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# Iodine-Catalyzed Iso-Nazarov Cyclization of Conjugated Dienals for the Synthesis of 2-Cyclopentenones

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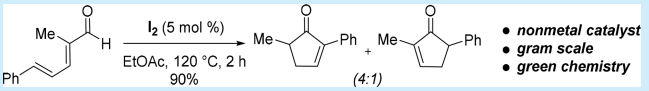
Supporting Information

**ABSTRACT:** Molecular iodine was identified as an efficient catalyst for the cycloisomerization of conjugated dienals to substituted 2-cyclopentenones. DFT calculations suggested an unexpected concerted character for this cyclization.




Cyclopentenones are unarguably distinguished chemical entities. From both marine[1] and terrestrial sources,[2] countless natural products bearing this structural motif have been isolated and found to possess interesting biological activities. Notable examples include jasmonoids such as *cis*-jasmone **1**, a volatile component of the oil of jasmine flowers used in perfumery and as a pesticide;[3] phorbol esters such as PMA **2** and prostratin, both potential treatments for acute myeloid leukemia and HIV, respectively;[4,5] and important biomolecules such as prostaglandins $A_2$ **3**, $B_2$, $C_2$, and $J_2$, which present hormone-type activity in animals (Figure 1).[6] In

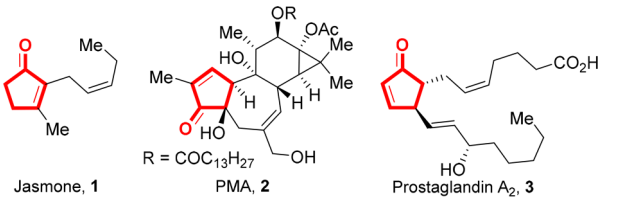
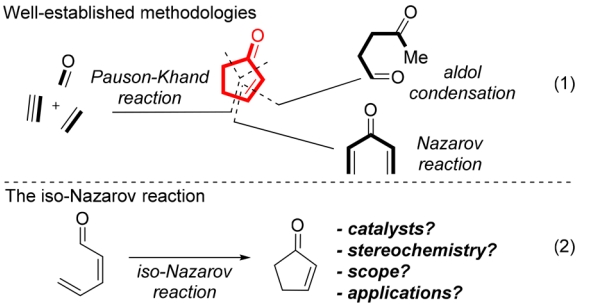



**Figure 1.** Distinguished natural 2-cyclopentenones.

particular, research on this last class of cyclopentenones has led to the discovery of novel potent anticancer drug candidates.[7] From a different chemical viewpoint, the ease with which selective chemical modifications can be executed at every corner of these carbocyclic systems makes them versatile building blocks in organic synthesis which is reflected in the number of natural products and derivatives synthesized using cyclopentenones as key intermediates.[8]

Undoubtedly, because of their importance, much attention has been given to the development of synthetic methodology for cyclopentenone construction.[9] The synthesis of cyclopentenones from acyclic precursors is generally carried out using standard well-established methods, namely the intramolecular aldol condensation,[10] the Pauson−Khand reaction,[11] and the Nazarov cyclization (Scheme 1, eq 1).[12]

**Scheme 1. Some Established Methodologies for Cyclopentenone Construction and the Iso-Nazarov Cyclization**




Notwithstanding the great advances in this field of research, all these transformations feature at least one of the following shortcomings. These methodologies involve harsh reaction conditions, toxic reagents, or the use of substrates which are difficult to prepare. As a result, an efficient and operationally simple procedure is lacking, particularly one that employs readily available materials. In this context, progress on nontraditional strategies to complement the well-established ones would be beneficial for synthetic organic chemists. Particularly in recent decades, the Nazarov reaction has witnessed considerable evolution.[13] Advancements include, among several, the extension of the chemistry to the use of linearly conjugated carbonyl compounds as substrates capable of affording the key hydroxy-pentadienyl cation intermediates en route to cyclopentenones (Scheme 1, eq 2).[14] This cycloisomerization of dienals, baptized as the iso-Nazarov reaction by Trauner et al.,[15−17] has been rarely explored.[18] Examples are limited and have mostly dealt with *cis*-dienals as

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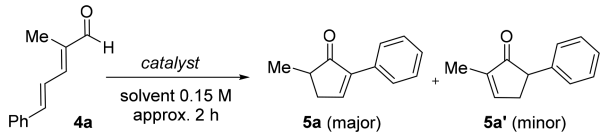
**Table 1. Optimization of the Iso-Nazarov Cyclization of Dienal 4a**




| entry | catalyst | solvent | $t$ (° C) | global yield[a] | approximate ratio 5a:5a′ |
|---|---|---|---|---|---|
| 1 | – | toluene | reflux | –[b] | – |
| 2 | *hν* (350 nm) | toluene | reflux | –[c] | – |
| 3 | TFA (5 mol %) | toluene | reflux | –[b] | – |
| 4 | $TsOH·H_2O$ (5 mol %) | toluene | reflux | 14%[d] | 5:1 |
| 5 | Aib (5 mol %) | toluene | reflux | –[b] | – |
| 6 | (*R*)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate (5 mol %) | toluene | reflux | –[b] | – |
| 7 | $PhB(OH)_2$ (5 mol %) | toluene | reflux | –[b] | – |
| 8 | $H_3PO_4$ (5 mol %) | toluene | reflux | –[b] | – |
| 9 | $CuCl_2·2H_2O$ (5 mol %) | toluene | reflux | –[b] | – |
| 10 | $AlCl_3$ (5 mol %) | toluene | reflux | –[b] | – |
| 11 | $FeCl_3$ (5 mol %) | toluene | reflux | –[b] | – |
| 12 | $FeCl_3$ (1 equiv) | toluene | reflux | 30% | 4:1 |
| 13 | $InCl_3$ (5 mol %) | toluene | reflux | –[b] | – |
| 14 | NIS (5 mol %) | toluene | reflux | –[b] | – |
| 15 | $I_2$ (5 mol %) | toluene | reflux | 67% | 5:1 |
| 16 | $I_2$ (5 mol %) | EtOH | 80 °C | –[b] | – |
| 17 | $I_2$ (5 mol %) | EtOH | 120 °C | 26%[e] | 5:1 |
| 18 | $I_2$ (5 mol %) | $H_2O$ | 120 °C | –[b] | – |
| 19 | $I_2$ (5 mol %) | THF | 120 °C | –[b] | – |
| 20 | $I_2$ (5 mol %) | *t*-BuOH | 120 °C | –[b] | – |
| 21 | $I_2$ (5 mol %) | EtOAc | 120 °C | **90%** | **4:1** |
| 22 | $I_2$ (10 mol %) | EtOAc | 120 °C | 74% | 4:1 |
| 23 | $I_2$ (5 mol %) | EtOAc | reflux | 74% | 5:1 |

[a]Isolated yields reported. Unless otherwise stated, conversion of **4a** was complete. [b]No conversion of **4a**. [c]Only isomerization of *γ*,*δ*-double bond was evidenced. [d]65% of **4a** was recovered. [e]Inseparable from side products. TFA = trifluoroacetic acid, Aib = 2-aminoisobutyric acid, NIS = *N*-iodosuccinimide.

substrates which are hard to prepare and are logically more prone to the cyclization.[15,19] Very little is known about substrate compatibility, appropriate catalysts, stereochemical requirements, and potential applications.

Herein, we report our studies which identified iodine as an efficient catalyst for this iso-Nazarov reaction of readily available all-*trans* dienals.

To initiate our studies, we prepared dienal **4a** as a model substrate via simple aldol condensation between cinnamaldehyde and propionaldehyde.[20] As shown in Table 1, thermal treatment did not promote any cycloisomerization of **4a**, nor irradiation with actinic lamps (Table 1, entries 1 and 2). Twelve readily available acids were then evaluated as potential catalysts for the desired transformation (Table 1, entries 3–15). These experiments were all performed in toluene at reflux and with a low amount of the catalyst (5 mol %). To our surprise, while most of these acids failed to catalyze the reaction, molecular iodine was found to efficiently promote the iso-Nazarov cycloisomerization of dienal **4a** toward conjugated 2-cyclopentenones **5a** and **5a′**, both separable and isolated in 56% and 11% yields, respectively, after column chromatography purification (Table 1, entry 15).

Of the other promoters assayed, only *p*-toluenesulfonic acid caused dienal **4a** to cycloisomerize to **5a**/**a′**, albeit in much lower yield than that attained by iodine (Table 1, entry 4 vs 15). Since toluenesulfonic acid is a cheap reagent, increasing amounts of this catalyst were screened, but without success. The same tests were performed with environmentally benign iron chloride which indeed promoted the reaction when used stoichiometrically although unsatisfactorily (Table 1, entries 11 and 12). Once iodine was chosen as a suitable catalyst for the transformation, other solvents, some of them greener than toluene, were evaluated (Table 1, entries 16–20). No reaction was observed when water, THF, or *t*-BuOH were used as solvents at 120 °C for 2 h. In ethanol, on the other hand, whereas no reaction occurred at 80 °C, at 120 °C the substrate did undergo transformation but cyclopentenone products **5a**/**a′** were produced accompanied by inseparable side products. Ethyl acetate proved to be the best substitution for toluene in the reaction, providing cyclopentenones **5a**/**a′** in an overall 90% yield (Table 1, entry 21). No further increase in yield was observed when the amount of catalyst iodine was doubled (10 mol %) (Table 1, entry 22). It should be noted that the reaction could also be performed under refluxing conditions, and although conversion was complete in 2 h, slightly lower yields were then obtained (74% yield) (Table 1, entry 23). Under these conditions, a gram scale attempt using 1.29 g of aldehyde **4a** was assayed without any deleterious effect on yields or selectivity (2 h; 72%; ratio **5a**/**5a′** = 5:1).

With these optimized reaction conditions in hand, we then set out to test the scope of the process. To this aim, several conjugated dienals **4** were acquired from commercial suppliers or prepared from simple aldehydes using standard and facile aldol and vinylogous aldol condensations or Horner–Wadsworth–Emmons reactions followed by reduction and oxidation. Branched dienals underwent successful cyclizations to the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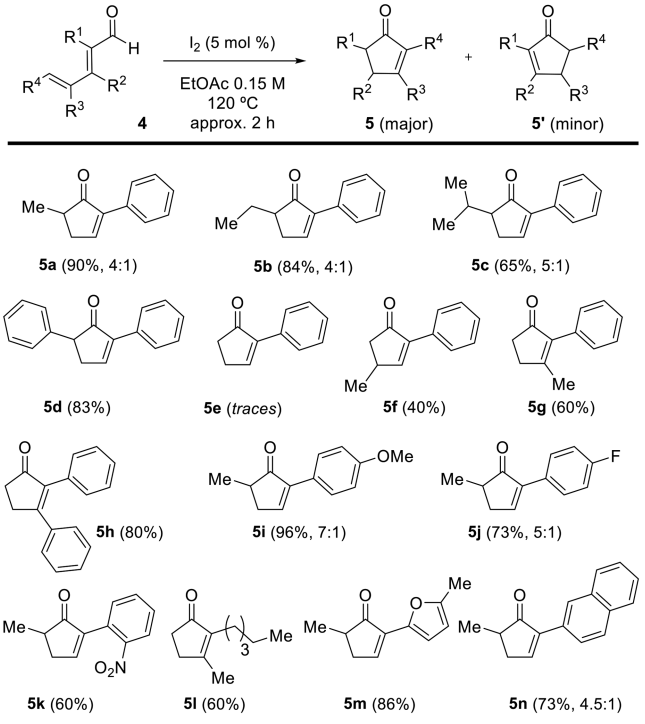
desired 2-cyclopentenones in good yields, regardless of the position of the substituents ($\alpha$-, $\beta$-, and $\gamma$-branching) (Scheme 2). Only traces of 2-cyclopentenones were observed in the

**Scheme 2. Scope of the Iso-Nazarov Cyclization of Dienals**



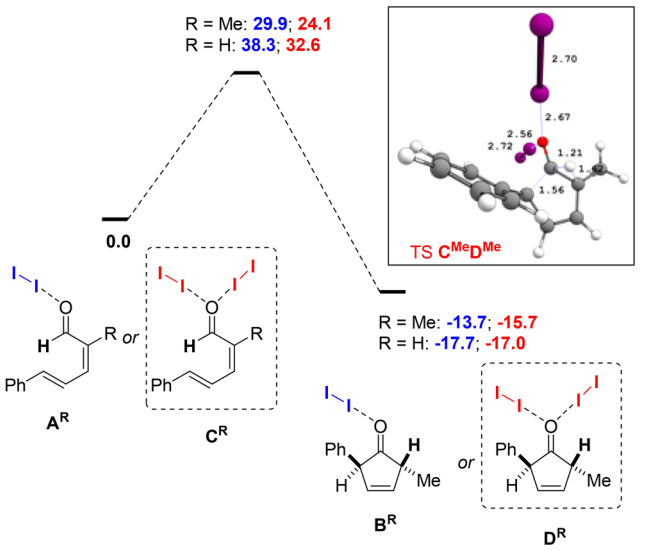

Yields after chromatography purification in parentheses. In cases in which regioisomer **5'** is formed, global yields and **5/5'** ratios are informed in parentheses and only major isomer **5** is shown.

reaction crude mixtures when unsubstituted dienals were used as substrates. Whereas unbranched 5-phenyl-2,4-pentadienal (**4e**) was chiefly inert to the reaction conditions (**5e**, Scheme 2), commercially available hexa- and decadienal underwent extensive decomposition toward a colored gum (not shown). This unwanted process could not be overcome by reducing the amount of catalyst or running the reaction at lower temperatures. As shown, alkyl and aryl substituents were compatible with the transformation, decorating the dienal substrates along the conjugated chain (products **5a**−**n**). In particular, the end of the polyene chain was compatible with alkyl groups, heteroaromatics such as furan, and substituted phenyl groups with both electron-donating and -withdrawing groups (**5i**−**n**). Gratifyingly, natural product dihydrojasmone **5l** could also be obtained among the cyclopentenone products in 60% yield. In this manner, a new synthesis of this aromatic compound used in perfumery was achieved.[21] As shown in Scheme 2, all reactions were highly regioselective, with the more substituted and conjugated cyclopentenones being produced either exclusively or predominantly.

Interestingly, apart from **5l**, some of the other obtained cyclopentenones **5** have also been prepared before by other methodologies. For instance, 2,5-diphenyl-cyclopent-2-enone (**5d**) was prepared before in low yield by Pauson and Khand using their well-known reaction.[22] 2,3-Diphenyl-cyclopent-2-enone (**5h**), obtained in 80% yield, was prepared several times before via different strategies including the aldol condensation,[23] a Nazarov-type cyclization,[24] and a Zr-promoted Pauson−Khand-type reaction.[25] However, in all these cases, yields were lower than that obtained using this new approach.

Catalysis by iodine, and halogen-bonding catalysis in general, has been receiving considerable interest recently.[26] Remarkably, to the best of our knowledge, the catalysis of Nazarov-type reactions by environmentally friendly and inexpensive molecular iodine appears to be largely unknown.[27] To gain insight into the carbonyl mode of activation observed for dienals **4**, DFT computations were performed (see Supporting Information for full details). Assuming that the *trans*,*trans*-dienals **4** first isomerize into the 2*Z*-dienals to make the cyclization possible,[28] the $I_2$-catalyzed cyclization via halogen bonding of the model dienal (2*Z*)-**4a** ($\mathbf{A^R}$, R = Me) was first studied (Scheme 3). We could only identify an

**Scheme 3. Calculated Energy Profile ($\Delta G_{393}$, kcal/mol) for the Iodine-Catalyzed Cycloisomerization of Dienals**




unexpected concerted process leading directly to the cyclopent-3-enone $\mathbf{B^{Me}}$ product. This product is more stable than $\mathbf{A^{Me}}$ by 13.7 kcal/mol, but the transition state lies as high as 29.9 kcal/mol on the potential energy surface (PES). Interestingly, with two iodine molecules instead of one to activate the carbonyl as in $\mathbf{C^{Me}}$, this barrier is reduced to 24.1 kcal/mol, which seems accessible at the reaction temperature. The resulting product $\mathbf{D^{Me}}$ is also obtained in an exergonic fashion (−15.7 kcal/mol). From $\mathbf{D^{Me}}$, it is easily conceivable that the C═C bond will spontaneously and rapidly shift to give a cyclopent-2-enone, with this migration being obviously more favorable toward the Ph group, as it gives a more conjugated product (**5a** vs **5′a**) (Table 1 and Scheme 2). As a comparison, the uncatalyzed reaction was also analyzed (not shown). It was found to be a concerted process as well, yet the corresponding transition state lies at 38.1 kcal/mol on the PES ($\Delta G_{393}$ −14.1 kcal/mol). Thus, $I_2$ can be dramatically effective as a catalyst, and clearly two iodine molecules are better than one. When R = H (substrate **4e**, activated dienal $\mathbf{C^H}$), although the use of two iodine molecules significantly lowers the computed cyclization barrier compared to just one (from 38.3 to 32.6 kcal/mol), it remains too high to be crossed under the reaction conditions and this is in line with the experimental findings (Scheme 2, **5e**).

The concerted character of this reaction is puzzling. Standard behavior, within the carbocationic paradigm, would



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comprise a conrotatory 4$\pi$-electrocyclization followed by a suprafacial [1,2]-H shift.[29] The resulting stereochemistry of this two-step process would have been the same as the one obtained for $\mathbf{B}^{Me}$ or $\mathbf{D}^{Me}$. The geometries and transition vectors of the computed transition states actually correspond to the [1,2]-H shift only. The new C−C bond is virtually fully formed (1.56−1.58 Å), and the quite large imaginary frequencies (−719 $cm^{-1}$ for $TS\mathbf{C}^{Me}\mathbf{D}^{Me}$) are typical from a hydrogen shift. This suggests that the putative intermediate that precedes the [1,2]-H shift is actually not stable and collapses to the cyclopent-3-enone. It should be noted that this is not an artifact due to the $\omega$B97X-D functional used. We obtained the same concerted cyclization using the B3LYP and the M06-L functionals. Indeed a possible zwitterionic intermediate converged with the PBE0 functional, but its transformation into the cyclopent-3-enone was found to be barrierless. Thus, even in this case, in contrast to standard Lewis acid catalyzed Nazarov/Wagner−Meerwein reactions of divinylketones,[30] the formation of a cyclopent-3-enone via iodine-catalyzed cycloisomerization can be considered as a concerted process according to computations.

In summary, the iso-Nazarov reaction of 2,4-dienals was studied both experimentally and theoretically. Molecular iodine was identified as a suitable catalyst for the cycloisomerization of *trans*-2,4-dienals, and hence, an environmentally benign, efficient, and simple protocol was achieved allowing the preparation of valuable 2-cyclopentenones in good to excellent yields. Among the products, dihydrojasmone (**5l**) was prepared from the corresponding dienal, thus providing a new synthesis of this remarkable substance. As aryl-substituted cyclopentenones of type **5** are expected to show antitumor activity,[31] we believe the present work may help and promote future biological studies on this notable and promising carbocyclic system.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03229.

General experimental procedures, $^1H$, $^{13}C$, and 2D NMR spectra of all new products, computational details, coordinates and energies of the computed structure (PDF)

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### Notes

The authors declare no competing financial interest.

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