Face-selective Diels–Alder reactions of (1*R*,5*R*)-3-formyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one

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The stereofacially differentiated enone aldehyde **11** was chosen to study the effects of steric and electronic influence on the Diels–Alder reaction. Under Lewis acid catalysis, **11** adds to dienes at low temperatures at a reasonable rate. Yields of desired chiral adducts are good to high with zinc chloride and boron trifluoride etherate catalysis. In all cases only products of addition to the *Re* face of general type **27** were observed. The regiochemistry of the adducts is exclusively that predicted by the *ortho* and *para* rules. The stereochemistry shows a very high selectivity in favour of aldehyde-*endo* transition state products. Unusual by-products were also obtained in some examples and mechanisms of these unexpected reactions are discussed.

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On a choisi le cétoaldéhyde insaturé **11**, différencié stéréofacialement, pour étudier les effets stériques de l'influence électronique sur la réaction de Diels–Alder. En présence d'un catalyseur de Lewis et à basse température, le composé **11** s'additionne sur les dièenes avec un rendement raisonnable. Les rendements en adduits chiraux désirés varient de bon à élevé avec le chlorure de zinc et l'éthérate trifluorure de bore comme catalyseurs. Dans tous les cas, on n'observe que les produits d'addition sur la face *Re* du type général **27**. La régiochimie des adduits est exclusivement celle prédite par les règles *ortho* et *para*. La stéréochimie montre une très grande sélectivité en faveur d'un aldéhyde-*endo* dans l'état de transition. On a également obtenu des produits secondaires inhabituels dans certains cas et on discute des mécanismes de ces réactions inattendues.

[Traduit par la rédaction]

Introduction

In recent years we have reported on a series of Diels–Alder reactions of 4,4-dimethyl-2-cyclohexenones **1** (1), **2** (1, 2), **3** (1, 3, 4), **4** (5) and several closely related cross-conjugated cyclic unsaturated carbonyl compounds **5** (6), **6** (7), **7** (8, 9), **8** (10, 11), **9** (12), and **10** (12). These studies showed that structural features in the dienophile and the nature of the Lewis acid strongly influence the regio- and stereoselectivity of the reaction. The use of various directing components such as cross-conjugated carbalkoxy groups or additional double bonds has provided a probe into the effect of structural, steric, and electronic features on the course of Diels–Alder additions by the study of their influence on the relative stabilities of the various possible orientational transition states. We also explored diastereofacial selectivity of some of these dienophiles (**8–10**). Additions to **8** and **9** ($n = 1, 2$) take place preferentially from the less hindered face while additions to **9** ($n = 0$) and **10** are from the more hindered face.

One of the most interesting features apparent in comparing this assemblage of dienophiles is the effect of the carbonyl directing substituents on the *exo* or *endo* orientation of addition. Dienophiles **4–8** exhibit preferential additions with diene orientation *endo* to the exocyclic ester directing substituent. Compounds **3** and **10** are preferentially keto-*endo* directed while the few examples we have reported to date for **9** ($n = 0$) exhibit reversal of selectivity depending on the diene used. Although the unusual behavior of **9** ($n = 0$) remains to be thoroughly explored and reported, the contrasting *exo–endo* orientation differences between the other groups of dienophiles raise important questions. What is the relative directing influence of the possible exocyclic substituents (alkyl, ketone, ester, aldehyde, halogen, nitrile, heteroatom, etc.)? Is the contribution of additional conjugation to the endocyclic carbonyl (such as the second cyclic double bond of **3** and **10**) the principal directing influence, overriding any contribution from the exocyclic directing substituent (in the same qualitative way that *ortho*-rule addition tyically supersedes *para*-rule addition of appropriately substituted dienes)? From a theoretical perspective, could secondary orbital effects really be the sole mechanism through which these orientational effects are manifested? From a practical viewpoint, can semi-empirical or theoretically based rules be identified to predict products in various novel systems in such a way as to allow strategic placement of directing influences into synthetic plans?

As a lead-in to the wider examination of Diels–Alder reactivity that these questions demand, and to improve on the stereoselectivity and yields of additions to **8**, we have turned our attention to enone aldehyde **11**. The formyl group is more strongly electron withdrawing and sterically smaller than the corresponding ester group in **8**. On these accounts alone the aldehyde-*endo* transition state **11***a* should be more strongly favoured over the keto-*endo* transition state **11***b* than the preference (11) for the corresponding ester-*endo* transition state of **8***a* over its keto-*endo* transition state **8***b*. The study also offers an interesting opportunity for comparison of the secondary oribital effect between the ester and aldehyde substituents. The elaboration[3] or removal[4] of the formyl group from the adducts can be addressed with a wider variety of methods than the carbalkoxy group so that **11** might prove to be even more synthetically useful than **8**.[5] The results of our investigations of Diels–Alder reactions of **11** are presented.

Results and discussion

*1. Preparation of enone aldehyde **11***

Enone aldehyde **11** was synthesized in high yield from (−)-

[1]Taken in part from the M.Sc. thesis of Y. Li, the University of Alberta, 1993.

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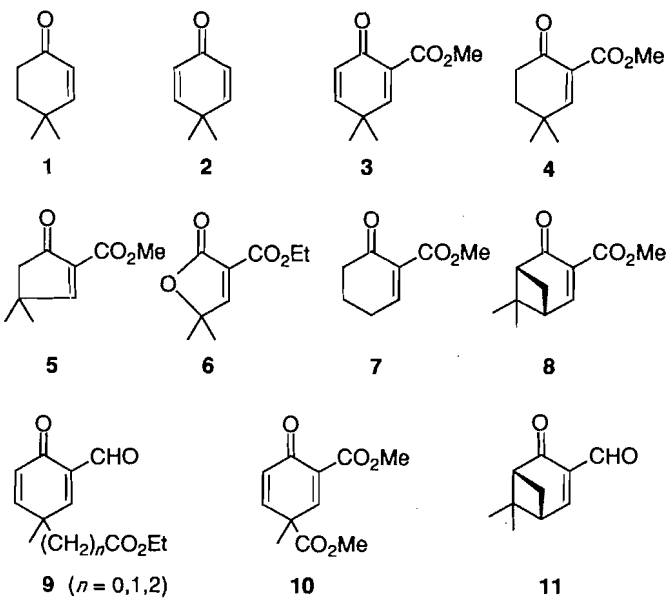
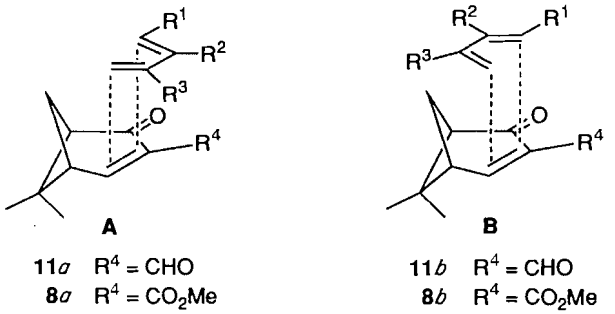
[3]For selected examples see refs. 13–17.

[4]For selected example see refs. 18–21.

[5]The full synthetic application of **8** and **11** to natural product targets will be reported in separate publications.





11*a* R^4 = CHO
8*a* R^4 = CO_2Me

11*b* R^4 = CHO
8*b* R^4 = CO_2Me

β-pinene **12**[6] in three steps (Scheme 1). We have already described the ozonolysis of β-pinene and its hazards[7] in reporting on the preparation of enone ester **8**. In the present study a modified procedure for ozonolysis of (−)-β-pinene in dichloromethane–methanol at higher concentration followed by reductive work-up with dimethyl sulfide gave (+)-nopinone (**13**) in an improved yield of 93%. Its spectral data were identical to those previously reported (11). We repeated the preparation several times and once, instead of chromatography, carried out purification by vacuum distillation without incident. The problems reported by others (22, 23) might be due to incomplete reduction of the ozonolysis products or improper handling of the work-up procedure. The following are some important precautions to consider in conducting this reaction: (*i*) A persistent blue or purple colour of the reaction solution can not serve as an indication of completion of the ozonolysis. We found that even when the purple colour remained, there was still considerable starting material remaining in the reaction mixture. Typically, only about 78% yield of product was formed (11). On the other hand, when tlc analysis showed the complete consumption of starting material, ketone **13** was obtained in 93% isolated yield. (*ii*) After the ozonolysis is complete, oxygen gas must be blown through the reaction mixture (5–10 min) to remove the excess of ozone. (*iii*) The reducing agent (dimethyl sulfide) must be added at low temperature (−78°C) and then the reaction mixture should be allowed to warm slowly over 2–4 h to room temperature. (*iv*) The amount of the reducing agent should be in excess and the reduction time should be suficiently long (overnight) to ensure the completion of the reaction.

The formyl group was introduced by the method of Watt and co-workers (24), treating **13** with sodium hydride and ethyl formate. The reaction was catalyzed by a few drops of ethanol and proceeded smoothly to give keto aldehyde **14** in 93% yield. Spectral data indicated that compound **14** was a mixture (7:2.5:1) of its tautomer and epimers. The ratio of the three components varied with the purity of the compound or with different solvents or temperatures. Dehydrogenation of **14** was carried out in two steps using the approach of Liotta et al. (25): phenylselenenylation followed by oxidative elimination of the resulting selenide to give enone aldehyde **11** in about 70% yield.

The desired product was always accompanied by epoxide **15**, presumably as a result of overoxidation. The epoxidation was very sensitive to the pH of the reaction media. When the oxidation was carried out under neutral conditions, the amount of epoxide increased rapidly and even became the major product (**11**:**15** = 1:1.2). When the selenide solution was oxidized immediately after washing with 1 N hydrochloric acid, only a small amount of epoxide was formed (**11**:**15** = 8:1). Compounds **11** and **15** were not separable by either column chromatography or bulb-to-bulb distillation. Pure epoxide **15** was recovered after the subsequent Diels–Alder reaction in which enone aldehyde **11** was totally consumed.

The mechanism for the generation of epoxide **15** remains unclear. The accepted mechanism for epoxidation of an α,β-unsaturated ketone or aldehyde by hydrogen peroxide, by 1,4-addition of hydroperoxide followed by ring closure with elimination of hydroxide (26–28), does not fit very well in this case. An alkaline medium would be required to deprotonate hydrogen peroxide and generate the hydroperoxide. In this case, there was no base present. If any hydroperoxide was present, it must have come from equilibrium dissociation of hydrogen peroxide (29). Such a process would not be sufficient to induce epoxidation of a normal α,β-unsaturated ketone or aldehyde. But in compound **11** the double bond is doubly activated and thus more highly reactive to Michael addition. Under neutral conditions, once the epoxidation is initiated by a trace of hydroperoxide, the epoxidation could be catalyzed by the hydroxide generated in the ring closure reaction. This process could lead to epoxide **15** as the major product. When the reaction is carried out under acidic conditions the hydroxide would be neutralized, the epoxidation process inhibited, and epoxide **15** would be obtained as only a minor by-product.

Recently, Reich suggested an alternative mechanism for the oxidation step.[8] In his opinion the rate of oxidation of the selenide to selenoxide is relatively slow. The observed rapid oxidation rate usually observed is attributed to perseleninic acid ($RSeO_3H$), which is generated during the reaction (30). It is perseleninic acid that acts as the true oxidant which enables the reaction to proceed at the fast rate observed. This is reasonable since perseleninic acid is a very strong oxidant. It should be possible to accelerate the oxidation by adding seleninic acid to the reaction mixture as a catalyst, thus reducing the amount of epoxidation so that a higher yield of the desired product may be achieved. To confirm this proposal several reactions were carried out using benzeneseleninic acid as a reagent. The results

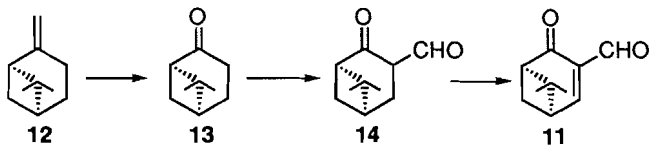
[6]Commercial (−)-β-pinene was obtained from Aldrich Chemical Co. and had an optical purity of 92%.

[7]See footnote 11 in ref. 11.

[8]H.J. Reich. Personal communication.

TABLE 1. Oxidation of the selenide in the presence of benzeneseleninic acid

	With $PhSeO_2H$ added				Control		
Entry	$PhSeO_2H$ (equiv.)	Time (min)	Yield (%)	Ratio (**26**:**30**)	Time (min)	Yield (%)	Ratio (**26**:**30**)
1	0.1	60	65	8:1	120	66	7:1
2	0.5	35	67	5:1	100	61	7:1



SCHEME 1

are listed in Table 1. We did observe a significant increase in the reaction rate but no obvious improvement in yield or product ratio. It is conceivable that the seleninic acid catalyzed both oxidation and epoxidation and thus the rates of both reactions increased to about the same extent. In fact, when 0.5 equivalents of seleninic acid was used, the ratio of the two products dropped to 5:1. Of many runs using this preparation, the best **11**:**15** ratio obtained was 12:1 after purification by bulb-to-bulb distillation.

Another side reaction also occurred during the oxidation. A small amount (3–8%) of **14** was always recovered. The intermediate selenide and selenoxide are both sterically congested at the C-3 position and may be relatively labile. Attack by a nucleophile such as hydrogen peroxide at the selenium atom could result in displacement of the selenium center, leaving a carbanion **16** and leading to formation of **14** after protonation. Several other methods were examined to improve on the production of enone aldehyde **11**, including 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (31), sodium periodate (30), magnesium mono-perphthalate (MMPP),[9] hydrogen peroxide (30), and ozone (30) oxidation of **14** as well as non-oxidative elimination of the selenide (32). These alternative procedures gave no useful yield of product.

*2. Diels–Alder reactions of enone aldehyde **11***

A variety of Lewis acids and conditions were explored for the Diels–Alder reaction of enone aldehyde **11** with isoprene. The results of these investigations are summarized in Table 2. The particular Lewis acids chosen were previously noted as particularly suitable catalysts for related cross-conjugated enone dienophiles (6, 33). The Diels–Alder reaction of **11** was very sensitive to the choice of Lewis acid catalyst. The milder Lewis acid catalysts gave better yields. Good yields of product **17** were obtained with zinc chloride and boron trifluoride etherate. When ferric chloride and stannic chloride were used, the yields dropped drastically. This result may be due to greater stability of the strained ring system of the reactant and the product under the relatively mild acidic conditions of boron trifluoride etherate and zinc chloride catalysis and degradation by the stronger Lewis acids. In further investigations of the scope of the Diels–Alder reaction of **11**, only boron trifluoride etherate and zinc chloride were used as catalysts. Adducts were obtained in good to high yields and the results are summarized in Table 3.

[9]The experiment was made using MMPP in the manner used in ref. 30 for *m*-chloroperbenzoic acid.

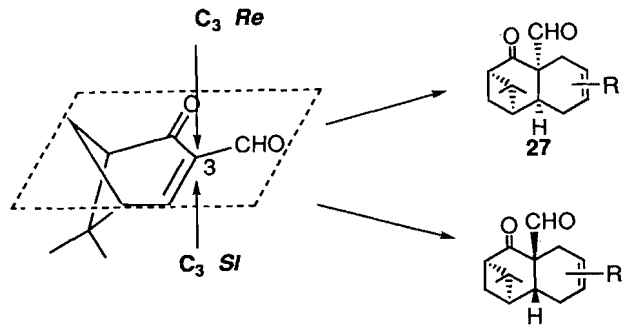
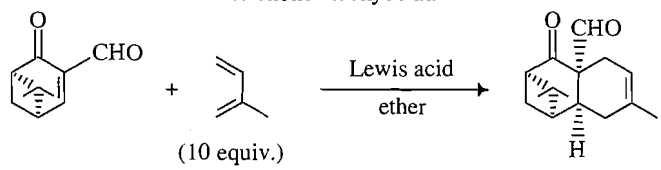


TABLE 2. Lewis acid catalyzed Diels–Alder addition of isoprene to enone aldehyde **11**



11 **17**

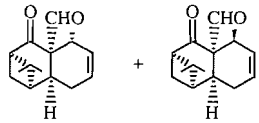
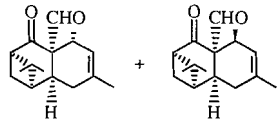
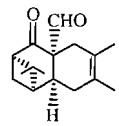
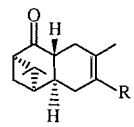
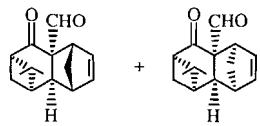
Lewis acid (equiv.)	Temp. (°C)	Time (h)	Yield (%)
$ZnCl_2$ (2.0)	–20	18	74
$ZnCl_2$ (1.0)	–20	18	71
$ZnCl_2$ (1.0)	–20 + 25	15 + 2	72
$SnCl_4$ (1.0)	–20	6	0
$FeCl_3$ (1.0)	–20	1	19
$BF_3{\cdot}OEt_2$ (1.0)	–20	2	84

In principle, Diels–Alder addition to enone aldehyde **11** could occur from either the sterically more hindered *Si* face or the less hindered *Re* face to give stereochemically distinct products (Scheme 2). In all cases, only the products of the addition to the *Re* face (general structure **27**) were obtained. The *gem*-dimethyl group in **11** presumably served to direct the Diels–Alder addition to the less hindered *Re* face, as indicated by the stereochemistry of the ring junction of the adducts. The structures of the adducts were established using spectroscopic methods including ^1H nmr, ^1H decoupling, and nOe experiments. The results of the nOe experiments are summarized in Table 4.

A. Addition to isoprene

The reaction of enone aldehyde **11** with isoprene under zinc chloride catalysis in ether at –20°C gave the adduct in 74% yield after 18 h. When boron trifluoride etherate was used as a

TABLE 3. Diels–Alder additions of dienes to enone aldehyde **11**

Entry	Diene (equiv.)	Lewis acid (1 equiv.)	Temp (°C)	Time (h)	Product(s)	(Ratio)	Yield (%)
1	 (10)	$ZnCl_2$	−20	16	 **18** + **19**	(170:1)	60
2		$BF_3{\cdot}OEt_2$	−20	1		(64:1)	71
3	 (10)	$BF_3{\cdot}OEt_2$	−40	3	 **20** + **21**	(133:1)	82
4	 (10)	$BF_3{\cdot}OEt_2$	−20	1.5	 **22**		92
5	 (10)	$ZnCl_2$	−20	4			70
6	R (5)	$ZnCl_2$	−40 → −15	3.5 1.5			68
	R = OTBDMS **23**				R = OTBDMS **24**		
7	 (10)	$BF_3{\cdot}OEt_2$	−20	1.5	 **25** + **26**	(20:1)	0
8		$BF_3{\cdot}OEt_2$	−40	0.5			0
9		$ZnCl_2$	−20	4			52

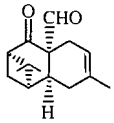
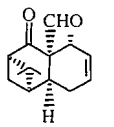
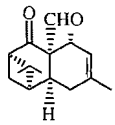
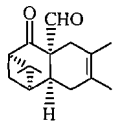
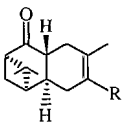
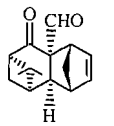
catalyst the reaction was finished in 2 h to give 84% yield of the adduct. Structure **17** could be assigned to the adduct if the Diels–Alder addition followed the normal *para* rule. However, orientational reversal, in violation of the *para* rule, in the Diels–Alder reaction of a 2-substituted diene has been observed (1, 2, 4). To rule out the possibility that the addition of isoprene to **11** could produce the regioisomer **28**, extensive ^1H decoupling experiments were carried out and all the protons of the adduct were assigned. A doublet of doublets assigned to H4e was observed to couple to H5 with a coupling constant of 7.0 Hz, as expected for the $CH_3C{=}CH_xCH_yH$ system (J_{xy} = 4–10 Hz). The regioisomeric adduct **28** would be expected to show a smaller coupling constant for the $CH_x{=}C(CH_3)CH_yH$ system (J_{xy} = 0–3 Hz) (34). On the basis of this ^1H nmr spectral data, structure **17** rather than **28** was assigned to the Diels–Alder adduct.

The stereochemistry of the ring junction was determined by nOe experiments. Irradiation of the ring junction proton (H8) signal at δ 2.94 resulted in enhancements of the formyl proton and the *endo*-methyl protons at δ 0.73. This implied that the formyl group and the *gem* dimethyl were on the same face as the ring junction proton. Thus the addition of isoprene obeyed the *cis* principle and occurred on the less hindered *Re* face of **11** to give adduct **17**. When the methyl at δ 1.32 was irradiated, nOe enhancements of H1, H11*exo*, H9 and the *endo*-methyl at δ 0.73 were observed. From this experiment, the *gem*-dimethyl and the *exo* and *endo* protons of the methylene bridge were assigned. The appearance of the *exo* methyl signal further down field than the *endo* methyl signal is probably due to shielding of the *endo* methyl by the ketone carbonyl. The signal at δ 2.52 (H11*exo*, dddd) was coupled to H1 (J = 5.5 Hz), H9 (J = 8.5 Hz), H11*endo* (J = 11.0 Hz) and H8 (W-coupling, J = 2.0 Hz). On the other hand the signal at δ 1.89 (H11*endo*), which was strongly shielded relative to H11*exo*, appeared as a readily recognizable doublet (J = 11.0 Hz) as the dihedral angles of H11*endo* to H1 and H9 were each about 90°.

B. Addition to trans*-piperylene*

When enone aldehyde **11** was reacted with *trans*-piperylene at −20°C under zinc chloride catalysis two adducts in a ratio of 170:1 were obtained in 60% yield. With boron trifluoride etherate catalysis two adducts in a ratio of 64:1 were formed in 71% yield. The adducts showed only one spot on the tlc plate and could not be separated by flash chromatography. The adducts displayed two sets of signals in the ^{13}C nmr APT spectrum and in the ^1H nmr spectrum. Since the product obtained was a mixture of two inseparable diastereomers the specific rotation was not measured. If the Diels–Alder reaction followed the normal *ortho* rule, then the structures of the adducts could tentatively be assigned as **18** and **19**. To conclusively determine the regiochemistry of the adducts, extensive ^1H decoupling experiments were carried out on the major isomer and a complete spectral assignment was made. The ring junction proton (H8), which appeared as a dddd at δ 2.80, was coupled to H7ax (J =

TABLE 4. The nOe data for Diels–Alder adducts

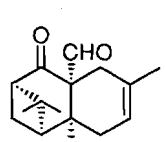
Compound	Irradiation	δ (ppm)	% Enhancement (H)
 **17**	H8	2.94	3.7 (CHO), 2.7 (*endo* CH_3)
	exo CH_3	1.32	4.7 (*endo* CH_3), 14.5 (H1), 17.7 (H11*exo*), 18.4 (H9)
	C6-CH_3	1.74	9.2 (H5), 16.0 (H7)
 **18**	H8	2.80	4.8 (H7), 3.9 (H9), 5.8 (*endo* CH_3),
	endo CH_3	0.71	4.8 (*exo* CH_3), 7.0 (H8)
	C4-CH_3	1.40	9.7 (CHO), 9.8 (H5), 9.3 (H4)
 **20**	H8	2.82	5.8 (*endo* CH_3)
	C4-CH_3	1.40	5.3 (H5), 6.4 (CHO), 5.9 (H4)
 **22**	*endo* CH_3	0.71	3.7 (CHO), 5.3 (H8) 4.9 (*exo* CH_3)
 R = OTBDMS **24**	*exo* CH_3	0.89	16.5 (H1), 10.2 (H9) 13.0 (H11*exo*)
	C5-CH_3	1.43	5.6 (H4), 2.8 (Si-CH_3)
 **25**	*endo* CH_3	0.82	2.3 (CHO), 8.2 (*exo* CH_3), 6.8 (H8)

10.5 Hz), H7e (J = 7.5 Hz), H9 (J = 2.0 Hz), and H11*exo* (W-coupling, J = 2.0 Hz). This coupling pattern indicated that two hydrogen atoms were attached to C7. Thus the methyl substituent could only be located at C4 and the major isomer was assigned the regiochemistry of structure **18**.

The stereochemistry of **18** was determined by nOe experiments. Irradiation of the *endo* methyl (δ 0.71) resulted in nOe enhancement of H8. According to the *cis* principle the formyl group should be on the same face as H8. This indicated that the addition of *trans* piperylene occurred from the *Re* face. Saturation of the methyl doublet (δ 1.40) produced enhancement of the formyl proton, indicating that the C4 methyl is on the same face as the aldehyde group. These experiments conclusively established the stereochemistry of the major adduct as that shown by **18**.

The presence of a trace amount of a minor isomer could only be detected by high-resolution nmr. Some ^{1}H nmr signals of the minor isomer were separated from those of the major isomer. The rest were buried under the signals of the major isomer. Therefore nOe and decoupling experiments were not performed on the minor adduct since it was impossible to complete all the spectral assignments. Compared to previous results obtained from our group (11), the two adducts should be epimers, so the minor isomer was tentatively assigned structure **19**.

In addition to adducts **18** and **19**, an unexpected product was formed during the Diels–Alder reaction between enone aldehyde **11** and *trans*-piperylene, with either boron trifluoride etherate or zinc chloride catalysis, in 14 and 15% isolated yield, respectively. This compound showed an intense spot under the uv lamp (short wavelength) on a tlc plate and greater polarity than the Diels–Alder adducts. It was isolated as a white crystalline compound by column chromatography. Based on the spectral data, structure **29** was assigned to the by-product, which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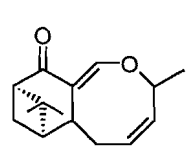
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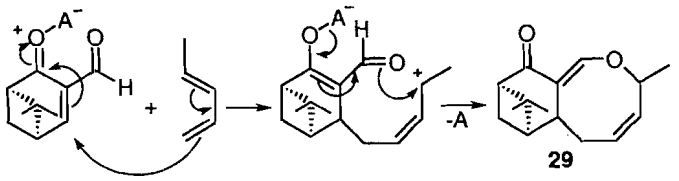
might have formed by a stepwise 1,4-cyclization process (see Scheme 3) instead of a Diels–Alder reaction. The reason for generation of this unexpected type of by-product in this partic-



SCHEME 3

ular case and not in any other example described here is not clear to us at this time.

C. Addition to trans-*2-methyl-1,3-pentadiene*

At –40°C the boron trifluoride etherate catalyzed Diels–Alder reaction of enone aldehyde **11** with *trans*-2-methyl-1,3-pentadiene proceeded smoothly to give a colourless liquid in 82% yield. Although the products showed only one spot on tlc and could not be separated by flash chromatography, the ^{1}H nmr spectrum indicated the presence of two compounds in a ratio of 133:1. Assuming that the reaction followed the normal *ortho* and *para* rules, the structures of the two adducts could be tentatively assigned as keto aldehydes **20** and **21**. Previous observations indicated that the coupling pattern of the ring junction proton (H8) could be used to determine the regiochemistry of the Diels–Alder adducts of 1-substituted dienes. Detailed ^{1}H decoupling experiments of the major isomer showed that irradiation of the signal at δ 2.82 (H8, dddd) led to a change in multiplicity of the signals at δ 2.47 (H11*exo*), 2.10–2.30 (two protons, H7ax and H9), and 1.98 (H7e). As for the previous cases, this coupling pattern indicated that two hydrogen atoms were attached to C7 and consequently the methyl substituent must be at C4, confirming the regiochemistry of the major isomer as shown by structure **20**.

To determine the stereochemistry of the ring junction and the C4 methyl, nOe experiments were carried out on the major isomer. When proton H8 (δ 2.82) was irradiated, enhancement on the *endo* methyl (δ 0.66) was observed. This indicated that the H8 proton was on the same face as the *gem*-dimethyl group and therefore the addition of the diene occurred from the *Re* face of **11**. The stereochemistry of the formyl group was then assigned in accordance with the *cis* principle. When the signal at δ 1.40 (C4 methyl) was irradiated nOe enhancements of H5, H4 and the formyl proton signals were observed. This confirmed the position and the stereochemistry of the methyl substituent of the major isomer as that specified by structure **20**.

The ^{1}H nmr spectral data of the minor isomer were incomplete. Therefore we could not unambiguously assign the structure of the minor isomer. The tentative assignment as structure **21** was based on the previous findings on a similar system (11).

D. Addition to 2,3-dimethylbutadiene

Enone aldehyde **11** reacted with 2,3-dimethylbutadiene using boron trifluoride etherate as a catalyst to give a colourless liquid in 92% yield. The spectral data were consistent with the proposed structure **22**. Again the stereochemistry was determined by nOe experiments. Irradiation of the *endo* methyl at δ 0.71 resulted in enhancement of H8 (δ 2.88), the formyl proton (δ 9.71), and the *exo* methyl (δ 1.70). These findings supported the assigned stereochemistry of **22** resulting from the addition of the diene exclusively from the *Re* face of enone aldehyde **11**.

E. Addition to 2-tert-*butyldimethylsiloxy-3-methyl-1,3-butadiene*

To examine the addition of more highly functionalized dienes we considered silyloxydiene **23**. We previously observed (6) that silyloxy dienes such as **23** and **30** are extremely sensitive to the acidity of some Lewis acids and only zinc chloride produces useful yields. The reaction of **23** (10 equiv.) with **11** catalyzed by zinc chloride was much faster than other additions to **11** reported here. The product was obtained in 70% yield after purification by column chromatography. The spectral data supported the general structural features of the expected Diels–Alder adduct except that the formyl group was absent. Evidently the formyl group was eliminated during the reaction or work-up and so the *cis* principle could not be applied directly to the structure assignment. In addition, several signals were at unexpected downfield shifts in the ^{1}H nmr spectrum.

To determine the regio- and stereochemistry of this adduct, nmr decoupling studies were carried out. Irradiation of the protons at δ 4.00 (H4e and H7e) led to a change in multiplicity of the signals at δ 3.38 (H4ax), 2.34 (H7ax) and 1.43 (C5-CH_3). When the signal at δ 3.31 (H8) was irradiated, the signal at δ 3.38 (H4ax) was also irradiated, due to their close proximity. Changes in multiplicity of the signals at δ 4.00 (H4e), 3.71 (H3), 1.94 (H9), and 1.43 (C5-CH_3) were observed. Irradiation of the proton at δ 2.29 (H1) led to a change in multiplicity of the signals at δ 1.94 (H9) and 1.73 (H11*exo*). These results confirmed that structure **24** expressed the correct regiochemistry of the adduct.

To determine the stereochemistry of the ring junction, nOe experiments were carried out. From the spectral data of other compounds in this series the methyl singlet at higher field (δ 0.89 for this compound) usually represented the *endo* methyl group. When the singlet at δ 0.89 was irradiated, nOe enhancements of the signals at δ 2.29 (H1), δ 1.94 (H9), and δ 1.73 (H11*exo*) were observed. These results indicated that the methyl singlet at δ 0.89 was due to the *exo* methyl. The absence of the formyl group could cause the exchange of the chemical shifts between the two geminal methyl groups. We tried to irradiate proton H8 at δ 3.31; however, proton H4ax at δ 3.38 was so close to H8 that it was also irradiated and the results of this experiment were inconclusive. Therefore the stereochemistry of the ring junction could not be determined by nOe experiments. The large coupling constant (11 Hz) observed for H3 suggested a *trans* ring junction as depicted by structure **24**; however, we do not consider this assignment to be conclusive since this coupling could be to the adjacent H4ax.

Since the diene **23** was used in large excess (10 equiv.), 19.4% of the diene was recovered intact after column chromatography. Diels–Alder dimerization of diene **23** also occurred during the reaction and 12% yield of the dimeric adduct **31** was obtained. We wanted to determine if the formyl group was lost from an initial adduct such as **32** to give **24**. It could have been eliminated during the reaction or during the work-up. Also, since this addition was faster than other zinc chloride catalyzed additions of **11**, there was a possibility that the excess of the relatively costly diene **23** could be reduced without lowering the yield. We ran the reaction again with 5 equivalents of diene **23**. The reaction was monitored carefully to observe when the formyl group was removed. After complete conversion a sample of the reaction mixture was concentrated and the ^{1}H nmr spectrum of the residue was recorded before addition of saturated sodium bicarbonate solution. The spectrum showed the absence of a formyl group in the crude mixture, indicating its loss during the cycloaddition reaction. The yield of product **24** was not affected by the reduction in the amount of the diene used.

F. Addition to 1,3-cyclopentadiene

Attempts to induce addition of 1,3-cyclopentadiene to **11** with boron trifluoride etherate as catalyst were unsuccessful due to rapid polymerization of the diene. When zinc chloride was used, the Diels–Alder reaction produced a mixture of two inseparable adducts (20:1 by ^{1}H nmr) in 52% yield. Preliminary analysis of the spectral data indicated that the structures of the adducts could be assigned as **25** and **26**. Extensive ^{1}H decoupling experiments on the major isomer led to the assignment of all its protons. The ring junction proton (H8) appeared at δ 3.17 as a multiplet. Irradiation of the signals at δ 3.01 (H7) and 2.30 (H9) led to a small change in multiplicity of the signal at δ 3.17. In an nOe experiment, when the *endo* methyl at δ 0.82 of the major isomer was irradiated, enhancement of the signals at δ 3.17, δ 9.81 and δ 1.32 were observed. Therefore the major product was assigned with both H8 and the formyl group in the α-orientation. Previous observations indicated that the addition of dienes to enone aldehyde occurred exclusively from the *Re* face of **11**. It was therefore expected that exclusive addition of cyclopentadiene to the *Re* face of **11** would also occur, so the minor isomer would most likely contain an α-H8 and an α-formyl group as well.

The stereochemistry of the methylene bridge of the bicyclo[2.2.1]heptene ring system was determined by comparing the difference in chemical shifts between the two vinylic protons with the known compounds **33** and **34** (11). Since the major isomer exhibited a larger difference in chemical shift between the two vinylic protons (Δδ 0.30) than the minor isomer (Δδ 0.11), it was assigned structure **25** while the minor isomer was assigned structure **26**.

G. endo*-Selectivity of the addition*

All dienes in this study added to enone aldehyde **11** with very high diastereomeric excess and mention of this *endo*-selectivity is appropriate. As we have described for related dienophiles (1, 7, 8, 11), there are two dienophilic components in **11**: the α,β-unsaturated ketone (**11***c*) and the α,β-unsaturated aldehyde (**11***d*). It would be unnecessary to distinguish between these two moieties except in certain cases for 1- and 4-substituted dienes. *endo*-Addition to either the enone or the α,β-unsaturated aldehyde moiety would give stereochemically distinguishable products. Determining which dienophilic moiety would control the reaction pathway should be a function of the secondary orbital overlap with the diene. The addition of 1-substituted dienes (Table 3, Entries 1–3 and 9) to **11** occurred predominantly with secondary orbital overlap with the aldehyde (as in aldehyde-*endo* transition state **11***a*) rather than with the ketone carbonyl (as in keto-*endo* transition state **11***b*). Comparison of the two transition states indicates that the addition by **11***b* would encounter some steric interaction between the C2–C3 zone of the diene and the methylene bridge of the dienophile. We believe that the enhanced aldehyde-*endo* selectivity exhibited by **11** over the moderate ester-*endo* selectivity of keto-ester **8** is a reflection of improved secondary orbital effect participation by the aldehyde carbonyl. The dramatic increase in reaction rate for additions to **11** over additions to **8** reflects the greater electron-withdrawing character of the aldehyde group of **11** over the ester group of **8** which we had predicted.

H. Optical purity

The (−)-β-pinene used to prepare enone aldehyde **11** had an optical purity of 92%. Optically active nmr shift reagents such as Eu(hfc)$_3$ have been used to evaluate the optical yield of reactions (35, 36). Direct application of Eu(hfc)$_3$ to adduct **17** showed separation of the signals for the *gem*-dimethyl groups. The chemical shift difference (Δδ) increased with an increase in the amount of Eu(hfc)$_3$ added. In all experiments the integrals of the split signals were consistently in the ratio of 96:4. Thus the optical purity of the starting material (92%) was retained in the Diels–Alder adducts. The enantiomeric set of adducts that would be obtained from the relatively unavailable enantiomeric (+)-β-pinene could nevertheless be prepared easily using the conversion of (+)-α-pinene to (−)-nopinone reported by Lavallee and Bouthillier (37). The (−)-nopinone so obtained would provide the enantiomer of **11** by the method we have described.

3. Removal of the formyl group

Having successfully generated various Diels–Alder adducts of enone aldehyde **11**, we wished to demonstrate that the formyl group, as an effective tool for controlling stereoselectivity, is not only easily introduced but also easily removed. Treatment of **17** with saturated aqueous potassium carbonate in a methanol mixture at room temperature for 18 h gave a single product in quantitative yield. The spectral data for this product were comparable with those previously reported for ketone **35** (11).

Treatment of the mixture of adducts **18** and **19** (64:1) under the same conditions for 18 h did not give any detectable amount of product. The starting material was recovered intact. However, after refluxing for 15 h a colourless liquid was isolated in 92% yield. After chromatographic separation, two products were obtained in a ratio of 1:6. Based on the spectral data and the ratio of the two products, structures **36** and **37** were assigned to the two compounds. Starting with a 64:1 mixture of **18** and **19**, it is impossible that the minor product in the 6:1 mixture originated from the minor component of the starting material. The two deformylation products must both be derived from the major starting material and must be epimeric at C3. The stereochemistry of C3 remained to be determined. Extensive ^{1}H COSY experiments of the major isomer resulted in the assignment of all the protons. The ring junction proton (H8) appeared at δ 2.71 as a multiplet. Its multiplicity changed when the H3 (δ 2.55) and H11*exo* (δ 2.40) protons and the multiplet at δ 1.98–2.20 (H9, H7, and other) were irradiated individually. Attempted nOe irradiation of proton H8 at δ 2.71 did not provide useful information since H3 was simultaneously irradiated. However, the ^{1}H nmr spectrum showed proton H3 as a doublet of doublets with coupling constants of 12.0 and 5.5 Hz. This large coupling constant (12 Hz) indicated that the major isomer had a *trans* ring junction (**36**) while the minor isomer could be assigned with a *cis* ring junction (**37**).

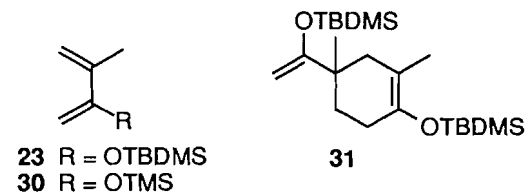
Conclusion

The Diels–Alder reaction of enone aldehyde **11** with various dienes provided good to high yields of chiral adducts in very high diastereomeric excess with complete diastereofacial selectivity. The observed regiochemistry was as predicted by the *ortho* and *para* rules. The formyl substituent of the adducts can be removed or elaborated to achieve synthetic goals. Enone aldehyde **11** is a potentially versatile intermediate for chiral synthesis by asymmetric Diels–Alder reactions.

Experimental

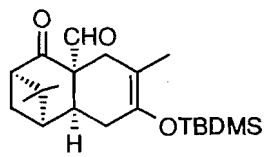
General

Melting points were recorded on a Kofler hot stage apparatus and are not corrected. Elemental analyses were performed by the microan-



23 R = OTBDMS
30 R = OTMS

31



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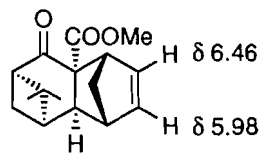

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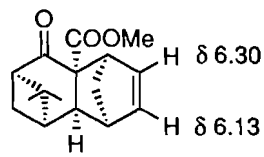

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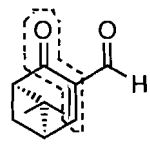
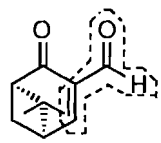
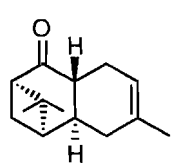


11*c*



11*d*



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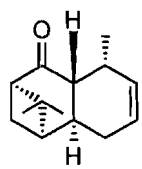

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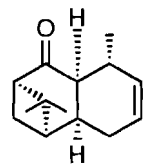

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alytical laboratory of this department. Fourier transform infrared spectra (ir) were recorded on a Nicolet 7199 or Nicolet MX-1 FT-IR spectrophotometer, and unless otherwise stated, were obtained in chloroform cast. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-80, Bruker WH-200, Bruker WH-300, Bruker WH-400, or Bruker AM-400 spectrometer using deuteriochloroform ($CDCl_3$) as solvent unless otherwise stated. Tetramethylsilane (TMS) was used as an internal reference. Coupling constants are reported to ±0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, δ = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH-300 (75 MHz) or Bruker WH-400 (125 MHz) spectrometer, and were obtained on solutions in deuteriochloroform as the internal reference, setting the central peak at 77.00 ppm. The ^{13}C nmr multiplicities were derived from APT (Attached Proton Test) experiments (38, 39). Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbons, and carbonyl groups appear in phase (p) with it. Nuclear Overhauser enhancement (nOe) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing antiphase with respect to the irradiated signal. Samples for nOe measurements were deoxygenated with argon gas for 10 min. High resolution electron impact mass spectra (ms) were recorded using an A.E.I. model MS-50 mass spectrometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Specific rotations ($[\alpha]_D$) are reported in degrees at the specified temperature and concentration (*c*) is given in grams per 100 millilitre in the specified solvent.

All reactions were carried out under slight positive pressure of argon. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. Flash chromatography (40) was used routinely for purification and separation of product mixtures using silica gel (Merck, 230–400 mesh). All solvents for chromatography were distilled prior to use. Concentrations of solvent systems used in column chromatography are given by volume. Analytical thin layer chromatography (tlc) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with Merck silica gel 60 F_{254}. Ultraviolet-active materials were detected by visualization under a uv lamp (254 or 350 nm). Visualization of tlc chromatograms was completed by dipping in an ethanol solution of vanillin (5% w/v) and sulfuric acid (5% v/v), followed by charring on a hot plate. Alternatively, an aqueous solution of phosphomolybdic acid (3% w/v) containing ceric sulfate (0.5% w/v) and sulfuric acid (3% v/v) was used as the dipping solution, followed by charring on a hot plate.

Materials

Anhydrous reaction solvents were distilled under argon from the appropriate drying agents before use. Tetrahydrofuran (THF) was freshly distilled from a solution of sodium and benzophenone. Pyridine and dichloromethane were distilled from calcium hydride. Ether was distilled from lithium aluminum hydride. Reactions requiring anhydrous conditions were performed in oven- or flame-dried glassware that was assembled and allowed to cool while being purged with argon. Argon was passed through a column of 4 Å molecular sieves and self-indicating silica gel. Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions.

*(1R,5S)-(+)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (**13**)*

WARNING: See footnote 11 in ref. 11. Ozone was passed through a −78°C solution of (1*S*,5*S*)-(−)-β-pinene[6] (10.0 g, 73.5 mmol) in dichloromethane–methanol (1:1, 30 mL). After 3.5 h a persistent blue

colour appeared. The reaction was stopped after a further 40 min when tlc showed no starting material remaining. Excess ozone was purged with oxygen for 10 min and the reaction mixture turned colourless. Dimethyl sulfide (27.5 mL, 0.37 mol) was added to the reaction mixture at –78°C, then the mixture was allowed to gradually warm to room temperature while stirring overnight. The solvent was removed under reduced pressure on a rotary evaporator. Flash chromatography of the residue, eluting with 2–10% ether in petroleum ether, gave pure **13** (7.2 g) as a colourless oil. A second chromatography of impure fractions gave additional **13** (2.2 g, total yield 9.4 g, 93%): $[\alpha]_D^{23}$ +15.0 (neat), +29.6 (*c* 1.32, $CHCl_3$);[10] ir: 1708 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 2.47–2.64 (complex, 3H), 2.34 (ddd, 1H, *J* = 19.0, 9.0, 2.5 Hz, C-3 H_α), 2.21 (m, 1H), 1.87–2.10 (complex, 2H), 1.55 (d, 1H, *J* = 10.0 Hz), 1.40 (s, 3H, *exo* CH_3), 0.82 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 215.0 (C=O), 58.0 (*C*HC=O), 41.2 (CMe_2), 40.5 (*C*HCMe$_2$), 32.8 (*C*H$_2$C=O), 25.9 (*exo* CH_3), 25.3 (CH_2), 22.2 (*endo* CH_3), 21.5 (CH_2); ms M^+ calcd. for $C_9H_{14}O$: 138.1045; found: 138.1046. Anal. calcd. for $C_9H_{14}O$: C 78.21, H 10.21; found: C 78.06, H 10.21.

*(1R,5R)-3-Formyl-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**14**)*

Sodium hydride (60% oil dispersion, 800 mg, 20.0 mmol) was suspended in tetrahydrofuran (30 mL) under argon. Ethyl formate (25 mL, 0.31 mol) was added at 0°C and stirred for 10 min. A solution of nopinone (**13**) (1.38 g, 10.0 mmol) in tetrahydrofuran (25 mL) containing 98% ethanol (7 drops) was added dropwise at 0°C over 30 min. The reaction mixture was allowed to gradually warm to room temperature. After 3 h at room temperature a saturated aqueous solution of ammonium chloride (25 mL) was added. The mixture was separated and the aqueous phase was extracted with ether – petroleum ether (1:1, 3 × 20 mL). The combined organic phases were washed with water and saturated aqueous sodium chloride, dried, filtered, and concentrated. Flash chromatography of the residue, eluting with 5–10% ether in petroleum ether, gave keto aldehyde **14** (1.55 g, 9.34 mmol, 93% yield) as a colourless oil that solidified on standing. This compound was a 7:2.5:1 mixture of isomers. The major isomer gave the following signals: ^1H nmr (300 MHz) δ: 13.35 (br s, 1H, enol *OH*), 7.18 (br s, 1H, enol =*CH*), 2.41–2.58 (complex, 6H), 1.41 (s, 3H, *exo* CH_3), 0.90 (s, 3H, *endo* CH_3). The two minor isomers also showed distinguishable signals in the nmr spectrum: δ 9.65, 9.40 (s, 1H each, C*H*O), 1.44, 1.40 (s, 3H each, *exo* CH_3), 0.93, 0.82 (s, 3H each, *endo* CH_3). The mixture also gave the following analytical data: ir: 3310 (enol OH), 1725 (CHO), 1713 (C=O), 1653 (chelated β-hydroxy-α,β-unsaturated ketone carbonyl), 1598 (C=C) cm^{-1}; ^{13}C nmr (75 MHz) δ: 209.4 (C=O), 163.9 (=CHOH), 107.2 (=*C*C=O), 54.1 (*C*HC=O), 39.6 (*C*Me$_2$), 39.4 (*C*HCMe$_2$), 27.5 (CH_2), 26.0 (CH_3), 25.3 (CH_2), 21.5 (CH_3); ms M^+ calcd. for $C_{10}H_{14}O_2$: 166.1004; found: 166.1009. Anal. calcd. for $C_{10}H_{14}O_2$: C 72.25, H 8.49; found: C 72.43, H 8.73.

*(1R,5R)-3-Formyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**11**) and (1R,3R,5S,6R)-3-formyl-7,7-dimethyl-4-oxatricyclo-[4.1.1.0^{3,4}]heptan-2-one (**15**)*

Pyridine (0.53 mL, 6.5 mmol) was added to a solution of phenylselenenyl chloride (1.37 g, 7.15 mmol) in dichloromethane (30 mL) at 0°C under argon. The colour of the solution changed from dark red to yellow-brown and white fumes were generated. After stirring for 10 min a solution of keto aldehyde **14** (1.08 g, 6.5 mmol) in dichloromethane (10 mL) was added. At the end of the addition, which took about 3 min, an instantaneous colour change from yellow-brown to bright yellow occurred, indicating completion of the selenenylation reaction; tlc analysis confirmed that no starting material remained. After 5 min the reaction mixture was washed with aqueous 1 N hydrochloric acid (2 × 30 mL). The organic layer was cooled to 0°C and aqueous 30% hydrogen peroxide solution (0.5 mL) was added dropwise. After stirring for 5 min aqueous 30% hydrogen peroxide (0.5 mL) was added. Another portion of aqueous hydrogen peroxide solution (15%, 1.0 mL) was added dropwise 7 min later. The resulting mixture was stirred for 1.5 h, then water (5 mL) was added and the phases were separated. The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried, filtered, and concentrated. Flash chromatography of the residue, eluting with 2–30% ether in petroleum ether, gave a light yellow oil (746 mg) as a mixture of enone aldehyde **11** and epoxide **15** (7:1, ca. 70% yield). The following nmr data were attributed to the enone aldehyde **11**: ^1H nmr (300 MHz) δ: 10.00 (s, 1H, C*H*O), 8.31 (dd, 2H, *J* = 6.5, 1.5 Hz, =C*H*), 2.75–2.95 (complex, 3H, C*H*CHH_{exo}C*H*), 2.12 (d, 1H, *J* = 9.0 Hz, CHH_{endo}), 1.57 (s, 3H, *exo* CH_3), 1.02 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 200.7 (C=O), 168.6 (CHO), 165.4 (CH=), 132.2 (C=), 58.3 (*C*HC=O), 54.8 (C), 44.7 (*C*HCMe$_2$), 40.4 (CH_2), 26.6 (CH_3), 21.5 (CH_3). The mixture showed the following spectral data: ir: 2830, 2710 (CHO, weak), 1724, 1691, 1657 (saturated and conjugated C=O), 1593 (C=C) cm^{-1}; ms M^+ calcd. for $C_{10}H_{12}O_2$: 164.0833; found: 164.0837; calcd. for $C_{10}H_{12}O_3$: 180.0786; found: 180.0781. Epoxide **15** was recovered in pure form from a typical Diels-Alder reaction mixture after dienophile **11** was totally consumed. It showed the following spectral data: ir: 1741 (CHO), 1710 (C=O), 1100 (C-O) cm^{-1}; ^1H nmr (300 MHz) δ: 9.65 (s, 1H, C*H*O), 3.89 (d, 1H, *J* = 4.5 Hz, CHC*H*O), 2.71 (dd, 1H, *J* = 11.0, 6.0 Hz, CHH_{exo}), 2.58 (dd, 1H, *J* = 6.0, 6.0 Hz, C*H*C=O), 2.38 (ddd, 1H, *J* = 11.0, 6.0, 4.5 Hz, C*H*CMe$_2$), 2.09 (dd, 1H, *J* = 11.0, 11.0 Hz, CHCH_{endo}), 1.49 (s, 3H, *exo* CH_3), 1.09 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 201.8 (C=O), 194.7 (CHO), 58.9 (CH), 56.7 (*C*HC=O), 50.0 (C), 40.7 (*C*HCMe$_2$), 26.5 (CH_3), 21.1 (CH_3), 20.7 (CMe_2), 20.4 (CH_2); ms M^+ + 1 calcd. for $C_{10}H_{13}O_3$: 181.0865; found: 181.0863.

General procedure for boron trifluoride etherate catalyzed reactions

The Diels–Alder reactions of enone aldehyde **11** with boron trifluoride etherate as catalyst were carried out in a manner similar to the following example.

*(1R,3R,8S,9R)-(−)-3-Formyl-6,10,10-trimethyltricyclo-[7.1.1.0^{3,8}]-undec-5-en-2-one (**17**)*

Isoprene (0.54 mL, 5.4 mmol, 10 equiv.) in ether (7 mL) was added to a solution of a mixture of **11** and **15** (9:1, 100 mg) at –20°C under argon, followed by addition of boron trifluoride etherate (0.07 mL, 0.54 mmol). After stirring for 2 h a saturated aqueous sodium bicarbonate solution (7 mL) was added. The mixture was separated and the aqueous layer was extracted with ether (3 × 7 mL). The combined organic layers were washed with water and brine, dried, filtered, and concentrated. Flash chromatography of the residue, eluting with 2–30% ether in petroleum ether, gave **17** as a colourless oil (105.2 mg, 84% yield): $[\alpha]_D^{23}$ –115.87 (*c* 0.75, $CHCl_3$); ir: 1730 (CHO), 1698 (C=O), 1600 (C=C) cm^{-1}; ^1H nmr (300 MHz) δ: 9.70 (s, 1H, C*H*O), 5.33 (m, 1H, C*H*=), 2.94 (dddd, 1H, *J* = 10.0, 7.5, 2.0, 2.0 Hz, CHC*H*CH$_2$), 2.83 (dd, 1H, *J* = 16.0, 7.0 Hz, CHH_{ax}CH=), 2.61 (dd, 1H, *J* = 5.5, 5.5 Hz, C*H*C=O), 2.52 (dddd, 1H, *J* = 11.0, 8.5, 5.5, 2.0 Hz, CHH_{exo}), 2.22 (dddd, 1H, *J* = 16.0, 8.0, 2.5, 2.5 Hz, CHH_eCH=), 2.15 (complex, 2H, C*H*CMe$_2$, CHH_{ax}C=), 1.91 (m, 1H, CHH_eC=), 1.89 (d, 1H, *J* = 11.0 Hz, CH*Hendo*), 1.74 (br s, 3H, CH_3C=), 1.32 (s, 3H, *exo* CH_3), 0.73 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 212.9 (C=O), 200.9 (CHO), 139.8 (CH_3C=), 116.4 (CH=), 68.2 (C), 61.9 (C), 57.5 (*C*H), 47.8 (CH), 33.4 (CH_2), 33.0 (CH_2), 30.4 (CH), 26.5 (=C*C*H$_3$), 25.3 (CH_2), 23.1 (CH_3), 21.7 (CH_3); ms M^+ calcd. for $C_{15}H_{20}O_2$: 232.1464; found: 232.1462. Anal. calcd. for $C_{15}H_{20}O_2$: C 77.55, H 8.68; found: C 77.43, H 8.94.

General procedures for zinc chloride, ferric chloride, and stannic chloride catalyzed reactions

The Diels–Alder reactions of enone aldehyde **11** with isoprene using ferric chloride and stannic chloride as catalysts were carried out by the method of the example procedure described above. Specific temperatures and times are reported in Table 4. The general procedure for zinc chloride catalyzed reactions was slightly different from the boron trifluoride catalyzed reactions. Zinc chloride (91.4 mg, 0.67 mmol, 1 equiv.) was flame-dried under vacuum and dissolved in ether (5 mL) at room temperature under argon to give a clear solution. A solution of a

[10]See analytical data and footnote 15 in ref. 11.

mixture of **11** and **15** (10:1, 110 mg, 0.60 mmol of **11**) in ether (2 mL) was added dropwise and a thick pale yellow precipitate formed. After a few minutes, the precipitate stuck onto the wall of the round-bottomed flask and the solution became clear again. After stirring for 10 min, the reaction mixture was cooled to –20°C and then isoprene (0.7 mL, 6.7 mmol, 10 equiv.) was added. The work-up procedure and purification were the same as those described above. Specific times and temperatures are reported in Tables 2 and 3.

*(1R,3R,4R,8S,9R)-3-Formyl-4,10,0-trimethyltricyclo[7.1.1.0^{3,8}]-undec-5-en-2-one (**18**) and (1R,3R,4S,8S,9R)-3-formyl-4,10,10-trimethyltricyclo[7.1.1.0^{3,8}]undec-5-en-2-one (**19**)*

After purification, the reaction with *trans*-piperylene gave a mixture of isomers **18** and **19** (64:1 ratio). The nmr spectra showed two sets of signals; the major set for isomer **18**: ^{1}H nmr (300 MHz) δ: 10.04 (s, 1H, C*H*O), 6.00 (m, 1H, C*H*═), 5.42 (ddd, 1H, *J* = 9.5, 3.0, 3.0 Hz, ═C*H*), 2.80 (dddd, 1H, *J* = 10.5, 7.5, 2.0, 2.0 Hz, CHC*H*CH$_2$), 2.62 (dd, 1H, *J* = 5.5, 5.5 Hz, C*H*C═O), 2.58 (m, 1H, CH$_3$C*H*CH═), 2.48 (dddd, 1H, *J* = 11.0, 5.5, 5.5, 2.0 Hz, CHH_{exo}), 2.34 (ddd, 1H, *J* = 15.0, 7.5, 7.5 Hz, CHH_eCH═), 2.10 (ddd, 1H, *J* = 5.5, 5.5, 2.0 Hz, C*H*CMe$_2$), 1.89 (d, 1H, *J* = 11.0 Hz, CHH_{endo}), 1.85 (m, 1H, CHH_{ax}CH═), 1.40 (d, 3H, *J* = 7.5 Hz, CH_3CH), 1.31 (s, 3H, *exo* CH_3), 0.71 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 211.0 (C═O), 204.3 (CHO), 130.9 (═CH), 127.9 (CH═), 68.3 (CH), 57.6 (CH), 56.2 (CH), 50.3 (C), 41.9 (CMe$_2$), 39.7 (CH), 32.4 (CH$_3$), 28.1 (CH$_2$), 26.3 (CH$_3$), 24.2 (CH$_2$), 21.4 (CH$_3$); the minor set for isomer **19**: ^{1}H nmr (300 MHz) δ: 9.63 (s, 1H, C*H*O), 6.00 (m, 1H, C*H*═), 5.75 (dddd, 1H, *J* = 9.5, 6.0, 1.5, 1.5 Hz, ═C*H*), 3.0 (m, 1H, CHC*H*CH$_2$), 2.88 (ddd, 1H, *J* = 14.0, 7.0, 7.0 Hz, CH$_3$C*H*CH═), 2.20 (ddd, 1H, *J* = 15.5, 7.0, 7.0 Hz, C*H*HCH═), 2.03 (ddd, 1H, *J* = 6.0, 6.0, 2.5 Hz, C*H*CMe$_2$), 1.32 (s, 3H, *exo* CH_3), 1.05 (d, 3H, *J* = 7.0 Hz, CH_3CH), 0.66 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 131.1, 128.3 (CH═CH), 71.5 (CH), 57.2 (CH), 48.1 (CH$_3$), 40.7 (CH), 26.7 (CH$_3$), 26.5 (CH$_2$), 20.8 (CH$_2$), 19.1 (CH$_3$). The following data are reported for the mixture of **18** and **19**: ir: 1723 (CHO), 1693 (C═O) cm^{-1}; ms M$^+$ calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1461. Anal. calcd. for $C_{15}H_{20}O_2$: C 77.55, H 8.68; found: C 77.30, H 8.77.

*(1R,10S,11R)-6,12,12-Trimethyl-5-oxatricyclo[9.1.1.0^{3,10}]undeca-3,7-dien-2-one (**29**)*

Compound **29** (colourless crystals): ir: 1684 (C═O), 1602 (C═C) cm^{-1}; ^{1}H nmr (300 MHz) δ: 7.40 (s, 1H, ═C*H*-O), 5.82 (m, 1H, C*H*═), 5.53 (dddd, 1H, *J* = 15.5, 7.0, 7.0, 1.5 Hz, ═C*H*), 4.59 (dddd, 1H, *J* = 12.0, 7.0, 3.0, 1.5 Hz, O-C*H*Me), 2.81 (ddd, 1H, *J* = 12.0, 4.5, 2.0 Hz, CHC*H*CH$_2$), 2.36–2.50 (complex, 2H, CH_2CH═), 2.10 (dd, 1H, *J* = 5.5, 5.5 Hz, C*H*C═O), 1.73 (complex, 3H, CH_2C*H*), 1.39 (d, 3H, *J* = 7.5 Hz, CHCH_3), 1.35 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); ^{13}C nmr (75 MHz) δ: 203.8 (C═O), 151.8 (═CH-O), 129.8, 129.6 (CH═CH), 113.0 (C═), 79.1 (CH), 56.3 (CH), 43.2 (CH), 40.9 (C), 32.4 (CH), 31.4 (CH$_2$), 26.5 (CH$_3$), 24.2 (C), 21.5 (CH$_3$), 17.8 (CH$_3$); ms M$^+$ calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1462.

*(1R,3R,4R,8S,9R)-3-Formyl-4,6,10,10-tetramethyltricyclo-[7.1.1.0^{3,8}]undec-5-en-2-one (**20**) and (1R,3R,4S,8S,9R)-3-formyl-4,6,10,10-tetramethyltricyclo[7.1.1.0^{3,8}]undec-5-en-2-one (**21**)*

Compounds **20** and **21** were obtained as a 133:1 mixture (colourless oil) after flash chromatography. The nmr spectra displayed two sets of signals. The major set for isomer **20**: ^{1}H nmr (300 MHz) δ: 10.04 (s, 1H, C*H*O), 5.08 (m, 1H, ═C*H*), 2.82 (dddd, 1H, *J* = 10.0, 8.0, 2.0, 2.0 Hz, CHC*H*CH$_2$), 2.61 (dd, 1H, *J* = 5.5, 5.5 Hz, C*H*C═O), 2.56 (m, 1H, CH$_3$C*H*CH═), 2.47 (m, 1H, CHH_{exo}), 2.10–2.30 (complex, 2H, CHH_eC═, C*H*CMe$_2$), 1.98 (dm, 1H, *J* = 14.5 Hz, CHH_{ax}C═), 1.90 (d, 1H, *J* = 11.0 Hz, CHH_{endo}), 1.78 (br s, 3H, CH_3C═), 1.41 (d, 3H, *J* = 7.5 Hz, CHCH_3), 1.32 (s, 3H, *exo* CH_3), 0.66 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 211.9 (C═O), 204.2 (CHO), 138.5 (C), 124.6 (CH═), 64.1 (C), 55.8 (CH), 48.0 (CH), 42.0 (CMe$_2$), 40.3 (CH), 33.5 (CH$_2$), 32.4 (CH), 26.4 (CH$_3$), 24.1 (CH$_2$), 22.8 (CH$_3$), 21.4 (CH$_3$), 16.2 (CH$_3$); the minor set for isomer **21**: ^{1}H nmr (300 MHz) δ 9.63 (s, 1H, C*H*O), 5.37 (m, 1H, C*H*═), 3.05 (m, 1H, CHC*H*CH$_2$), 2.93 (dd, 1H, *J* = 7.5, 7.5 Hz, C*H*C═O), 1.89-2.00 (m, 3H), 1.82 (d, 1H, *J* = 10.5 Hz, CHH_{endo}), 1.73 (br s, 3H, CH_3C═), 1.33 (s, 3H, *exo* CH_3), 1.20 (d, 3H, *J* = 7 Hz, CHCH_3), 1.02 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ 129.4 (C═), 123.6 (CH═), 61.6 (C), 57.3 (CH), 41.5 (CH), 31.5 (CH$_2$), 26.8 (CH$_3$), 23.1 (CH$_3$), 21.0 (CH$_3$), 20.7 (CH$_2$), 18.8 (CH$_3$). The following data are reported for the mixture of **20** and **21**. ir 1713 (CHO), 1694 (C═O cm^{-1}); ms M$^+$ 246.1619 (calcd. for $C_{16}H_{22}O_2$: 246.1619);

*(1R,3R,8S,9R)-(+)-3-Formyl-5,6,10,10-tetramethyltricyclo-[7.1.1.0^{3,8}]undec-5-en-2-one (**22**)*

Adduct **22** (colourless oil): $[\alpha]_D^{23}$ +25.0 (*c* 1.0, CHCl$_3$); ir: 1729 (CHO), 1698 (C═O) cm^{-1}; ^{1}H nmr (300 MHz) δ: 9.71 (s, 1H, C*H*O), 2.88 (dddd, 1H, *J* = 10.5, 6.0, 2.0, 2.0 Hz, CHC*H*CH$_2$), 2.67 (d, 1H, *J* = 15.0 Hz, CCHH_{ax}C═), 2.61 (dd, 1H, *J* = 5.5, 5.5 Hz, C*H*C═O), 2.51 (dddd, 1H, *J* = 11.0, 6.0, 5.5, 2.0 Hz, CHH_{exo}), 2.33 (br d, 1H, *J* = 15.0 Hz, CCHH_eC═), 1.97-2.17 (complex, 3H, CHC*H*HC═, CHCH*H*C═, C*H*CMe$_2$), 1.86 (d, 1H, *J* = 11 Hz, CHH_{endo}), 1.70 (br s, 3H, CH_3C═), 1.61 (br s, 3H, CH_3C═), 1.31 (s, 3H, *exo* CH_3), 0.71 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 213.4 (C═O), 200.6 (CHO), 130.0 (CH$_3$C═), 122.7 (CH$_3$*C*═), 63.0 (C), 57.5 (CH), 47.5 (CH), 41.3 (C), 39.9 (CH$_2$), 34.7 (CH$_2$), 30.2 (CH), 26.5 (CH$_3$), 25.1 (CH$_2$), 21.7 (CH$_3$), 19.1 (CH$_3$), 19.0 (CH$_3$); ms M$^+$ calcd. for $C_{16}H_{22}O_2$: 246.1619; found: 246.1619. Anal. calcd. for $C_{16}H_{22}O_2$: C 78.01, H 9.00; found: C 77.95, H 8.87.

*(1R,3R,8S,9R)-6-(tert-Butyldimethylsiloxy)-5,10,10-trimethyl-tricyclo[7.1.1.0^{3,8}]undec-5-en-2-one (**24**)*

Ketone **24** (colourless oil): ir: 1715 (C═O) cm^{-1}; ^{1}H nmr (300 MHz, C_6D_6)[11] δ: 4.00 (complex, 2H, CHH_e(CH$_3$)C═, CHH_eCOSi), 3.71 (dd, 1H, *J* = 11.0, 3.5 Hz, O═CC*H*CH$_2$), 3.38 (dm, 1H, *J* = 15.0 Hz, CHH_{ax}(CH$_3$)C═), 3.31 (m, 1H, CHC*H*CH$_2$), 2.34 (dm, 1H, *J* = 15.0 Hz, CHH_{ax}COSi), 2.29 (dd, 1H, *J* = 6.0, 6.0 Hz, C*H*C═O), 2.01 (d, 1H, *J* = 10.5 Hz, CHH_{endo}), 1.94 (m, 1H, C*H*CMe$_2$), 1.73 (m, 1H, CHH_{exo}), 1.43 (br s, 3H, CH_3C═), 1.01 (s, 3H, *endo* CH_3), 0.98 (s, 9H, C(CH_3)$_3$), 0.89 (s, 3H, *exo* CH_3), 0.22 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3); ^{13}C nmr (75 MHz, C_6D_6) δ: 204.2 (C═O), 140.9 (═C-OSi), 109.3 (CH$_3$*C*═), 75.7 (CH), 69.3 (CH$_2$), 58.6 (CH), 58.2 (C), 57.6 (CH), 49.0 (C), 40.9 (CH), 32.2 (CH$_2$), 34.7 (CH$_2$), 26.5 (CH$_3$), 25.1 (3 × CH$_3$), 21.7 (2 × CH$_3$), 19.1 (CH$_3$), 18.99 (CH$_3$); ms M$^+$ calcd. for $C_{20}H_{34}O_2Si$: 334.2328; found: 334.2324.

*1-(tert-Butyldimethylsiloxy)-4-[1-(tert-butyldimethylsiloxy)-ethenyl]-2,4-dimethylcyclohexene (**31**)*

Compound **31** (colourless oil): ^{1}H nmr (300 MHz) δ: 4.20 (d, 1H, *J* = 3.0 Hz, ═C*H*H), 4.18 (d, 1H, *J* = 3.0 Hz, ═CH*H*), 1.39 (s, 3H, CH_3C═), 1.30 (complex, 6H), 1.03 (s, 3H, CCH_3), 0.89 (s, 9H, C(CH_3)$_3$), 0.84 (s, 9H, C(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3).

*(1R,3R,4S,7R,8S,9R)-3-Formyl-10,10-dimethyltetracyclo-[7.1.1.1.^{4,7}0^{3,8}]dodec-5-en-2-one (**25**) and (1R,3R,4R,7S,8S,9R)-3-Formyl-10,10-dimethyltetracyclo[7.1.1.1.^{4,7}0^{3,8}]dodec-5-en-2-one (**26**)*

The nmr spectra of the two inseparable products (as a colourless oil) exhibited two sets of signals: the major set for isomer **25**: ^{1}H nmr (300 MHz) δ: 9.81 (s, 1H, C*H*O), 6.40 (dd, 1H, *J* = 5.5, 3.0 Hz, CHCHC*H*═), 6.10 (dd, 1H, *J* = 5.5, 3.0 Hz, CCHC*H*═), 3.33 (m, 1H, CHC*H*CH═), 3.17 (m, 1H, CHC*H*CH), 3.01 (br s, 1H, CC*H*CH═), 2.42 (d, 1H, *J* = 12.0 Hz, CHH_{endo}), 2.36 (dd, 1H, *J* = 6.6, 6.0 Hz, C*H*C═O), 2.19–2.35 (complex, 2H, CHH_{exo}, CH$_2$C*H*CH), 1.70 (br d, 1H, *J* = 8.5 Hz, CHCH*H*CH), 1.32 (s, 3H, *exo* CH_3), 1.27 (ddd, 1H, *J* =

[11]The ^{1}H nmr spectrum of **24** in deuteriochloroform gave an unexpectedly complex pattern. When the solution in the nmr tube was examined by tlc, two new spots appeared, indicating that the adduct had decomposed under the mildly acidic conditions of deuteriochloroform. Subsequent nmr spectra of **24** were run in deuteriobenzene.

8.5, 4.0, 2.0 Hz, CHC*H*HCH), 0.82 (s, 3H, *endo* CH_3); ^{13}C nmr (125 MHz) δ: 217.7 (C=O), 199.9 (CHO), 142.3 (HC=), 134.0 (=CH), 68.2 (C), 65.9 (C), 57.8 (CH), 52.3 (CH), 48.2 (CH), 47.2 (CH_2), 45.4 (CH), 39.1 (CH), 27.0 (CH_3), 22.4 (CH_2), 15.3 (CH_3); the minor set for isomer **26**: ^1H nmr (300 MHz) δ: 10.08 (s, 1H, C*H*O), 6.21 (m, 1H, C*H*=), 6.10 (m, 1H, C*H*=), 1.31 (s, 3H, CH_3), 0.81 (s, 3H, CH_3); ^{13}C nmr (125 MHz) δ: 130.9 (HC=), 128.8 (=CH), 71.6 (C), 43.3 (C), 38.8 (CH), 30.4 (CH_2), 29.0 (CH_2), 14.1 (CH_3), 11.0 (CH_3). The mixture also showed the following spectral data: ir: 1723 (CHO), 1694 (C=O) cm^{-1}; ms M^+ calcd. for $C_{15}H_{18}O_2$: 230.1307; found: 230.1308.

(1R,3R,8S,9R)-(−)-6,10,10-Trimethyltricyclo[7,1,1,0^{3,8}]undec-5-en-2-one (35)

Keto aldehyde **17** (70 mg, 0.30 mmol) was dissolved in methanol (10 mL). A saturated aqueous potassium carbonate solution (10 mL) was added. After stirring for 18 h at room temperature, the reaction mixture was extracted with a solution of ether and petroleum ether (1:1; 3 × 10 mL). The combined organic layers were washed with water and brine, dried, filtered, and concentrated. Flash chromatography of the residue, eluting with 0–3% ether in petroleum ether, gave **35** (60 mg, 0.295 mmol, 98% yield); $[\alpha]_D^{23}$ –47.7 (*c* 2.286, $CHCl_3$); mp 53–54°C (crystallization from petroleum ether); ir: 1713 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 5.48 (br s, 1H, =C*H*), 2.60 (dd, 1H, *J* = 5.0, 5.0 Hz, C*H*C=O), 2.30-2.50 (complex, 3H), 1.83–2.20 (complex, 6H), 1.71 (br s, 3H, =CCH_3), 1.38 (s, 3H, *exo* CH_3), 0.79 (s, 3H, *endo* CH_3); ^{13}C nmr (125 MHz) δ: 214.8 (C=O), 135.4 (=C), 121.2 (=CH), 58.6 (CH), 46.4 (CH), 45.0 (CH), 44.7 (C), 36.6 (CH_2), 36.5 (CH), 26.8 (CH_3), 25.0 (CH_2), 24.0 (CH_2), 23.7 (CH_3), 22.0 (CH_3); ms M^+ calcd. for $C_{14}H_{20}O$: 204.1514; found: 204.1511. Anal. calcd. for $C_{14}H_{20}O$: C 82.29; H 9.87; found: C 82.04, H 9.97.

(1R,3R,4R,8S,9R)-4,10,10-Trimethyltricyclo[7.1.1.0^{3,8}]undec-5-en-2-one (36) and (1R,3S,4R,8S,9R)-4,10,10-trimethyltricyclo[7,1,1,0^{3,8}]undec-5-en-2-one (37)

A mixture of keto aldehydes **18** and **19** (64:1, 45.0 mg, 0.194 mmol) was dissolved in methanol (20 mL). Saturated aqueous potassium carbonate (20 mL) was added. After refluxing for 15 h, the reaction mixture was cooled to room temperature and extracted with ether and petroleum ether (1:1; 3 × 15 mL). The combined organic phases were washed with water and brine, dried, filtered, and concentrated. Flash chromatography of the residue, eluting with 0–3% ether in petroleum ether, gave isomer **37** (5.2 mg, 0.025 mmol, 13% yield): ir: 1710 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 5.55 (m, 1H, =C*H*), 5.49 (m, 1H, C*H*=), 2.60 (dd, 1H, *J* = 5.0, 5.0 Hz, C*H*C=O), 2.30–2.45 (complex, 3H), 2.00–2.15 (complex, 4H), 1.70 (d, 1H, *J* = 11.0 Hz, CHH_{endo}), 1.37 (s, 3H, *exo* CH_3), 1.22 (d, 3H, *J* = 7.0 Hz, CHCH_3), 0.78 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 215.7 (C=O), 135.3 (HC=), 130.0 (=CH), 59.2 (CH), 52.6 (CH), 45.3 (CH), 45.0 (C), 36.3 (CH), 31.6 (CH_2), 30.1 (CH), 26.8 (CH_3), 24.2 (CH_2), 21.5 (CH_3), 16.0 (CH_3); ms M^+ calcd. for $C_{14}H_{20}O$: 204.1514; found: 204.1512. Continued elution gave isomer **36** (31.2 mg, 0.153 mmol, 79% yield): ir 1714 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 5.77–5.63 (complex, 2H, C*H*=C*H*), 2.71 (m, 1H, CHC*H*CH_2), 2.64 (dd, 1H, *J* = 5.0, 5.0 Hz, C*H*C=O), 2.55 (dd, 1H, *J* = 12.0, 5.5 Hz, O=CC*H*CH), 2.40 (m, 1H, CHH_{exo}), 1.98–2.20 (complex, 4H, C*H*CMe_2, C*H*HCH=, CH*H*CH=, MeC*H*CH=), 1.82 (d, 1H, *J* = 11 Hz, CHH_{endo}), 1.36 (s, 3H, *exo* CH_3), 1.10 (d, 3H, *J* = 7.0 Hz, CHCH_3), 0.87 (s, 3H, *endo* CH_3); ^{13}C nmr (75 MHz) δ: 214.6 (C=O), 134.3 (HC=), 126.0 (HC=), 58.5 (CH), 49.4 (CH), 45.1 (CH), 44.5 (C), 32.3 (CH), 31.5 (CH_2), 29.9 (CH), 27.2 (CH_3), 24.4 (CH_2), 21.5 (CH_3), 15.5 (CH_3); ms M^+ calcd. for $C_{14}H_{20}O$: 204.1514; found: 204.1513.

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