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Rapid Access to 2-Methylene Tetrahydrofurans and γ-Lactones: A Tandem Four-Step Process

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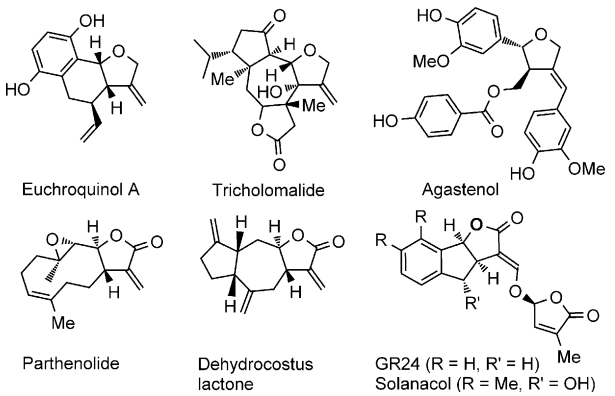
Abstract: *A one-pot tandem process involving hydrolysis, Knoevenagel condensation, Michael addition, and Conia-ene (HKMC) reactions has been developed for the rapid synthesis of indanone-fused 2-methylene tetrahydrofurans from the reaction of enynals and propynols. In this process, two rings and four bonds are generated with 100 % atom-economy and high step-efficiency. The resulting tetrahydrofurans were readily oxidized into α-methylene γ-lactones, which are one of the most important substructures in natural and bioactive compounds.*

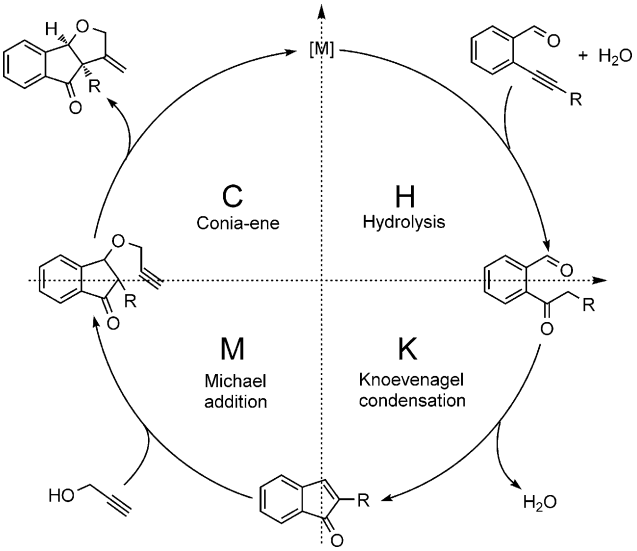
Although great achievements in both theoretical and practical aspects of organic synthesis have been made in the past century, chemists are still facing the challenge of reaction efficiency (atom- and step-efficiency).[1] To meet this challenge, a popular trend has been to move away from traditional step-by-step strategies and instead focus on multistep tandem processes.[2] In such processes, multiple rings and bonds can be generated with high atom- and step-economy.

2-Methylene tetrahydrofurans and γ-lactones are core structures of large varieties of natural and bioactive compounds, including lignans, terpenes, steroids, and even nucleosides.[3] In many cases, these skeletons are fused with other cyclic units to form polycyclic structures, such as euchroquinol A,[4] tricholomalide A,[3c,5] parthenolide,[6] dehydrocostus lactone,[7] GR24,[8] and solanacol[9] (Scheme 1). Among them, tricholomalide A is a fused tetracyclic neurotrophic diterpene and shows neurotrophic activity.[9] GR24, an indanone-fused 2-methylene γ-lactone, is a synthetic analogue of the strigolactones, which stimulate mitosis and growth of the arbuscular mycorrhizal fungus *Gigaspora rosea* by boosting its energy metabolism.[10] Despite ongoing efforts, construction of 2-methylene tetrahydrofurans and γ-lactones, particularly for those fused with polycyclic structures, typically require multistep syntheses with low atom- and step-economy.[11] Therefore, the development of efficient and useful methods for the synthesis of polycyclic compounds bearing 2-methylene tetrahydrofuran and γ-lactone units would be of great importance.



Scheme 1. Natural or bioactive compounds bearing 2-methylene tetrahydrofurans and α-methylene γ-lactones.

As part of our continuing efforts to develop a highly efficient tandem reaction based on enynal/enynone chemistry,[12] we envisioned that indanone-fused 2-methylene tetrahydrofuran, the core structure of GR24 and Solanacol, might be rapidly accessed through a tandem four-step process by using the reaction of an enynal with propynol, and it involves hydrolysis,[12c,13] Knoevenagel condensation, Michael addition, and Conia-ene (HKMC) reactions (Scheme 2). In this process, molecular complexity would be achieved rapidly with



Scheme 2. Tandem four-step process.

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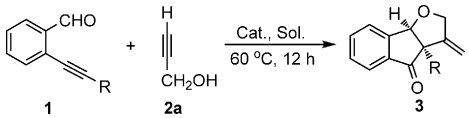
two rings and four chemical bonds being generated in a single synthetic operation. The design and implementation of this tandem reaction would face several challenges, such as the compatibility of catalyst with the four sequential reactions, and undesired cross-reactions between substrates and intermediates.

Initial efforts were made to systematically investigate various catalytic reaction conditions for the cyclization of the enynal **1** and propynol (**2a**; Table 1). Silver salts were firstly chosen as the catalysts because they were typically regarded as good catalysts for the activation of carbonyl groups and C≡C bonds. The terminal enynal **1a** was initially tested for the cyclization by treating it with 2.0 equivalents of **2a**. When the reaction was conducted in DCE at 60 °C with 5 mol% of $AgNTf_2$ as catalyst, the desired product **3a** was not detected (entry 1). Similarly, 2-(phenylethynyl)-benzaldehyde (**1b**) did not furnish the desired product **3b** (entry 2). It is supposed that the reactions of both **1a** and **1b** underwent 6-*endo*-dig-cyclization rather than the desired 5-*exo*-dig-cyclization.[14] In contrast, we reasoned that electron-deficient enynal may undergo the desired 5-*exo*-dig-cyclization because of electronic effects.[12c,g,15] For this reason, the electron-deficient enynal **1c** was then employed as the substrate. As expected, the desired product **3c** was obtained in 12% yield under the same reaction conditions (entry 3). $IMesAuNTf_2$ gave similar results as those obtained with $AgNTf_2$ (entry 4). It is well known that zinc and indium salts are good catalysts for the Conia-ene reaction.[16] Therefore, several zinc and indium salts were tested for this transformation. As shown in entries 5 and 6, both $ZnCl_2$ and $Zn(OTf)_2$ performed better than silver and gold salts, thus giving **3c** in 34 and 18% yield, respectively. The results were enhanced further when $InCl_3$ and $In(OTf)_3$ were applied, with the yields of 41 and 68%, respectively (entries 7 and 8). Different solvents were also examined (entries 9–13). The reaction could be carried out in $MeNO_2$, PhMe, and $CHCl_3$, but with inferior results (entries 9–11). CH_3CN and THF were proved to be superior solvents, thus leading to **3c** with yields of 76 and 85%, respectively (entries 12 and 13). Additional experiments indicated that either a smaller amount of **2a** or lower temperature gave inferior results (entries 14 and 15). When 4 Å molecular sieves were added to the reaction system, to remove the adventitious water introduced by solvent, catalyst and substrate, only trace amounts of product were detected. The addition of 1.0 equivalent of H_2O furnished a similar result (entry 17). When a mixed solvent of THF/H_2O (5:1) was used for this transformation, however, a complex system resulted. No desired **3c** could be detected. Presumably, there are unknown cross-reactions between H_2O and reaction intermediates. This outcome indicated that the adventitious water introduced by solvent, catalyst, and substrate is enough for this transformation, and is consistent with the proposed reaction mechanism, in which water is required only in a catalytic amount (Scheme 2). Brønsted acids, such as TfOH, CF_3COOH, TsOH, and HBF_4 cannot catalyze this transformation (Table 1, entry 19; see the Supporting Information for more details). The addition of a proton scavenger, 2,6-di-*tert*-butylpyridine (DTBP),[17] has no effect on the reaction efficiency (Table 1, entry 20; see the Supporting Information). All these results indicated that this reaction is not a Brønsted acid catalyzed process.

Table 1: Optimization of the reaction conditions.[a]



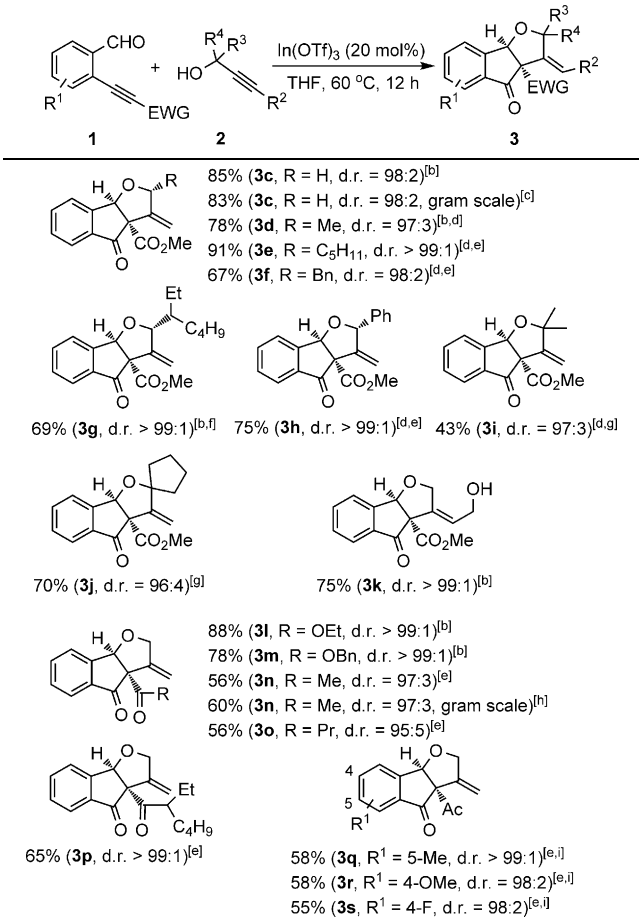
1 2a 3

Entry	R (**1**)	Cat.	Sol.	Yield [%][b]
1	H (**1a**)	$AgNTf_2$ (5 mol%)	DCE	n.d. (**3a**)
2	Ph (**1b**)	$AgNTf_2$ (5 mol%)	DCE	n.d. (**3b**)
3	CO_2Me (**1c**)	$AgNTf_2$ (5 mol%)	DCE	12 (**3c**)
4	CO_2Me (**1c**)	$IMesAuNTf_2$ (5 mol%)	DCE	10 (**3c**)
5	CO_2Me (**1c**)	$ZnCl_2$ (20 mol%)	DCE	34 (**3c**)
6	CO_2Me (**1c**)	$Zn(OTf)_2$ (20 mol%)	DCE	18 (**3c**)
7	CO_2Me (**1c**)	$InCl_3$ (20 mol%)	DCE	41 (**3c**)
8	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	DCE	68 (**3c**)
9	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	$MeNO_2$	36 (**3c**)
10	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	PhMe	30 (**3c**)
11	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	$CHCl_3$	54 (**3c**)
12	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	CH_3CN	76 (**3c**)
13	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF	85 (**3c**)[c]
14[d]	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF	58 (**3c**)
15[e]	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF	trace (**3c**)
16[f]	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF	trace (**3c**)
17[g]	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF	84 (**3c**)[c]
18[h]	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF/H_2O	complex (**3c**)
19	CO_2Me (**1c**)	TfOH (20 mol%)	THF	complex (**3c**)
20[i]	CO_2Me (**1c**)	$In(OTf)_3$ (20 mol%)	THF	85 (**3c**)[c]

[a] **1** = 0.25 mmol, **2a**:**1** = 2.0, [**1**] = 0.25 M. [b] Yield determined by NMR spectroscopy. [c] Yield of isolated product; d.r. = 98:2 (determined by ^1H NMR spectroscopy). [d] 1.2 equiv of **2a**. [e] Room temperature. [f] 100 mg 4 Å M.S. was added. [g] 1.0 equiv H_2O was added. [h] V_{THF}/V_{H_2O} = 5:1. [i] 0.2 equiv 2,6-di-*tert*-butylpyridine (DTBP) was added. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

With the optimized reaction conditions in hand (Table 1, entry 13), the substrate scope was examined. As shown in Table 2, a variety of propynol derivatives served as effective substrates (**3c–k**). The yields were typically higher than 70%. For example, in addition to primary alcohols, secondary alcohols with alkyl or aryl substituents functioned well for this transformation (**3d–h**). Both substrates with linear and branched alkyl groups afforded the desired products in satisfactory yields. Furthermore, even bulky tertiary alcohols could be successfully converted into tricyclic products as well (**3i,j**). Interestingly, the spiroproduct **3j** was formed in 70% yield when 1-ethynylcyclopentanol was utilized as the substrate. Surprisingly, as internal alkyne such as that found in butyne-1,4-diol, which represents a challenging substrate for the Conia-ene reaction, could also be cyclized, thus affording the desired product **3k** in 75% yield as a single isomer. Other internal propynol derivatives, such as 3-phenylprop-2-yn-1-ol or but-2-yn-1-ol, did not work. Presumably, the additional hydroxy group in butyne-1,4-diol may assist the activation of the intermediate through the chelation of the hydroxy group and C≡C bond in the course of Conia-ene reaction.[18] Furthermore, the tandem reaction could also proceed smoothly when *o*-alkynyl benzaldehydes (**1**) having different electron-withdrawing groups on the alkyne were used as

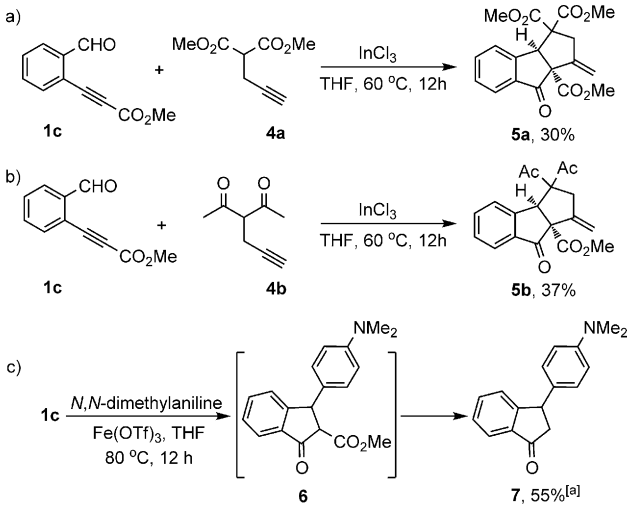
Table 2: Substrate scope.[a]



[a] Performed at 60 °C for 12 h under N_2; **1** (0.25 mmol), [**1**] = 0.25 M; yield of the isolated product. The stereochemistry of the products was determined by using the two-dimensional nOe spectrum of **3d**. [b] 2.0 equiv of **2** was used. [c] **1c** (12 mmol, 2.26 g). [d] 40 h. [e] 3.0 equiv of **2** was used. [f] 36 h. [g] 5.0 equiv of **2** was used. [h] **1d** (12 mmol, 2.06 g). [i] 16 h. EWG = electron-withdrawing group.

substrates (**3l**–**p**). The enynals with ethyl and benzyl ester worked, as well as those with a methyl ester (**3l**,**m**). The results also showed that enynals bearing acyl groups did not function as well as those with ester groups (**3n**–**p**), and led to yields ranging from 56–65%. It seems that the steric hindrance of the ketone moiety has little effect on the reaction yields. It was also noted that both electron-donating and electron-withdrawing groups on the phenyl rings of the enynals had little effect upon the product yields (**3q**–**s**). It is noteworthy that the d.r. ratio for all products in Table 2 were higher than 95:5. Furthermore, the reaction could be conducted on gram scale as well, thus giving the products in similar yields (**3c** and **3n**) as those obtained for reactions run on a 0.25 mmol scale. The product structure was further confirmed by the X-ray diffraction analysis of **3s** (see the Supporting Information).[19]

Aside from the propynol substrates, several other nucleophiles were also tested to trap the potential Michael acceptor intermediate. For example, both a homopropargyl diester (**4a**) and diketone (**4b**) served as carbon nucleophiles



Scheme 3. The reaction of the enynal **1c** with either a homopropargyl diester or diketone (**4**): **1c** (0.25 mmol), **4** (0.50 mmol), $InCl_3$ (20 mol%), THF (1.0 mL), 60 °C, 12 h. Yield is that of the isolated product. [a] $Fe(OTf)_3$ (20 mol%), *N*,*N*-dimethylaniline (2.0 equiv).

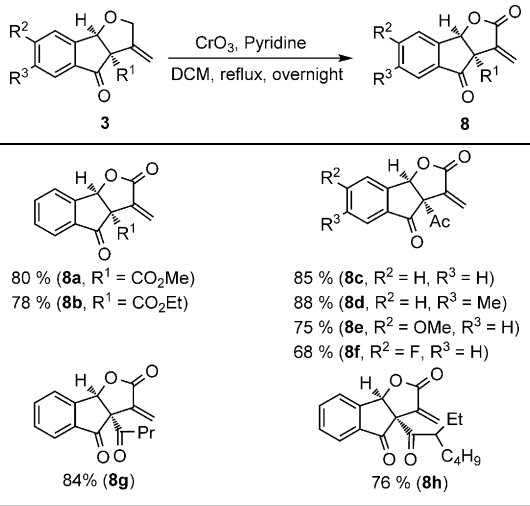
to realize a similar tandem process, albeit resulting in somewhat lower yields (Scheme 3a,b). In this reaction, an interesting indanone-fused cyclopentane tricyclic skeleton was obtained instead. $InCl_3$ proved to be a superior catalyst to $In(OTf)_3$ (see the Supporting Information). When a nonpropargyl nucleophile was used as a nucleophile instead, the reaction was terminated at the Michael addition step. For example, when *N*,*N*-dimethylaniline was added to the reaction system, 3-(4-(dimethylamino)phenyl)-indanone (**7**) was obtained in 55% yield by using $Fe(OTf)_3$ as the catalyst (Scheme 3c). The indanone **7** arises from de-esterification of the ester **6**.

With indanone-fused 2-methylene tetrahydrofuran products (**3**) in hand, additional chemical transformations were also carried out to demonstrate the potential applications of these molecules. As mentioned above, 2-methylene γ-lactones are one of the most important substructures in natural and bioactive compounds, such as parthenolide, dehydrocostus lactone, GR24, and solanacol (Scheme 1). As shown in Table 3, the 2-methylene tetrahydrofurans **3** can be selectively oxidized into the desired 2-methylene γ-lactones **8** with CrO_3/pyridine.[20] In all cases, the products **8** were obtained in good to excellent yields (68–88%).

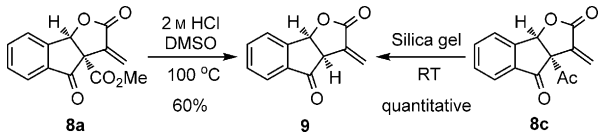
Furthermore, both the ester or acetyl groups of the products **8** were easily removed under acidic conditions. For example, the ester group of **8a** was removed in HCl/DMSO, thus affording the desired product **9** in 60% yield (Scheme 4). The same product **9** could also be attained by deacylation of **8c** in quantitative yield. The tricyclic compound **9** shares almost the same ring-skeleton with GR24, solanacol, and amentotaxin WB.[21]

In summary, we have developed a highly efficient one-pot system for the synthesis of indanone-fused 2-methylene tetrahydrofurans tricyclic framework from the reaction of electron-deficient enynals (**1**) and propynols (**2**). The reaction is believed to proceed through a tandem hydrolysis, Knoevenagel condensation, Michael addition, and Conia-ene reac-

Table 3: Further transformations.[a]



[a] **3** = 0.25 mmol, CrO_3 (28 equiv), pyridine (34 equiv), DCM (2.0 mL). Yield is that of the isolated product. DCM = dichloromethane.



Scheme 4. De-esterification of **8a** and deacylation of **8c**. DMSO = dimethylsulfoxide.

tion. The resulting 2-methylene tetrahydrofurans **3** are readily and selectively oxidized into the desired 2-methylene γ-lactones **8** with CrO_3/pyridine in excellent yields. In this process, two rings and four bonds are generated with 100% atom-economy and high step-efficiency. Owing to good substrate scope, mild reaction conditions, and high atom- and step-economy, this tandem reaction holds considerable potential for the construction of natural or bioactive compounds containing indanone-fused 2-methylene tetrahydrofurans or γ-lactones moiety. Investigations on the asymmetric version and additional applications of this reaction are underway in our laboratory.

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