Shackles Off: A Kilo Scale Synthesis of Rawal's Diene

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ABSTRACT: Despite superior reactivity compared to Danishefsky's diene, Rawal's diene suffered from low commercial availability, limited scalability, and obscure stability issues. Herein, we present an optimized, scalable synthetic protocol that achieves yields suitable for the diene's semi-industrial production, with adjustments to reagent concentrations, reaction conditions, and isolation procedures to enhance the efficiency of the synthetic protocol. Complementing synthetic advancements, this work explores the diene's physicochemical stability under diverse storage conditions. Rigorous quality control methodologies exploiting NMR and IR spectroscopy facilitate precise monitoring of purity and degradation pathways, establishing robust analytical standards.

Additionally, the work demonstrates the utility of Rawal's diene in multigram syntheses of 2-alkyl-2,3-dihydro-4*H*-pyran-4-ones, showcasing its applicability for medicinal chemistry purposes. The findings disclosed in the paper establish a foundation for the broader adoption and commercialization of Rawal's diene, enabling its integration into academic and industrial workflows.

INTRODUCTION

Organic reactions, methods, and reagents can be likened to living organisms – they continually evolve to provide researchers with efficient tools that meet the modern demands of fine organic synthesis. Once these processes achieve a certain level of reliability, they become an integral tool of industrial protocols, including, but not limited to, API production.[1]

The development of (*E*)-1-methoxy-3-trimethylsilyloxy-buta-1,3-diene marked a significant milestone in the classical (*hetero*)-Diels-Alder reaction (**Figure 1**). Exactly half a century ago, *Samuel Danishefsky* and *Takeshi Kitahara* released a communication note highlighting the synthesis and potential application of the diene in [4+2] cycloadditions with electron-deficient alkenes.[2] Further investigations revealed substantial advantages in using the diene for the preparation of pyrans and piperidines securing high regioselectivity of the transformations and yielding products amenable to further functional group manipulations.[3] These advantages have given rise to numerous research papers and reviews that clarified its reactivity profile.[4] Today, Danishefsky's diene is a well-established commercially available building block with a reported "200+ grams" synthetic approach.[5]

However, while Danishefsky's diene is useful for synthesizing (hetero)cyclic motifs, it presents challenges, particularly regarding its insufficient reactivity toward certain functionalities (e.g., aliphatic aldehydes without proper activation).[3d,6] This demand has spurred the development of

even more reactive 1-amino-substituted dienes. Although such dienes have been important in the evolution of the Diels-Alder reaction since the 1940s,[7] the incorporation of both 3-siloxy and 1-amino substituents into the 1,3-butadiene structure received surprisingly little attention until the late 1990s, when *Viresh Rawal* and *Sergey Kozmin* explored this area. Their works on the total synthesis of dehydrotubifoline,[8] strychnine,[9] and possible precursors to lepadiformine and cylindracines led them to the idea that aminosiloxy dienes could serve as advantageous alternatives to Danishefsky-type dienes.

Among others, 1-(dimethylamino)-3-(dimethyl-*tert*-butylsiloxy)-1,3-butadiene (commonly known as Rawal's diene) gained the most popularity. It was first reported in a seminal paper by *Kozmin* and *Rawal*,[10] which emphasized its unique structural features and potential as a building block. The presence of enamine and enol ether units in synergistic positions endows Rawal's diene with remarkable reactivity in Diels-Alder processes.[11] Initial and subsequent assessment of the relative reactivity of Rawal's and Danishefsky's dienes concluded that the aminosiloxy diene is 25-to-3000 times more reactive than the 1-methoxy 3-siloxy diene.[10,12]

Despite the growing popularity of Rawal's diene and numerous projects utilizing it (though much lower than for Danishefsky's diene[13]), Sigma-Aldrich remains the only reliable commercial supplier, offering a 5 g package for €220 as of October 28, 2024.[14] Furthermore, most reactions involving the aminosiloxy diene have been conducted on a mmol scale, even though it was considered valuable for drug development. Evidently, the status quo stems from the absence of a large-scale protocol for its preparation, thus restricting research flexibility. Unlike Danishefsky's diene, Rawal's counterpart has been prepared with a reported maximum one-run yield of just 20.4 g.[15] Even if the protocol were to be scaled up, stability issues remain a significant challenge that must be addressed for its broader commercial application. In this work, we present our findings

that aim to overcome the limitations associated with Rawal's diene in synthetic research, making it more accessible to a wider range of scientists and paving the way for its commercialization.

This research is built on three pillars. The first is the development of a scalable, hundred-gram synthetic protocol for Rawal's diene, including exploration of factors influencing its performance. The second one involves establishing robust quality control measures for the substance. Finally, the third pillar focuses on a comprehensive investigation into the stability of Rawal's diene under various conditions. Together, these efforts are expected to create clear guidelines for its proper handling and storage, ensuring its reliability and usability in both research and commercial settings.

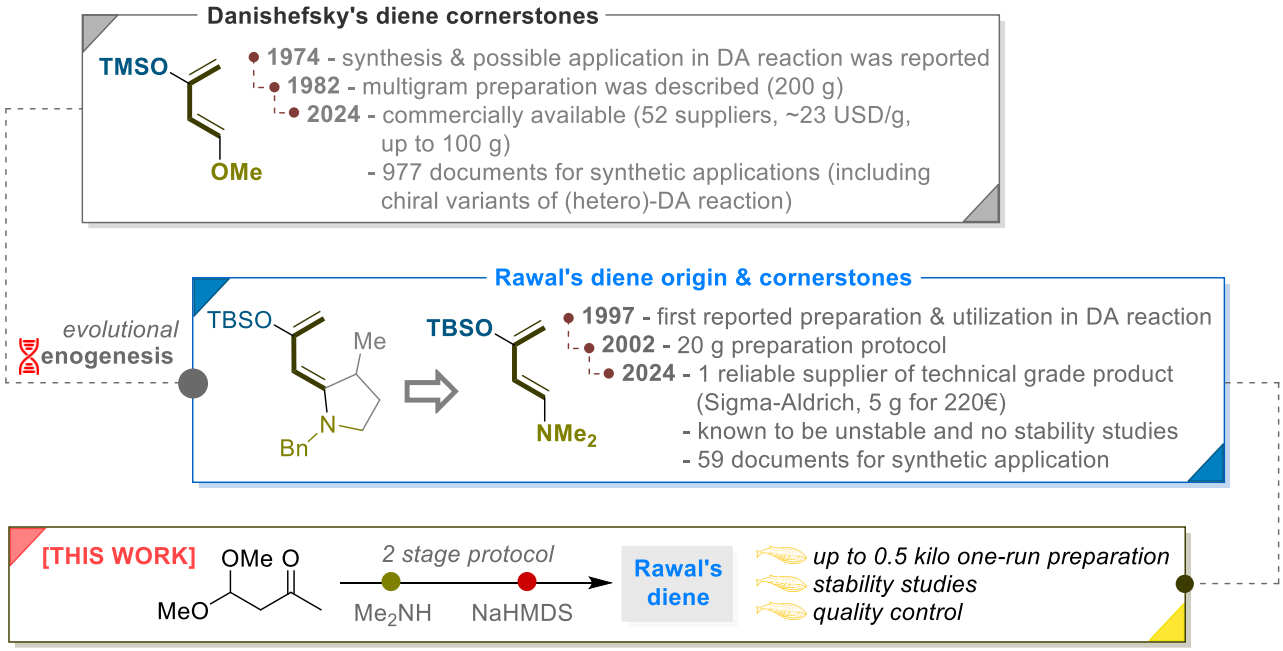


Figure 1. Background and synopsis of the work

RESULTS AND DISCUSSION

Synthesis and scale-up

The gram-scale synthesis of Rawal's diene has been predominantly guided by the method developed by *Kozmin et al.* and detailed in *Organic Syntheses* in 2002.[15] Their approach employs

a two-step process starting with acetylacetaldehyde dimethyl acetal (**1**), which reacts sequentially with dimethylamine and *tert*-butylchlorodimethylsilane (**Scheme 1**). Before scaling-up to produce larger quantities, we carefully evaluated the original method. Our trials confirmed that the reported procedure consistently produced the desired product with indicated purity and yield. While experimenting, we identified several enhancements that improved the process efficiency. Notably, replacing the original 2M dimethylamine in methanol with a corresponding 40% (*w*/*w*) aqueous solution maintained the reaction yield while improving cost- and resource efficiency of a large-scale protocol. An additional aspect we noticed during primary experiments concerned acetylacetaldehyde dimethyl acetal quality. Commercial-grade acetylacetaldehyde dimethyl acetal (**1**) (95%) could be used directly without the need for distillation, thus making the process more practical. In general, scaling-up loading to 1.42 kg of dimethyl acetal yielded 1.09 kg (90%) of enaminone, obtained as an orange oil that darkened slightly over time but required no specific storage conditions and remained stable and usable without further purification prior to introduction into the next step.

The second step involved the generation of the enamine enolate with a base and introducing a TBS (*tert*-butyldimethylsilyl) protecting group using TBSCl. The original protocol employed a 1M solution of NaHMDS to form the enolate. To improve scalability, we switched to a more concentrated, commercially available 2M NaHMDS solution in THF. This adjustment not only reduced the reaction volume but also made handling the reaction mixture far more practical and efficient. While 1M KHMDS was also tested successfully, for the mentioned reasons, NaHMDS demonstrated superior practicality. The higher concentration of 2M NaHMDS allowed us to increase the dilution of enaminone **2** to 0.6M in THF, compared to the 2M concentration used in

the original procedure. This step provided better control of the internal temperature while adding TBSCl (exothermic process).

In comparison to the method described by *Kozmin et al.*, we also modified the order of reagent addition. Instead of adding the enaminone to the base, we introduced the base into a pre-prepared THF solution of enaminone **2**. This change addressed viscosity issues associated with the solubility of NaHMDS in THF at low temperatures, making the reaction mixture easier to handle. Another key reason for this adjustment was to maintain homogeneity in the reaction mixture while adding the base to the enaminone. It is important as the formation of a precipitate is undesirable and may cause a drop in diene's yield. In turn, premature precipitation may result from the rapid addition of the base or excessively low internal temperatures. By reordering the reagent addition, we ensured that the precipitate formed only after the complete addition of TBSCl, as the reaction warmed to room temperature.

Another practical aspect concerns conditions for the generation of the enolate. Experiments indicated that elevating the internal temperature to -40°C and maintaining it for one hour prior to TBSCl addition resulted in higher yields of the diene. For further refinements, we also optimized the ratios of NaHMDS and TBSCl relative to the classical method. Through experimentation, we achieved the highest reaction yield by performing the silylation with 1.10 equiv of NaHMDS and 1.15 equiv of TBSCl, as opposed to the original ratios of 1.00 and 1.05 equiv, respectively.

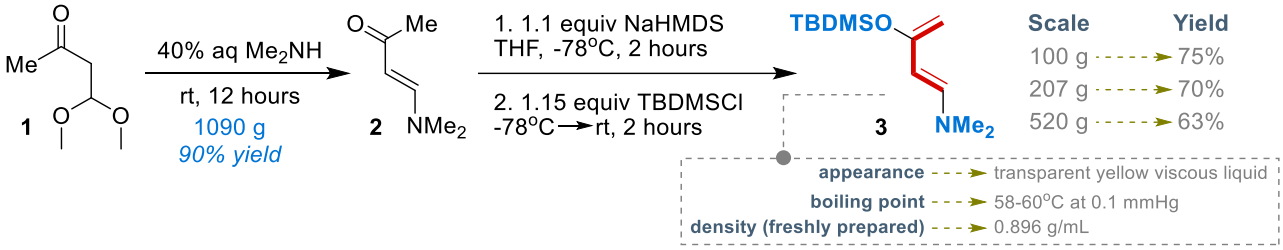
The second stage of introducing the silyl-protecting group produces sodium chloride as a by-product. While NaCl is indifferent toward components of the reaction mixture in most organic reactions, in the case of generating Rawal's diene, it is extremely important to qualitatively filter the finely dispersed precipitate of NaCl since it worsens the quality and yield of the product **3**. Analysis of the product contaminated with NaCl evidenced desilylation of the diene molecule

because of the backward S_N2 process, leading to an inseparable mixture of the starting enaminone **2** and product **3**. The best-found way to efficiently get rid of NaCl was the dilution of the reaction mixture with the same volume of *t*BuOMe and leaving it in a fridge for 12 hours to let the precipitate mature. This step and the following procedures are required for as quick as possible filtration of the mixture, which is crucial for achieving high yields of the diene (*vide infra*). For small batches (20–50 g), filtration through Na_2SO_4 pads tightly packed in a glass funnel filter was effective (water jet pump vacuum). The main limitation lies in the filtration efficiency, which decreases for larger loads (becomes slow), requiring frequent pad replacements. This, in turn, prolongs the diene's unwanted exposure to air. To avoid moisture contamination, it is also crucial to use high-quality, freshly calcined anhydrous sodium sulfate, ensuring the product remains protected from water absorption. In the case of larger batches, a much better way was filtering the reaction mixture through cotton wool placed in a glass funnel (first gravity filtration, than vacuum filtration with a water jet pump). In this scenario, the filtration process is faster (occasionally, the cotton wool should be loosened), thus minimizing exposure of the diene to air and preserving its stability.

Following filtration, the solution was concentrated under reduced pressure, with bath temperatures kept within the range of 30-35°C to avoid TBS group degradation. For large-scale preparations (hundreds of grams), we combined filtration and concentration steps to improve process efficiency. The crude product (a mixture of the diene with HMDS) was then distilled *in vacuo*, collecting the fraction boiled at 58-60ºC (0.1 mmHg). To streamline the process, most of the HMDS should first be removed under a low vacuum (has a lower bp of 126ºC at 1 atm), and then a deeper vacuum should be applied to distill the diene, minimizing trap changes and distillation time.

While proceeding along the scaling-up ladder, we noticed a gradual drop in the yield of diene **3**, from 90% at 11 g of the starting enaminone to 63% at 420 g (**Scheme 1**). This drop correlated with prolonged filtration times required for larger batches, which increased the product's exposure to air. Given Rawal's diene's electron-rich nature, it must be highly susceptible to oxidation by air oxygen, thus lowering the content of the diene in the solution and leading to reduced yields. Moreover, air moisture absorption during handling can further exacerbate diene's degradation (see *SI file*), emphasizing the need for an inert environment and rapid processing.

Thus, through targeted optimizations, the synthesis of Rawal's diene was transformed into a reproducible, moderate-yield process suitable for semi-industrial applications. Possibly, these advancements will pave the way for broader adoption of Rawal's diene in synthetic and pharmaceutical research.

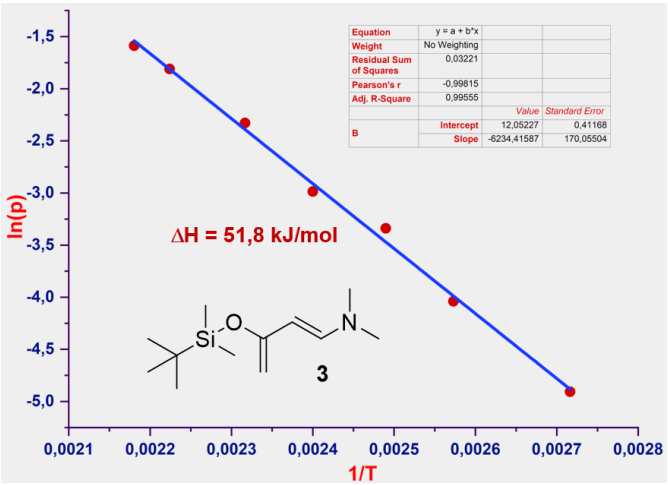


Scheme 1. Overview of the Rawal's diene synthesis

When shifting from lab-scale preparation to industrial production, the distillation stage may become a cornerstone for efficient process development.[16] In this way, knowing vapor pressure behavior is an invaluable instrument as it helps in designing distillation columns and understanding separation efficiency because it governs the volatility of components, phase equilibria, and separation dynamics. A plot of the *Clausius-Clapeyron equation* provides valuable insights into the relationship between vapor pressure and temperature and is a powerful tool for studying the thermodynamic and physical properties of a substance across temperature ranges. **Table 1** depicts

the results of our measurements of the "vapor pressure *vs* temperature" correlation for Rawal's diene. They indicate linear dependence ln*p*–1/*T* within the temperature range of 95-459 °C. Calculated vaporization enthalpy for the linear section is 51.8 kJ/mol, which is, for instance, comparable to 1,2-propanediol (52.4 kJ/mol, 96-223 °C), diethylene glycol methyl ether (51.9 kJ/mol, 122-193 °C,) and benzylamine (51.8 kJ/mol, 29-185 °C).[17] At higher than 0.2 bar values of pressure, the dependence loses its linearity that, among others, may indicate potential decomposition processes, reinforcing the need for precise pressure control during scale-up.

Table 1. *Clausius-Clapeyron* equation plot for Rawal's diene



ln*p* = -6234/T + 12.05				
p, bar	***T*, °C**	***T*, K**	**1/*T***	**ln(*p*)**
0.0074	95	368.15	0.002716	-4.90628
0.0176	115.5	388.65	0.002573	-4.03986
0.0355	128.5	401.65	0.00249	-3.33822
0.0505	143.5	416.65	0.0024	-2.98578
0.0975	158.5	431.65	0.002317	-2.3279
0.1635	176.5	449.65	0.002224	-1.81094
0.2045	185.5	458.65	0.00218	-1.58719

Quality control

Ensuring the quality of chemical reagents is essential for achieving reliable and reproducible results in scientific, industrial, and commercial applications. High-quality reagents are crucial across diverse fields, including pharmaceuticals, biotechnology, materials science, and analytical chemistry, and directly impact process performance. In industrial settings, the use of high-quality reagents minimizes waste, enhances efficiency, and reduces costs by preventing incomplete reactions, low yields, or additional purification steps. Maintaining consistently high-quality reagents supports smooth production workflows, optimizes resources, and maximizes profitability.

Given Rawal's diene's high reactivity – especially its sensitivity to moisture and atmospheric oxygen – keeping its purity through proper preparation and storage is critical. Recognizing this, we focused on developing robust analytical methods to assess its quality, providing essential guidelines for suppliers and researchers handling this compound.

Early testing revealed that chromatography methods were unsuitable for evaluating Rawal's diene purity due to its chemical and thermal instability. While LC-MS has clear limitations in the analysis of Rawal's diene, GC-MS failed to provide meaningful data as well. Instead, we focused on NMR spectroscopy, a widely used and reliable analytical tool, to assess purity. Selecting the appropriate solvent for NMR analysis was a key focus. We started by evaluating the most important deuterated solvents – dimethyl sulfoxide (DMSO-d_6) and chloroform ($CDCl_3$). Initial tests with commercial samples of DMSO-d_6 quickly revealed its unsuitability, as partial degradation of the diene into enaminone **2** *via* hydrolysis occurred almost immediately after dissolution (see *SI file*). The degradation process accelerated over time, as evidenced by increasing proton signals corresponding to enaminone in the spectra recorded at 2, 24, and 72 hours (closed NMR ampoule, **Table 2**). Commercial deuterated chloroform proved more effective, yielding clean NMR spectra of diene **3** immediately after its dissolution without any detectable enaminone contamination. However, gradual hydrolysis still occurred due to residual water in the solvent and, likely, slight acidity of chloroform, leading to nearly the same degradation level two hours after dissolution as we observed in DMSO-d_6. While overall the rate of degradation in $CDCl_3$ was slower than in DMSO-d_6, it still posed challenges for prolonged analysis. Nevertheless, $CDCl_3$ remains an option (though rough) for the evaluation of the diene quality. To address these limitations, we turned our attention to deuterated benzene (C_6D_6). Tests demonstrated that Rawal's diene remained stable in C_6D_6 for at least four days without any signs of decomposition. This

stability, coupled with high spectral clarity, made C_6D_6 the optimal solvent for assessing the quality and purity of Rawal's diene.

Table 2. Content of enaminone **2** (%) in the deuterated solvents over time (the same sample of freshly prepared Rawal's diene) according to ^{1}H NMR (400 MHz)

Solvent	2 hours	24 hours	72 hours	96 hours
DMSO-*d*$_6$	11	36	55	-
$CDCl_3$	10	19	50	-
C_6D_6	0	-	-	0

Stability and storage

After establishing reliable methods to evaluate the quality of Rawal's diene, we shifted focus to assessing its stability under different storage conditions. The central question was how long Rawal's diene could be stored without significant degradation and under what conditions it retained its purity. This issue is vital for its further integration into commercial chemical space. To evaluate stability, we monitored the diene over time at intervals of 7 days, 14 days, and 1.5 years. Samples were stored in various conditions – open and closed vials, under air and argon atmospheres, and at temperatures of 4°C and 25°C. Degradation levels were tracked using ^{1}H NMR spectroscopy in C_6D_6 solutions, as detailed earlier (for ^{1}H NMR copies, see *SI file*). The results are summarized in **Table 3**. They highlight that open-air storage (7 days) is unsuitable due to moisture absorption, which leads to hydrolysis and the formation of enaminone **2** as the major product. For closed vials (7 days), both under air at 25°C and argon at 4°C or 25°C, the diene largely maintained its quality. However, the air-stored sample developed about 3% of an unidentified impurity, visible as two distinct doublets at 5.53 and 7.59 ppm, unrelated to hydrolysis (provided that each doublet corresponds to 1H integral intensity). Visual inspection (**Figure 2**) of

7-day samples revealed color changes of the substance, with diene darkening from pale yellow to orange and eventually to brown.

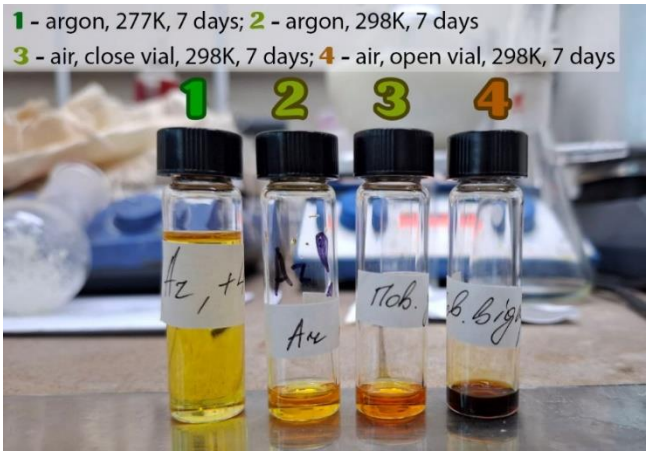


Figure 2. Rawal's diene stored for 7 days under different conditions

For another step, 14 days, we excluded open-air conditions due to the rapid degradation of the diene. Closed vials stored at 25°C in air and argon continued to perform well, although the levels of the non-identified admixture in the air-stored sample rose to 11%, compared to 4% in the argon-flushed sample. This unidentified impurity likely resulted from slow oxidation by atmospheric oxygen (or oxygen traces present in argon), and further tests confirmed it did not compromise the diene's performance in *hetero*-Diels-Alder reactions. Likewise, the enaminone could stem from the absorption of residual water present in commercial argon gas. Thus, extra care should be taken to ensure the purity of the inert gas.

Overall, the tests indicate the possibility of storing the reagent under ambient conditions without tangible degradation for a short time. To understand the long-term prospects of Rawal's diene storage, we kept the diene in a fridge at 4°C under argon for 1.5 years. ^{1}H NMR ($CDCl_3$) of the product showed the sample retained of *ca.* 83% purity, suggesting this setup is viable for extended storage.

Table 3. Relative content (%) of main components in a Rawal's diene sample stored under different conditions (according to ^{1}H NMR, 400 MHz, C_6D_6)

	Ar, 4°C, 7 days	Ar, 25°C, 7 days	Air, closed vial, 25°C, 7 days	Air, open vial, 25°C, 7 days	Ar, 25°C, 14 days	Air, closed vial, 25°C, 14 days	Ar, 4°C, 1.5 years*
Rawal's diene (**3**)	100	100	100	0	100	100	100
Enaminone (**2**)	0	0	0	100	2	2	9
The unknown admixture**	0	0	3	1	4	11	11

Notes: *^{1}H NMR was taken in a $CDCl_3$ solution; **Featuring doublets at 5.53 and 7.59 ppm

Figure 3 illustrates key stacked NMRs for the diene samples compared to enaminone.

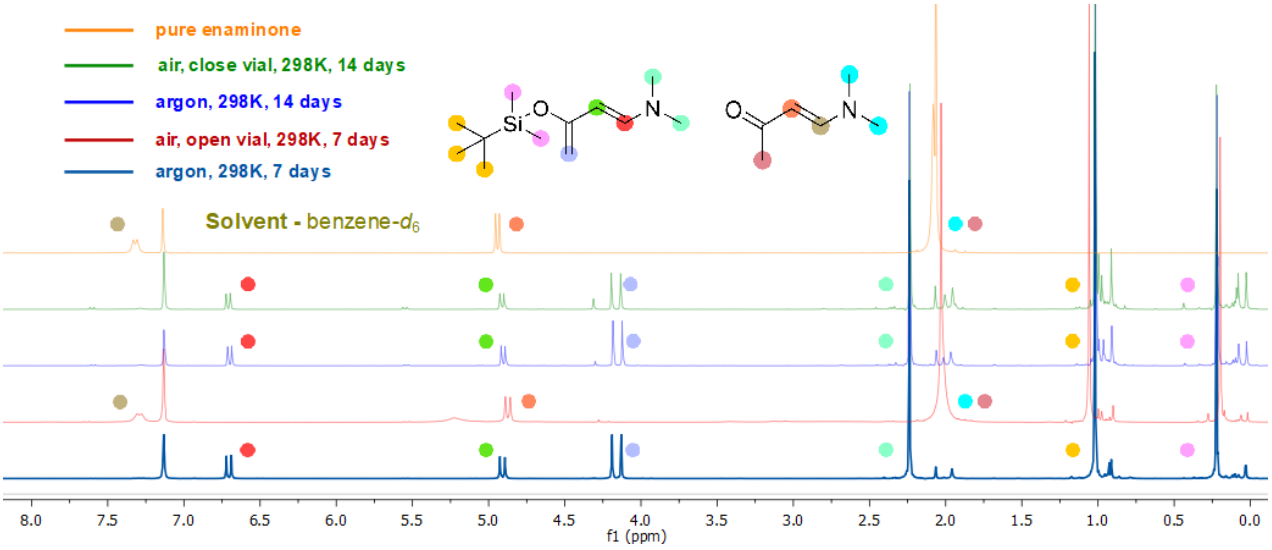


Figure 3. NMR spectra of Rawal's diene samples compared to the enaminone (for details, see *SI files*)

It is worth noting that assessing the quality of the same sample of Rawal's diene using ^{1}H NMR in $CDCl_3$ and C_6D_6 (recorded simultaneously after dissolution) often yielded slightly different results. Chloroform solutions typically showed a lower content of the main compound and a higher amount of the hydrolyzed product. Therefore, while deuterochloroform is generally the solvent of choice, using deuterated benzene for QC of Rawal's diene helps avoid misleading data.

Although the NMR method is a leading technique for structure elucidation and the detection of impurities and has become accessible to most chemical facilities, some other methods still keep their importance due to time and cost efficiency. IR spectroscopy is definitely one of such instrumental approaches. Process development departments of pharmaceutical companies routinely use IR spectrometry to assess the quality of supplied substances and intermediate products in synthetic routes. For that reason, we acquired IR spectra from various samples of Rawal's diene and compared them to the IR spectrum of the main degradation product – enaminone **2**.

In the functional group region, the pure diene exhibited distinct C-H stretching bands between 2950 and 2800 cm^{-1} and a strong C=C stretch at 1645 cm^{-1}. At the same time, most signals appeared within the fingerprint part of the spectrum (see *SI file*). Importantly, the IR spectrum of enaminone **2** is clearly different, especially at wavenumbers below 1600 cm^{-1} (an intensive broad band at ~1560 cm^{-1} is especially characteristic), which allows for easy identification of its presence in the mixture. Interestingly, comparisons between the air-stored and argon-stored samples (both after 14 days) revealed a notable difference: the air-stored sample displayed an unusually high-intensity band at 1580 cm^{-1}. Given that the "closed, air" sample is characterized by the relatively high content of the unknown admixture (two doublets at 5.53 and 7.59 ppm), one can suspect that the band is indicative of its presence in the substance. These patterns may establish IR spectroscopy as a well-suited method for the express analysis of the diene samples, despite the preconception that the method is not as sensitive and reliable as the NMR.

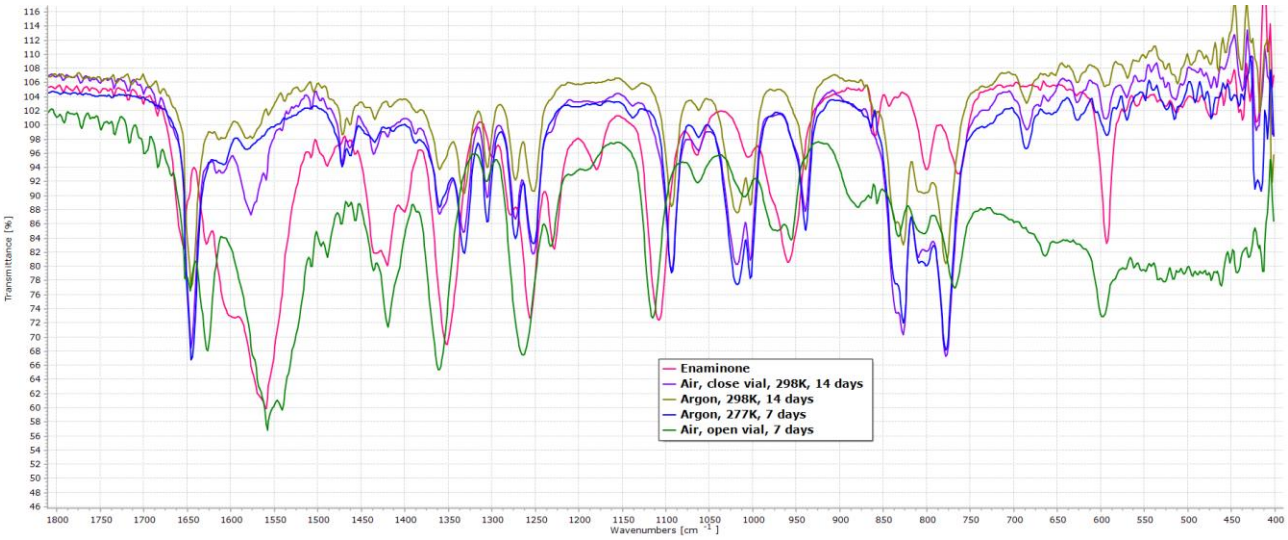


Figure 4. IR spectra of Rawal's diene samples compared to the enaminone (for details, see *SI files*)

Utility of Rawal's diene for the multigram preparation of 2-alkyl-2,3-dihydro-4*H*-pyran-4-ones

The seminal paper describing the preparation of 1-amino-3-siloxy-1,3-butadienes[10] has shown Rawal's diene as appreciably more reactive than a 1-methoxy-3-siloxy-1,3-butadiene and uncovered its utility in the construction of functionalized cyclohexanes *via* [4+2] cycloaddition. The following works revealed its prospects for a one-step assembling 2,3-dihydro-4*H*-pyran-4-ones in reaction with easily available carbonyls under particularly mild conditions. However, Rawal's diene and its application in organic synthesis remained mostly a matter of academic research and was not accepted by the industry. For instance, AstraZeneca's project on the elaboration of a synthetic route to a 5-LOX inhibitor,[18] which included 2-methyltetrahydropyran-4-one as an intermediate (**Scheme 2**), marked the latter as a challenging molecule to synthesize due to its sensitivity to acidic, basic, and Lewis acidic reaction media. The Diels-Alder reaction approach employing Danishefsky's diene followed hydrogenation was reasonably refused due to the necessity of using a Lewis acid catalysis, and Rawal's diene, in turn, was dismissed because

of insufficient stereoselectivity of the process. Instead, a five-step synthesis was used utilizing a chiral starting material and giving a 19% overall yield of the target pyranone on a 100-gram scale. Further improvement in the way made by Bristol-Myers Squibb chemists provided a 4-step multikilogram process,[19] though in moderate 35% yield and involving a Pd-catalyzed stage that reduces overall cost-efficiency of the approach. Recently, researchers from Pfizer made a particular breakthrough in the issue.[20] They applied a biocatalytic approach to resolve a racemic 2-methylpyran-4-one by reducing the undesired ketone using a ketone reductase enzyme on a multikilogram scale. This discovery opens up a great opportunity for a more concise route to a chiral 2-methyl-2,3-dihydro-4*H*-pyran-4-one, including a one-step process of interacting Rawal's diene with acetaldehyde. Notably, we found a single paper reporting such a *hetero*-Diels−Alder reaction in 1 mmol scale and 75% yield.[21]

In this work, we provide our results on multigram preparation of racemic 2-methyl-2,3-dihydro-4*H*-pyran-4-one supported by the elaborated multigram route to the diene (**Scheme 2**). Experiments confirmed that the first step of the reaction (formation of **5**) is thermally controlled and proceeds smoothly in a toluene solution at room temperature without the need for additives, such as Lewis acids, to activate the carbonyl component. While the mentioned study by *Unni et al.* suggested running the reaction with aliphatic aldehydes at low temperatures (down to -40°C), possibly to enhance enantioselectivity, we found that it performs just as efficiently at room temperature (water bath), with no noticeable exothermic effects. ^{1}H NMR monitoring in C_6D_6 verified that the reaction reached completion within 12 hours. Under the given conditions, a certain excess of the aldehyde component was needed. We found that the use of 1 equiv of the aldehyde resulted in the crude mixture containing unreacted Rawal's diene. In contrast, employing a 4-fold excess of acetaldehyde ensured complete consumption of the diene within 12 hours. The use of

the aldehyde excess did not pose a problem as it was easily removed by evaporation at the isolation stage.

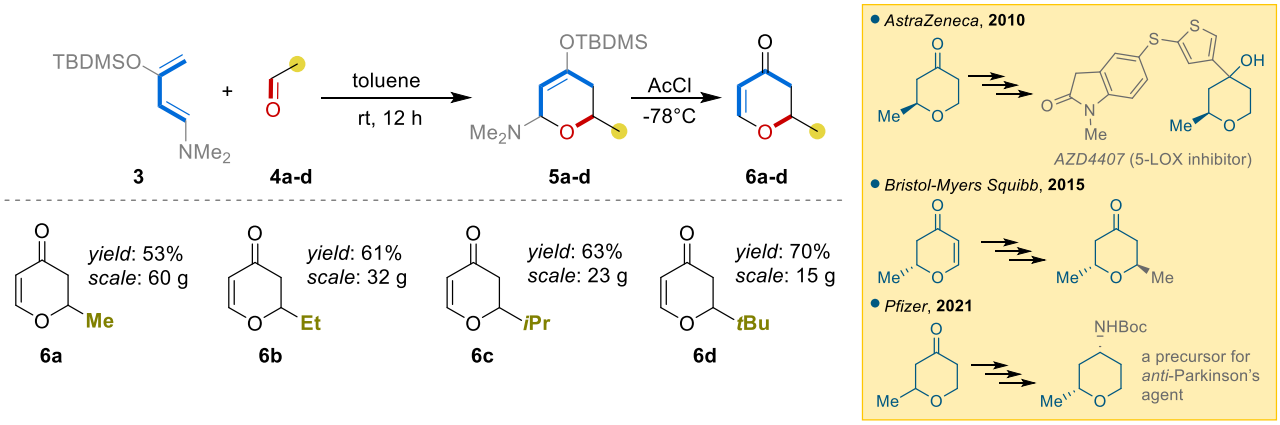
According to literature reports, cycloadduct **5** was not isolated but instead carried directly into the "deprotection" step, which was efficiently performed using acetyl chloride at a low temperature. This process simultaneously removed the dimethylamino and TBS groups, yielding the target 2-methylpyranone **6a** after purification by flash chromatography (see *Experimental section*). Notably, we see the chromatography step to be the only factor that could limit the scalability of this reaction due to its inherent constraints. In our experiments, the yield was nearly independent of the reaction scale and ranged from 52 to 55% for 0.1 to 1.0 mol of the diene used. Thus, we managed to obtain 60 grams of 2-methylpyranone **6a** in a single run with an overall 53% yield. It's worth noting that, while fractional distillation of the crude product after deprotection may seem more convenient than chromatography, it's not a viable option for isolating pyranones **6**. During distillation, the target pyranones form an azeotropic mixture with a TBS-containing byproduct (likely TBS-OH), preventing the enrichment of the distillate with compound **6**. For this reason, the method proved unproductive.

With all the achievements of this work and the findings of other groups, [4+2] the Diels-Alder way to 2-metrhylpyran-4-one has a chance to take its place in the mentioned and future MedChem programs. In this way, to provide evidence that this method is a general one for other less electrophilic aliphatic aldehydes, we carried out multigram experiments for the next three linear and branched members of the series. The results (**Scheme 2**, aldehydes **4b-d**) support the potential and applicability of the reaction to produce the target objects **6b-d**. We observed no reduction in the reaction efficiency on multigram scales, and the yields slightly increased while proceeding to the higher homologs.

Previously, *Huang & Rawal* demonstrated that the *hetero*-Diels-Alder reactions employing diene **3** and different carbonyl compounds are greatly accelerated in hydrogen-bonding solvents compared to aprotic ones.[11c] The hydrogen bond catalysis worked well with simple, unreactive ketones, which are much poorer heterodienophiles than the aldehyde carbonyl group due to steric and electronic reasons. Among others, butan-2-ol showed perfect results, yielding the corresponding pyranones in moderate to high yields. Along with ketones, an improvement was also achieved with the hindered aldehyde, pivaldehyde (1.5 hours, 77%), compared to the reported earlier reaction in chloroform, which afforded the product in 54% yield after 2 days. Given that, we decided to validate the applicability of the hydrogen-bond catalysis for the multigram access to 2-alkylpyranones based on aldehydes **4a-d**. Initially, the reaction was carried out on a 0.01 mol scale of the diene in butan-2-ol solution at room temperature for 12 hours according to the general procedure (see *Experimental part*). The reaction progress was monitored by means of ^{1}H NMR and GC-MS, and analysis was performed for a crude product **6** not purified by chromatography. For the first two members, acetaldehyde and propionaldehyde, we did not detect even traces of the pyranones in the analyzed mixtures by any applied method (see *SI file*). Isobutyraldehyde (**4c**) gave pyranone **6c** in only a small amount, which was evidenced by ^{1}H NMR. Pivaldehyde under used conditions showed the most encouraging results, with compound **6d** being the major component in the mixture, however, the method did not possess advantages in terms of yield and purity of the target pyranone.

Therefore, Rawal's diene demonstrates remarkable utility for synthesizing 2-alkyl-2,3-dihydro-4*H*-pyran-4-ones, offering a simple and scalable approach that bypasses the complexities of the earlier multi-step processes. Unlike previous strategies that required costly catalysts and lengthy

reaction sequences, the described method preserves high efficiency and reproducibility, making it suitable for large-scale preparations.



Scheme 2. Application of Rawal's diene in a large-scale synthesis 2-alkyl-2,3-dihydro-4*H*-pyran-4-ones

CONCLUSION

In summary, this study is trying to overcome the longstanding barriers limiting the scalability, stability, and broader utilization of Rawal's diene, advancing its prospects for the adoption in synthetic academic and industrial chemistry. We developed and validated a scalable, reproducible synthetic protocol that achieves a reasonable total yield of 57% while accommodating semi-industrial production demands for the preparation of up to 520 g of the diene in a single run.

Investigations into the stability of Rawal's diene revealed its vulnerability to hydrolysis and possibly oxidation, necessitating stringent storage protocols under inert atmospheres and low temperatures. However, for a short period, Rawal's diene can be safely stored at room temperature, either in an argon atmosphere or in a tightly sealed container, without significant loss of its quality. Analytical methods, particularly ^{1}H NMR and IR spectroscopy, were optimized to ensure precise quality control, enabling the reliable assessment of purity and degradation pathways.

Deuterobenzene was found to be the most suitable solvent for the NMR analysis ensuring stability of the analyte during the analysis.

The practical application of Rawal's diene was exemplified through its utility in multigram syntheses of four 2-alkylpyranone derivatives, reinforcing its role as a valuable precursor for pyran-containing molecular frameworks. Especially mild reaction conditions, coupled with easy purification protocol, validate its suitability for drug development and other medicinal chemistry workflows.

We hope that the results outlined herein will further solidify the role of Rawal's diene as a valuable reagent, facilitating advancements in synthetic methodologies and accelerating innovations in synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

General. The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 (400 MHz) or a Bruker 170 Avance 500 (500 MHz) instrument; ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 (126 MHz) or an Agilent ProPulse 600 (151 MHz) spectrometer. The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and 13C nuclei, respectively, in $CDCl_3$, and 7.13 and 127.6 ppm for ^{1}H and ^{13}C nuclei, respectively, in C_6D_6. IR spectra were taken on an IR5 FTIR spectrometer (Edinburgh Instruments) in KBr pellets. GCMS analyses were performed with the assistance of an Agilent 5890 Series II 5972 GCMS instrument (electron impact (EI) ionization (70eV)). Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were in good agreement (±0.4%) with the calculated values.

NMR spectra were analyzed using MestReNova software (version 12.0.0-20080), and IR spectra were processed with a Spectragryph tool (version 1.2.16.1).

Multigram 2-step protocol for the synthesis of Rawal's diene

Step 1. (E)-4-(dimethylamino)but-3-en-2-one (2)

Acetylacetaldehyde dimethyl acetal (1 kg, 7.567 mol) was placed in a 3-liter flask equipped with a magnetic stirring bar. Then 40% water solution of dimethylamine (937.5 g, 8.324 mol) was added to the flask in one portion. The resulting yellow solution, which darkens over time, was left to stir at room temperature for 12 hours (the start of the reaction was accompanied by heating of the reaction mixture to ~50ºC). After, the obtained mixture was concentrated on a rotary evaporator to remove most of the water. The remaining oily liquid was then dissolved in ethyl acetate, and sodium sulfate was added to the solution to remove residual water. The ethyl acetate solution was concentrated on a rotary evaporator, and the residue was distilled *in vacuo* (0.1 mmHg, distillation temperature 76ºC), furnishing 770 g (90%) of the title enone as an oily orange liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 12.7 Hz, 1H, CH–N), 4.94 (d, *J* = 12.8 Hz, 1H, CH–C=O), 2.93 (br. s, 3H,CH_3–N), 2.78 (br. s, 3H, CH_3–N), 1.99 (s, 3H, CH_3–C=O) ppm. ^{13}C NMR (126 MHz, Cloroform-*d*) *δ* 195.2 (C=O), 152.7 (C–N), 96.7 (C–C=O), 44.7, 37.0, 28.1 ppm. GCMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_6H_{11}NO$ 113.1; Found 113.1. Anal. Calcd for $C_6H_{11}NO$, %: C 63.69, H 9.80, N 12.38. Found, %: C 63.85, H 9.74, N 12.30.

Step 2. (E)-3-((tert-butyldimethylsilyl)oxy)-N,N-dimethylbuta-1,3-dien-1-amine (Rawal's diene, **3***)*

(*E*)-4-dimethylamino-3-buten-2-one from *Step 1* (412 g, 3.64 mol) was placed in a pre-dried 10-liter 3-necked reactor equipped with a mechanical stirrer, and THF (6 L) was added. Then, the flask was equipped with a pressure-equalizing funnel and an argon adapter. The apparatus was

flushed with argon, the solution was cooled to -78°C, and a 2.0 M solution of NaHMDS in THF (2 L, 4.0 mol) was added dropwise. The resulting solution was stirred for 1-1.5 hours at -78°C. A solution of TBSCl (631 g, 4.21 mol) in THF (700 mL) was added dropwise to the reaction mixture at -78°C. After the addition, a finely dispersed precipitate of NaCl appeared. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature (requires ~2-2.5 h). The reaction mixture was in portions poured into a container containing 8 L of MTBE. The container was covered with plastic wrap, and the resulting suspension was allowed to stand in the refrigerator for 12 hours for completing sedimentation (+4°C). The suspension was then filtered through cotton wool. While filtering, the cotton wool might be clogged with fine sediment (that significantly complicates filtering) and must be replaced. The filtered portions were simultaneously concentrated on a rotary evaporator (bath temperature 30-35°C). Upon completion, the obtained "raw" dark red product containing hexamethyldisilazane was purified by vacuum distillation (0.1 mmHg, distillation temperature 58-60°C) to afford 520 g (63%) of the title diene as a transparent yellow oil.

^{1}H NMR (400 MHz, Benzene-d_6) δ 6.71 (d, J = 13.2 Hz, 1H, CH–N), 4.91 (d, J = 13.2 Hz, 1H, C<u>H</u>=CH–N), 4.19 (s, 1H, CH_2), 4.13 (s, 1H, CH_2), 2.24 (s, 6H, $N(CH_3)_2$), 1.02 (s, 9H, $C(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.55 (d, J = 13.2 Hz, 1H, CH–N), 4.77 (d, J = 13.2 Hz, 1H, C<u>H</u>=CH–N), 3.90 (s, 1H, CH_2), 3.82 (s, 1H, CH_2), 2.68 (s, 6H, $N(CH_3)_2$), 0.95 (s, 9H, $C(CH_3)_3$), 0.17 (s, 6H, $Si(CH_3)_2$). ^{13}C{^{1}H} NMR (151 MHz, benzene-d_6) δ 156.6 (C–O), 140.6 (Csp^2–N), 96.8 (=<u>C</u>H–C=), 86.3 (CH_2=), 39.8 ($N(CH_3)_2$), 25.8 ($C(\underline{C}H_3)_3$), 18.2 ($\underline{C}(CH_3)_3$), -4.7 ($Si(CH_3)_2$). IR (KBr) ν_{max}/cm^{-1} 2954, 2929, 2884, 2857, 2799, 1645 (C=C), 1472, 1360, 1332, 1350, 1273, 1252, 1093, 1018, 939, 827, 778.

General procedure for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones (6)

An aliphatic aldehyde (4.0 equiv) was dissolved in toluene (550 mL for 1 mol of the aldehyde) under an argon atmosphere, followed by Rawal's diene (1.0 equiv) added dropwise at room temperature (water bath). The reaction mixture was allowed to stir overnight and then the volatiles were removed on a rotary evaporator under reduced pressure. The residue was dissolved in methyl *tert*-butyl ether (550 mL for 1 mol of the aldehyde), and the solution was cooled to -78ºC under argon. Acetyl chloride (2.0 equiv) was added to the solution slowly, keeping the temperature at -78ºC. Then, the cooling bath was removed, and the mixture was allowed to attain 0ºC and poured into the saturated solution of $NaHCO_3$ (the resulting pH must be above 7). The organic layer was separated, and the water fraction was extracted with methyl *tert*-butyl ether again. The combined organic fraction was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained crude product was purified by flash-chromatography (hexane/methyl *tert*-butyl ether, 100:0→80:20→50:50). The first eluted fraction (100:0) contains non-identified components, the second (80:20) – TBS-containing by-products (^{1}H NMR), the target product comes out with the most polar eluent (50:50). The presence of the pyranones in the eluted fractions was controlled by TLC, hexane/methyl *tert*-butyl ether 4:1, staining reagent – $KMnO_4$, R_f ~0.3.

2-Methyl-2,3-dihydro-4H-pyran-4-one (**6a**)

Yield – 53% (60 g from 227 g of diene **3**). Light-brown oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (d, J = 5.9 Hz, 1H, =CH–O), 5.38 (d, J = 6.0 Hz, 1H, =CH–C=O), 4.63 – 4.46 (m, 1H, C<u>H</u>CH$_3$), 2.58 – 2.36 (m, 2H, CH$_2$–C=O), 1.44 (d, J = 6.3 Hz, 3H, CH$_3$) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 192.6 (C=O), 163.3 (=C–O), 106.9 (<u>C</u>=C–O), 76.0 (Csp^3–O), 43.5 (CH$_2$), 20.3 (CH$_3$) ppm. GCMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_6H_8O_2$ 112.1; Found 112.1. Anal. Calcd for $C_6H_8O_2$, %: C 64.27, H 7.19. Found, %: C 64.11, H 7.23.

2-Ethyl-2,3-dihydro-4H-pyran-4-one (**6b**)

Yield – 61% (32 g from 93 g of diene **3**). Colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 (d, J = 6.0 Hz, 1H, =CH–O), 5.39 (d, J = 5.9 Hz, 1H, =CH–C=O), 4.40 – 4.27 (m, 1H, Csp^{3}H–O), 2.59 – 2.37 (m, 2H, CH_2–C=O), 1.89 – 1.67 (m, 2H, C$\underline{H}_2$CH$_3$), 1.02 (t, J = 7.4 Hz, 3H, CH$_2$C$\underline{H}_3$) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 192.8 (C=O), 163.3 (=C–O), 106.9 (C=C–O), 80.7 (Csp^3–O), 41.4 (CH_2 in-ring), 27.4 (C$\underline{H}_2$CH$_3$), 9.1 (CH$_2$C$\underline{H}_3$) ppm. GCMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_7H_{10}O_2$ 126.1; Found 126.0. Anal. Calcd for $C_7H_{10}O_2$, %: C 66.65, H 7.99. Found, %: C 66.73, H 8.04.

2-Isopropyl-2,3-dihydro-4H-pyran-4-one (**6c**)

Yield – 63% (23 g from 60 g of diene **3**). Yellow oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, J = 6.0 Hz, 1H, =CH–O), 5.39 (d, J = 5.9 Hz, 1H, =CH–C=O), 4.15 (ddd, J = 14.5, 5.9, 3.4 Hz, 1H, Csp^{3}H–O), 2.53 (dd, J = 16.7, 14.5 Hz, 1H, CH_2), 2.38 (dd, J = 16.7, 3.3 Hz, 1H, CH_2), 2.07 – 1.92 (m, J = 6.9, 6.4 Hz, 1H, C$\underline{H}$(CH$_3$)$_2$), 1.00 (dd, J = 11.5, 6.8 Hz, 6H, 2×CH$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 192.5 (C=O), 163.0 (=C–O), 106.3 (C=C–O), 83.6 (Csp^3–O), 38.4 (CH_2), 31.2 (C$\underline{H}$CH$_3$), 17.3 (CHC$\underline{H}_3$), 17.0 (CHC$\underline{H}_3$) ppm. GCMS (EI) m/z: $[M]^{+\bullet}$ Calcd for $C_8H_{12}O_2$ 140.1; Found 140.1. Anal. Calcd for $C_8H_{12}O_2$, %: C 68.55, H 8.63. Found, %: C 68.41, H 8.70.

2-tert-Butyl-2,3-dihydro-4H-pyran-4-one (**6d**)

Yield – 70% (15 g from 32 g of diene **3**). Light-yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, J = 5.9, 0.8 Hz, 1H, =CH–O), 5.41 (dd, J = 5.9, 1.3 Hz, 1H, =CH–C=O), 4.04 (dd, J = 15.1, 3.3 Hz, 1H, Csp^{3}H–O), 2.54 (dd, J = 16.6, 15.1 Hz, 1H, CH_2), 2.41 (ddd, J = 16.6, 3.3, 1.3 Hz, 1H, CH_2), 1.01 (s, 9H, 3×CH$_3$) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 193.7 (C=O), 163.9 (=C–O), 106.6 (C=C–O), 86.9 (Csp^3–O), 37.2 (CH_2), 33.8 (C$\underline{C}$(CH$_3$)$_3$), 25.4 (C(C$\underline{H}_3$)$_3$) ppm. GCMS

(EI) m/z: $[M]^{+\bullet}$ Calcd for $C_9H_{14}O_2$ 154.1; Found 154.1. Anal. Calcd for $C_9H_{14}O_2$, %: C 70.10, H 9.15. Found, %: C 70.19, H 9.08.

ASSOCIATED CONTENT

The following files are available free of charge *via* www.pubs.acs.org.

Copies of ^1H, ^{13}C NMR and IR spectra of compounds **3** and **6**, also including results of stability studies for Rawal's diene (PDF file)

Original NMR (FID files) and IR (TXT files) packed in ZIP archive.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interests.

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