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Letter

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Cyclopentanoids by Uncatalyzed Intramolecular Carbonyl Ene (ICE) Reaction of α-Keto Esters

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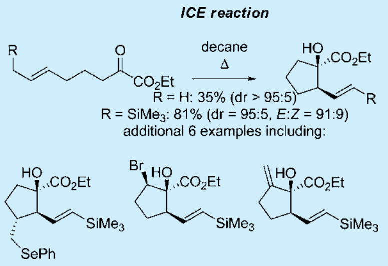
Supporting Information

ABSTRACT: The uncatalyzed intramolecular carbonyl ene (ICE) reaction of substituted ε,ζ-unsaturated α-keto esters to terpenoid-related building blocks has been studied. We found a beneficial effect of a silyl substituent at the ene segment on the kinetics of the ICE reaction. A generalizable and scalable synthesis of ε,ζ-unsaturated α-keto esters from allylic alcohols was developed.



The uncatalyzed intramolecular carbonyl ene (ICE) reaction of an ε,ζ-unsaturated α-keto ester (**1**) has recently been exploited to access the highly substituted cyclopentanoid **2**, which was pivotal in the total synthesis of jatrophane diterpenoids (e.g., **5**) from plants of the genus *Euphorbia* (Figure 1).[1]

Notably, the catalyst-free ICE reaction to afford **2** in decane required 180 °C, and the stereochemical outcome of the bond-forming event was thermodynamically controlled.[2] To further probe for the scope of the ICE reaction, including an application in a projected total synthesis of the marine sesquiterpenoid menverin C (**4**),[3] we have synthesized a range of ε,ζ-unsaturated α-keto esters (**1a–i**) and studied the influence of substituents on the ICE reaction. In particular, we envisioned that a $SiMe_3$ substituent at the ene segment would increase the thermodynamic driving force of the ICE reaction and, assuming that the Bell–Evans–Polanyi principle is operative, favorably bias the kinetics as well.[4−6] The results of our study are summarized in this letter.

Despite the many methods known for the preparation of the α-oxo ester functionality,[7] a general and robust synthetic excess to substituted ε,ζ-unsaturated α-keto esters **1** that would serve the purpose of this study was not available. Therefore, we were prompted to develop a route starting from readily available allylic alcohols (Table 1).[8] On the basis of the work of Schlaf as well as Wei,[9,10] we subjected the secondary allylic alcohols **6b–d** to a telescoped process consisting of (bphen)Pd(tfa)$_2$-catalyzed vinyl ether metathesis and subsequent Hurd–Claisen rearrangement[11] under modified conditions to deliver the corresponding aldehydes in 85–89% yield.[12−14] Unfortunately, the telescoped process was low-yielding (25%) for the allylic alcohol **6a**, and the vinyl ether metathesis failed for ethyl 1-propenylether; hence, a sequence of Johnson–Claisen rearrangement[15] and subsequent DIBAH reduction was utilized to access the aldehydes **7a** and **7e**. With the requisite aldehydes **7a–e** in hand, we turned toward the introduction of the α-keto ester moiety. Thus, Horner–Wadsworth–Emmons-type olefination using ethyl 2-acetoxy-2-(diethoxyphosphoryl)acetate[16] (**8**) under previously reported conditions provided the vinyl acetates **9a–e** (Table 1, entries 1–5).[1] In our hands, this procedure proved to be generalizable and scalable for aliphatic aldehydes.[17]

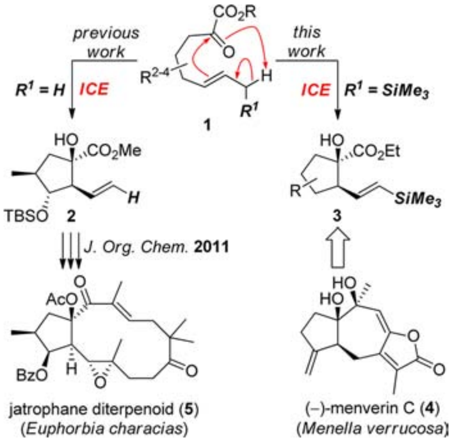


Figure 1. Intramolecular carbonyl ene (ICE) reaction for the synthesis of terpenoid building blocks.

We turned next to elaboration of the vinyl acetates **9a–e** into the desired α-keto esters **1a–g** (Table 2). Using **1b** for initial exploration and optimization, we first tested our established transesterification conditions (0.1 equiv K_2CO_3, MeOH, 0 °C),[1] but without measurable success. Instead of the desired α-keto ester **1b**, we detected the product of a homocondensation process between the α-keto ester **1b** and its potassium enolate, which arises as primary product of the potassium methoxide-triggered transesterification. As expected, shortening the reaction time or lowering the reaction temperature suppressed homocondensation, albeit at the expense of an incomplete conversion.

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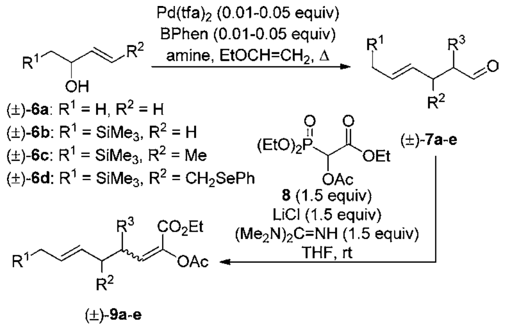
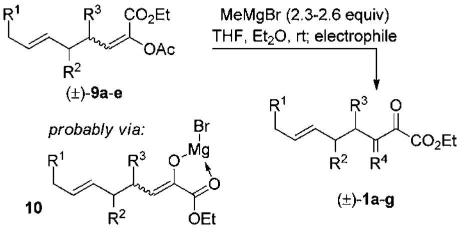
Table 1. Synthesis of Vinyl Acetates from Allylic Alcohols via Aliphatic Aldehydes[a]



entry	aldehyde	R^1	R^2	R^3	vinyl acetate	E:Z[b]	yield of **9** from **6** (%)[c]
1	**7a**[d]	H	H	H	**9a**	69:31	51 (806 mg)
2	**7b**[e]	$SiMe_3$	H	H	**9b**	67:33	81 (920 mg)
3	(±)-**7c**[f]	$SiMe_3$	Me	H	(±)-**9c**	58:42	77 (745 mg)
4	(±)-**7d**[g]	$SiMe_3$	CH_2SePh	H	(±)-**9d**	66:34	66 (2.047 g)
5	(±)-**7e**[d]	$SiMe_3$	H	Me	(±)-**9e**	75:25	49 (2.179 g)

[a] BPhen = 4,7-diphenyl-1,10-phenanthroline, bathophenanthroline. [b] Determined by NMR; double-bond configuration assigned on the basis of ^{13}C,^1H long-range coupling constant analysis. [c] Yield (isolated mass) after purification by chromatography. [d] Prepared by Johnson–Claisen rearrangement and DIBAH reduction; see the Supporting Information. [e] Amine = DABCO (0.1 equiv). [f] Amine = DABCO (0.14 equiv). [g] Amine = 2,6-lutidine (1 equiv).

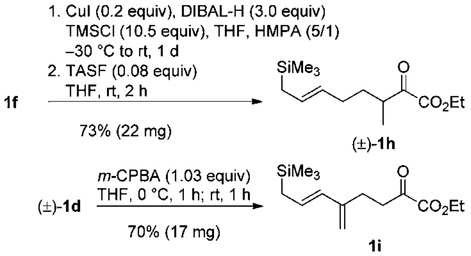
Table 2. Vinyl Acetate Elaboration: Synthesis of ε,ζ-Unsaturated α-Keto Esters



entry	electrophile	product	R^1	R^2	R^3	R^4	yield (%)[a]
1	H_2O	**1a**	H	H	H	H,H	61
2	H_2O	**1b**	$SiMe_3$	H	H	H,H	75
3	H_2O	(±)-**1c**	$SiMe_3$	Me	H	H,H	80
4	H_2O	(±)-**1d**	$SiMe_3$	CH_2SePh	H	H,H	76
5	H_2O	(±)-**1e**	$SiMe_3$	H	Me	H,H	91
6	$H_2C{=}NMe_2I$	**1f**	$SiMe_3$	H	H	CH_2	86
7	NBS	(±)-**1g**	$SiMe_3$	H	H	H,Br	84

[a] Isolated yield (100–900 mg) after purification by chromatography.

Scheme 1. Structural Diversification: Synthesis of the α-Keto Ester 1h,i



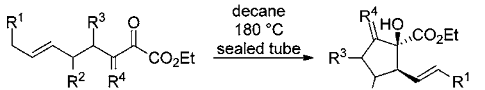
Next, a Brønsted acid mediated process (1 equiv PTSA, MeOH, rt) was explored; however, we obtained low yields (45–55%) and observed decomposition. We then opted for conditions that would prevent the coexistence of the α-keto ester and its enol or enolate. Thus, exposure of the vinyl acetate **9b** to commercially available MeMgBr solution (1 M in Et_2O) with subsequent aqueous workup afforded the α-keto ester **1b** in a synthetically useful yield (Table 2, entry 2).[18,19] The success of this procedure probably hinges on the intermediacy of the stable chelated magnesium enolate **10**. As outlined in Table 2, the developed procedure was general and, furthermore, could be extended to other electrophiles as well (entries 6 and 7). Notably, the aminomethylation using Eschenmoser's salt[20] enabled elimination already during workup without the necessity for quatenarization and, hence, formation of the β-methylidene α-keto ester **1f**. However, the methylation (MeI, Me_2SO_4) of the proposed magnesium enolate **10** of **1b** failed to afford the desired β-methyl-substituted α-keto ester (**1h**).

In an effort to access an even greater diversity of the desired ε,ζ-unsaturated α-keto esters (**1**), we sought to implement a 1,4-reduction to convert the β-methylidene α-keto ester **1f** into the elusive β-methyl-substituted α-keto ester **1h** (Scheme 1). After much experimentation, we found that a two-step procedure consisting of 1,4-hydrosilylation followed by TASF-catalyzed silyl enol ether cleavage delivered **1h** in an useful yield (73%) on an explorative scale.[21,22] Also on a small scale, the δ-methylidene α-keto ester **1i** was made accessible by treatment of the phenyl selenide **1d** with *m*-CPBA (1 equiv).[23]

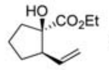
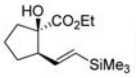
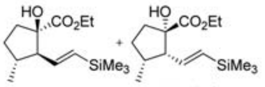
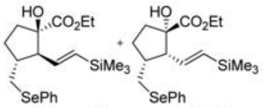
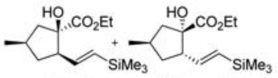
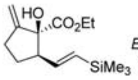
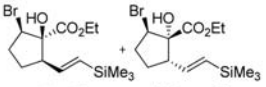
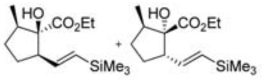
With the requisite nine α-keto esters **1a–i** in hand, the influence of substitutents on the outcome of the ICE reaction was explored (Table 3). All experiments were performed using decane as the solvent in a sealable glass pressure tube with a Teflon screw cap. Thus, upon heating (180 °C) the reference compound **1a** lacking the silyl substituent at the ene, we obtained the cyclopentanoid **3a** as a single *cis*-configured diastereomer in low yield (35%) along with substantial amounts of starting material (entry 1).

Subjecting the α-keto ester **1b** featuring the Me_3Si-substituted ene to the identical conditions markedly increased the yield (81%), and **3b** was obtained in high diastereoselectivity (dr = 95:5) and as a E:Z = 91:9 mixture of double bond isomers with respect to the vinyl silane moiety (entry 2).[24] To shed some light on the influence on the $SiMe_3$ substituent on the kinetics of the ICE reaction, the conversion was tracked by ^1H NMR spectroscopy for **1a** and **1b**. The resulting conversion-versus-time profiles nicely illustrate the improved kinetics of the ICE reaction of **1b** compared to **1a**.[25] For instance, after 1 d at 180 °C, we obtained a 15% conversion of **1a** to **3a** but a 64% conversion of **1b** to **3b**. The substrate-induced diastereoselectivity was investigated next.[26] The ICE reaction (180 °C, 3 d) of the δ-methyl branched α-keto ester **1c** delivered **3c** in very good yield (86%) and with a significant (dr = 89:11) induced diastereoselectivity (entry 3).[27] A comparable result (92%, dr = 91:9) was obtained for the δ-$PhSeCH_2$-substituted α-keto ester **1d** (entry 4).[28] The δ-methylene α-keto ester **1i** very reluctantly underwent the ICE reaction, and extensive decomposition was observed rendering this transformation synthetically unattractive. Hence, and considering the efficiency of the ICE reaction of **1d** to **3d**, we decided to access the desired cyclopentanoid **3i** by a post-ICE transformation of **3d** (vide infra). In striking contrast to the synthetically useful induced diastereoselectivities obtained

Table 3. Substituent Effects on the ICE Reaction

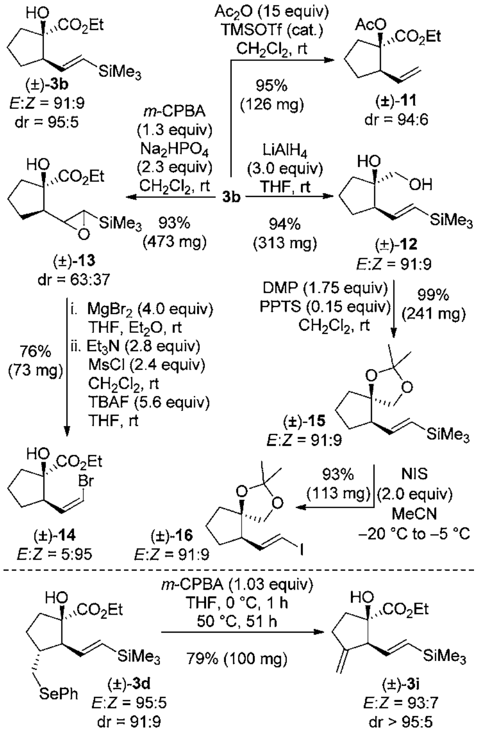


(±)-**1a-h** (±)-**3a-h**

entry	substrate	time (h)	product(s)[a]	yield (%)[b]
1	**1a**	84	 (±)-**3a** dr > 95:5	35[c] (24 mg)
2	**1b**	84	 (±)-**3b** E:Z = 91:9 dr = 95:5	81 (65 mg)
3	**1c**	72	 (±)-*trans*-**3c** E:Z = 92:8 (±)-*cis*-**3c** E:Z = 91:9 dr = 89:11	86 (69 mg)
4	**1d**	72	 (±)-*trans*-**3d** E:Z = 95:5 (±)-*cis*-**3d** E:Z > 95:5 dr = 91:9	92 (183 mg)
5	**1e**	72	 (±)-*cis*-**3e** E:Z = 92:8 (±)-*trans*-**3e** E:Z = 91:9 dr = 53:47	93 (75 mg)
6	**1f**	144[d]	 (±)-**3f** E:Z = 87:13 dr > 95:5	50[e] (25 mg)
7	**1g**	77[d]	 (±)-*cis*-**3g** E:Z = 95:5 (±)-*trans*-**3g** E:Z > 95:5 dr = 82:18	80 (56 mg)
8	**1h**	72	 (±)-*cis*-**3h** E:Z = 92:8 (±)-*trans*-**3h** E:Z > 95:5 dr = 86:14	94 (66 mg)

[a] Ratios determined by NMR; relative configuration assigned by NOE experiments. [b] Yield (isolated mass) after purification by chromatography. [c] Unconsumed **1a** (25%) was reisolated. ^{1}H NMR of the reaction mixture and TLC (baseline) indicates formation of unidentified byproducts. For a procedure on larger scale, see the Supporting Information. [d] Reaction conducted at 140 °C. [e] Along with 30% (15 mg) of a dimer from a hetero-Diels–Alder reaction between **1f** and **3f** as well as 14% (7 mg) of **1f**; see Supporting Information.

Scheme 2. Post-ICE Transformations of 3b and 3d



for **1c** and **1d**, the ICE reaction (180 °C, 3 d) of the γ-methyl branched α-keto ester **1e** (entry 5), despite being high-yielding (93%), proceeded without notable induced diastereoselectivity (dr = 53:47).[29] We continued our study with the β-bromo- and β-methyl-substituted α-keto esters **1g** and **1h** (entries 6 and 7). The ICE reaction (77 h, 140 °C) of **1g** delivered **3g** in good yield (80%) and with a moderate induced diastereoselectivity (dr = 82:18). On one hand, the conversion of **1g** to **3g** slowly proceeded already at 120 °C, indicating that the β-bromo substituent exerts the most significant rate effect yet detected; on the other hand, however, the ICE reaction of **1g** at 180 °C was accompanied by HBr elimination and concomitant protodesilylation. The ICE reaction (180 °C, 3 d) of the β-methyl α-keto ester **1h** delivered **3h** in excellent yield (94%) and good induced diastereoselectivity (dr = 86:14). Heating (140 °C) of the β-methylidene α-keto ester **1f** led to a mixture consisting of unconsumed **1f** (14%), the expected cyclopentanoid **3f** (50%), as well as a homodimer from a hetero-Diels–Alder reaction between **1f** and **3f** (30%) as a single diastereomer (entry 6).[30]

Having gained access to terpenoid-related building blocks (**3**) by ICE reaction of ε,ζ-unsaturated α-keto esters (**1**), we subsequently focused on the development of post-ICE transformations of the vinyl silane moiety (Scheme 2). Using **3b** (E:Z = 91:9) for initial exploration, we found that a mixture of TMSOTf and Ac_2O mediates acetylation of the tertiary hydroxyl group as well as protodesilylation to deliver the vinyl cyclopentanoid **11** (95%).[31] Iododesilylation with retention of double bond configuration required upstream LAH reduction of the α-hydroxy moiety to the diol **12** (94%) and acetalization to afford the acetonide **15** (99%); subsequent treatment of **15** with NIS delivered the vinyl iodide **16** (93%, E:Z = 91:9).[32] A stepwise bromodesilylation with inversion of the double bond configuration was accomplished by initial epoxidation of **3b** to afford the silyl oxirane **13** (93%) as a mixture of diastereomers; treatment of **13** with $MgBr_2$ delivered the crude bromohydrin which was subjected to a telescoped process consisting of mesylation and TBAF-mediated elimination to provide the vinyl bromide **14** (76%, E:Z = 5:95).[33] Finally, and thereby completing the circle to our initial proposal (Figure 1), treatment of the selenide **3d** with 1 equiv of m-CPBA under carefully optimized conditions delivered the methylene cyclopentanoid **3i** (79%, dr >95:5, E:Z = 93:7) representing a promising building block for menverin C (**4**).

In summary, substituent effects on the uncatalyzed intramolecular carbonyl ene (ICE) reaction of ε,ζ-unsaturated α-keto esters were investigated. Most notably, the presence of a silyl substituent at the ene exerts an enabling beneficial effect on the kinetics of the ICE reaction. High simple diastereoselectivities, enforced by the concertedness of the bond reorganization process, were observed. The extent of the induced diastereoselectivity depends on the position of substituents at the tether atoms between ene and enophile. Central to the study of the ICE reaction was the development of a robust and generalizable synthetic access to aliphatic α-keto esters from allylic alcohols.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, characterization data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) In our hands, the optimum conditions for the Pd(II)-catalyzed vinyl ether metathesis were dependent on the substrate structure, particularly with respect to the nature of the amine base.

(13) $Hg(OAc)_2$ or $Hg(tfa)_2$ (0.1−0.2 equiv) were less effective catalysts; see: Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828−2833.

(14) A catalytic cycle for the Pd(II)-catalyzed vinyl ether metathesis is proposed in the Supporting Information.

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(17) Attempts to subject a methyl ketone to this olefination reaction were unsuccessful.

(18) The α-keto esters **1a** and **1b**, in our hands, possessed the propensity to undergo homocondensation during chromatographic purification. See also: Boehlow, T. R.; Harburn, J. J.; Spilling, C. D. *J. Org. Chem.* **2001**, *66*, 3111−3118. In order to circumvent this problem on larger scale, the α-keto ester **1b** was subjected to the conditions of the ICE reaction unpurified; for instance, 1.9 g of **9b** delivered 75% of **3b** from **9b**.

(19) In contrast to the transesterification conditions (K_2CO_3, MeOH), the ethyl instead of the methyl α-keto ester is formed under the conditions of the nucleophilic vinyl acetate degradation (MeMgBr).

(20) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330−331.

(21) Optimized reductive procedure according to: Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537−540.

(22) Attempted HF-mediated silyl enol ether cleavage led to decomposition. We propose a TASF-catalyzed 1,3-retro-Brook rearrangement of the silyl enol ether to deliver the β-trimethylsilyl α-keto ester, followed by protodesilylation during aqueous workup. A catalytic cycle is proposed in the Supporting Information.

(23) Optimized procedure according to: Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250−3252.

(24) The relative configuration was assigned based on NOE experiments with **12** (Scheme 2); see Supporting Information. NOE experiments using the corresponding diol accessible from **3a** support the assignment. The relative configuration of **3c**−**h** was assigned in analogy.

(25) See the Supporting Information for details. We currently tend to believe that the rate-accelerating effect of the $SiMe_3$ group is caused by an increased thermodynamic driving force, rather than an intrinsic transition-state stabilizing effect of the $SiMe_3$ substituent.

(26) Kinetic studies by NMR indicate that the reported substrate-induced diastereoselectivities are thermodynamically controlled. A combined experimental and computational study on this issue will be reported in due course.

(27) Scaled to 1.3 g of **1c** (86% yield).

(28) Scaled to 1.0 g of **1d** (88% yield).

(29) Scaled to 0.8 g of **1e** (90% yield).

(30) The homodimer was purified and characterized and its configuration is deduced from NOE experiments; see the Supporting Information.

(31) Acylation without protodesilylation, see: Procopiou, A. P.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342−2347.

(32) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647−8650.

(33) See the Supporting Information for a mechanistic proposal that accounts for the stereochemical result of the stepwise bromodesilylation. For a two-step procedure for the conversion of α,β-epoxysilanes to vinylbromides (HBr; $F_3B{\cdot}OEt_2$), see: Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993−1996.