Diastereoselective intramolecular Diels–Alder reactions of the furan diene: the synthesis of (±)-1,4-epoxycadinane

CHRISTINE ROGERS AND BRIAN A. KEAY[1]

Department of Chemistry, University of Calgary, Calgary, Alta., Canada T2N 1N4

Received October 9, 1992

CHRISTINE ROGERS and BRIAN A. KEAY. Can. J. Chem. **71**, 611 (1993).

The diastereoselective intramolecular Diels–Alder reactions of the furan diene (IMDAF), in which the side arm comprises four carbon atoms and is substituted by a methyl group adjacent to, or one carbon removed from, the furan ring, are described. Adducts are formed in moderate to excellent yields when treated with either Florisil in methylene chloride at room temperature or methylaluminum dichloride in methylene chloride at −78°C. Florisil is most effective for substrates containing unsubstituted dienophiles. An equimolar quantity (1.1 equivalents) of methylaluminum dichloride is most effective for precursors having methacrolein-type dienophiles, while a catalytic quantity (0.1 equivalent) is effective for crotonaldehyde-type dienophiles. Only the adducts with the side arm orientated *syn* with respect to the oxygen bridge are detected and isolated. The major diastereomer is the one in which the methyl group (initially on the side arm) is situated equatorially on the newly formed six-membered ring. An application of the diastereoselective IMDAF reaction to the synthesis of (±)-1,4-epoxycadinane is described, beginning with 2-methylfuran.

CHRISTINE ROGERS et BRIAN A. KEAY. Can. J. Chem. **71**, 611 (1993).

On décrit les réactions diastéréosélectives de Diels–Alder intramoléculaires du furane (DAIMF) agissant comme dième et dans lequel la chaîne latérale comporte quatre atomes de carbone et est substituée par un groupe méthyle sur le carbone en α ou en β par rapport au noyau furanique. Les adduits se forment avec des rendements allant de moyens à excellents lorsqu'on les traite soit avec du Florisil dans le chlorure de méthylène à la température ambiante soit avec du dichlorure de méthylaluminium dans le chlorure de méthylène à −78°C. Le Florisil est le plus efficace pour les substrats contenant des diénophiles qui ne sont pas substitués. Une quantité équimolaire (1,1 équivalents) de dichlorure de méthylaluminium est le plus efficace pour des diénophiles précurseurs du type méthacroléine alors qu'une quantité catalytique (0,1 équivalent) est efficace pour les diénophiles du type crotonaldéhyde. On n'a détecté et isolé que les adduits dont la chaîne latérale est orientée en *syn* par rapport au pont oxygéné. Le diastéréoisomère principal est celui dans lequel le groupe méthyle (initialement dans la chaîne latérale) est en position équatoriale dans le cycle à six chaînons nouvellement formé. On décrit une application de la réaction diastéréosélective Diels–Alder intramoléculaire du furane pour la synthèse du (±)-1,4-époxycadinane à partir du 2-méthylfurane.

[Traduit par la rédaction]

The intramolecular Diels–Alder reaction of the furan diene (IMDAF) has been studied by many groups since it was first reported in 1978 (1). These investigations have attempted to define the scope and limitations of the IMDAF reaction with respect to (*i*) the effect of varying the length of the tether linking the diene and dienophile,[2,3] (*ii*) the effect of substituting heteroatoms for carbon on the tether,[2,3] (*iii*) the effect of varying the type and placement of substituents on both the furan ring and dienophile,[2,3] (*iv*) the development of methods to overcome the unfavourable equilibrium towards product,[2,3] and, lastly, (*v*) utilization of the adducts in the synthesis of natural products (7).

Our efforts have concentrated on defining the scope and limitations of the IMDAF reaction of systems containing a four-carbon-atom side arm (8–10). Precursors containing substituted dienophiles have an equilibrium favouring starting material, and therefore we examined methods to shift the equilibrium toward adduct formation. We recently showed (9) that the IMDAF reaction of precursors having a four-carbon-atom side arm was accelerated by methylaluminum dichloride in methylene chloride at −78°C (Scheme 1). The oxatricyclo adducts were obtained in good to excellent yield after only 2–8 h. In addition, the reaction was shown to be 100% stereoselective; only the adducts in which the side arm was orientated *syn* with respect to the oxygen bridge were isolated. Thus, adducts were prepared containing up to four asymmetric centres of known stereochemistry depending on the substituent pattern of the dienophile (i.e., Scheme 1: R^1 = Me, R^2 = H, R^3 = H or Me).

Placement of a single substituent on the side arm of the IMDAF precursor could lead to two diastereomers. The major isomer was expected to be that with the substituent in the equatorial position of the newly formed six-membered ring (Scheme 1: R^1 = H, R^2 = R^3 = Me), since the above IMDAF reactions were shown to be under thermodynamic control. This modification would result in adducts having up to five asymmetric centres of known relative stereochemistry (i.e., Scheme 1: R^1 = R^2 = R^3 = Me), which would be useful as intermediates for the synthesis of natural products, such as 1,4-epoxycadinane **1**.

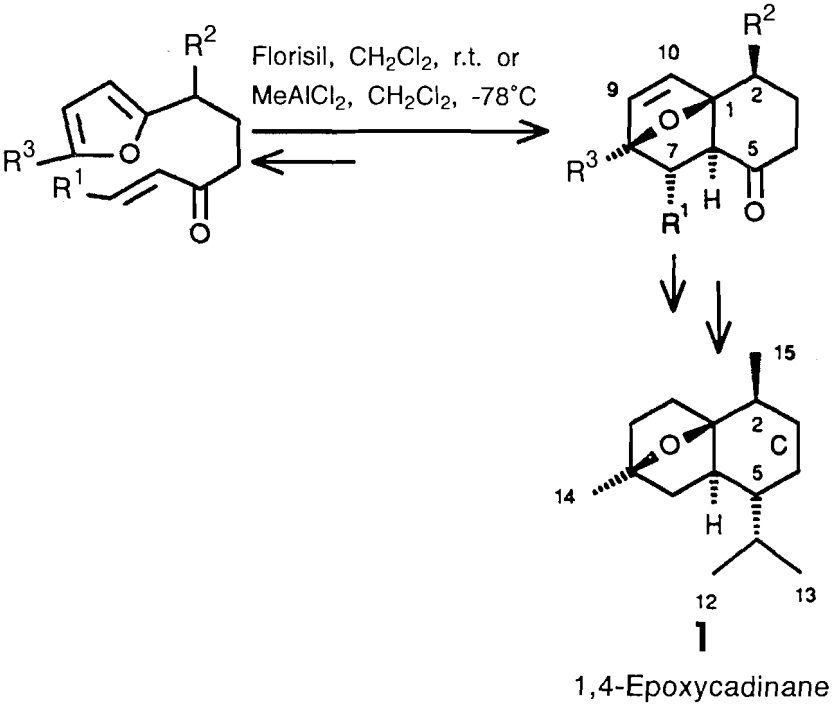
We recently reported (11) that stirring various IMDAF precursors possessing a methyl-substituted four-carbon-atom tether with Florisil in methylene chloride for 0.5–19 days provided oxatricyclo adducts in which the major diastereomer had the methyl group situated in the equatorial position on the newly formed six-membered ring.[4] The adducts with the side arm *syn* to the oxygen bridge were the only isomers detected (by ^{1}H NMR) and isolated (i.e., Scheme 1: R^1 = H, R^2 = R^3 = Me). Since methylaluminum dichloride is an effective Lewis acid for accelerating the IMDAF reaction, we studied the effect of methylaluminum dichloride on the diastereomeric ratios of a number of IMDAF precursors having monosubstituted tethers. We herein provide (*i*) a full

[1]Author to whom correspondence may be addressed.

[2]For reviews, see ref. 2.

[3]For work reported on IMDAF reactions containing side arms with (*a*) heteroatoms, (*b*) three carbon atoms, (*c*) four carbon atoms, and (*d*) five carbon atoms, see refs. 3, 4, 5, and 6, respectively.

[4]Related diastereoselective IMDAF reactions have since been reported, see refs. 4*a*, 7*g*, and 12.



SCHEME 1

account of both the effect of Florisil and methylaluminum dichloride on the IMDAF reaction of precursors containing a single substituent on the tether, and (*ii*) the application of this methodology to the synthesis of (±)-1,4-epoxycadinane **1** (Scheme 1).[5]

Preparation of monosubstituted IMDAF precursors

The synthesis of the precursors with monosubstituted tethers was accomplished as outlined in Scheme 2. Friedel–Crafts alkylation (13) of 2-methylfuran **2** with either methacrolein or crotonaldehyde, in the presence of a trace of concentrated sulfuric acid, provided aldehydes **3** (53%) and **4** (36%), respectively. Although the yields were low, the starting materials are inexpensive, the reactions could be run on large scale, and the products were easily purified by distillation. The aldehydes **3** and **4** were converted into their respective iodides **5** and **6** by (*i*) reduction of the aldehydes with sodium borohydride in ethanol to the corresponding alcohols, (*ii*) conversion of the alcohols into tosylates, and (*iii*) displacement of the tosylate moiety by iodide in refluxing acetone. Treatment of iodides **5** and **6** with 2.2 equivalents of *tert*-butyllithium at −78°C (14), followed by trapping of the resulting carbanion with either acrolein, methacrolein, or crotonaldehyde, provided the allylic alcohols **7**–**12** in good yield. Alcohols **7**, **8**, **10**, and **11** were isolated as mixtures of diastereomers that were not separated, but were oxidized under Swern conditions (15) to provide enones **13**, **14**, **16**, and **17**, respectively. Alcohols **9** and **12** were oxidized to enones **15** and **18**, respectively, with Fétizon's reagent (16), since the Swern conditions provided low yields of the desired enones and a mixture of unidentified by-products.

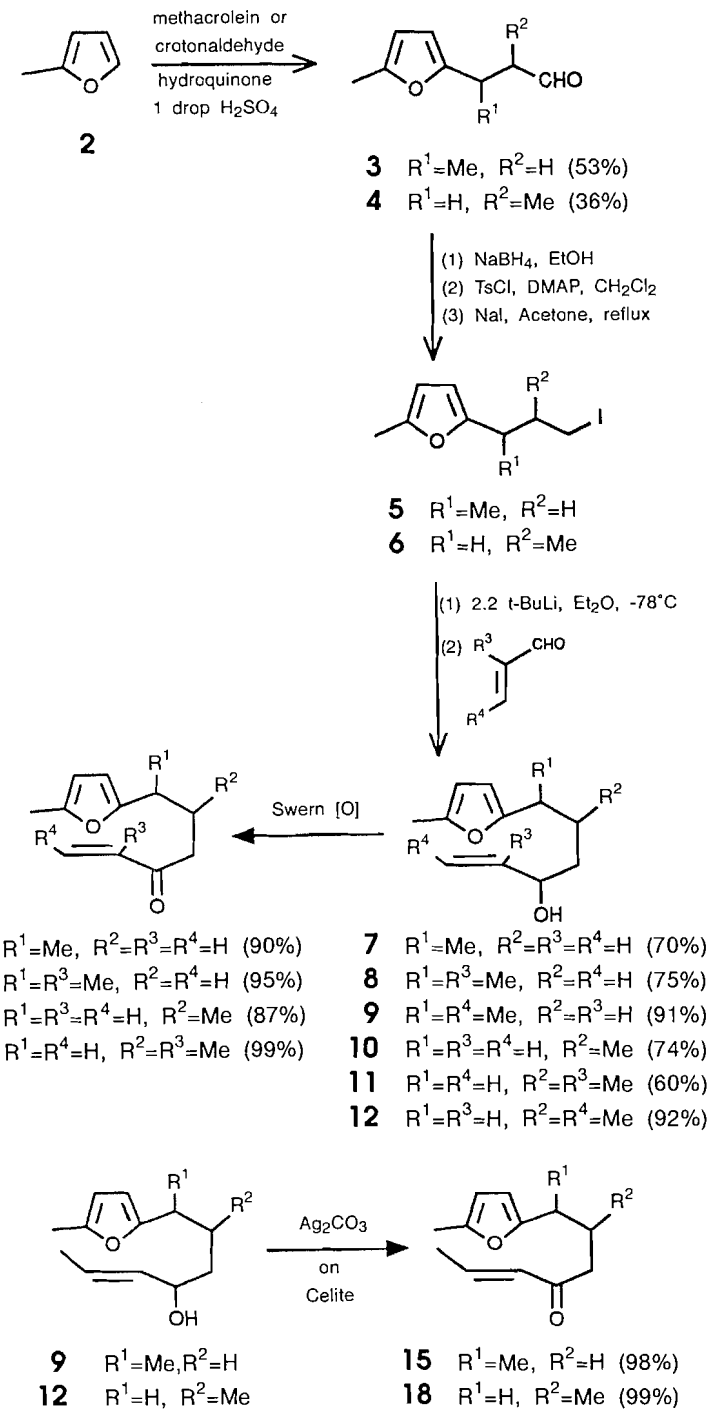
IMDAF reactions with Florisil in methylene chloride

A study was performed to determine the optimum quantity of Florisil necessary for accelerating the IMDAF reaction. Compound **13** was studied as a model since previous work had shown (8, 9*c*) that the IMDAF reaction of precursors with unsubstituted dienophiles and side chains was accelerated by Florisil. Thus, furan **13** (100 mg) was treated with various quantities of Florisil (100–200 mesh) at room temperature, and aliquots were removed at various intervals to determine the ratio of starting material to adduct (SM : A) by integration of the ^1H NMR spectrum of the mixture. Gas chromatography was not used since some of the adducts cyclo-reversed on the column. The results of this study are summarized in Table 1 and several points are noteworthy. First, the presence of Florisil was required for the IMDAF reaction to occur. Secondly, two isomeric products **19**e and **19**a were formed, with the proportion of **19**e increasing over time. Both isomers had the side chain orientated *syn* with respect to the oxygen bridge (at C-6)[6] due to an *exo* mode of attack; however, the methyl group at C-2 was positioned equatorially (*syn* to the oxygen bridge) in the major isomer (**19**e) and axially (*anti* to the oxygen bridge) in the minor isomer (**19**a) (*vide infra*). Thirdly, equilibrium was attained more rapidly as the quantity of Florisil was increased; however, the use of greater than 10 weight equivalents led to low recoveries. Finally, the equilibrium was shifted completely toward adduct formation when 10 weight equivalents of Florisil were employed, and the reaction was stirred for 19 days.

Precursors **14**–**18** were therefore treated under the optimized conditions in methylene chloride at room temperature. The results are summarized in Table 2. The IMDAF

[5]The numbering of all oxatricyclo adducts in this paper will follow the IUPAC nomenclature rules. The natural product 1,4-epoxycadinane was originally numbered as a decahydronaphthalene system and thus the "1,4" numbering in the name does not follow the IUPAC numbering.

[6]See ref. 9*c* for details regarding the assignment of the stereochemistry of the side arm relative to the oxygen bridge in oxatricyclo adducts.



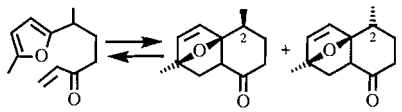
SCHEME 2

reactions of precursors **13–15** were less diastereoselective than those of the corresponding precursors **16–18** (diastereoselectivity will refer to the stereocenter on the side chain (i.e., C-2 or C-3)). Only the adducts in which the side chain was orientated *syn* to the oxygen bridge (at C-6) were detected (by ^{1}H NMR) and isolated.

Precursors **13–15** always provided a mixture of two diastereomers with the major isomer having the side-chain methyl equatorially positioned (*syn* to the oxygen bridge). The stereochemistry of the C-2 methyl group was determined as follows, using adducts **19**e and **19**a as representative examples. Irradiation of the C-2 methyl doublet resulted in the collapse of the C-2 hydrogen signal to a doublet of doublets and a triplet for compounds **19**e and **19**a, respectively. The measured coupling constants of 4.5 Hz (axial–equatorial) and 13.0 Hz (axial–axial) for the C-2 proton in compound **19**e indicated that it was axial. The coupling constant of 4.6 Hz (equatorial–equatorial and equatorial–axial) for the triplet indicated that the C-2 hydrogen was equatorial in compound **19**a.

Compounds **16–18** yielded only one isomer in which the methyl on the side chain was equatorially positioned (*anti* to the oxygen bridge). The stereochemistry of the C-3 methyl group was determined as follows using adduct **22**e as an ex-

TABLE 1. Optimization of quantity of Florisil



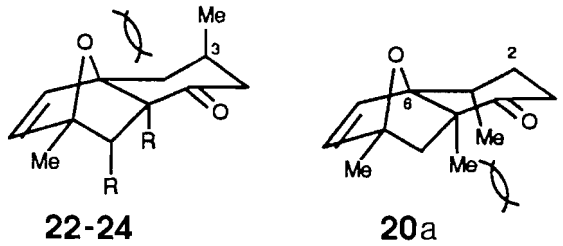
13 19e 19a

Quantity of Florisil (g)	Time (h)	Ratio **13**:**19e**:**19a**
0.0	2	100:0:0
	4	100:0:0
	9	100:0:0
	24	100:0:0
0.1	2	100:0:0
	4	78:12:10
	9	82:9:9
	24	64:20:16
0.5	2	71:12:17
	4	68:17:15
	9	44:27:29
	24	36:29:35
	48	22:41:37
	72	25:43:32
	480	18:66:16
1.0	24	30:37:33
	48	25:46:29
	456	0:87:13

ample. Since the C-3 hydrogen was "buried" in the 300 MHz ^{1}H NMR spectrum, the stereochemistry of the C-3 hydrogen atom was assigned by measuring the vicinal coupling constants of the adjacent C-2 and C-4 protons. For example, the doublet of doublets (12.0 Hz to H-3 and 14.5 Hz (germinal)) at δ 1.92 was assigned to H-2α by a combination of one- and two-dimensional NMR techniques. The large vicinal coupling constant of 12.0 Hz indicated that the C-3 hydrogen was axial, thus placing the methyl group equatorial.

A possible reason for the increased diastereoselectivity observed with compounds **16**–**18** may be due to an unfavourable 1,3-diaxial interaction, which would exist between the C-3 side-chain methyl group and the oxygen atom of the ether bridge if the methyl group were axial in adducts **22**–**24** (Fig. 1); this 1,3-diaxial interaction is absent in adducts **19**–**21**. This unfavourable interaction may promote the retro-Diels–Alder reaction, and thus equilibration occurs to provide the thermodynamically more stable equatorially substituted adduct.

The IMDAF reactions of precursors **14** and **17** also resulted in the formation of the desired adducts, although the SM:A ratios were in favour of starting material. The lower SM:A ratios relative to those of **13** and **16** may be a result of either unfavourable steric interactions in the transition state due to substitution of the dienophile, or decreased reactivity of the dienophile, which would be more electron rich than the unsubstituted dienophile due to the electron-donating methyl group (17). Substitution of the tether with a single methyl group accelerated the IMDAF reaction relative to that of the corresponding unsubstituted precursors, which showed no reaction in the presence of Florisil (8, 9*c*). Again, the IMDAF reaction of precursor **17** was more diastereoselective than that of compound **14** (*vide supra*). A higher proportion of equatorial to axial isomers was obtained for product **20** relative to adduct **19** (12:1 for compound **20** versus 7:1 for compound **19**). A very strong 1,3-diaxial interaction exists in adduct **20a** between the C-2 and C-6 methyl groups (Fig. 1), which could promote the retro-Diels–Alder reaction and thus favour equilibration to the equatorial isomer **20e**.



22-24 **20a**

FIG. 1. 1,3-Diaxial interaction in compounds **22**–**24** and **20a**.

Compounds **15** and **18** showed even less propensity to undergo the IMDAF reaction than the methacrolein precursors **14** and **17**. The reduced reactivity is likely due to steric interaction between the methyl groups on the terminus of the dienophile and on the 5-position of the furan ring in the transition state. Again, the major adducts produced (**21e** and **24e**, respectively) had the methyl group oriented equatorially on the newly formed six-membered ring.

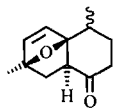
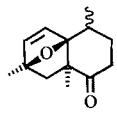
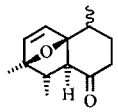
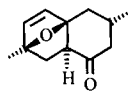
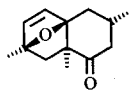
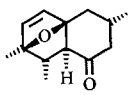
It is interesting to note that heating precursors **13**, **17**, and **18** to 40°C resulted in acceleration of the rate at which the IMDAF equilibrium was attained. This result is in contrast to the behaviour of the adducts derived from precursors with unsubstituted side arms, which revert to starting material upon heating (8, 9*c*). This method provided equilibrium ratios within 1 day similar to those obtained at room temperature after 19 days and is therefore more synthetically useful.

IMDAF reactions with methylaluminum dichloride in methylene chloride

We have reported that methylaluminum dichloride accelerates the IMDAF reaction of precursors having unsubstituted side chains (9). Both 1.1 and 0.1 equivalents of methylaluminum dichloride were shown to be effective; precursors with a substituted dienophile provided a higher ratio of adduct when the catalytic quantity of methylaluminum dichloride was employed. Precursors **13**–**15**, **17**, and **18** were therefore treated with methylaluminum dichloride, and the results are summarized in Table 2. The use of 1.1 equivalents of methylaluminum dichloride was found to be very effective for accelerating the IMDAF reaction of compounds **13**, **14**, and **17**. The products were formed stereoselectively in favour of the adduct with the methyl group situated equatorially on the newly formed cyclohexanone ring. In all cases the side chain was orientated *syn* with respect to the oxygen bridge due to an *exo* mode of attack. The reaction was complete within 15 min at −78°C compared to the 4–14 days required for equilibrium to be achieved with Florisil (Table 2), and provided the adducts in excellent yields (81–88%). Thus methylaluminum dichloride is much superior to Florisil in accelerating the IMDAF reaction.

Precursors **15** and **18**, having a terminally substituted dienophile, provided SM:A ratios of 79:21 and 42:58, respectively, with 1.1 equivalents of methylaluminum dichloride. The ratios were improved to 17:79 and 11:89 by treating precursors **15** and **18** with 0.1 equivalent of

TABLE 2. IMDAF reaction of monosubstituted precursors with Florisil and $MeAlCl_2$ (MAC)

Starting material	Lewis Acid	Time	Temperatures	SM: Adduct ratio (SM:Eq.:Ax.)	Yield[a] (%)	Adduct
13	Florisil	13 d	rt	0:87:13	70	
	Florisil	24 h	40°C	<1:84:16	67	
	Florisil	48 h	40°C	7:75:18	60	
	MAC					
	1.1 equiv.	15 min	−78°C	0:90:10	88	**19**e and **19**a
14	Florisil	24 h	rt	73:27:<1	22	
	Florisil	4 d	rt	65:35:<1	28	
	Florisil	13 d	rt	48:47:4	38	
	MAC					
	1.1 equiv.	5 min	−78°C	9:88:3	81	**20**e and **20**a
15	Florisil	24 h	rt	93:6:0	—	
	Florisil	4 d	rt	89:11:<1	9	
	Florisil	13 d	rt	73:19:8	15	
	MAC					
	1.1 equiv.	5 min	−78°C	79:16:5	15	
	0.1 equiv.	2 h	−65°C	17:75:4	74	**21**e and **21**a
16	Florisil	6 d	rt	0:100:0	85	 **22**e
17	Florisil	5 d	rt	62:38:0	—	
	Florisil	9 d	rt	52:48:0	—	
	Florisil	19 d	rt	50:50:0	40	
	Florisil	24 h	40°C	62:38:0	—	
	Florisil	48 h	40°C	56:44:0	37	
	MAC					
	1.1 equiv.	5 min	−78°C	11:89:0	88	**23**e
18	Florisil	5 d	rt	85:15:0	—	
	Florisil	8 d	rt	80:20:0	16	
	Florisil	24 h	40°C	85:15:0	13	
	MAC					
	1.1 equiv.	5 min	−65°C	61:31:8	30	
	0.1 equiv.	2 h	−65°C	11:87:2	83	**24**e

[a]Isolated yield of the major adduct.

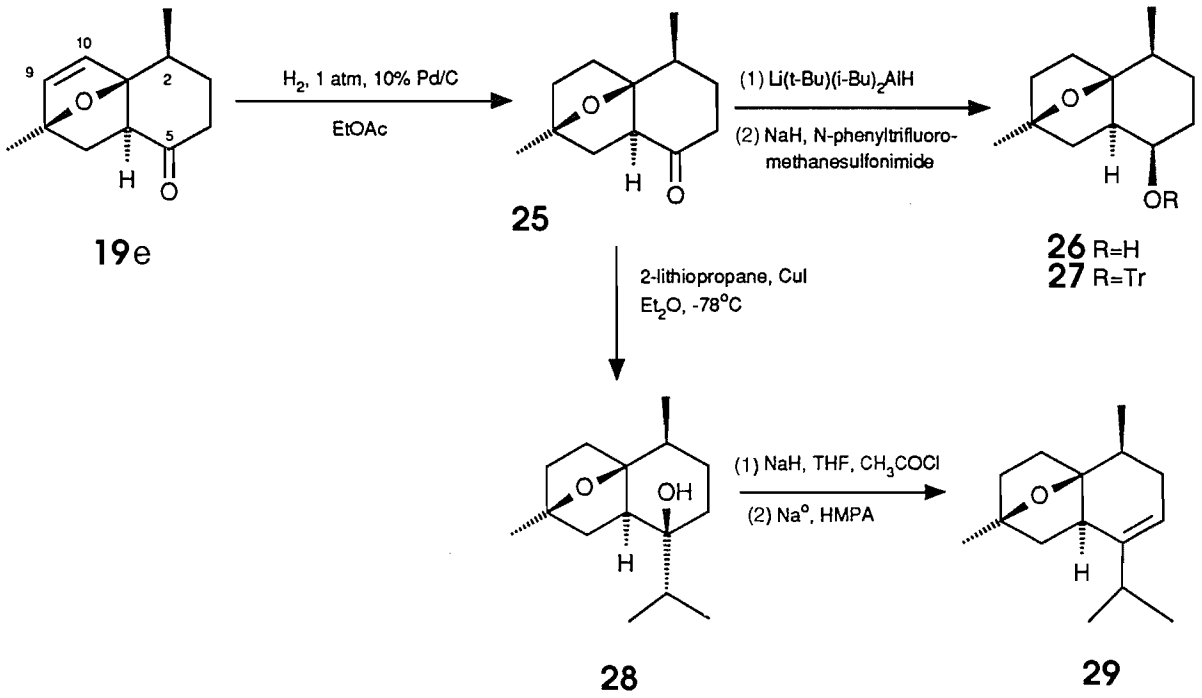
methylaluminum dichloride at −65°C for 2 h.[7,8] The major adducts (**21**e and **24**e) were those with the methyl group on the side arm in the equatorial position on the newly formed six-membered ring. The major adducts were formed in excellent yield (73% and 85%, respectively) and were easily separated from the minor adduct and starting material by flash chromatography.

Conclusions

The Florisil-mediated diastereoselective IMDAF reaction was optimized with 10 weight equivalents of Florisil in methylene chloride. Optimized results with methylaluminum dichloride were obtained at −78°C when 1.1 equivalents were employed with either unsubstituted or α-substituted dienophiles; β-substituted dienophiles gave the best results with 0.1 equivalent of methylaluminum dichloride. The IMDAF reactions with Florisil and methylaluminum dichloride were highly diastereoselective. Only the adducts with the side arm orientated *syn* with respect to the oxygen bridge were detected and isolated. In addition, the major adduct had the methyl substituent in the equatorial position of the newly formed six-membered ring, and reactions that resulted in the substituent in the C-3 position were more diastereoselective than those with the substituent in the C-2 position. Finally, the use of methylaluminum dichloride was superior to that of Florisil since the reaction time was reduced from up to 19 days with Florisil to a couple of hours with methylaluminum dichloride. In addition, higher yields of the adducts were obtained and lower temperatures were required when methylaluminum dichloride was employed. The reaction time with

[7]Catalytic quantities of $MeAlCl_2$ were not used on compounds **14** and **17** since the results with 1.1 equivalents provided the adducts in excellent yield.

[8]A paper describing competitive complexation NMR studies with $MeAlCl_2$ has recently been submitted, which provides evidence to support our hypothesis (ref. 9) on why catalytic quantities of $MeAlCl_2$ provide higher ratios of adduct to starting material than when 1.1 equivalents of $MeAlCl_2$ are used.



SCHEME 3

Florisil, however, could be reduced from 19 days to 1 day by refluxing the mixture at 40°C in methylene chloride.

Thus, these reactions constitute the first examples of diastereoselective IMDAF reactions with the diene and dienophile connected by a four-carbon-atom tether. In addition, adducts containing up to five asymmetric centers, all of known relative stereochemistry, were formed in one step from an acyclic precursor. The accompanying synthesis of 1,4-epoxycadinane illustrates the synthetic usefulness of the above IMDAF reactions.

The synthesis of (±)-1,4-epoxycadinane

The natural product 1,4-epoxycadinane **1** (Scheme 1) was isolated as a crystalline, optically active, solid from the brown alga *Dilophus fasciola* in 1979 (18*a*). 1,4-Epoxycadinane **1** is a sesquiterpene containing the cadinane ring (18*b*, 18*c*) system with five asymmetric centres and an oxygen ether linkage between carbons 1 and 8 (IUPAC numbering). While there have been many reported syntheses of natural products containing the cadinane ring system, 1,4-epoxycadinane has not been synthesized (19).

The methyl group at C-2 and the isopropyl group at C-5 are both equatorially positioned on ring C of 1,4-epoxycadinane. In addition, the C-2 methyl group and C-6 hydrogen are *syn* and *anti*, respectively, to the oxygen bridge. Since the IMDAF reaction of precursor **13** provided adduct **19e**, which contains four of the five asymmetric centres present in 1,4-epoxycadinane, as the major product (Table 2), we investigated the conversion of adduct **19e** into 1,4-epoxycadinane. The synthesis of 1,4-epoxycadinane would therefore entail (1) reduction of the C9—C10 double bond and (2) stereoselective conversion of the C-5 ketone into the equatorially positioned isopropyl group.

The first step in the synthesis of 1,4-epoxycadinane was routine. Compound **19e** was hydrogenated using 10% palladium on carbon in ethyl acetate to provide compound **25** in 95% yield (Scheme 3) (20). The absence of the vinyl protons at δ 6.08 and 6.18 in the ^{1}H NMR spectrum indicated the carbon–carbon double bond had been reduced, while the presence of the absorption at 1713 cm^{-1} in the IR spectrum confirmed that the ketone had not been reduced to the alcohol.

The conversion of the carbonyl moiety into the equatorially positioned isopropyl group proved to be more troublesome than initially expected. Our first approach involved (1) a stereoselective reduction of the ketone to an axial alcohol, (2) conversion of the alcohol into a good leaving group, and (3) an S_N2 displacement of the leaving group with an isopropyl moiety. Reduction of ketone **25** with lithium *tert*-butyldiisobutylaluminum hydride in THF at −78°C provided a single compound **26** in which the alcohol group was axial (Scheme 3). The attempted conversion of alcohol **26** into the triflate **27**, employing a variety of conditions (21), provided only starting material upon work-up, although TLC indicated that the alcohol had reacted. Since it was possible that the triflate was being hydrolyzed during work-up, the above reaction was repeated and the mixture added directly to an ethereal solution of isopropylmagnesium chloride in the presence of copper(I) iodide to attempt an *in situ* displacement of the triflate. Again, only starting material was recovered. Attempts to prepare the tosylate of alcohol **26** were equally unsuccessful under a variety of conditions (22). An alternative approach was therefore required.

Since the bulky reducing agent lithium *tert*-butyldiisobutylaluminum hydride reduced the ketone in compound **25** exclusively from the α face, attack by isopropyl nucleophile should provide alcohol **28** having the isopropyl group in the equatorial position (Scheme 3). Removal of the tertiary hydroxyl group with retention of stereochemistry would then complete the synthesis. Although compound **25** did not react with isopropylmagnesium chloride (quantitative recovery of starting material) it did react smoothly with the less basic, higher order, cuprate (23) of 2-lithiopropane (24)

(prepared by adding 2-lithiopropane (8 equivalents) to copper(I) iodide (3 equivalents)) in ether at 0°C to provide a single alcohol **28**. Treatment of compound **28** under a variety of conditions reported for the deoxygenation of tertiary alcohols (25) did not provide 1,4-epoxycadinane. Either starting material **28** was recovered or eliminated product **29** was isolated and was inert to catalytic hydrogenation (H_2, PtO_2, or 10% Pd/C) (Scheme 3).

Since the shorter synthetic routes for the conversion of the ketone carbonyl into an isopropyl group failed, a longer sequence was utilized (Scheme 4). This synthetic strategy takes advantage of the fact that the presence of the oxygen bridge in compound **25** does not allow the adjacent cyclohexanone ring to undergo chair interconversions. Thus, elaboration of the ketone in compound **25** to an aldehyde group via Wittig chemistry should provide an equatorially disposed aldehyde under thermodynamic conditions (see compound **31**, Scheme 4). The aldehyde (at C-5) would therefore be *trans* to the methyl group at C-2, thus providing the correct relative stereochemistry at C-5.

Wittig reaction of ketone **25** with the ylid of (methoxymethyl)triphenylphosphonium chloride provided compound **30** (82%) as a 2:3 mixture of double bond isomers. No attempt was made to separate these isomers. The mixture was treated immediately with dilute HCl in THF to provide aldehyde **31** (63%) as a single isomer (26). The stereochemistry of the aldehyde was determined by decoupling experiments. Irradiation of the aldehyde signal resulted in a collapse of the signal centered at δ 2.18 to a doublet (3.3 Hz) of triplets (10.9 Hz). These coupling constants are indicative of a vicinal axial–equatorial and two axial–axial couplings, respectively. Therefore the C-5 hydrogen was axial, establishing the aldehyde in the desired equatorial position.

The aldehyde **31** was converted into the methyl ketone **33** in two steps. Treatment of **31** with excess methyllithium at −78°C for 1.5 h provided compound **32** (97%) as a 7:3 mixture of diastereomers. The mixture was smoothly oxidized to the methyl ketone **33** (90%) under Swern conditions (15). The stereochemistry at C-5 was again confirmed by measuring the coupling constants of the C-5 hydrogen (δ 2.3, doublet of triplets). The single coupling constant of 3.1 Hz (doublet, axial–equatorial) and two 10.4 Hz couplings (triplet, axial–axial) established that the C-5 hydrogen in compound **33** was axial.

Wittig reaction of ketone **33** with a 20-fold excess of the ylid of methylenetriphenylphosphorane (27) provided compound **34** (74%) and some unreacted starting material (20%). The mixture was easily separated and the unreacted starting material was recycled. Finally, vinyl compound **34** was hydrogenated (H_2, PtO_2, 1 atm (1 atm = 101.3 kPa)) to provide 1,4-epoxycadinane in 93% yield. Although the ^{13}C and ^1H NMR spectra of synthetic 1,4-epoxycadinane agreed very well with the data reported for the authentic sample (Table 3), irradiation of the proton at δ 1.81 did not result in a collapse of the methyl doublets at δ 0.73 and δ 0.89 as reported by Fattorusso *et al.* (i.e., the isopropyl methine hydrogen) (18*a*). Through 2D-NMR techniques the isopropyl methine hydrogen was assigned to the signal at δ 1.58. Fattorusso informed us that the reported irradiation of the peak at δ 1.81 was a typographical error and should have been δ 1.58.

Thus, (±)-1,4-epoxycadinane was synthesized in 14 steps from 2-methylfuran in 9% overall yield. The relative stereochemistry of four of the five stereocentres was controlled by the IMDAF reaction, while the rigidity of the oxatricyclo adduct was used effectively to control the stereochemistry of the fifth stereocentre. This synthesis clearly illustrates the synthetic usefulness of the IMDAF reaction for the preparation and control of remote stereocentres.

Experimental

General methods

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Boiling points refer to the air-bath temperature using Kugelrohr distillation apparatus, and are also uncorrected. Infrared spectra were obtained as thin films (oils) on either NaCl or KBr plates or as KBr pellets (solids). The infrared spectra were recorded on either a Nicolet 5-DX FT-IR spectrophotometer or a Mattson model 4030 FT-IR.

Nuclear magnetic resonance spectra were obtained on one of three instruments: Bruker AC-300 (^1H 300 MHz, ^{13}C 75 MHz), Bruker ACE-200 (^1H 200 MHz, ^{13}C 50 MHz), or a Bruker AM-400 spectrometer (^1H 400 MHz). Deuterochloroform was used both as the solvent, and as the internal standard (^1H, δ 7.27, ^{13}C, δ 77.0), unless otherwise stated. All ^1H NMR spectra listed will have the following format: chemical shift (in ppm), (multiplicity, number of protons, coupling constants (Hz), assignment). The abbreviations used to describe the multiplicities are as follows: br = broadened, s = singlet, d = doublet, t = triplet, q = quartet, and ABq refers to a quartet due to an AB spin system. The ^{13}C NMR spectra listed will have the following format: chemical shift (in ppm), (number of attached protons as determined by DEPT experiments).

Low-resolution mass spectra were recorded using either a Varian CH5 spectrometer or a VG 7070 instrument. The data are listed as mass (*m/e*), (relative intensity, assignment). The spectra were obtained either by the electron-impact (EI) method or field ionization (FI), and the method will only be listed if FI was used. High-resolution mass spectra were recorded on a Kratos MS80. Microanalyses were performed either by Guelph Chemical Laboratories Limited, Guelph, Ontario, or by Mrs. D. Fox, Department of Chemistry, University of Calgary.

Solvents were either dried by standard methods (28), then distilled prior to use, or were purchased as anhydrous solvents in Sure-Seal® bottles from the Aldrich Chemical Company. THF was dried over sodium and benzophenone, as was diethyl ether. Methylene chloride, diisopropyl amine, and triethylamine were dried over CaH_2. Methanol was refluxed with Mg^0 metal for 12 h, then distilled. DMSO was dried over NaOH. Acetonitrile, DMF, and diethyl ether were purchased as anhydrous solvents, and HPLC-grade acetone was used.

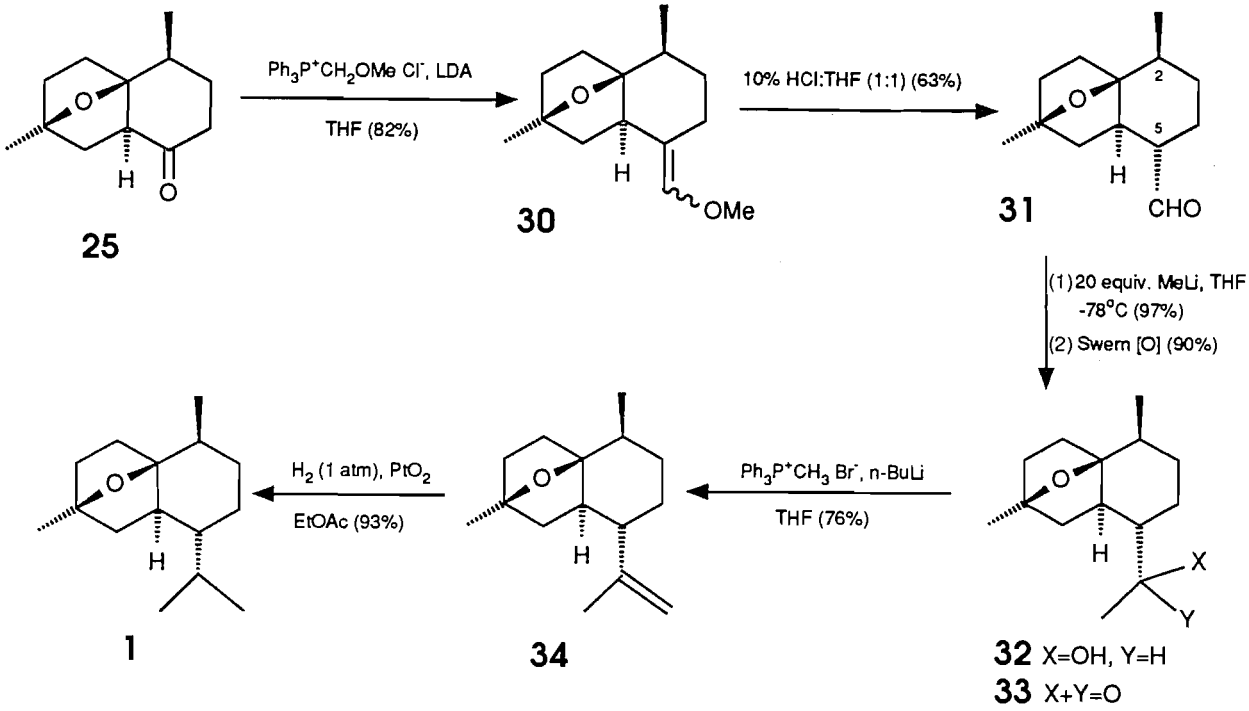
All glassware and syringes were dried in a 120°C oven for at least 4 h, then cooled under a stream of argon, or in a desiccator containing Drierite. Reactions that were sensitive to moisture or atmospheric conditions were performed under an argon atmosphere. Compounds were purified by flash chromatography using various ratios of petroleum ether and ethyl acetate.

The experimental procedures for the preparation of compounds **3–17** have been deposited as Supplementary Material.[9]

General procedure 1: IMDAF reactions in Florisil

The freshly distilled enone (1 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and placed in an argon-purged round-bottom flask. To this was added Florisil (100–200 mesh, 10 weight equivalents to the enone). The reaction was wrapped in foil and stirred at the appropriate temperature for the required length of time. The reaction was then filtered, the Florisil washed well with EtOAc (20 mL), and the

[9]Supplementary material mentioned in the text may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0S2.



SCHEME 4

TABLE 3. A comparison of the ^{13}C and ^{1}H NMR spectra of natural and synthetic 1,4-epoxycadinane **1**

Multiplicity	Natural product	Synthetic product
	^{13}C NMR data	
Quartet	15.96	15.99
Quartet	16.22	16.22
Quartet	21.61	21.61
Quartet	21.79	21.83
Triplet	24.46	24.37
Triplet	31.84	31.81
Triplet	34.69	34.64
Triplet	37.54	37.50
Triplet	44.76	44.68
Doublet	27.47	27.38
Doublet	34.82	34.78
Doublet	48.15	48.08
Doublet	48.66	48.60
Singlet	83.32	83.27
Singlet	88.02	86.97
	Selected ^{1}H NMR data	
Me-12	0.73	0.74
Me-13	0.89	0.89
Me-15	1.05	1.06
Me-14	1.44	1.45

solvent removed *in vacuo* without external heating to provide the crude product, which could be purified by flash chromatography (pet. ether: EtOAc).

General procedure 2: IMDAF reactions using Lewis acid

The freshly distilled enone (0.2 mmol) was dissolved in dry CH_2Cl_2 (10 mL), placed in an argon-purged 3-necked flask, and cooled to the appropriate temperature. Methylaluminum dichloride (1.0 M in hexane) was added to the cooled enone solution, and the reaction was stirred for the appropriate length of time. The reaction was quenched with 10% $NaHCO_3$ (10 mL), and warmed until no frozen material remained. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), then the organic layer was washed with H_2O (15 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* without external heating to provide the crude product, which was purified by flash chromatography (pet. ether: EtOAc).

*(6αH)-2β,8β-Dimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (**19e**) and (6αH)-2α,8β-dimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (**19a**)*

Enone **13** (380.1 mg) was stirred with Florisil (4.0 g) according to general procedure 1 for 13 days at room temperature under argon to provide a mixture of **13**:**19e**:**19a** in a ratio of 0:87:13. The isolated yields were **19e**: 70% (239 mg) and **19a**: 71% (29 mg).

Enone **13** (48.8 mg, 0.254 mmol) was treated with excess $MeAlCl_2$ (280 μL, 0.280 mmol) according to general procedure 2 at −78°C for 15 min to provide a mixture of **13**:**19e**:**19a** in a ratio of 0:90:10 with quantitative recovery (**19e**: 88% (40 mg); **19a**: 90% (4.2 mg)). The above mixtures were separated using flash chromatography (9:1, pet. ether: EtOAc).

*Compound **19e** (colourless oil)*: IR (neat): 1709, 1108 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.06(d, 3H, J = 7.0 Hz, C-2-CH_3), 1.52(s, 3H, C-8-CH_3), 1.55(dd, 1H, $J_{7\alpha,6\alpha}$ = 8.3 Hz, J_{gem} = 11.8 Hz, H-7α), 1.73(dq, 1H, $J_{3\beta,4\beta}$ = 5.6 Hz, $J_{3\beta,2\alpha}$ = 13.0 Hz, $J_{3\beta,4\beta}$ = 13.0 Hz, J_{gem} = 13.0 Hz, H-3β), 1.88(ddd, 1H, $J_{3\alpha,2\alpha}$ = 4.5 Hz, J_{gem} = 13.0 Hz, H-3α), 2.10(dd, 1H, $J_{7\beta,6\alpha}$ = 3.4 Hz, J_{gem} = 11.8 Hz, H-7β), 2.28(dd, 1H, $J_{6\alpha,7\beta}$ = 3.4 Hz, $J_{6\alpha,7\alpha}$ = 8.3 Hz, H-6α), 2.35(ddq, 1H, $J_{2\alpha,3\alpha}$ = 4.5 Hz, $J_{2\alpha,12}$ = 7.0 Hz, $J_{2\alpha,3\beta}$ = 13.0 Hz, H-2α), 2.28–2.45(overlapping m, 2H, H-4α and H-4β), 6.07 and 6.17(ABq, 2H, J = 5.5 Hz, H-9 and H-10); ^{13}C NMR (75 MHz) δ: 16.32(q), 18.68(q), 29.68(t), 33.58(d), 35.65(t), 41.61(t), 53.46(d), 85.61(s), 93.62(s), 137.17(d), 140.89(d), 209.70(s); mass spectrum, *m/e*: 192(4, M^+), 122(100, $M-C_4H_6O$, retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{12}H_{16}O_2$: 192.1151; found: 192.1154.

*Compound **19a** (colourless oil)*: IR (neat): 1710 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.30(d, 3H, $J_{12,2\beta}$ = 7.2 Hz, C-2-CH_3), 1.52(s, 3H, C-8-CH_3), 1.58(dd, 1H, $J_{7\alpha,6\alpha}$ = 8.4 Hz, J_{gem} = 11.8 Hz, H-7α), 1.69(m, 1H, $J_{3\alpha,2\beta}$ = 4.4 Hz, $J_{3\alpha,4\beta}$ = 4.4 Hz, $J_{3\alpha,4\alpha}$ = 5.6 Hz,

J_{gem} = 13.6 Hz, H-3α), 2.10(dd, 1H, $J_{7\beta,6\alpha}$ = 3.4 Hz, J_{gem} = 11.7 Hz, H-7β), 2.10(overlapping ddt, 1H, H-3β), 2.32(dt, 1H, $J_{4\beta,3\alpha}$ = 4.6 Hz, $J_{4\beta,3\beta}$ = 4.6 Hz, J_{gem} = 15.3 Hz, H-4β), 2.34(m, 1H, H-2β), 2.37(dd, 1H, $J_{6\alpha,7\beta}$ = 3.4 Hz, $J_{6\alpha,7\alpha}$ = 8.4 Hz, H-6α), 2.51(ddd, 1H, $J_{4\alpha,3\alpha}$ = 5.5 Hz, $J_{4\alpha,3\beta}$ = 11.8 Hz, J_{gem} = 15.5 Hz, H-4α), 6.22 and 6.29(ABq, 2H, J = 5.7 Hz, H-9 and H-10); ^{13}C NMR (75 MHz) δ: 16.18(q), 18.64(q), 27.85(t), 30.35(d), 35.79(t), 36.63(t), 51.32(d), 85.61(s), 93.71(s), 135.04(d), 141.44(d), 210.41(s); mass spectrum, *m/e*: 192(10, $M^{+\cdot}$), 122(100, $M-C_4H_6O$. retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{12}H_{16}O_2$: 192.1151; found: 192.1147.

2β,6α,8β-Trimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (20e)

Enone **14** (108.0 mg) was stirred with Florisil (1.1 g) according to general procedure 1 for 13 days at room temperature under argon to provide a mixture of **14**:**20**e:**20**a in a ratio of 48:47:4 in quantitative yield. The starting material **14** could be separated from the adducts by flash chromatography (9:1); however, the minor isomer **20**a could not be completely separated from the major isomer **20**e. Only the major isomer could therefore be characterized.

Enone **14** (79.5 mg, 0.385 mmol) was treated with excess $MeAlCl_2$ (424 μL, 0.424 mmol) according to general procedure 2 at −78°C for 5 min to provide a mixture of **14**:**20**e:**20**a in a ratio of 9:88:3 with quantitative recovery. IR (KBr): 1707 cm^{-1}; ^{1}H NMR (400 MHz) δ: 1.07(s, 3H, C-6-CH_3), 1.07(d, 3H, J = 6.8 Hz, C-2-CH_3), 1.12(d, 1H, J_{gem} = 11.7 Hz, H-7α), 1.52(s, 3H, C-8-CH_3), 1.76(m, 1H, $J_{3\beta,4\beta}$ = 3.0 Hz, $J_{3\beta,2\alpha}$ = 11.7 Hz, $J_{3\beta,4\alpha}$ = 13.1 Hz, J_{gem} = 13.1 Hz, H-3β), 1.82–1.89(m, 1H, H-3α), 2.38(ddq, 1H, $J_{2\alpha,3\alpha}$ = 4.2 Hz, J = 6.8 Hz, $J_{2\alpha,3\beta}$ = 11.7 Hz, H-2α), 2.40(dt, 1H, $J_{4\beta,3\alpha}$ = 4.1 Hz, $J_{4\beta,3\beta}$ = 4.1 Hz, J_{gem} = 14.6 Hz, H-4β), 2.54(d, 1H, J_{gem} = 11.7 Hz, H-7β), 2.65(dt, 1H, $J_{4\alpha,3\alpha}$ = 6.0 Hz, $J_{4\alpha,3\beta}$ = 14.3 Hz, J_{gem} = 14.3 Hz, H-4α), 6.13 and 6.26(ABq, 2H, J = 5.6 Hz, H-9 and H-10); ^{13}C NMR (50 MHz) δ: 16.59(q), 18.95(q), 22.40(q), 29.19(t), 38.31(t), 30.39(d), 44.03(t), 57.17(s), 85.55(s), 95.29(s), 135.37(d), 141.30(d), 213.72(s); mass spectrum, *m/e*: 206(5, $M^{+\cdot}$), 122(100, $M-C_5H_8O$, retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1306.

(6αH)-2β,7α,8α-Trimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (21e) and (6αH)-2α,7α,8α-trimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (21a)

Enone **15** (95.4 mg) was stirred with Florisil® (0.95 g) according to general procedure 1 for 13 days at room temperature under argon to provide a mixture of **15**:**21**e:**21**a in a ratio of 73:19:8 in quantitative yield.

Enone **15** (145.2 mg, 0.704 mmol) was treated with excess $MeAlCl_2$ (774 μL, 0.774 mmol) according to general procedure 2 at −78°C for 5 min to provide a mixture of **15**:**21**e:**21**a in a ratio of 79:16:5 with quantitative recovery.

Enone **15** (350.1 mg, 1.70 mmol) was treated with catalytic $MeAlCl_2$ (170 μL, 0.17 mmol) at −65°C for 2 h to provide a mixture of **15**:**21**e:**21**a in a ratio of 17:75:4 with 98% recovery. Flash chromatography (9:1) provided the compounds **15** (4.0 mg), and **21**e (250 mg) and **21**a (2.0 mg).

Major isomer 21e: mp 55–56°C; IR (neat): 1709 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.94(d, 3H, J = 7.0 Hz, C-7-CH_3), 1.10(d, 3H, J = 6.9 Hz, C-2-CH_3), 1.52(s, 3H, C-8-CH_3), 1.73(dq, 1H, $J_{3\beta,4\beta}$ = 3.9 Hz, $J_{3\beta,2\alpha}$ = 13.6 Hz, $J_{3\beta,4\alpha}$ = 13.6 Hz, J_{gem} = 13.6 Hz, H-3β), 1.83(d, 1H, $J_{6\alpha,7\beta}$ = 4.2 Hz, H-6α), 1.89(m, 1H, $J_{3\alpha,4\beta}$ = 3.3 Hz, $J_{3\alpha,2\alpha}$ = 5.0 Hz, $J_{3\alpha,4\alpha}$ = 5.0 Hz, J_{gem} = 13.6 Hz, H-3α), 2.33(m, 1H, $J_{2\alpha,3\alpha}$ = 4.2 Hz, J = 6.9 Hz, $J_{2\alpha,3\beta}$ = 13.6 Hz, H-2α), 2.41(dq, 1H, $J_{7\beta,6\alpha}$ = 4.2 Hz, J = 7.0 Hz, H-7β), 2.30–2.42(m, 1H, H-4α), 2.49(dt, 1H, $J_{4\beta,3\alpha}$ = 3.6 Hz, $J_{4\beta,3\beta}$ = 3.6 Hz, J_{gem} = 14.4 Hz, H-4β), 6.17 and 6.23 (ABq, 2H, J = 5.6 Hz, H-9 and H-10); ^{13}C NMR(50 MHz) δ: 16.21(q), 17.07(q), 17.15(q), 29.42(t), 33.66(d), 41.60(t), 43.47(d), 61.36(d), 88.41(s), 93.07(s), 138.38(d), 138.66(d), 210.28(s); mass spectrum, *m/e*: 206(14, $M^{+\cdot}$), 122(100, $M-C_5H_7O$, retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1315.

Minor isomer 21a: IR (neat): 1708 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.96(d, 3H, J = 7.0 Hz, C-7-CH_3), 1.31(d, 3H, J = 7.3 Hz, C-2-CH_3), 1.52(s, 3H, C-8-CH_3), 1.70–1.80(m, 1H), 1.92(d, 1H, $J_{6\alpha,7\beta}$ = 4.2 Hz, H-6α), 2.00–2.20(overlapping m, 2H), 2.30(m, 1H, $J_{2\alpha,3\alpha}$ = 4.8 Hz, $J_{2\alpha,3\beta}$ = 4.8 Hz, J = 7.3 Hz, H-2β), 2.30–2.44(overlapping m, 2H), 2.40(dq, 1H, $J_{7\beta,6\alpha}$ = 4.2 Hz, J = 7.2 Hz, H-7β), 2.45–2.56(m, 1H), 6.22(d, 1H, $J_{10,9}$ = 5.7 Hz, H-10), 6.45(d, 1H, $J_{9,10}$ = 5.7 Hz, H-9); ^{13}C NMR(50 MHz) δ: 16.26(q), 17.08(q), 17.16(q), 29.70(t), 36.62(t), 30.67(d), 43.69(d), 65.82(d), 88.22(s), 93.19(s), 136.24(d), 139.09(d), 210.85(s); mass spectrum, *m/e*: 206 (23, $M^{+\cdot}$); HRMS (EI) calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1301.

(6αH)-3α,8α-Dimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (22e)

Enone **16** (372.8 mg) was stirred with Florisil (3.79 g) according to general procedure 1 for 6 days at room temperature under argon to provide a mixture of **16**:**22**e in a ratio of 0:100 in 75% yield after purification by flash chromatography (3:1). The product was obtained as a white crystalline solid (280.0 mg), mp 62–64.5°C; IR (KBr): 1700 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.05(d, 3H, J = 6.1 Hz, C-3-CH_3), 1.56(s, 3H, C-8-CH_3), 1.59(dd, 1H, $J_{7\alpha,6\alpha}$ = 8.2 Hz, J_{gem} = 11.8 Hz, H-7α), 1.92(dd, 1H, $J_{2\alpha,3\beta}$ = 12.0 Hz, J_{gem} = 14.5 Hz, H-2α), 2.12–2.20(m, 2H, H-3β and H-4α), 2.18(dd, 1H, $J_{7\beta,6\alpha}$ = 3.4 Hz, J_{gem} = 11.8 Hz, H-7β), 2.30(dd, 1H, $J_{6\alpha,7\beta}$ = 3.4 Hz, $J_{6\alpha,7\alpha}$ = 8.2 Hz, H-6α) 2.38(dt, 1H, $J_{2\beta,3\beta}$ = 3.2 Hz, $J_{2\beta,4\beta}$ = 3.2 Hz, J_{gem} = 14.5 Hz, H-2β), 2.45(ddd, 1H, $J_{4\beta,2\beta}$ = 2.2 Hz, $J_{4\beta,3\beta}$ = 3.2 Hz, J_{gem} = 10.2 Hz, H-4β), 6.15 and 6.21(ABq, 2H, J = 7.9 Hz, H-9 and H-10); ^{13}C NMR (75 MHz) δ: 18.67(q), 21.94(q), 29.08(d), 35.42(t), 37.15(t), 50.02(t), 52.87(d), 85.99(s), 90.36(s), 137.61(d), 141.15(d), 209.19(s); mass spectrum, *m/e*: 192(4, $M^{+\cdot}$), 122(100 $M-C_4H_6O$, retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{12}H_{16}O_2$: 192.1151; found: 192.1148.

3α,6α,8α-Trimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (23e)

Enone **17** (75.7 mg) was stirred with Florisil (760 mg) according to general procedure 1 for 19 days at room temperature under argon to provide a mixture of **17**:**23**e in a ratio of 50:50 in quantitative recovery.

Enone **17** (79.5 mg, 0.385 mmol) was treated with excess $MeAlCl_2$ (424 μL, 0.424 mmol) according to general procedure 2 at −78°C for 5 min to provide a mixture of **17**:**23**e in a ratio of 11:89 with quantitative recovery. Flash chromatography (9:1) provided the compounds **17** (4.5 mg), and **23**e (84.7 mg) as a white crystalline solid, mp 45–49°C; IR (KBr): 1705 cm^{-1}; ^{1}H NMR (400 MHz) δ: 1.04(d, 3H, J = 6.2 Hz, C-3-CH_3), 1.08(s, 3H, C-6-CH_3), 1.14(d, 1H, J_{gem} = 11.8 Hz, H-7α), 1.51(s, 3H, C-8-CH_3), 1.89(dd, 1H, $J_{2\alpha,3\beta}$ = 12.0 Hz, J_{gem} = 14.1 Hz, H-2α), 2.18(m, 1H, $J_{3\beta,2\beta}$ = 4.2 Hz, $J_{3\beta,4\beta}$ = 4.2 Hz, J = 6.2 Hz, $J_{3\beta,2\alpha}$ = 12.0 Hz, $J_{3\beta,4\alpha}$ = 12.0 Hz, H-3β), 2.23(dt, 1H, $J_{2\beta,4\beta}$ = 2.1 Hz, $J_{2\beta,3\beta}$ = 4.2 Hz, J_{gem} = 14.1 Hz, H-2β), 2.32(t, 1H, $J_{4\alpha,3\beta}$ = 12.3 Hz, J_{gem} = 12.3 Hz, H-4α), 2.38(ddd, 1H, $J_{4\beta,2\beta}$ = 2.1 Hz, $J_{4\beta,3\beta}$ = 4.2 Hz, J_{gem} = 13.6 Hz, H-4β), 2.57(d, 1H, J_{gem} = 11.7 Hz, H-7β), 6.14 and 6.29(ABq, 2H, J = 5.6 Hz, H-9 and H-10); ^{13}C NMR (50 MHz) δ: 18.78(q), 21.87(q), 22.12(q), 28.02(d), 34.43(t), 43.40(t), 46.52(t), 85.68(s), 91.79(s), 135.74(d), 141.53(d), 212.89(s); mass spectrum, *m/e*: 206(3, $M^{+\cdot}$), 122(100, $M-C_5H_8O$, retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1316.

(6αH)-3α,7α,8α-Trimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (24e)

Enone **18** (233.8 mg) was stirred with Florisil (2.4 g) according to general procedure 1 for 8 days at room temperature under argon to provide a mixture of **18**:**24**e in a ratio of 80:20 in 68% yield.

Enone **18** (103.6 mg, 0.500 mmol) was treated with excess $MeAlCl_2$ (552 μL, 0.552 mmol) according to general procedure 2

at −65°C for 5 min to provide a **18**:**24**e ratio of 42:58 with 96% recovery. Flash chromatography (9:1) provided the compounds **18** (32.8 mg), and **24**e (37.8 mg) as oils.

Enone **17** (60.5 mg, 0.293 mmol) was treated with catalytic $MeAlCl_2$ (30 μL, 0.03 mmol) at −65°C for 9 min to provide, after flash chromatography (9:1), **17** (41.6 mg), **24**e (12.5 mg), and **24**a (2.5 mg) with 93% recovery. Compound **24**a was always contaminated with compound **24**e and therefore could not be characterized. Compound **24**e: IR (neat): 1710 cm^{-1}; ^1H NMR (400 MHz) δ: 0.94(d, 3H, J = 7.1 Hz, C-7-CH_3), 1.05(d, 3H, J = 6.2 Hz, C-3-CH_3), 1.50(s, 3H, C-8-CH_3), 1.82(d, 1H, $J_{6\alpha,7\beta}$ = 4.1 Hz, H-6α), 1.85(dd, 1H, $J_{2\alpha,3\beta}$ = 11.9 Hz, J_{gem} = 14.6 Hz, H-2α), 2.07(dd, 1H,$J_{4\alpha,3\beta}$ = 13.0 Hz, J_{gem} = 13.0 Hz, H-4α), 1.90–2.16(m, 1H, H-3β), 2.33(dt, 1H, $J_{2\beta,3\beta}$ = 3.1 Hz, $J_{2\beta,4\beta}$ = 3.1 Hz, J_{gem} = 14.6 Hz, H-2β), 2.45(dt, 1H, $J_{4\beta,2\beta}$ = 3.1 Hz, $J_{4\beta,3\beta}$ = 3.1 Hz, J_{gem} = 13.0 Hz, H-4β), 2.46(dq, 1H, $J_{7\beta,6\alpha}$ = 4.1 Hz, J = 7.1 Hz, H-7β), 6.20 and 6.23(ABq, 2H, J = 5.6 Hz, H-9 and H-10); ^{13}C NMR (50 MHz) δ: 16.96(q), 17.02(q), 21.91(q), 28.77(d), 37.30(t), 43.17(d), 49.94(t), 60.65(d), 88.69(s), 89.87(s), 138.72(d), 138.84(d), 209.48(s); mass spectrum, *m/e*: 206(2, $M^{\cdot+}$), 122(100, M−C_5H_8O, retro IMDAF–McLafferty rearrangement); HRMS (EI) calcd. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1307.

(6αH)-2β,8α-Dimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undecan-5-one (25)

Ketone **19**e (0.13 g, 0.65 mmol) was dissolved in EtOAc (10 mL) and a small spatula tip of 10% palladium on carbon was added. The flask was evacuated, then filled with hydrogen gas three times via a hydrogen-filled balloon attached to a three-way stopcock. The reaction was stirred at room temperature for 1 h, filtered through Celite®, and the solvent removed *in vacuo* to produce the hydrogenated ketone **25** (0.12 g, 0.62 mmol) as a colourless oil in 95% yield, bp 58–62°C/0.025 Torr (1 Torr = 133.3 Pa), IR (neat): 1713, 1088 cm^{-1}; ^1H NMR (300 MHz) δ: 1.10(d, 3H, J = 6.9 Hz, C-2-CH_3), 1.42(s, 3H, C-8-CH_3), 1.45–2.00(overlapping m, 7H), 2.11(ddq, 1H, $J_{2\alpha,3\alpha}$ = 4.4 Hz, J = 6.9 Hz, $J_{2\alpha,3\beta}$ = 12.4 Hz, H-2α irradiation of methyl doublet at δ 1.10 resulted in collapse of signal to dd), 2.00–2.20(m, 1H), 2.30–2.50(overlapping m, 3H); ^{13}C NMR (75 MHz) δ: 15.21(q), 20.94(q), 30.93(t), 33.94(t), 37.24(t), 37.62(t), 41.42(t), 33.94(d), 57.04(d), 83.26(s) 89.87(s), 210.61(s); mass spectrum, *m/e*: 194(73, $M^{\cdot+}$); Anal. calcd. for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.29, H 9.51.

(E)- and (Z)-(6αH)-2β,8α-Dimethyl-5-(methoxymethylene)-11-oxatricyclo[6.2.1.0^{1,6}]undecane (30)

(Methoxymethyl)triphenylphosphonium chloride (0.82 g, 2.38 mmol) was suspended in dry THF (30 mL) and cooled to −78°C. To this was added LDA (1.59 mL, 2.38 mmol), and the reaction was stirred for 10 min at −78°C, then warmed to 0°C for 30 min and subsequently to room temperature for 30 min before being cooled to 0°C once more. Ketone **25** (0.11 g, 0.54 mmol) was dissolved in THF (6 mL), added dropwise to the anion, and stirred overnight. The reaction was quenched with wet Et_2O (10 mL), and the solvent was removed *in vacuo* to yield a crude brown oil. The product was purified by a filter column (5:1), then flash chromatography (9:1), then distillation to yield compound **30** as a clear, colourless oil (98.4 mg, 0.44 mmol) in 82% yield as a mixture of isomers, bp 56–60°C/0.06 Torr; IR (neat): 1676, 1102 cm^{-1}; ^1H NMR (300 MHz) δ: 1.02 and 1.03(d, 3H each, J = 6.9 Hz, C-2-CH_3), 1.41 and 1.44(s, 3H each, C-8-CH_3), 1.20–2.80(overlapping multiplets, 24H), 3.47 and 3.51(s, 3H each, vinyl methoxy CH_3), 5.65 and 5.58(m, 1H each, vinyl-H); ^{13}C NMR (75 MHz) δ: 16.06(q), 16.22(q), 21.35(q), 21.46(q), 24.20(t), 25.85(t), 30.21(t), 30.29(t), 30.87(t), 32.12(t), 36.21(t), 37.01(t), 42.06(t), 43.81(t), 34.23(d), 34.40(d), 46.08(d), 46.33(d), 59.28(q), 59.40(q), 82.56(s), 82.89(s), 88.00(s), 88.20(s), 125.49(s), 119.57(s), 140.37(d), 141.37(d); mass spectrum, *m/e*: 222(1, $M^{\cdot+}$); HRMS calcd. for $C_{14}H_{22}O_2$: 222.1621; found: 222.1624.

(6αH)-2β,8α-Dimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undecane-5-carboxaldehyde (31)

The mixture of methyl enol ethers **30** (98.4 mg, 0.44 mmol) was dissolved in THF (4 mL) and 10% HCl (3 mL) and stirred at room temperature for 1 h. The solution was neutralized to pH 7 (monitored with universal pH paper) with saturated Na_2CO_3, then the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried (over Na_2SO_4), filtered, and the solvent was removed *in vacuo* to yield a crude yellow oil. Distillation yielded compound **31** (57.8 mg, 0.28 mmol) as a clear, colourless oil (62%), bp 60°C/0.03 Torr; IR (neat): 2706, 1722, 1094 cm^{-1}; ^1H NMR (300 MHz) δ: 1.05(d, 3H, J = 6.6 Hz, C-2-CH_3), 1.17(dt, 1H, J = 3.0 Hz, J = 3.0 Hz, J = 12.4 Hz), 1.30–1.50(overlapping m, 4H), 1.43(s, 3H, C-8-CH_3), 1.52–1.78(overlapping m, 3H), 1.80–2.05(overlapping m, 3H), 2.18(dddd, 1H, $J_{5\beta,11}$ = 1.6 Hz, $J_{5\beta,4\beta}$ = 3.4 Hz, $J_{5\beta,6\alpha}$ = 10.5 Hz, $J_{5\beta,4\alpha}$ = 12.4 Hz, H-5β, assignment confirmed since irradiation of H-11 at δ 9.57 caused collapse to ddd with 1.6 Hz coupling removed), 9.57(d, 1H, J = 1.6 Hz, H-11); ^{13}C NMR (75 MHz) δ: 15.76(q), 21.32(q), 25.26(t), 30.58(t), 33.91(t), 37.67(t), 44.19(t), 34.06(d), 44.07(d), 56.62(d), 83.93(s), 85.90(s), 204.31(d); mass spectrum, *m/e*: 208(9, $M^{\cdot+}$), 179(100, M−CHO); Anal. calcd. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 74.81, H 9.73.

(6αH)-5α-(1-Hydroxyethyl)-2β,8α-dimethyl-11-oxatricyclo[6.2.1.0^{1,6}]undecane (32)

Freshly distilled aldehyde **31** (49.2 mg, 0.24 mmol) was dissolved in THF (5 mL) and the solution was cooled to −78°C. Methyllithium (1.00 mL, 1.40 mmol) was added; the reaction was stirred for 1.5 h at −78°C, then was allowed to warm to room temperature and was quenched with saturated NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layer was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The resulting crude oil was purified by flash chromatography (5:1) to produce compound **32** (51.6 mg, 0.23 mmol) as a mixture of two isomers in 97% yield, bp 80°C/0.024 Torr (data listed for 1 isomer only); IR (neat): 3422, 1092 cm^{-1}; ^1H NMR (300 MHz) δ: 1.02(d, 3H, J = 6.6 Hz, C-2-CH_3), 1.15(d, 3H, J = 6.5 Hz), 1.41(s, 3H, C-8-CH_3), 3.68(dq, 1H, J = 1.2 Hz, J = 6.5 Hz), 1.10–1.40(overlapping m, 6H), 1.41–1.75(overlapping m, 6H), 1.80–1.92(overlapping m, 2H); ^{13}C NMR (75 MHz) δ: 16.03(q), 21.69(q), 21.88(q), 23.31(t), 31.32(t), 34.50(t), 37.64(t), 44.66(t), 34.61(d), 46.71(d), 49.42(d), 67.66(d), 83.55(s), 87.05(s); mass spectrum, *m/e*: 224 ($M^{\cdot+}$); HRMS (EI) calcd. for $C_{14}H_{24}O_2$: 224.1777; found: 224.1780.

(6αH)-2β,8α-Dimethyl-5α-(1-oxoethyl)-11-oxatricyclo[6.2.1.0^{1,6}]undecane (33)

Oxalyl chloride (11 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and cooled to −60°C (Dry Ice/chloroform) in an argon-purged 3-neck round-bottom flask equipped with a dropping funnel. Freshly distilled alcohol **32** (21.6 mg, 10 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and placed in the dropping funnel. DMSO (22 mmol) was added neat (by syringe) to the oxalyl chloride solution, the reaction was stirred for 2 min, and then the alcohol solution was added within 5 min. The mixture was stirred an additional 15 min; then Et_3N (50 mmol) was added and stirring was continued for another 5 min before warming the reaction to room temperature. Water (50 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic layers were washed with 5% HCl (15 mL), 5% Na_2CO_3 (15 mL), and water (15 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to provide the crude product. This was purified by flash chromatography, then distilled to provide compound **33** (19.2 mg, 0.086 mmol) as a clear, colourless oil in 90% yield after purification by flash chromatography (5:1), bp 58–60°C/0.03 Torr; mp 63.5–64.5°C; IR (neat): 1702, 1087 cm^{-1}; ^1H NMR (300 MHz) δ: 0.97(dt, 1H, $J_{7\beta,6\alpha}$ = 2.9 Hz, $J_{7\beta,9\beta}$ = 2.9 Hz, J_{gem} = 11.8 Hz, H-7β), 1.04(d, 3H, J = 6.6 Hz, C-2-CH_3), 1.21(dq, 3H, J = 2.6 Hz, J = 12.8 Hz, J = 12.8 Hz), 1.30–

1.49(overlapping m, 3H), 1.41(s, 3H, C-8-CH_3), 1.50–1.72(overlapping m, 3H), 1.80–1.95(overlapping m, 3H), 2.00(ddd, 1H, $J_{6\alpha,7\beta}$ = 2.9 Hz, $J_{6\alpha,7\alpha}$ = 8.1 Hz, $J_{6\alpha,5\beta}$ = 10.6 Hz, H-6α), 2.10(s, 3H, $COCH_3$), 2.31(ddd, 1H, $J_{5\beta,4\beta}$ = 3.1 Hz, $J_{5\beta,6\alpha}$ = 10.2 Hz, $J_{5\beta,4\alpha}$ = 13.1 Hz, H-5β); ^{13}C NMR (75 MHz) δ: 15.76(q), 21.42(q), 29.31(q), 28.61(t), 31.39(t), 34.00(t), 37.70(t), 44.74(t), 34.00(d), 45.57(d), 57.75(d), 83.73(s), 86.09(s), 211.83(s); mass spectrum, *m/e*: 222(28, $M^{+\cdot}$), 179(38, M−MeCO); HRMS (EI) calcd. for $C_{14}H_{22}O_2$: 222.1621; found: 222.1625.

*(6αH)-2β,8α-Dimethyl-5α-(1-methylethenyl)-11-oxatricyclo[6.2.1.0^{1,6}]undecane (**34**)*

Methyltriphenylphosphonium bromide (Aldrich Chemical Co.) was purified by washing with hot toluene, then dried under high vacuum for 8 h. The purified phosphonium salt (0.88 g, 2.45 mmol) was suspended in dry THF (10 mL), and cooled to 0°C. Butyllithium (0.98 mL, 2.48 mmol) was added dropwise by syringe, and the reaction was warmed to room temperature and stirred for 20 min. A solution of ketone **33** (27.6 mg, 0.124 mmol) in THF (3 mL) was added to the orange anion solution, and the reaction was refluxed overnight. The reaction was cooled, quenched with wet Et_2O (10 mL), and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography (5:1) to yield starting material (9.0 mg) and product **34** (30.9 mg) as a mixture with an aromatic-containing impurity. The mixture was further purified by flash chromatography (20:1) to yield compound **34** (20.8 mg, 71%), bp 50–60°C/0.04 Torr; IR (KBr): 1088 cm^{-1}; ^1H NMR (300 MHz) δ: 0.90–1.4(overlapping m, 6H), 1.04(d, 3H, J = 6.6 Hz, C-2-CH_3), 1.42(s, 3H, C-8-CH_3), 1.48–1.82 (overlapping m, 5H), 1.85–1.96(m, 1H), 1.62(m, 3H, J = 1.0 Hz, vinyl-CH_3), 4.63 and 4.67(m, 2H, J_{gem} = 1.4 Hz, J = 2.5 Hz); mass spectrum, *m/e*: 220(15, $M^{+\cdot}$); HRMS (EI) calcd. for $C_{15}H_{24}O$: 220.1828; found: 220.1827.

*(6αH)-2β,8α-Dimethyl-5α-(1-methylethyl)-11-oxatricyclo[6.2.1.0^{1,6}]undecane (epoxycadinane) (**1**)*

Compound **34** (8.8 mg, 0.04 mmol) was dissolved in absolute ethanol (5 mL). Platinum(IV) oxide (28.5 mg, 0.126 mmol) was added, then the flask was evacuated and filled with hydrogen gas three times by way of a hydrogen-filled balloon attached to a three-way stopcock. The reaction was stirred at room temperature for 1 h; then the catalyst was removed by filtration and the solvent was removed *in vacuo* to yield compound **1** (6.0 mg, 0.027 mmol) as a colourless oil in 93% yield, bp 42–50°C/0.06 Torr; IR (neat): 2964–2869, 1376, 1367, 1094 cm^{-1}; ^1H NMR (300 MHz), see Table 4; ^{13}C NMR (75 MHz), see Table 4; mass spectrum, *m/e*: 222(3, $M^{+\cdot}$), 179(100, M−$CHMe_2$); HRMS (EI) calcd. for $C_{15}H_{26}O$: 222.1984; found: 222.1986.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the University of Calgary Research Board for financial support. In addition we thank NSERC for a postgraduate scholarship (to C.R.).

1. K. A. Parker and M. R. Adamchuk. Tetrahedron Lett. **19**, 1689 (1978).
2. D. Craig. Chem. Soc. Rev. **16**, 187 (1987); K. Hayakawa and K. Kanematsu. J. Synth. Org. Chem. Jpn. **44**, 109 (1986); D. F. Taber. Intramolecular Diels–Alder reactions and Alder ene reactions. Springer-Verlag, New York. 1984; E. Ciganek. Org. React. **32**, 1 (1984); A. G. Fallis. Can. J. Chem. **62**, 183 (1984); R. Sustman and J. Sauer. Angew. Chem. Int. Ed. Engl. **19**, 779 (1980); G. Brieger and J. N. Bennett. Chem. Rev. **80**, 63 (1980).
3. (*a*) W. Blokzul, M. R. Blandamer, and J. B. F. N. Engberts. J. Am. Chem. Soc. **113**, 4241 (1991); (*b*) M. E. Jung and J. Gervay. J. Am. Chem. Soc. **113**, 224 (1991); (*c*) M. E. Jung. Synlett, 186 (1990); (*d*) K. H. Dotz, R. Noack, K. Harms, and G. Muller. Tetrahedron, **46**, 1235 (1990); (*e*) H. Finch, L. M. Harwood, G. M. Robertson, and R. C. Sewell. Tetrahedron Lett. **30**, 2585 (1989); (*f*) Y. Yamaguchi, H. Yamada, K. Hayakawa, and K. Kanematsu. J. Org. Chem. **52**, 2040 (1987); (*g*) W. M. Best and D. Wege. Aust. J. Chem. **39**, 635 (1986); **39**, 647 (1986); (*h*) J. Moursounidis and D. Wege. Tetrahedron Lett. **27**, 3045 (1986).
4. (*a*) B. L. Feringa, O. J. Gelling, and L. Meesters. Tetrahedron Lett. **31**, 7201 (1990); (*b*) K. Fischer and S. Hunig. J. Org. Chem. **52**, 564 (1987); (*c*) A. P. Kozikowski and W. Tuckmantel. J. Org. Chem. **56**, 2826 (1991); (*d*) A. Padwa, Y. S. Kulkarni, and L. W. Terry. J. Org. Chem. **55**, 2478 (1990); (*e*) T. Ghosh and H. Hart. J. Org. Chem. **54**, 5073 (1989); (*f*) S. Cauwberghs, P. J. De Clercq, B. Tinant, and J. P. Declercq. Tetrahedron Lett. **29**, 2493 (1988); (*g*) D. D. Sternbach, D. M. Rossana, and K. D. Onan. Tetrahedron Lett. **26**, 591 (1985); (*h*) B. M. Trost, M. Lautens, M.-H. Hung, and C. S. Carmichael. J. Am. Chem. Soc. **106**, 7641 (1984); (*i*) D. D. Sternbach, D. M. Rossana, and K. D. Onan. J. Org. Chem. **49**, 3427 (1984).
5. (*a*) L. M. Harwood, S. A. Leeming, N. S. Isaacs, G. Jones, J. Pickard, R. M. Thomas, and D. A. Watkin. Tetrahedron Lett. **29**, 5017 (1988); (*b*) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin. Tetrahedron Lett. **29**, 5825 (1988); (*c*) P. Missiaen and P. J. De Clercq. Bull. Soc. Chem. Belg. **96**, 105 (1987); (*d*) L. A. Van Royen, R. Mijngheer, and P. J. De Clercq. Tetrahedron, **41**, 4667 (1985); (*e*) L. A. Van Royen, R. Mijngheer, and P. J. De Clercq. Bull. Soc. Chem. Belg. **93**, 1019 (1984).
6. S. J. Burrell, A. E. Derome, M. S. Edenborough, L. M. Harwood, S. A. Leeming, and N. S. Isaacs. Tetrahedron Lett. **26**, 2229 (1985), and refs. 4*a*, 4*b*, and 3*a* above.
7. (*a*) F. Nuyttens, G. Appendino, and P. J. De Clercq, Synlett, 526 (1991); (*b*) L. M. Harwood, T. Ishikawa, H. Phillips, and D. Watkin. J. Chem. Soc. Chem. Commun. 527 (1991); (*c*) P. Missiaen and P. J. De Clercq. Bull. Soc. Chem. Belg. **99**, 271 (1990); (*d*) L. M. Harwood, B. Jackson, G. Jones, K. Prout, R. M. Thomas, and F. J. Witt. J. Chem. Soc. Chem. Commun. 608 (1990); (*e*) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin. J. Chem. Soc. Chem. Commun. 605 (1990); (*f*) G. Appendino, J. Hoflack, P. J. De Clercq. G. Chiari, and M. Calleri. Tetrahedron, **44**, 4605 (1988); (*g*) S. G. Cawberghs and P. J. De Clercq. Tetrahedron Lett. **29**, 6501 (1988); (*h*) W. M. Grootaert and P. J. De Clercq. Tetrahedron Lett. **27**, 1731 (1986); (*i*) W. M. Grootaert and De Clercq. Tetrahedron Lett. **23**, 3291 (1982).
8. B. A. Keay. J. Chem. Soc. Chem. Commun. 419 (1987).
9. (*a*) C. Rogers and B. A. Keay. Synlett, 353 (1991); (*b*) Tetrahedron Lett. **32**, 6477 (1991); (*c*) Can. J. Chem. **70**, 2929 (1992).
10. P. W. Dibble and B. A. Keay. Tetrahedron Lett. **30**, 1045 (1989).
11. C. Rogers and B. A. Keay. Tetrahedron Lett. **30**, 1349 (1989).
12. E. Bovenschulte, P. Metz, and G. Henkel. Angew. Chem. Int. Ed. Engl. **28**, 202 (1989).
13. Y. K. Yur'ev, N. S. Zefirov, and A. A. Shteinman. Chem. Abstr. **59**, 11395d (1963).
14. W. F. Bailey, T. T. Nurmi, J. J. Patricia, and W. Wang. J. Am. Chem. Soc. **109**, 2442 (1987).
15. A. J. Mancuso and D. Swern. Synthesis, 165 (1981).
16. A. McKillop and D. W. Young. Synthesis, 401 (1979).
17. W. G. Dauben and H. O. Krabbendroft. J. Am. Chem. Soc. **98**, 1992 (1976).
18. (*a*) E. Fattorusso, S. Magno, and L. Mayol. Gazz. Chim. Ital. **109**, 589 (1979); (*b*) M. Bordoloi, V. S. Shukla, S. C. Nath, and R. P. Sharma. Phytochemistry, **28**, 2007 (1989); (*c*) B. M. Fraga. Nat. Prod. Rep. **9**, 217 (1992).
19. T.-L. Ho. Enantioselective synthesis. Wiley Interscience, New York. 1992. pg. 226; H. Irie, R. Matsumoto, M. Nishimura, and Y. Zhang. Chem. Pharm. Bull. **38**, 1852 (1990); B. S.

Davidson, K. A. Plavcan, and J. Meinwald. J. Org. Chem. **55**, 3912 (1990); J. ApSimon. Total Synth. Nat. Prod. **5**, 157 (1983); B. M. Fraga. Nat. Prod. Rep. **9**, 557 (1992).
20. R. A. Augustine. Catalytic hydrogenation. M. Dekker, New York. 1965.
21. J. A. Hendrickson and R. Bergeron. Tetrahedron Lett. **46**, 4607 (1973).
22. E.-I. Negishi, L. D. Boardman, H. Sawada, V. Bagheri, A. T. Stoll, J. M. Tour, and C. L. Rand. J. Am. Chem. Soc. **110**, 5383 (1988).
23. B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski. Tetrahedron, **40**, 5005 (1984).
24. H. Gilman, W. Langham, and F. W. Moore. J. Am. Chem. Soc. **62**, 2327 (1940).
25. R. E. Ireland, D. C. Muchmore, and U. Hengartner. J. Am. Chem. Soc. **94**, 5098 (1972); S. C. Dolan and J. MacMillan. J. Chem. Soc. Chem. Commun. 1588 (1985); A. G. M. Barrett, C. R. A. Godfrey, D. M. Hollinshead, P. A. Prokopiou, D. H. R. Barton, R. B. Boar, L. Joukhadar, J. F. McGhie, and S. C. Misra. J. Chem. Soc. Perkin Trans. 1, 1501 (1981); A. G. M. Barrett, P. A. Prokopiou, D. H. R. Barton, R. B. Boar, and J. F. McGhie. J. Chem. Soc. Chem. Commun. 1173 (1979); W. Hartwig. Tetrahedron, **39**, 2609 (1983); G. Hofle, W. Steglich, and H. Vorbruggen. Angew. Chem. Int. Ed. Engl. **17**, 5691 (1978); H. Deshayes, J.-P. Pete, C. Portella, and D. Scholler. J. Chem. Soc. Chem. Commun. 439 (1975); H. Deshayes and J.-P Pete. J. Chem. Soc. Chem. Commun. 567 (1978).
26. L. A. Paquette, P. C. Bulman-Page, P. D. Pansegrau, and P. E. Wiedeman. J. Org. Chem. **53**, 1450 (1988).
27. E. Piers and G. L. Jung. Can. J. Chem. **63**, 996 (1985).
28. D. D. Perrin and W. L. F. Armarego. Purification of laboratory chemicals. 3rd ed. Pergamon Press, Toronto. 1988.