with 20%ee (entry 15). Recently, Nishida introduced a new axially chiral catalyst **25**, which gave good yields and high ee's with Danishefsky's diene **2** and oxazolidinone-substituted enoates.[23] Unfortunately these promising results could not be confirmed when this new BINAMIDE complex **25** was used in the asymmetric Diels-Alder reaction of 2-methyl-2-cyclopentenone **9b** and Danishefsky's diene **2**, giving rise to an enantiomeric excess of 7%.



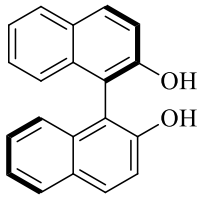
20a R = H
20b R = *n*-Bu
20c R = 3,5-$(CF_3)C_6H_3$

LA = BH_3, BF_3, CF_3SO_3H



21a $R_1 = R_2$ = Ph
21b R_1 = Ph, R_2 = 1-naphthyl
21c $R_1 = R_2$ = 2-naphthyl
21d $R_1 = R_2$ = Me

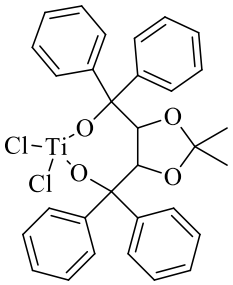
LA = $AlBr_3$, CF_3SO_3H



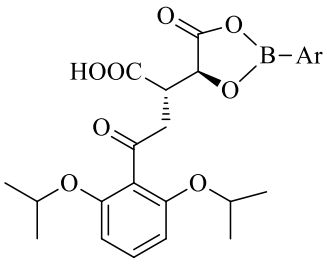
(*R*)-BINOL

[(*R*)-BINOL (1 equiv)
$TiCl_2(O^iPr)_2$ (1 equiv)
4 Å MS (5 - 15% H_2O)]

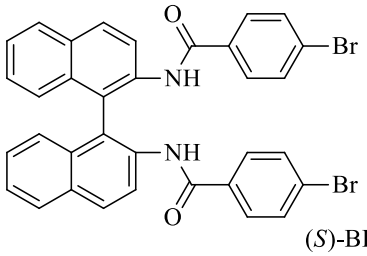
22 (Mikami's catalyst)



23



24a Ar = 3,5-$(CF_3)C_6H_3$
24b Ar = Ph
24c Ar = *p*-tolyl



(*S*)-BINAMIDE

[$Yb(OTf)_3$ (1 equiv)
(*S*)-BINAMIDE (1.2 equiv)
DBU (2.4 equiv)]

25

Scheme 6. Chiral Lewis acids employed in the Diels-Alder reaction of **9b** and **2.**

Table 3. Diels-Alder reaction of 2-methyl-2-cyclopentenone **9b** with Danishefsky's diene **2** in the presence of chiral Lewis acids

Entry[a]	Lewis acid	Solvent	Temperature [°C]	Time	Conv. [%]	GC-Yield [%]	%ee	Yield[b] [%]
(1)	**20a**·BH_3	CH_2Cl_2	-15	7 h	20	76	0	
(2)	**20a**·BF_3	CH_2Cl_2	-78	1 h	70	93	0	
(3)	**20a**·CF_3SO_3H	CH_2Cl_2	-78	10 min	70	11	0	
(4)	**20b**·BF_3	CH_2Cl_2	-78	10 min	80	66	0	
(5)	**20a**·CF_3SO_3H	CH_2Cl_2	-78	10 min	25	31	0	
(6)	**20c**·BF_3	CH_2Cl_2	-78	10 min	50	65	0	
(7)	**20c**·CF_3SO_3H	CH_2Cl_2	-78	10 min	25	15	0	
(8)	**21a**·CF_3SO_3H	CH_2Cl_2	-78	5 min	40	35	0	
(9)	**21a**·$AlBr_3$	CH_2Cl_2	-15	10 min	100	95	0	90
(10)	**21b**·$AlBr_3$	CH_2Cl_2	-15	1 h	50	95	0	46
(11)	**21c**·$AlBr_3$	CH_2Cl_2	-15	3 h	75	95	0	60
(12)	**21d**·$AlBr_3$	CH_2Cl_2	-15	1 h	50	65	0	
(13)[c]	**22**	CH_2Cl_2	22	4 h	30	70	0	
(14)	**23**	CH_2Cl_2	-7	2 h	50	30	0	
(15)[d]	**24a**	C_2H_5CN	0	5 min	24	82	20	81
(16)	**24b**	C_2H_5CN	50	2 h	100	10	0	
(17)	**24c**	C_2H_5CN	50	1,5 h	100	9	0	
(18)[d]	**25**	CH_2Cl_2	-78	36 h	10	10	7	

[a]Catalyst loading: 10 mol%. [b]Yields of products after purification. [c]20mol% of the catalyst was used. [d]Enantiomeric ratio determined on a Amidex B capillary column (length: 20 m, diameter: 0.25 mm, 0.35 bar H_2), initial temperature 40 °C, 1 min isothermal, heating rate 2.5 °C/min, end temperature 200 °C, Rt_1 = 25.46 min, Rt_2 = 26.19 min.

Conclusions

The formation of tetrahydro-1*H*-indenediones **10**, **18** by Lewis acid-catalyzed Diels-Alder reaction of 2-cyclopentenone **9a** or 2-methyl-2-cyclopentenone **9b** and Danishefsky's diene **2** was explored. The cycloaddition of 2-cyclopentenone **9a** suffers from rapid C=C bond isomerization from the C6/C7 enone **10** to the C7/C7a enone **12**, thus making any attempts towards an enantioselective route unsuccessful. In contrast, the reaction of 2-methyl-2-cyclopentenone **9b** gave exclusively one regioisomer **18**. However, the stereochemical control turned out to be very challenging, giving only 20%ee and 7%ee with the chiral Lewis acids **24** and **25** respectively, whereas all other chiral Lewis acids produced only racemic compound **18**.

The results suggest that the development of novel chiral Lewis acids presumably operating via cooperative catalysis[24] is highly desirable.

Experimental Section

General. ^{1}H-NMR and ^{13}C-NMR spectra were obtained at 300 MHz or 500 MHz and 75 MHz or 125 MHz respectively, using a Bruker Avance 300 or Avance 500 spectrometer with tetramethylsilane as the internal standard. Nuclear Overhauser effect (NOESY), homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY) and inverse gradient heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HSQC and HMBC) were obtained using the standard Bruker pulse sequence for structural assignment of NMR spectra. Chemical shift values (δ) were given in ppm. Mass spectra and HRMS data were recorded on a Finnigan MAT 95 instrument for chemical ionisation (CI) and on a Varian MAT 711 instrument for electron impact ionisation (EI). The melting points were determined on an SMP 20 melting point apparatus (Büchi). Infrared spectra were obtained on a Bruker Vector 22 FT-IR spectrometer. Enantiomeric ratios were detected on a GC HRGC Mega 8560 (Fisons) or a GC HRGC 5300 (Carlo Erba Strumentazione). The exact conditions are reported in connection with each analyzed substance. Preparative HPLC was performed on a Shimadzu system with the following modules: DGU-20A5 Prominence Degasser, LC-20AT Prominence Liquid Chromatograph, SIL-20A Prominence Auto Sampler and a Kromasil 100 Si 5μm column (Knauer). The progress of the reactions was routinely monitored by GC analysis (HP 6890, capillary column HP-5, 80 °C initial temperature, heating rate 16 °C/min and final temperature 300 °C) or thin layer chromatography (TLC) on Silica gel 60 F254 (Merck) and the products were visualized with an ultraviolet lamp (254 and 365 nm) or an alcoholic anisaldehyde solution. Flash column chromatography was carried out on silica gel 60 (Fluka). All solvents were dried by standard methods and distilled before use. 2-Cyclopentenone **9a** and 2-methyl-2-cyclopentenone **9b** were purchased from Sigma Aldrich and were distilled before use.

The following compounds were prepared following literature procedures:
trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **2** (Danishefsky's diene)[25]; oxazaborolidinones **20a-c**[26]; Seebach's titanium TADDOLate complex **23**[21]; chiral acyloxyborane complexes **24a-d**[22]; Nishida's BINAMIDE complex **25.**[23]

For details of the synthesis of catalysts **21a-d**, see supplementary information.

General procedure for the Lewis acid-catalyzed Diels-Alder reaction of 2-cyclopentenones (9a), (9b) with Danishefsky's diene (2)
2-Cyclopentenone **9a** (0.04 mL, 0.04 g, 0.48 mmol) was placed in a dry Schlenk flask and dissolved in 2 mL of CH_2Cl_2, 0.05 mmol of $BF_3{\cdot}Et_2O$ was added and the resulting mixture was stirred for 15 min. After cooling the reaction to the indicated temperature 0.12 mL (0.01 g, 0.58

mmol) *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**2)** was added. After 5 min the end of reaction was detected using GC analysis. It was hydrolyzed with 2 mL 1N HCl and stirred heavily for 15 min at room temperature. The layers were separated and the aqueous layer was extracted with 3 x 3 mL of dichloromethane. Combined organic layers were washed with 5 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$ and the solvents were removed under reduced pressure.

***Cis*-2,3,3a,4-Tetrahydro-1*H*-indene-1,5(7a*H*)-dione (10). 2,3,3a,4-Tetrahydro-1*H*-indene-1,5(6*H*)-dione (12).** After purification by flash chromatography (silica, eluant: 4:1 hexanes/*i*PrOH) a product mixture of the two double bond isomers **10** and **12** (43:57 ratio according to ^{1}H-NMR) was obtained, which could not be further separated. Yellow oil, yield 14.3 mg (20%), R_f = 0.3 (4:1 hexanes/*i*PrOH, UV).

Isomer (10). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 – 1.26 (m, 1H, 3-H_a), 1.38 – 1.45 (m, 1H, 3-H_b), 1.57 – 1.64 (m, 1H, 2-H_a), 1.69 – 1.77 (m, 1H, 2-H_b), 1.90 – 2.08 (m, 3H, 3a-H, 4-H), 2.29 – 2.33 (m, 1H, 7a-H), 5.84 (dd, *J* = 10.1 Hz, *J* = 2.6 Hz, 1H, 6-H), 6.24 (ddd, *J* = 10.1 Hz, *J* = 4.2 Hz, *J* = 0.7 Hz, 1H, 7-H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 24.6 (C-3), 32.9 (C-3a), 35.6 (C-2), 37.7 (C-4), 48.4 (C-7a), 128.9 (C-6), 141,4 (C-7), 194.4 (C-5), 211.5 (C-1) ppm.

Isomer (12). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.70 (dddd, *J* = 20.5 Hz, *J* = 13.2 Hz, *J* = 10.9 Hz, 8.1 Hz, 1H, 3-H_a), 1.47 (dd, *J* = 14.4 Hz, *J* = 12.0 Hz, 1H, 4-H_a), 1.44 – 1.52 (m, 1H, 3-H_b), 1.69 – 1.77 (m, 2H, 2-H_a, 6-H_a), 1.90 – 2.08 (m, 1H, 2-H_b), 2.09 – 2.19 (m, 1H, 3a-H), 2.30 (dd *J* = 14.4 Hz, *J* = 5.4 Hz, 1H, 4-H_b), 2.39 (t, *J* = 3.7 Hz, 2H, 6-H_b), 6.33 (tdd, *J* = 3.7 Hz, *J* = 3.2 Hz, *J* = 0.7 Hz, 1H, 7-H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 26.6 (C-3), 35.9 (C-3a), 37.3 (C-2), 37.5 (C-6), 43.8 (C-4), 126.0 (C-7), 139.3 (C-7a), 200.8 (C-1), 204.3 (C-5) ppm. HRMS (EI): calcd. for $C_9H_{10}O_2$ 150.0681, found 150.0669 $[M]^+$. MS (EI, 70 eV) *m/z* (%): 151.1 $[M + H]^+$ (8), 150.1 $[M^+]$ (100), 122.1 (10), 109.1 (4), 108.1 (46), 107.1 $[M^+ – CH_3\text{-}C{=}O]$ (9), 95.1 (44), 94.1 (14), 80.1 (28), 79.0 (48), 66.1 (24), 55.0 (8), 39.0 (16). FT-IR (ATR): ν = 3426 (w), 2959 (m), 2367 (w), 2198 (w), 1975 (w), 1737 (s), 1714 (vs), 1676 (s), 1655 (vs), 1618 (m), 1456 (w), 1407 (m), 1386 (m), 1299 (w), 1245 (m), 1214 (s), 1182 (s), 1157 (s), 1108 (m), 1043 (m), 983 (m), 960 (m), 923 (w), 875 (m), 854 (m), 830 (m), 775 (m), 744 (m), 701 (w), 670 (w), 644 (w), 582 (w), 555 (w).

***Cis*-2,3,3a,4-Tetrahydro-7a-methyl-1*H*-indene-1,5(7a*H*)-dione (18).** Brown oil, 78.7 mg (100%). ^{1}H-NMR (500 MHz, C_6D_6): δ = 0.85 (s, 3H, CH_3), 1.00 – 1.15 (m), 1.48 – 1.69 (m), 1.75 -1.92 (m), and 2.00 – 2.20 (m) (7H, 2-H_2, 3-H_2, 3a-H, 4-H_2), 5.74 (dd, *J* = 10.1 Hz, *J* = 0.7 Hz, 1H, 6-H), 6.46 (ddd, *J* = 10.1 Hz, *J* = 1.8 Hz, *J* = 0.7, 1H, 7-H) ppm. ^{13}C-NMR (75 MHz, C_6D_6): δ = 21.4 (CH_3), 24.8 (C-3), 36.7 (C-3a), 37.8 (C-2), 41.5 (C-4), 51.1 (C-7a), 129.4 (C-6), 147.6 (C-7), 195.6 (C-5), 216.0 (C-1) ppm. HRMS (EI): calcd. for $C_{10}H_{12}O_2$ 164.0837, found 164.0840 $[M]^+$. MS (EI, 70 eV) *m/z* (%): 164.1 $[M]^+$ (28), 109.1 $[M^+ – COC_2H_5]$ (100), 80.1 (32), 79.1 (56).

***Cis*-Hexahydro-1*H*-inden-1,5(6*H*)-dione (13).** Compounds **10** and **12** (60.0 mg, 0.40 mmol) were placed in a dry Schlenk flask and dissolved in 4 mL of methanol. Triethylsilane (0.64 mL, 93.0 mg, 0.80 mmol) was added, followed by addition of 7.00 mg of $PdCl_2$ (4.00 μmol). The

mixture was stirred for 8 h at room temperature, then heated to 80 °C and stirred for 3h under reflux. The residue was filtered off and the remaining organic layer was diluted with 5 mL of CH_2Cl_2. It was washed with 5 mL of each, H_2O and brine. The solvents were evaporated under reduced pressure. Red liquid, 20 mg (33%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.71 – 1.81 (m, 1H, 3a-H), 1.94 – 2.54 (m, 10H, 2-H, 3-H, 7-H, 6-H, 4-H), 2.54 – 2.82 (m, 1H, 7a-H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.7, 26.4, 35.0, 37.4, 38.0, 42.9, 47.6 (C-2, C-3, C-3a, C-7a, C-7, C-6, C-4), 211.0 (C-5), 218.1 (C-1) ppm. Spectroscopic data were consistent with previously reported data for this compound.[12]

Ketalization of the double bond isomers (10, 12)

Compounds **10** and **12** (80.0 mg, 0.53 mmol), dissolved in 6 mL of benzene, were treated with 0.30 mL (0.33 g, 5.33 mmol) of ethylene glycol and 44.0 mg (0.18 mmol) of pyridinium *p*-toluenesulfonate. The solution was refluxed for 3 h. Another 0.30 mL (0.33 g, 5.33 mmol) ethylene glycol and 44.0 mg (0.18 mmol) PPTS were added and the resulting solution was refluxed for further 60 min. The solvents were concentrated in vacuo. The residue was dissolved in 20 mL of diethyl ether and washed with 10 mL of each, saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. After purification by flash chromatography (2:1 hexanes/ethyl acetate) an inseparable mixture of monoketal **14** and diketal **15** (50:50 according to GC analysis) was obtained (75%).

***cis*-2',3',3a',4'-Tetrahydrospiro[1,3-dioxolane-2,1'(1'*H*)-indene]-5'(7a'*H*)-one (14).** R_f = 0.3 (2:1 hexanes/ethyl acetate, UV). ^{1}H-NMR (300 MHz, C_6D_6): δ = 0.81 – 1.59 (m, 4H, 3-H, 3a-H, 7a′-H), 1.89 – 2.11 (m, 4H, 2-H, 4′-H), 2.94 – 3.25 (m, 6H, 1-H, 2-H, 7a-H, 5′-H), 5.76 (dd, *J* = 10.3 Hz, *J* = 2.3 Hz, 1 H, 6′-H), 6.18 (ddd, *J* = 10.3 Hz, *J* = 3.4 Hz, *J* = 0.9 Hz, 1H, 7′-H) ppm. ^{13}C-NMR(75 MHz, $CDCl_3$): δ = 24.8, 28.7, 33.9, 39.1, 45.5 (C-2, C-3, C-3a, C-4, C-7a), 62.7, 63.6 (C-1, C-2), 116.8 (C-1), 129.5 (C-6), 143.8 (C-7), 195.9 (C-5). HRMS (ESI): calcd. for $C_{11}H_{14}O_3$ 195.1021, found 195.1016 $[M + H]^+$. MS (ESI) *m/z*: 217.1 $[M + Na]^+$, 295.1 $[M + H]^+$, 151.1, 133.1, 102.1. FT-IR (ATR): ν = 2929 (m), 2882 (m), 1720 (s), 1695 (s), 1605 (s), 1548 (s), 1430 (w), 1406 (m), 1320 (w), 1297 (w), 1244 (s), 1200 (w), 1103 (m), 1033 (m), 1021 (m), 950 (w), 833 (w), 802 (w), 759 (w), 688 (w), 645 (w), 577 (w), 497 (w).

***cis*-2',3',3a',4'-Tetrahydrospiro[1,3-dioxolane-2,1'(1'*H*)-indene-5'(7a'*H*),2''-1,3-dioxolane] (15).** R_f = 0.5 (2:1 hexanes/ethyl acetate, UV). ^{1}H-NMR (300 MHz, C_6D_6): δ = 1.11 – 1.65 (m, 6H, 2′-H, 3′-H, 3′a-H, 4′-H_a), 1.81 (dd, *J* = 13.07 Hz, *J* = 9.9 Hz 1H, 4′-H_b), 2.48 – 2.58 (m, 1H, 7a′-H), 3.28 – 3.51 (m, 8H, H-1, H-2, H-1′, H-2′), 5.61 (ddd, *J* = 10.2 Hz, *J* = 1.6 Hz, *J* = 0.7 Hz, 1H, 7-H), 5.67 (dd, *J* = 10.2 Hz, *J* = 3.1 Hz, 1H, 6-H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.2, 32.2, 34.0, 35.7, 45.1 (C-2, C-3, C-3a, C-4, C-7a), 62.7, 63.0, 63.2, 63.6 (C-1, C-2, C-1′, C-2′), 104.5 (C-5), 116.4 (C-1), 129.0 (C-6), 133.3 (C-7). HRMS (ESI): calcd. for $C_{13}H_{18}O_4Na^+$ 261.1103, found 261.1095. MS (ESI) *m/z*: 261.1 $[M + Na]^+$, 239.1 $[M + H]^+$, 219.1, 177.1, 133.1, 127.1. FT-IR (ATR): ν = 2927 (m), 2878 (m), 1697 (s), 1598 (s), 1536 (s), 1487 (w), 1452 (m), 1406 (m), 1334 (w), 1303 (w), 1228 (s), 1196 (w), 1124 (m), 1087 (m), 1055 (m), 1027 (m), 950 (w), 835 (w), 803 (w), 749 (w), 699 (w), 646 (w), 572 (w), 505 (w).

Synthesis of the hydrazones (16, 17)

2,4-Dinitrophenylhydrazine (0.52 g, 2.62 mmol) was dissolved in 2.50 mL concentrated H_2SO_4 and 3.75 mL of water were slowly added to this solution followed by addition of 12.5 mL ethanol. A solution of the two double bond isomers **10**, **12 (**78.0 mg, 0.52 mmol) in 5 mL of ethanol was then added. Immediately the precipitation of a red solid could be observed which was filtered off, washed with water and dried over P_2O_5 in vacuo. Using preparative HPLC (Kromasil; UV-detection; λ_{max} = 356 nm; flow rate 10 mL/min; hexane/isopropyl alcohol 98:2) 2 mg of the bishydrazone **17** and 2 mg of the monohydrazone **16** could be obtained as red solids.

2,3,3a,4 -Tetrahydro-1*H*-indene-1,5(7a*H*)-dione 5-[2-(2,4-dinitrophenyl)hydrazone] (16). Concerning the configuration of the C=N bond see ref. 13. R_f = 0.7 (1:1 hexanes/ethyl acetate, UV). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.78 – 1.90 (m), 2.34 – 2.48 (m), 2.56 – 2.86 (m) 2.87 – 3.21 (8H, 2-H, 3-H, 3a-H, 7a-H, 4-H), 6.12 (ddd, *J* = 10.0 Hz, *J* = 3.9 Hz, *J* = 0.7 Hz, 1H, 7-H), 6.46 (dd, *J* = 10.0 Hz, *J* = 2.7 Hz, 1H, 6-H), 8.01 (d, *J* = 9.5 Hz, 1H, 2′-H), 8.29 – 8.37 (m, 1H, 3′-H), 9.09 – 9.17 (m, 1H, 5′-H), 11.31 (br, 1H, NH) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.6 (C-3), 26.8 (C-3a), 33.1 (C-2), 37.4 (C-4), 50.0 (C-7a), 112.4, 116.3, 116.7, 128.4, 131.1, 144.6 (Ar), 123.4 (C-6), 130.1 (C-7), 150.3 (C-5), 215.4 (C-1) ppm. HRMS (ESI): calcd. for $C_{15}H_{14}N_4O_5Na^+$ 353.0862, found 353.0864. MS (ESI) *m/z*: 353.1 $[M + Na]^+$, 331.1 $[M + H]^+$, 304.3, 276.2. FT-IR (ATR): ν = 3311 (w), 3102 (w), 2961 (w), 2306 (w), 1736 (m), 1610 (s), 1588 (s), 1501 (s), 1422 (m), 1327 (s), 1309 (s), 1223 (m), 1134 (m), 1088 (s), 922 (w), 833 (m), 798 (m).

2,3,3a,4 -Tetrahydro-1*H*-indene-1,5(7a*H*)-dione 1,5-bis[2-(2,4-dinitrophenyl)hydrazone] (17). Concerning the configuration of the C=N bond see ref. 13. R_f = 0.9 (1:1 hexanes/ethyl acetate, UV). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.75 – 0.99 (m), 1.16 – 1.40 (m), 1.83 – 2.95 (m) (8H, 2-H, 3-H, 3a-H, 7a-H, 4-H), 6.23 (ddd, *J* = 10.1 Hz, *J* = 3.6 Hz, *J* = 0.6 Hz, 1H, 7-H), 6.46 (dd, *J* = 10.1 Hz, *J* = 2.5 Hz, 1H, 6-H), 7.96 – 8.03 (m, 2H, 2′-H, 2′-H), 8.35 (m, 2H, 3′-H, 3′-H), 9.15 (m, 2H, 5′-H, 5′-H), 10.87, 11.32 (s, 2H, NH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 25.2 (C-3), 26.9 (C-3a), 29.6 (C-2), 34.8 (C-4), 44.8 (C-7a), 112.4, 116.3, 116.7, 127.7, 130.12, 134.3 (Ar), 123.50 (C-6), 130.17 (C-7), 165.4 (C-5), 173.0 (C-1) ppm. HRMS (APCI): calcd. for $C_{21}H_{18}N_8O_8$ 511.1326, found 511.1315 $[M + H]^+$. MS (APC) *m/z*: 511.1 $[M + H]^+$, 491.1, 477.1, 413.1, 342.1, 328.1, 294.1, 279.1. FT-IR (ATR): ν = 3310 (w), 3102 (w), 2925 (w), 2358 (w), 2050 (w), 1981 (w), 1614 (s), 1589 (s), 1502 (s), 1420 (m), 1332 (s), 1310 (s), 1220 (m), 1080 (m), 973 (w), 921 (m), 832 (m), 762 (w), 742 (m), 717 (w), 686 (w), 639 (w), 568 (w).

General procedure for the preparation and use of chiral Diels-Alder catalysts (20a-c) and (21a-d)

A two necked, round bottom flask, equipped with a pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 4A molecular sieves) was charged with (*S*)-α,α-diphenyl-2-pyrrolidinemethanol **21a** (0.94 g, 3.71 mmol), tri-*o*-tolylboroxine (0.36 g, 1,01 mmol) and 35 mL of toluene. The resulting solution was heated to reflux. After 3 h toluene was directly distilled off using a Claisen bridge. This distillation protocol was repeated three times by

recharging with 3 x 30 mL of toluene. The following concentration in vacuo (0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil which was then dissolved in CH_2Cl_2 and used in Diels-Alder experiments.

To an aliquot of the oxazaborolidine precursor (0.07 mmol, theoretical) in 5 mL of CH_2Cl_2 at -78 °C was added triflic acid (0.2 M solution in CH_2Cl_2, freshly prepared, 300 μL, 0.06 mmol) dropwise. During the addition, the catalyst solution turned orange in color, but cleared up instantaneously. Near the end, a small amount of orange precipitate was observed. After 10 to 15 min at -78 °C, the orange precipitate disappeared and a yellow homogeneous solution was obtained. In the following 0.07 mL (0.07 g, 0.70 mmol) of 2-methyl-2-cyclopentenone **9b** was added and the reaction was stirred for further 15 min. Danishefsky's diene **2** (0.16 mL, 0.14 g, 0.84 mmol) was added and at the end of reaction, detected using GC analysis, it was hydrolyzed with 2 mL 1N HCl and stirred heavily for 15 min at room temperature. The layers were separated and the aqueous layer was extracted with 3 x 3 mL of CH_2Cl_2. Combined organic layers were washed with 5 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$ and the solvents were removed under reduced pressure.

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