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Total syntheses of melodienones by redox isomerization of propargylic alcohols†

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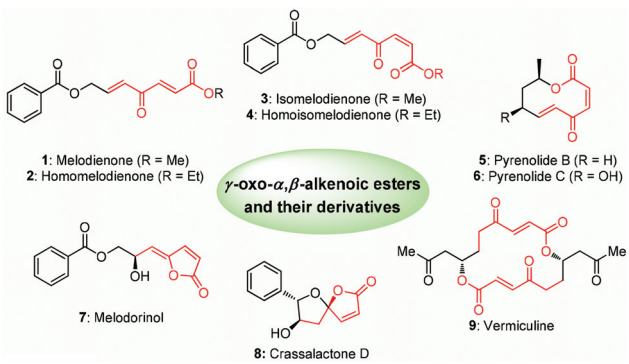
A remarkable base-promoted methodology for the rapid construction of the (*E*)- and (*Z*)-γ-oxo-α,β-alkenoic ester skeletons from readily accessible vinyl propargylic alcohols through modified redox isomerization was uncovered. This approach manifested its high simplicity and efficiency with excellent tolerance of functional substituents, which led to the straightforward structural modifications of various natural products and efficient total syntheses of melodienone, homomelodienone, isomelodienone, and homoisomelodienone within 4 linear steps.

Divergent organic synthesis has emerged as a promising strategy to discover biologically meaningful lead drugs in the pharmaceutical community, which is reflected by numerous unremitting efforts towards the development of efficient synthetic methodologies to prepare the common frameworks of the targeted bioactive molecules.[1] The (*E*)- and (*Z*)-γ-oxo-α,β-alkenoic esters have been widely used as ubiquitous and intriguing reactive intermediates in many types of organic reactions, including Diels–Alder cycloaddition[2–4] and cyclopropanation.[5] Moreover, these moieties also represent one of the most basic building blocks of various biologically meaningful pharmaceuticals[6] and natural products,[7–16] such as melodienone (**1**),[7] homomelodienone (**2**),[8] isomelodienone (**3**),[8] homoisomelodienone (**4**),[8] pyrenolide B (**5**),[12] pyrenolide C (**6**),[12] melodorinol (**7**),[14] crassalactone D (**8**),[13] and vermiculine (**9**)[10] (Scheme 1). Notwithstanding their ostensibly simple skeleton, these molecules showed a series of pharmaceutically potent biological activities including antibacterial and anticancer activities.[7–12] In particular, melodienones **1–4** exhibited significant anti-cancer activities with ED_{50} as low as 0.17 μg ml^{-1}, which was much better than that of the positive control adriamycin (IC_{50} = 3.45 μM).[17]

The intriguing structural diversity of γ-oxo-α,β-alkenoic esters has attracted considerable attention and led to outstanding progress in the synthetic community in the past few years.[18–21] Among them, Nineham and Raphael discovered an isomerization reaction of 4-hydroxy-4-phenyl-but-2-ynoic acid methyl ester with Et_3N to afford methyl (*E*)-4-oxo-4-phenylbut-2-enoate with high *E*-selectivity but a low yield.[18] Saiah reported a selective stereoisomerization method to generate methyl (*E*)-4-oxo-4-phenylbut-2-enoate through the use of air-sensitive tri-*n*-butylphosphine and 3 mol% $Rh(PPh_3)_3Cl$ at high temperature.[19] In 2006, Sonye and co-workers successfully established an efficient methodology to selectively generate *E*- or *Z*-enones in excellent yields by changing the base to DABCO, *i*-Pr_2NEt or $NaHCO_3$.[20,21a,b] Despite the apparent advantages of selective isomerization of propargylic alcohols to the corresponding (*E*)- and (*Z*)-enones, nearly all the reported methods were restricted to 1-phenyl substituted propargylic



Scheme 1 Representative natural products sharing γ-oxo-α,β-alkenoic ester motifs.

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alcohols. Thus, there is still further room for improvement to strategically advance their promising application in the synthesis of the aforementioned pharmaceutically or industrially meaningful molecules with such enone skeletons. Therefore, the development of a fairly efficient strategy toward the chemical diversity-oriented assembly of these (*E*)- or (*Z*)-enone cores will be a highly desirable and challenging task.

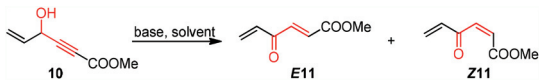
Motivated by the previous excellent contributions and our continuing efforts towards the efficient total syntheses of natural products,[4,22] we investigated the possibility of forging these 1-alkenyl enone scaffolds through the isomerization of 1-alkenyl propargylic alcohols, and if successful, it would boost the efficiency in terms of the diverse access to pharmaceutically significant natural products such as melodienone (**1**), homomelodienone (**2**), isomelodienone (**3**), and homoisomelodienone (**4**) in a highly efficient manner without further elaboration.

With this scenario in mind, readily accessible methyl 4-hydroxyhex-5-en-2-ynoate (**10**) was selected for the initial studies to implement the putative isomerization by a brief survey of several reaction parameters (Table 1). The well-established John's procedure (entry 1) was first tested, and only the starting material decomposed, whereas the inorganic base NaOH led to a successful conversion and delivered the desired product in a low yield with the ratio of the *Z* and *E* configurations of about 1 : 5 (entry 2). Other bases (entries 3–9) such as $NaHCO_3$, CH_3COONa, CH_3COONH_4, DMAP, Et_3N, *i*-Pr_2NEt, and DBU were evaluated, and Et_3N outperformed the others, leading to the targeted *Z* and *E* products with 49% yield in a 1 : 2 ratio (entry 7).

Although the desired products can be readily obtained with moderate yields in DMSO, its intractable reprocessing stemming from a high boiling point posed a challenge to achieve an operationally convenient process. Therefore, simple post-treatment solvents (entries 10–16) were further evaluated to optimize the reaction conditions. Interestingly, polar solvents seemed to outperform apolar ones in terms of the yield but were inferior in terms of the regioselectivity. In particular, the reaction occurred much faster in ACN (entry 14) than in other solvents and led to a significant increase in conversion, providing the desired product in 75% yield with a *Z*/*E* ratio of 1 : 1.5, thereby laying a solid foundation in terms of practicality and operational simplicity. Variation in the base loading of triethylamine (entries 17–19) did not dramatically affect the reaction profiles for both the reaction yield and regioselectivity. Although increasing the equivalents of the base provided products in faster rates and lower temperature seemed to benefit this transformation (entries 20 and 21),[23] we still decided to employ 1.0 equivalent of Et_3N in the following reactions so as to maintain an economical protocol.

With the above-defined reaction conditions established, the scope and versatility of this reaction with respect to propargylic alcohol derivatives with various vinyl substituents and diverse ester moieties were then surveyed. As presented in Table 2, the reactivity of this transformation appeared to be quite general, wherein the vinyl substituents could be excellently tolerated, and the corresponding (*E*)- or (*Z*)-enone products **13a–13k** were expectedly delivered in moderate to excellent yields under the standard conditions. Notably, a methyl moiety at the 1- or 2-position in the vinyl substituents in propargylic alcohols **12a–12d** did not seem to have a pivotal influence on the reac-

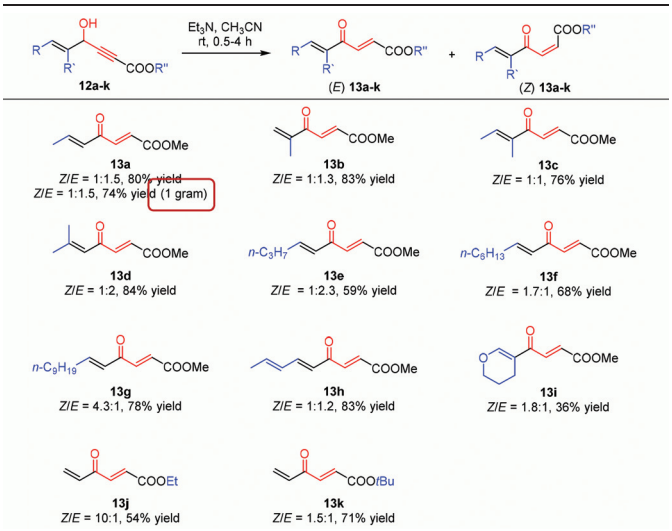
Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	Time	Yield	*Z*11/*E*11
1	DABCO	DMSO	3 h	0%	—
2	NaOH	DMSO	1 h	19%	1 : 5
3	$NaHCO_3$	DMSO	6 h	44%	2.5 : 1
4	CH_3COONa	DMSO	3 h	<10%	—
5	CH_3COONH_4	DMSO	3 h	<10%	—
6	DMAP	DMSO	1 h	<10%	—
7	Et_3N	DMSO	1 h	49%	1 : 2
8	*i*-Pr_2NEt	DMSO	12 h	43%	1.6 : 1
9	DBU	DMSO	1 h	27%	1 : 4
10	Et_3N	$CHCl_3$	1.5 h	28%	0.7 : 1
11	Et_3N	CH_2Cl_2	1.5 h	<10%	>20 : 1
12	Et_3N	THF	6 h	21%	1 : 10
13	Et_3N	Xylene	5 h	25%	1 : 10
14	Et_3N	CH_3CN	30 min	75%	1 : 1.5
15	Et_3N	1,4-Dioxane	1.5 h	53%	1 : 2
16	Et_3N	EtOAC	2.0 h	32%	1 : 3
17	Et_3N[b]	CH_3CN	30 min	83%	1 : 1.5
18	Et_3N[c]	CH_3CN	20 min	83%	1 : 1.5
19	Et_3N[d]	CH_3CN	18 min	82%	1 : 1.5
20	Et_3N[e]	CH_3CN	1 h	85%	1 : 1.5
21	Et_3N[f]	CH_3CN	15 min	<10%	—

[a] Conditions: **10** (0.2 mmol), base (0.1 mmol), solvent (1.0 mL), rt, isolated yield. [b] Et_3N (0.2 mmol). [c] Et_3N (0.3 mmol). [d] Et_3N (0.4 mmol). [e] 0 °C. [f] Reflux.

Table 2 Scope of Et_3N-mediated redox isomerizations[a]



[a] Conditions: **12** (0.6 mmol), Et_3N (0.6 mmol), CH_3CN (5.0 mL), rt, isolated yield.

tion efficiencies and (*E*)- or (*Z*)-isomeric selective ratios, thus generating the corresponding products ((*E*)-**13a–13d**, (*Z*)-**13a–13d**) with the ratio ranging from 1 : 1 to 1 : 2 in excellent yields. The reactivity of alcohols **12e–12g** with carbon chain extension was also evaluated, and it revealed that the extended carbon chain could obviously increase both the reaction yields and the stereoselectivities, and the difference in their stereoselectivities might be attributable to the steric hindrance of the carbon chain.

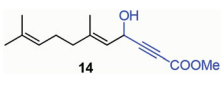
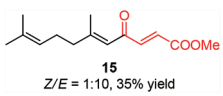
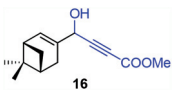
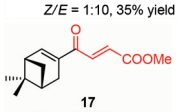
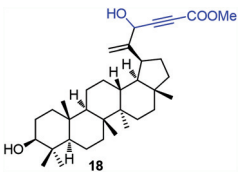
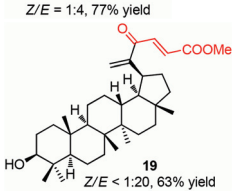
Moreover, when the enhanced conjugation system was induced in the vinyl propargylic alcohol skeleton, exemplified as **12h**, the related products *E*/*Z*-**13h** could be smoothly obtained with a high yield and excellent efficiency (less than 20 min). When the 3,4-dihydro-2*H*-pyran derivative **12i** was subjected to the standard reaction conditions, the corresponding products *E*/*Z*-**13i** were formed in 36% yield. To further verify the scope of its application, ethyl and *tert*-butyl propargylic alcohols **12j** and **12k** were selected to perform the redox isomerization reaction. Analogous to the methyl ester **10**, both of them could be readily converted to the corresponding isomerized products *E*/*Z*-**13j** and **13k** with excellent yields, thus showing the methodology to be promisingly tolerant towards different ester functionalities. Collectively, the established protocol could smoothly promote the redox transformation of various alkenyl-substituted alkenoic esters.

The synthetic utility of this intriguing redox isomerization could be further clarified by intelligent orchestration with straightforward structural modifications of many pharmaceutically meaningful natural products. As presented in Table 3, the potential bioactive citral derivative **14**, which was readily accessed through carbonyl addition using lithium methylpropiolate and commercially available citral, could be successfully converted to the targeted conjugated enone product **15** in 35% yield with a *Z*/*E* ratio of 0.1 : 1 as expected under the well-established redox isomerization conditions. Moreover, when the myrtenal derivative **16** was subjected to the reaction conditions, the corresponding desired product **17** was successfully isolated with excellent yield and stereoselectivity (77% yield, *Z*/*E* = 1 : 4). It merited attention that the treatment of complex lupeol derivative **18** could efficiently provide the expected product **19** in a stereospecific manner, providing *E*-enone **19** as a single product at room temperature. Therefore, these representative structural elaborations clarified the promising value to rapidly access a focused library of structural analogues bearing diversely modified functional moieties and opened up new avenues for aldehyde product modification.

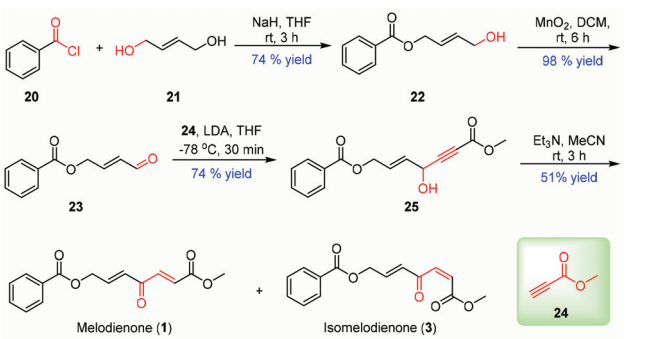
After exploring the substrate scope and versatility of the base-dependent methodology, the next step was then carried out to investigate its synthetic utility to the concise total syntheses of the biologically significant natural products melodienone (**1**), homomelodienone (**2**), isomelodienone (**3**), and homoisomelodienone (**4**), which have been previously prepared in multiple steps, under relatively harsh conditions or from complex raw materials.[24,25] The implementation of the concise total syntheses of melodienone (**1**) and isomelodienone (**3**) was commenced with the preparation of (*E*)-4-(benzoyloxy)-2-butenololine (**22**) using selective mono-esterification of (*E*)-2-butene-1,4-diol (**21**) and benzoyl chloride (**20**) in 74% yield by a previously reported procedure (Scheme 2).[26] The monobenzoate **22** was further oxidized with MnO_2 to provide the unsaturated aldehyde **23**,[27] which was treated with lithium methylpropiolate formed *in situ* at low temperature, generating the critical propargylic alcohol precursor **25** in an excellent yield.[28] Most gratifyingly, the transformation of the propargylic alcohol **25** through the well-established redox isomerization successfully proceeded, and the desired natural products **1** and **3** were obtained in 51% yield with a *Z*/*E* ratio of 1 : 1.1.

Similarly, when the critical precursor **23** was reacted with lithium ethylpropiolate at low temperature, it smoothly provided the desired propargylic alcohol **27** in an excellent yield as expected (Scheme 3). The final redox isomerization of the vinyl propargylic alcohol **27** under the aforementioned base-mediated reaction conditions was successfully performed to obtain the targeted natural products homomelodienone (**2**) and homoisomelodienone (**4**) in 42% total yield with a *Z*/*E* ratio of 1 : 1.2. To our delight, the NMR and HRESIMS spectra of the synthetic melodienone (**1**), homomelodienone (**2**), isomelodienone (**3**), and homoisomelodienone (**4**) were then

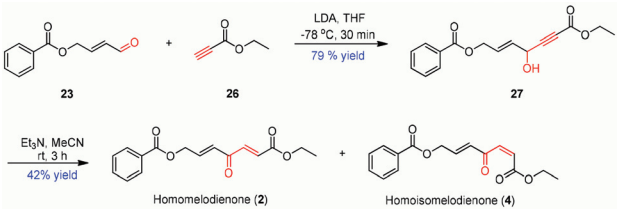
Table 3 Straightforward structural modifications of natural products[a]

Entry	Substrates	Time	Products (yield)
1	 **14**	8 h	 **15** *Z*/*E* = 1:10, 35% yield
2	 **16**	8 h	 **17** *Z*/*E* = 1:4, 77% yield
3	 **18**	10 h	 **19** *Z*/*E* < 1:20, 63% yield

[a] Conditions: Et_3N (1.0 eq.), CH_3CN, rt.



Scheme 2 Concise total syntheses of melodienone (**1**) and isomelodienone (**3**).

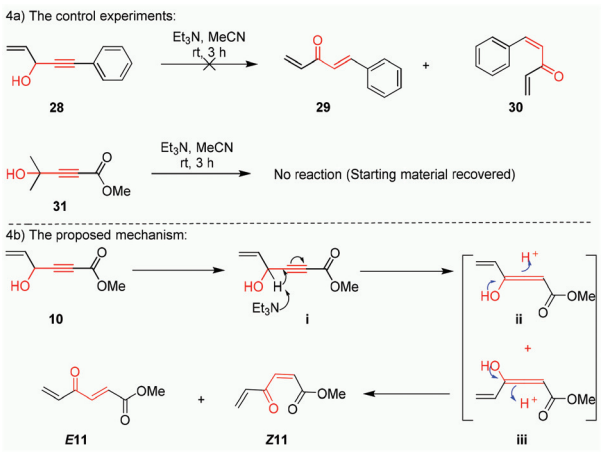


Scheme 3 Total syntheses of homomelodienone (**2**) and homoisomelodienone (**4**).

proved to be identical to those of the isolated natural products reported in the previous literature in all aspects, thus evidencing the successful concise total syntheses of these natural products in only 4 linear steps.

Mechanistic control experiments were also performed to shed light on the potential reaction pathway as shown in Scheme 4a. With the propargylic alcohols **28** and **31** as the tentative substrates, no obvious reactions took place under the standard reaction conditions for both of them, and almost all of the starting materials were recovered. These results collectively pointed to the fact that the electron-withdrawing ester group and the active proton in the propargylic position were critical for this transformation, thus suggesting that the deprotonation of the propargylic alcohol might be a crucial step for the transformation. With these issues in mind, the probable mechanism is proposed in Scheme 4b, which is similar to the previously proposed mechanisms in the reported literature.[20,29] Firstly, Et_3N abstracted the active propargylic proton from **10** to generate *trans*- and *cis*-allenols (**ii** and **iii**), which then abstracted protons from the reaction conditions to afford the desired products ***Z*11** and ***E*11**, respectively.

In summary, under the well-optimized reaction conditions, a base-mediated redox isomerization of vinyl propargylic alcohols was established, which provided an alternative convenient and practical methodology for the rapid stereodivergent construction of (*E*)- and (*Z*)-γ-oxo-α,β-alkenoic ester skeletons in a highly efficient fashion from readily accessible vinyl propargylic alcohol derivatives. Moreover, advancing the capacity for the strategic protocol successfully led to the efficient total synthesis of the biologically significant natural products melodienone (**1**), homomelodienone (**2**), isomelodienone (**3**), and homoisomelodienone (**4**). Its advantageous simplicity and efficiency would illuminate an actionable path to pursue the diversity-oriented total syntheses of other natural products in this family together with their structure optimization towards drug discovery. Further investigations directed toward these desired goals are currently underway and will be reported in due course.



Scheme 4 The control experiments and proposed mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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