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FULL PAPER

Synthesis of the Bicyclic Lactone Core of Leonuketal Enabled by a Telescoped Diels-Alder Reaction Sequence

Phillip S. Grant,[a] Margaret A. Brimble*[a,b] and Daniel P. Furkert*[a,b]

Abstract: The Diels-Alder cycloaddition is established as a fundamental approach for preparation of complex natural products, however application of the intermolecular reaction to the synthesis of particularly congested scaffolds remains surprisingly problematic. Inspired by the terpenoid spiroketal natural product, leonuketal, a challenging telescoped reaction sequence has been realized to successfully deliver access to the core [2.2.2]-bicyclic lactone ring system and its [3.2.1] isomer. The four-step, protecting group free process required detailed investigation to circumvent problems of adduct fragmentation and intermediate instability encountered en route. Successful solution of these practical issues along with unambiguous structural determination of the target structures provides useful insights that will facilitate further challenging application of the Diels-Alder cycloaddition to highly congested molecular scaffolds and ongoing synthetic efforts towards the natural product.

Introduction

In 2015, Peng and co-workers reported the isolation of the unique diterpenoid natural product leonuketal (**1**, Figure 1) from the herb *Leonurus japonicus*.[1] Leonuketal (**1**) displayed significant vasorelaxant activity against KCl-induced contraction of rat aorta (EC_{50} 2.32 μM), and was assigned an unprecedented tetracyclic structure.

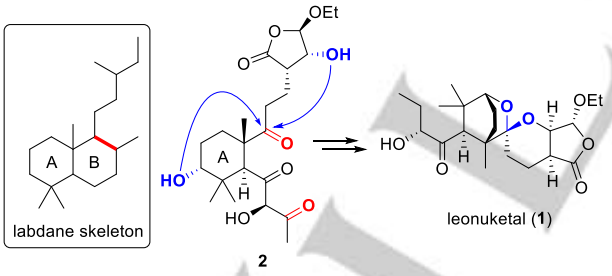
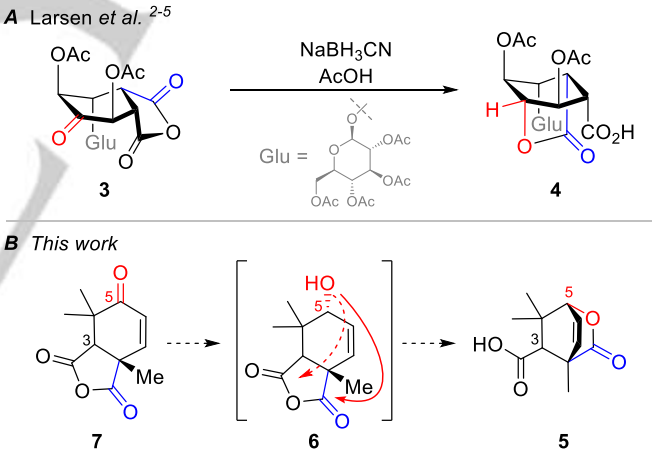


Figure 1. Biosynthesis of leonuketal (**1**) proposed by Peng.

The bridged spiroketal core of **1** was proposed by Peng and co-workers to arise from the oxidative cleavage of the B-ring of a labdane-type precursor containing a double bond, to give **2**, followed by spirocyclization. To date, no studies towards the preparation of leonuketal have been reported. The synthetic challenge posed by the unique and complex architecture of **1** attracted our interest, along with the potential for synthetic and pharmacological discovery. Our initial attention focused on identifying a viable route to access the key densely functionalized [2.2.2]-oxabicyclic core ring system. Larsen and co-workers had earlier reported the synthesis of bicyclic carbohydrate-derived [2.2.2] lactone **4** (Scheme 1A) from keto anhydride **3**.[2–5] These studies revealed that reduction of the C5 ketone (*red*) proceeded with complete diastereoselectivity to afford a single alcohol epimer, that underwent spontaneous 6-*exo*-trig cyclization at the distal carbonyl of the anhydride (*blue*, Scheme 1, A). This approach appeared to offer a plausible synthetic route for application to bicyclic lactone **5** that forms the core of leonuketal (Scheme 1, B) via analogous cyclization of alcohol **6**, if access to the requisite precursor ketone **7** could be secured.



Scheme 1. Proposed approach to the [2.2.2] bicyclic lactone core of **1** (*leonuketal numbering*).

Bicyclic anhydride **7**, or a suitable synthon, was anticipated to be accessible by Diels-Alder cycloaddition (Scheme 2). Cycloaddition of 1,1-dimethyl Danishefsky-type diene **8** with methyl-substituted fumarate **9** should lead to 3,4-*trans*-**10**, a synthetic equivalent of **7**, possessing the correct relative stereochemistry for leonuketal (**1**). The literature contains very few reports of successful cycloadditions involving such highly-substituted diene/*trans*-dienophile combinations. As a synthetic alternative, we also envisaged that cycloaddition of **8** with the more reactive commercially available cyclic *cis*-dienophile, citraconic anhydride (**11**) (*ca.* US$0.70/g), should give access to the fused cyclic anhydride, 3,4-*cis*-**7**, with the additional benefit of reducing the step count of the synthesis. The stereochemistry of

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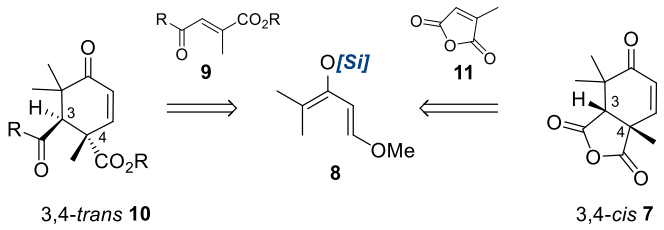
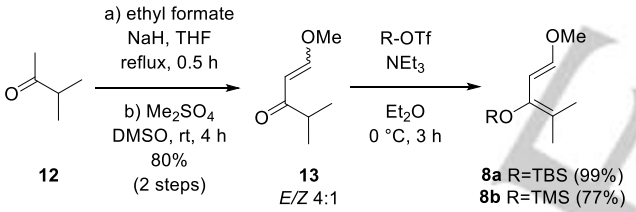
3,4-*cis*-**7** resulting from this latter sequence would be C3 epimeric with respect to **1**, therefore an epimerization step would be required later in the synthesis.



Scheme 2. Retrosynthetic analysis.

Results and Discussion

The requisite 2-silyloxy butadienes **8a** and **8b** were readily prepared by adaptation of a literature approach (Scheme 3).[6] Deprotonation of **12** with sodium hydride followed by treatment with ethyl formate and subsequent methylation afforded ketone **13** in high yield (*E/Z*, 4:1). Subsequent treatment of the *E/Z* mixture with the appropriate silyl triflate afforded the 2-silyloxy butadienes **8a**,**8b** as single stereoisomers. These modified conditions proved more successful and reliable in our hands than those previously reported.



Scheme 3. Preparation of dienes **8a** and **8b**.

At the outset of the Diels-Alder cycloaddition study, we anticipated two principal challenges; (a) high steric demand in forming two tertiary-quaternary C-C bonds and (b) possible regioisomeric mixtures due to the use of unsymmetrical 1,2-doubly activated dienophiles *e.g.* **11**. Literature precedent for [4+2] cycloadditions forming such densely substituted cyclohexenes is scarce, despite their abundance in terpenoid scaffolds.[7] Reports of related cycloadditions involving *either* a 1,1-dimethylated 2-silyloxy butadiene *or* a fumarate or citraconic anhydride (**11**) dienophile, suggest that all of these components are problematic reaction partners.[8] Indeed, at the outset of our studies Sarpong's work toward prenylated indole alkaloids had represented to our knowledge the only related example in which a 1,1-dimethylated 2-silyloxy butadiene system undergoes productive intermolecular cycloaddition with a trisubstituted dienophile.[9,10] During preparation of this manuscript a very closely related example involving an aryl-substituted maleic anhydride dienophile was described by the Dong group, forming the foundation of a highly efficient total synthesis of three complex natural products; (-)-enmein, (-)-isodocarpin and (-)-sculponin.[11] Interestingly, no problems of product fragmentation or instability were reported in the development of this reaction, which was successfully carried out on multigram scale. In general, [4+2] cycloadditions involving citraconic anhydride (**11)** are significantly rarer that those of the simpler symmetrical congener, maleic anhydride (**14**).[12–14]

Trans dienophiles

Our initial investigations towards the cycloaddition of dienes **8a** and **8b** proved disappointing (Table 1). Although cycloaddition of **8a** and the simple dienophile, methyl methacrolein (**15**), proceeded readily to directly afford the cyclic enone **16** in excellent yield (Table 1, Entry 1), reaction with the corresponding acrylate ester, methyl methacrolate (**17)** was unsuccessful, instead leading only to the diene dimerization product **18** (Table 1, Entry 2). Variation of the Lewis acid catalyst did not alter the course of this reaction. Thermal cycloaddition of **8a** with either of the *trans* dienophiles diethyl fumarate (**19)** (Table 1, Entry 3) or 3-methyl-4-oxocrotonate (**20)** (Table 1, Entry 4) failed to give any of the desired products. In the presence of the Lewis acid catalyst scandium triflate however, **8a** underwent undesired hetero-Diels-Alder addition to give **21** in moderate yield (Table 1, Entry 5). Given this lack of success with the *trans* dienophile series, our attention turned to the use of the *cis* alternatives; maleic anhydride (**14**) and citraconic anhydride (**11**).

Cis dienophiles

In contrast to the *trans* dienophiles, thermal reaction of **8a** with the model *cis* dienophile maleic anhydride (**14**) pleasingly proceeded cleanly to afford the corresponding cycloadduct **22** in 36% isolated yield (Table 1, Entry 6). More pleasingly, on heating with diene **8a** at 150 °C in toluene, citraconic anhydride (**11**) also underwent full conversion to the desired cycloaddition product **23**, as established by ^{1}H NMR (Table 1, Entry 7). Importantly, this result also revealed complete regioselectivity for the desired cycloadduct regioisomer, likely driven by unfavorable steric interactions between the 1,1-dimethyl groups of the diene and the methyl group of dienophile **11** in the transition state required for the undesired regioisomer. Notwithstanding this encouraging success, optimization of the reaction was hampered by concomitant desilylation of diene **8a** to give **13** during the reaction, and the instability of **23** to isolation and purification on silica, resulting in very low isolated yields (<5%). It was observed that desilylation of diene **8a** to give ketone **13** was less prevalent when using an equimolar amount of dienophile **11**, as opposed to a 2- or 4-fold excess (Table 1, Entry 7 *vs* 8 & 9). This suggested that an acidic impurity in the commercially-sourced dienophile **11**, possibly citraconic acid, was promoting the undesired side reaction. Accordingly, citraconic anhydride (**11**) was distilled prior to use, which was found to reduce diene desilylation in subsequent runs (Table 1, Entry 10 & 11). A subtle reduction in the reaction temperature proved to be beneficial (Table 1, Entry 10). These optimized conditions were also found to be compatible with TMS diene **8b** (Table 1, entry 11).

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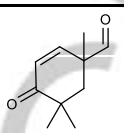
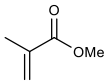
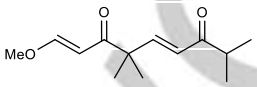
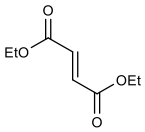
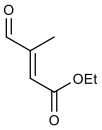
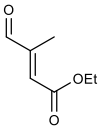
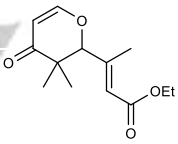
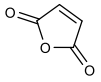
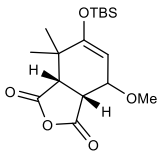
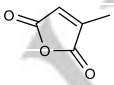
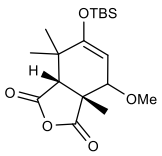
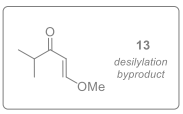
Table 1. Diels-Alder cycloadditions of 1,1-dimethyl butadienes **8a**,**8b** with a range of dienophiles.

Entry[a]	Dienophile		Conditions	Product		Result [*reaction type*]
1		**15**	$ZnCl_2$, CH_2Cl_2 0 °C, 3 h		**16**	84% [*Diels-Alder*]
2		**17**	$SnCl_4$, CH_2Cl_2 -78 °C for 3 h, *then* 0 °C for 1 h; Et_3N		**18**[b]	51% [*diene dimerization*]
3		**19**	40 h, 150 °C	-		-
4		**20**	40 h, 150 °C	-		-
5		**20**	$Sc(OTf)_3$, CH_2Cl_2, -78 °C for 3 h; NEt_3, rt.		**21**	43% [*hetero Diels-Alder*]
6		**14**	PhMe, 100 °C, 2 h		**22**	36% [*Diels-Alder*]
				Ratio of Diels-Alder product to desilylation byproduct		(**23**:**13**)
7			neat, 40 h, 150 °C			80:20[a]
8		**11**	neat, 16 h, 150 °C **11** (2 equiv.)		**23**	30:70[a,c]
9			neat, 16 h, 150 °C **11** (4 equiv.)			10:90[a,c]
10			**neat**, **16 h**, **140 °C**			**92**:**8**[a,d]
11			neat, 16 h, 140 °C			90:10[a,d,e]

[a] Product distribution by ^1H NMR at full conversion. [b] Dimerization product of diene **8a**. [c] BHT used instead of hydroquinone. [d] Distilled citraconic anhydride (**11**) used. [e] Diene **8b** used.

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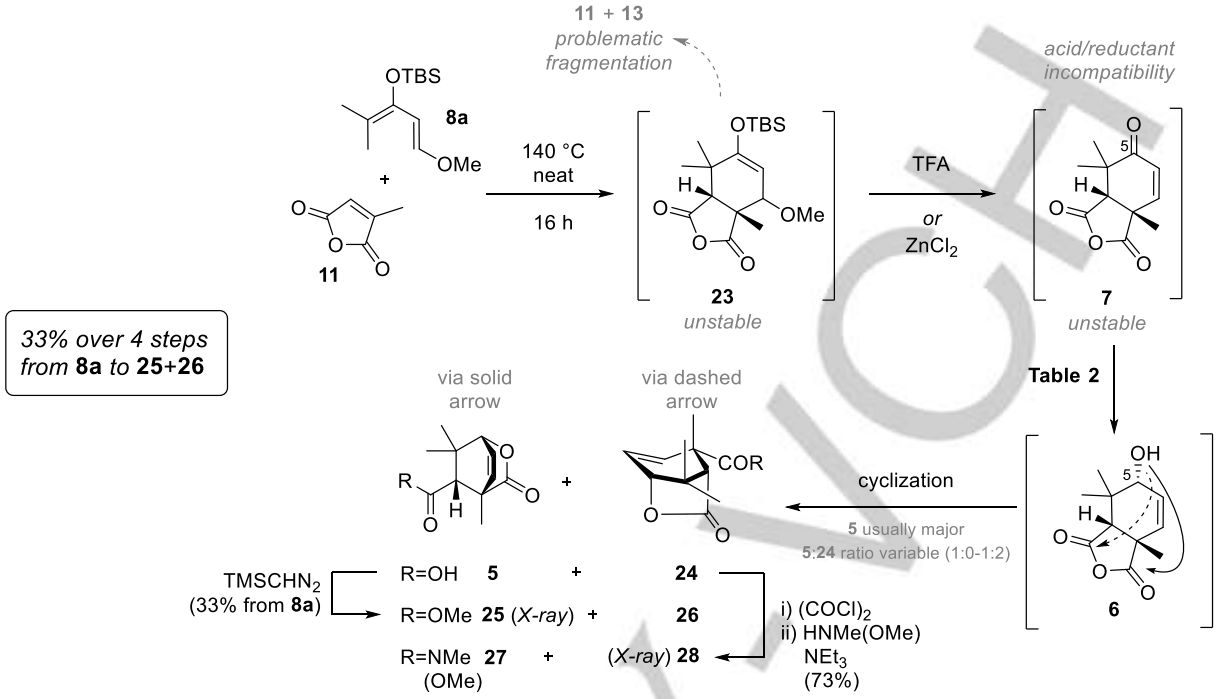


Scheme 4. Optimized telescoped four-step Diels-Alder sequence to afford the bicyclic lactone core of leonuketal (**1**).

With conditions for formation of the target Diels-Alder cycloadduct **23** identified, the problem of product isolation remained to be resolved, for productive routine synthesis. Difficulties were immediately encountered in the desilylation/elimination of cycloadduct **23** to ketone **7**. Following close investigation of the reaction process, it was determined that **23** underwent retro-Diels-Alder/diene desilylation to give citraconic anhydride (**11**) and ketone **13** upon cooling in the reaction solvent, toluene. This effect was not observed when the crude adduct was quickly redissolved in *d*-chloroform for NMR, implicating a solvent effect in the fragmentation process. Interestingly, maleic anhydride cycloadduct **22** (*see* Table 1, Entry 6) did not undergo retro-Diels-Alder/desilylation and was stable to purification on silica. This suggested that the angular methyl group at the ring fusion also contributed to fragmentation, and further demonstrated the increase in reaction difficulty moving from maleic to citraconic anhydride. After detailed dissection of the Diels-Alder procedure, it was eventually possible to circumvent these issues by conducting the cycloaddition step neat, to avoid the toluene-induced fragmentation. Subsequent direct treatment of the crude reaction mixture with TFA in chloroform successfully afforded ketone **7** (Scheme 4). This compound also proved unstable to purification on silica or alumina, and was accordingly used directly in the next step.

Table 2. Optimization of the reduction step (**7** to **6**) in the presence of $ZnCl_2$ for the telescoped sequence (Scheme 4).

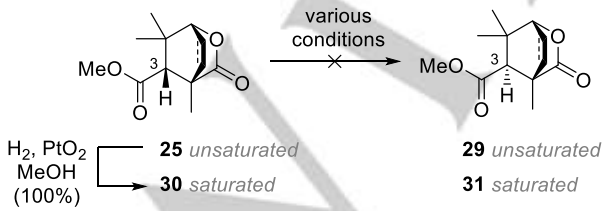
Entry	Reductant	Solvent	Yield (**5**+**24** from **11**)
1	$NaBH_4$	$CHCl_3$	-
2	$NaCNBH_3$	$CHCl_3$:THF (1:1)[a]	-
3	$NaCNBH_3$	$CHCl_3$:THF:AcOH (1:1:0.1)	33[b]
4	$NaCNBH_3$	$CHCl_3$:AcOH (1:1)	100[b]

[a] AcOH (1 drop) added. [b] Determined by NMR using an internal standard.

With access to crude ketone **7** established, formation of the [2.2.2] oxabicyclic core of leonuketal (**1**) was next undertaken. Reduction of the α,β-unsaturated ketone by treatment with sodium cyanoborohydride in acetic acid afforded an inseparable mixture of the desired product [2.2.2]-**5** and [3.2.1]-**24**. The reaction was observed to favor the formation of **5** in approximately a 2:1 ratio for most repetitions, however this selectivity proved somewhat

variable and was occasionally reversed, for reasons that remain to be identified.[15] The reduction step was found to proceed with complete *exo* selectivity to give a single C5 alcohol epimer **6**, but competing cyclisation at either carbonyl of the cyclic anhydride led to concomitant formation of either a 6-membered lactone (*solid arrow*) to give the favoured desired product [2.2.2]-**5**, or a 5-membered lactone (*dashed arrow*) to afford [3.2.1]-**24**. Similar competitive cyclization had been previously observed by Larsen on a substitution dependent basis.[5] It was recognized that [3.2.1]-**24** could still potentially prove a useful intermediate in later studies if necessary, via a trans-esterification step later in the synthesis. Carboxylic acids [2.2.2]-**5** and [3.2.1]-**24** were ultimately separable by derivatization to their respective esters **25** and **26**, that were obtained in 17% and 7% overall yield respectively, from citraconic anhydride. The corresponding Weinreb amides **27** and **28** were also prepared, by conversion of the crude mixture of acids **5** and **24** to the acid chlorides, followed by amide formation with dimethylhydroxlamine, in 24% combined yield from citraconic anhydride (Scheme 4). Single crystal *X*-ray structures of [2.2.2]-**25** and [3.2.1]-**28** were able to be obtained, representing both isomeric manifolds, that allowed unambiguous confirmation of the structural assignment and relative stereochemistry.

With synthetic methods to access bicyclic lactones **25**-**28** identified and their structures confirmed, from a process point of view it appeared that a telescoped reaction sequence for preparation of **25** and **26** directly from **11** and **8a** without isolation would avoid the purification issues encountered for cycloadduct **23** and ketone **7**. The key to achieving this involved identification of suitable conditions for formation of ketone **7** from the crude Diels-Alder reaction mixture that would be compatible with the subsequent reductive lactonization. After exploration of a number of alternative conditions for reduction of the C5 ketone (Table 2) it was found that desilylation of **23** could be effected with zinc chloride, that did not disrupt the subsequent reduction/lactonization step, if the latter was performed using sodium cyanoborohydride in acetic acid (Table 2, Entry 4,). Using this telescoped sequence, it proved possible to obtain **25** and **26** in a pleasing combined yield of 33% over 4 steps from diene **8a** with variable selectivity between [2.2.2]-**25** and [3.2.1]-**26** bicyclic products as previously observed for the multistep sequence.



Scheme 5. Attempted C3 epimerization of **25** and **30**.

Finally, focus was directed towards inversion of the C3 stereochemistry, required to access the correct relative stereochemistry for the bicyclic core of leonuketal (**1**). Unfortunately, despite an extensive screen of basic and other conditions to promote epimerization, it did not prove possible to access the target C3 epimer **29** (Scheme 5 and Table S1). Further, no deuterium inclusion was observed upon deuterium oxide quench of a mixture of **25** and sodium hydride that had been heated at reflux in 1,4-dioxane. In order to rule out the possibility of unfavorable π interactions of the endocyclic alkene, **25** was hydrogenated to the saturated analogue **30**. Unfortunately, **30** proved likewise recalcitrant to deprotonation. These data suggest that formation of the enolate is not possible due to either the high steric demand of deprotonation, or a prohibitively strained geometry requirement for the enolate. Inversion of the C3 stereochemistry via decarboxylative formation of an alkyl radical from activated esters of **5** was also briefly pursued, but ultimately also proved unfruitful.[16–21]

Conclusions

In summary, an efficient telescoped four-step protocol for synthetic access to highly congested bicyclic lactone ring systems similar to that possessed by leonuketal (**1**) has been developed, without reliance on protecting groups. The sequence proceeded through unstable intermediates highly prone to fragmentation and decomposition, and was only achieved after close dissection of each individual transformation. The structure and relative stereochemistry of the highly congested [2.2.2]- and [3.2.1]-bicyclic lactone products were unambiguously determined by *X*-ray crystallography. Surprisingly, it was not possible to effect the planned C3 epimerization to access the relative stereochemistry required for leonuketal. The insights gained in successfully realising this challenging approach should enable wider application of the Diels-Alder cycloaddition to highly congested molecular scaffolds and ongoing synthetic efforts towards the natural product.

Experimental Section

General

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried by passage through a column of activated alumina under N_2 using an LC Technology solvent purification system. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as the visualizing agent and potassium permanganate as a developing agent. Silica gel (60, 230−400 mesh) was used for flash column chromatography unless otherwise stated. NMR spectra were recorded at room temperature in $CDCl_3$ solution on either a spectrometer operating on a Bruker 400 MHz instrument. Chemical shifts are reported in parts per million on the δ scale, and coupling constants, J, are in Hertz. Multiplicities are reported as “s” (singlet), “br s” (broad singlet),

"d" (doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet), and "m" (multiplet). Where distinct from those due to the major diastereomer, resonances due to minor diastereomers are denoted by an asterisk. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, HMBC, and NOESY spectra. Infrared (IR) spectra were recorded using a thin film on a composite of zinc selenide and diamond crystal on an FT-IR system transform spectrometer. Melting points are uncorrected. High-resolution mass spectrometry (HRMS) was performed using a spectrometer operating at a nominal accelerating voltage of 70 eV or a TOF-Q mass spectrometer.

*Ketone **13**.* A suspension of 3-methyl-2-butanone (6.21 mL, 58.1 mmol), ethyl formate (8.58 mL, 116 mmol) and NaH (1.53 g, 63.9 mmol, 60% dispersion in mineral oil) in THF (120 mL) was heated to reflux and allowed to stir for 30 min. The solution turned cloudy grey to yellow, then was allowed to cool to rt before concentration *in vacuo*. The resultant yellow gum was dissolved in DMSO (120 mL) under an inert atmosphere, then dimethyl sulfate (5.51 mL, 58.1 mmol) was added and the reaction was left to stir for 4 h at rt. The reaction was quenched with H_2O (150 mL) then extracted with CH_2Cl_2 (3 × 150 mL); the collected organic fractions were then dried over $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by vacuum distillation (80 °C, 1.5 mbar) to give ketone **13** (5.92 g, 80%, *E/Z* 4:1) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 12.6 Hz, 1H), 6.40* (d, *J* = 7.2 Hz, 0.24H), 5.62 (d, *J* = 12.5 Hz, 1H), 5.08* (d, *J* = 7.2 Hz, 0.23H), 3.85* (s, 0.83H), 3.70 (s, 3H), 2.87* (dq, *J* = 13.9, 6.9 Hz, 0.23H), 2.65 (dq, *J* = 7.0 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.07* (s, 0.74H), 1.05* (s, 0.68H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 162.7, 158.2*, 105.3*, 103.5, 57.7, 41.2, 39.7*, 18.8, 18.6 *minor isomer. Spectroscopic data were in good agreement with those previously reported.[6]

*Diene **8a**.* To a stirred solution of ketone **13** (2.50 g, 15.6 mmol) and NEt_3 (6.52 mL, 46.8 mmol) in Et_2O (50 mL) at 0 °C under nitrogen was added TBSOTf (5.38 mL, 23.4 mmol) dropwise. After 10 min, the solution was allowed to warm to rt and stir for 3 h by which point two clear layers had formed. The bottom layer was removed by pipette and the top layer was concentrated *in vacuo*. The resultant crude oil was then purified by flash chromatography on neutral alumina (6% EtOAc in pet. ether) to give diene **8a** (3.75 g, 99%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, *J* = 12.3 Hz, 1H), 5.63 (d, *J* = 12.4 Hz, 1H), 3.58 (s, 3H), 1.67 (s, 6H), 0.99 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 140.2, 111.2, 101.0, 56.7, 26.2, 19.1, 19.0, 18.5, -3.3. A small impurity corresponding to TBS-X persists after purification as per report by Rawal *et al*. Spectroscopic data were in good agreement with those previously reported by Rawal *et al.* [6]

*Diene **8b**.* To a stirred solution of ketone **13** (1.00 g, 7.80 mmol) and NEt_3 (3.26 mL, 23.4 mmol) in Et_2O (90 mL) at 0 °C under nitrogen was added TMSOTf (1.55 mL, 8.58 mmol) dropwise. After 10 min, the solution was allowed to warm to rt and stir for a further 3 h. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ (30 mL) followed by pentane (30 mL). The organic layer was then separated and the aqueous phase was extracted with pentane (30 mL). The combined organic extracts were then washed with sat. aq. $NaHCO_3$ (2 × 30 mL), H_2O (2 × 30 mL), and brine (2 × 30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the resultant brown oil was purified by vacuum distillation (110 °C, 50 mbar) to afford diene **8b** (1.20 g, 77%) as a clear oil. IR (film) ν_{max} 2981, 2936, 1627, 1380, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, *J* = 12.6 Hz, 1H), 5.68 (d, *J* = 12.2 Hz, 1H), 3.58 (s, 3H), 1.66 (s, 3H), 1.66 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 140.6, 111.0, 101.2, 56.8, 18.9, 18.7, 0.82.

*Adduct **16**.* To a solution of methacrolein (30 μL, 0.33 mmol) and $ZnCl_2$ (4.5 mg, 0.033 mmol) at 0 ºC in CH_2Cl_2 (0.5 mL) was added diene **8a** (40 mg, 0.16 mmol). The resultant solution was stirred for 3 h then sat. aq. Na_2CO_3 (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were concentrated *in vacuo* and the crude oil was purified by flash chromatography (20% EtOAc in pet. ether) to give adduct **16** as a clear oil (23 mg, 84%). IR (film) ν_{max} 2971, 2931, 1711, 1457, 1386, 1369, 1240, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 6.72 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.04 (d, *J* = 10.2 Hz, 1H), 2.34 (dd, *J* = 14.5, 1.8 Hz, 2H), 1.82 (d, *J* = 14.5 Hz, 1H), 1.27 (s, 3H) 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 201.5, 148.0, 128.8, 48.6, 43.9, 41.4, 26.7, 25.7, 24.0; HRMS (ESI+) $[M + H]^+$ 167.0714 calcd for $C_{10}H_{15}O_2$ 167.1067.

*Ketone **18**.* To a solution of diene **8a** (40 mg, 0.16 mmol) and methyl methacrylate (35 μL, 0.32 mmol) in CH_2Cl_2 (0.5 mL) at -78 ºC was added $SnCl_4$ (0.1 M in CH_2Cl_2, 30 μL. 0.06 mmol). The resulting solution was stirred for 3 h at -78 °C, then warmed to 0 ºC and stirred for a further 1 h before addition of NEt_3 (69 μL, 0.49 mmol). The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography (20% EtOAc in pet. ether) to afford dimer **18** as a clear oil (yield). IR (film) ν_{max} 2973, 2936, 1672, 1270, 1032, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 12.1 Hz, 1H), 6.95 (d, *J* = 16.1 Hz, 1H), 6.21 (d, *J* = 16.0 Hz, 1H), 5.73 (d, *J* = 12.1 Hz, 1H), 3.71 (s, 3H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.30 (s, 6H), 1.12 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 199.8, 164.2, 150.2, 126.9, 100.7, 58.3, 49.6, 39.0, 23.9, 18.5.

*Adduct **21**.* To a solution of ethyl 3-methyl-4-oxocrotonate (44 μL, 0.33 mmol) and $Sc(OTf)_3$ (16 mg, 20 mol %) in CH_2Cl_2 at -78 °C was added diene **8a** (40 mg, 0.16 mmol). The resultant mixture was stirred for 3 h, then allowed to warm to rt and quenched with NEt_3 (69 μL, 0.49 mmol). The reaction mixture was extracted with sat. aq. NH_4Cl, washed with brine, and dried over Mg_4SO_4. The organic phase was then concentrated *in vacuo* and purified by flash chromatography (30% EtOAc in pet. ether) to give adduct **21** as a clear oil (23 mg, 43%). IR (film) ν_{max} 2978, 2937, 1716, 1466, 1385, 1369, 1269, 1162 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 6.6 Hz, 1H), 5.94 (q, *J* = 1.1 Hz, 1H), 5.39 (d, *J* = 5.9 Hz, 1H), 4.54 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.25 (d, *J* = 1.5, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.11 (s, 3H) 1.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 166.0, 161.5, 151.1, 120.7, 105.5, 90.4, 60.3, 44.8, 20.0, 19.0, 18.0, 14.4; HRMS (ESI+) [M + Na] 261.1091 calcd for $C_{13}H_{18}NaO_4$ 261.1097.

*Adduct **22**.* A solution of diene **8a** (61 mg, 0.25 mmol) and freshly sublimed maleic anhydride (49 mg, 0.50 mmol) in toluene (1 mL) was stirred at 100 °C in a round-bottom flask for 2 hours. After cooling to rt, the solution was concentrated *in vacuo* and purified by flash chromatography (15% EtOAc in pet. ether) to afford adduct **14** (31 mg, 36%) as a colorless oil. IR (film) ν_{max} 2933, 1715, 1637, 1255, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (d, *J* = 6.4 Hz, 1H), 4.25 (dd, *J* = 6.4, 5.0 Hz, 1H), 3.36 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.21 (s, 3H), 3.18 (d, *J* = 10.9 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 0.95 (s, 9H), 0.22 (d, *J* = 1.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.3, 163.1, 97.3, 71.5, 55.5, 49.4, 46.7, 36.8, 28.8, 25.7, 25.2, 18.3, -4.3, -5.1; HRMS (ESI+) $[M + Na]^+$ 363.1598; calc. for $C_{17}H_{28}NaO_5Si$ 363.1598.

*Lactone **25** & **26**.*

Method A. A mixture of diene **8a** (1.17 g, 4.82 mmol), distilled citraconic anhydride (400 mg, 3.57 mmol), and hydroquinone (9.8 mg, 0.09 mmol) was degassed in a Schlenk tube by prolonged evacuation followed by back-filling with nitrogen three times. The reaction mixture was then stirred at 140 °C overnight. After cooling to rt, chloroform (35 mL) and TFA (1.05 mL) were added and the resulting mixture was stirred for 5 min at rt, then concentrated *in vacuo*. The crude mixture was dissolved in AcOH (40 mL) and $NaCNBH_3$ (1.24 g, 17.9 mmol) was added. The reaction mixture was stirred at rt for 2 h before concentration *in vacuo*. The crude mixture was then dissolved in CH_2Cl_2 (150 mL) and washed with

1 M aq. HCl (100 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 × 100 mL). The collected organic phases were then washed with brine (1 × 150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a crude mixture of acids **5** and **24**. The crude mixture was suspended in MeOH/benzene (2:1, 30 mL) and TMS diazomethane (2.15 mL, 2 M in Et_2O) added. The resultant mixture was stirred for 15 min then quenched with AcOH. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (35% EtOAc in pet. ether) to afford a mixture of lactones **25** (136 mg, 17%) and **26** (60 mg, 7%) as yellow oils.

Method B (One pot optimized): A mixture of diene **8a** (141 mg, 0.58 mmol), distilled citraconic anhydride **11** (45 mg, 0.40 mmol), and hydroquinone (1 mg, 0.01 mmol) was degassed in a Schlenk tube by prolonged evacuation followed by back-filling with nitrogen three times. The reaction mixture was then stirred at 140 °C overnight. After cooling to rt, chloroform (5 mL) and $ZnCl_2$ (1.0 M in Et_2O, 150 μL) were added and the resulting mixture was stirred for 20 min before the addition of AcOH (2 mL) and $NaCNBH_3$ (182 mg, 2.9 mmol). The mixture was stirred at rt for a further 30 min before it was quenched with 1 M aq. HCl (10 mL). The resulting mixture was then extracted with CH_2Cl_2 (3 × 15 mL). The collected organic phases were then washed with brine (1 × 30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Esterification with TMS diazomethane and purification as per *method A* afforded a mixture of lactones **25** (8.0 mg, 9%) and **26** (22 mg, 24%) as yellow oils.

[2.2.2]-**25**: IR (film) ν_{max} 2957, 1436, 1353, 1211, 1100, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, J = 7.6, 5.0 Hz, 1H), 6.14 (dd, J = 7.6, 1.9 Hz, 1H), 4.58 (dd, J = 5.0, 2.0 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 1H), 1.41 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 171.7, 136.8, 133.1, 82.0, 56.6, 51.9, 46.2, 41.4, 29.5, 23.4, 17.2. HRMS (ESI+) $[M + Na]^+$ 247.0944 calcd for $C_{12}H_{16}NaO_4$ 247.0941; Crystals were obtained for XRD analysis by evaporation from chloroform-hexane, mp 104-107 °C.

[3.2.1]-**26**: IR (film) ν_{max} 2956, 1780, 1436, 1262, 1109, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 9.6, 5.8 Hz, 1H), 5.96 (ddd, *J* = 9.6, 1.7, 0.9 Hz, 1H), 4.26 (d, *J* = 5.9, 1H), 3.72 (s, 3H), 2.52 (s, 1H), 1.49 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 173.9, 133.7, 126.8, 80.4, 55.6, 52.8, 47.8, 43.4, 27.0, 22.6, 22.0; HRMS (ESI+) $[M + Na]^+$ 247.0949 calcd for $C_{12}H_{16}NaO_4$ 247.0941.

Weinreb amides **27** *and* **28**. To a solution of crude acids **5** and **24** (*ca.* 0.71 mmol obtained from method B) in CH_2Cl_2 (7.5 mL) under nitrogen were added oxalyl chloride (0.24 mL, 2.85 mmol) and DMF (1 drop) and the resulting mixture was allowed to stir at rt for 4 h before concentration *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (7.5 mL), then HN(Me)OMe.HCl (139 mg, 1.43 mmol) and NEt_3 (0.40 mL, 2.85 mmol) were added and the mixture was left to stir for 24 hours at rt. The reaction mixture was then washed with sat. aq. NH_4Cl (5 mL), then brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was then purified by flash chromatography (70% EtOAc in pet. ether) to afford Weinreb amide **27** (25 mg, 14% from citraconic anhydride) and Weinreb amide **28** (19 mg, 10% from citraconic anhydride) as white solids. Data for [2.2.2] Weinreb amide **27**: IR (film) ν_{max} 2944, 1777, 1745, 1646, 1089, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.13 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.51 (dd, *J* = 5.0, 2.0 Hz, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 2.61 (s, 1H), 1.39 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 172.9, 136.5, 133.5, 82.2, 61.4, 52.4, 46.6, 41.4, 32.4, 29.2, 24.0, 17.5; HRMS (ESI+) $[M + H]^+$ 254.1386 calcd for $C_{13}H_{20}NO_4$ 254.1387. Data for [3.2.1] Weinreb amide **28**: IR (film) ν_{max} 2960, 1760, 1643, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, *J* = 9.6, 5.7 Hz, 1H), 6.02 (ddd, *J* = 9.7, 1.7, 1.0 Hz, 1H), 4.24 (d, *J* = 5.8 Hz, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 2.91 (t, *J* = 1.6 Hz, 1H), 1.53 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 174.8, 135.5, 124.2, 80.6, 60.7, 54.4, 48.3, 43.7, 34.2, 27.2, 22.1, 22.0; HRMS (ESI+) $[M + H]^+$ 254.1390 calcd for $C_{13}H_{20}NO_4$ 254.1387; crystals were obtained for XRD analysis by evaporation from Et_2O; mp. 135-137 °C.

Lactone ***30***. A mixture of lactone **25** (9.4 mg, 0.042 mmol) and a catalytic amount of $PtO_2.H_2O$ in MeOH (1 mL) was stirred at rt under an atmosphere of H_2 (balloon pressure) for 16 h. The mixture was then filtered through Celite® and the filtrate was concentrated *in vacuo* to give ester **30** (10 mg, quant.) as an amorphous white solid. IR (film) ν_{max} 2953, 1755, 1367, 1098, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (dd, *J* = 3.8, 1.7 Hz, 1H), 3.68 (s, 3H), 2.51 (s, 1H), 2.12–2.02 (m, 1H), 1.94 (dddd, *J* = 14.5, 11.7, 6.6, 3.7 Hz, 1H), 1.81–1.60 (m, 2H), 1.22 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 171.3, 83.3, 60.5, 51.6, 40.2, 37.0, 30.6, 28.9, 24.0, 22.5, 19.6; HRMS (ESI+) $[M + H]^+$ 227.1271 calcd for $C_{12}H_{19}O_4$ 227.1278.

Associated Content

Experimental procedures, analytical data and copies of ^1H and ^{13}C NMR spectra for novel compounds and ORTEP structures of **25** and **28**.

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Keywords: leonuketal • natural products • cycloaddition • synthetic methods • multistep reaction

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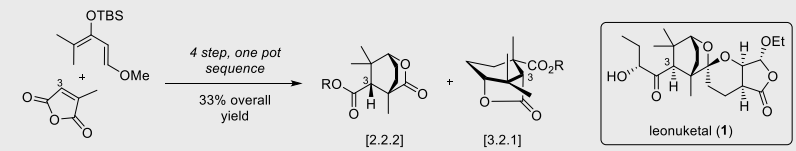

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