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A succinct access to ω-hydroxylated jasmonates via olefin metathesis

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Abstract: In higher plants, jasmonates are lipid-derived signaling molecules that control many physiological processes, including responses to abiotic stress, defenses against insects and pathogens, and development. Among jasmonates, ω-oxidized compounds form an important subfamily. The biological roles of these ω-modified derivatives are not fully understood, largely due to their limited availability. Herein, a brief (two-step), simple and efficient (>80% yield), versatile, gram-scalable, and environmentally friendly synthetic route to ω-oxidized jasmonates is described. The approach utilizes olefin cross-metathesis as the key step employing inexpensive, commercially available substrates and catalysts.

Keywords: cross-metathesis; gram scale synthesis; jasmonate; phytohormone; ω-hydroxylated jasmonate.

Dedication: This article is dedicated to the memory of Prof. Dr. Lothar Jaenicke.

1 Introduction

Jasmonates are signaling molecules that are ubiquitous in higher plants. They are key regulators of plant growth and development, as well as of responses to both biotic and abiotic stresses [1, 2]. Jasmonates are biosynthesized from α-linolenic acid, which, after several enzymatic steps, yields jasmonic acid [JA (**1**)] as the (3*R*,7*S*)-isomer (Scheme 1). However, some degree of epimerization at C7 may occur, and, moreover, the 7*R* epimer can be found within the cell [3]. Like JA (**1**), JA-derivatives exist *in planta* as a mixture of the 7*S* and 7*R* epimers. For instance, compound JKL (**7**) has been described as the 7*R* epimer [4, 5]. In response to environmental and developmental cues, JA (**1**) is activated by its conjugation to L-isoleucine (Ile) [6]. This reaction produces the most active jasmonate (3*R*,7*S*)-*N*-jasmonoyl-L-isoleucine (JA-Ile, **4**). The ω-oxidation of active JA-Ile (**4**) is carried out by members of the CYP94 family. This reaction produces the ω-hydroxylated acid 12-OH-JA-Ile (**8**) that is further converted into other ω-modified (12-modified) jasmonates (Scheme 1). Many 12-modified jasmonates (e.g. compounds **5–10**, Scheme 1) exist in relatively high abundance (compared to other jasmonates) in various plant species [7]; however, little is known about their physiological roles. These chemical species may be stored in cell compartments such as vacuoles and may contribute to maintaining the homeostasis of jasmonates within plant tissues, which is of crucial importance for plant fitness and defense [8]. On the one hand, naturally occurring 12-modified jasmonates are believed to be partially or completely inactive with regard to the canonical jasmonate pathway [9, 10]. However, 12-OGlc-JA (**5**) was found to activate leaf-closing movement in *Samaneasaman* [11]. The action mechanism of 12-OGlc-JA (**5**) is independent of the COI1-JAZ complex, the canonical jasmonate receptor. This suggests that endogenous 12-modified jasmonates may have biological roles beyond the classical jasmonate functions known to date. On the other hand, some synthetic 12-modified jasmonate derivatives have been described as inducers of plant defenses similarly to bioactive endogenous jasmonates [12]. Furthermore, these derivatives were recently employed to uncouple growth and defense in *Nicotiana attenuata* plants, opening a whole new field of research with potential application in agriculture [13]. Nonetheless, the production costs of 12-modified jasmonates (and jasmonates in general) must be sufficiently low if these compounds are to be employed in agricultural systems. The above-mentioned observations highlight the need to develop new synthetic strategies to prepare 12-modified jasmonates from a commercial product, such as methyljasmonate, in order to evaluate their mode of action and eventually to employ these compounds in agriculture.

The jasmonates' biological relevance made them the target of several synthetic approaches aiming to obtain not only naturally occurring compounds but also synthetic analogs; all of these contributed greatly to our understanding of how these phytohormones act [14–16]. A few studies have reported on the synthesis of 12-modified

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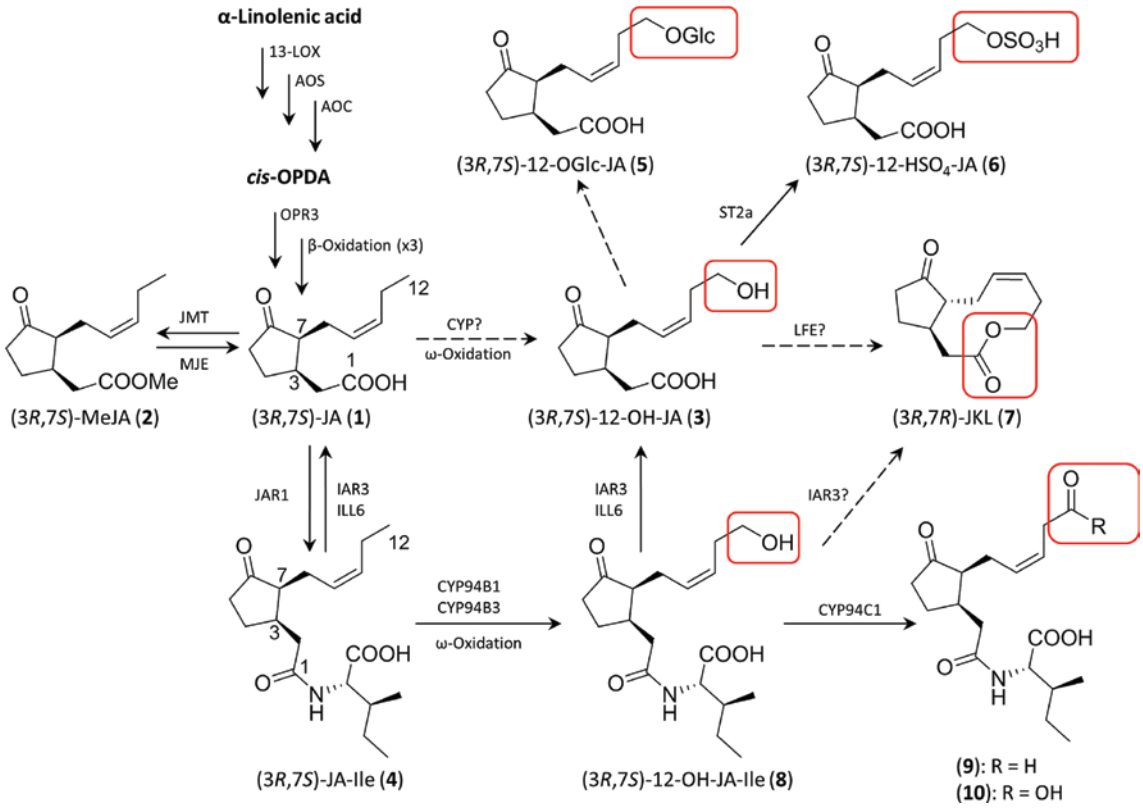
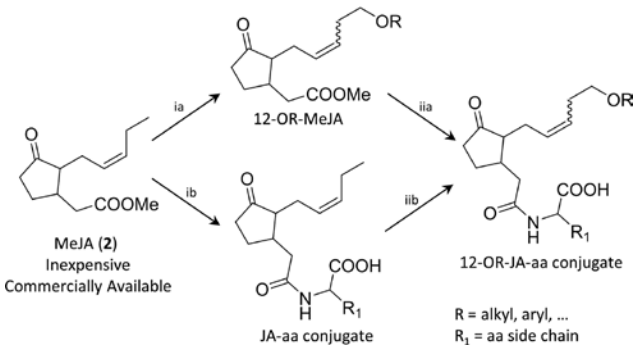


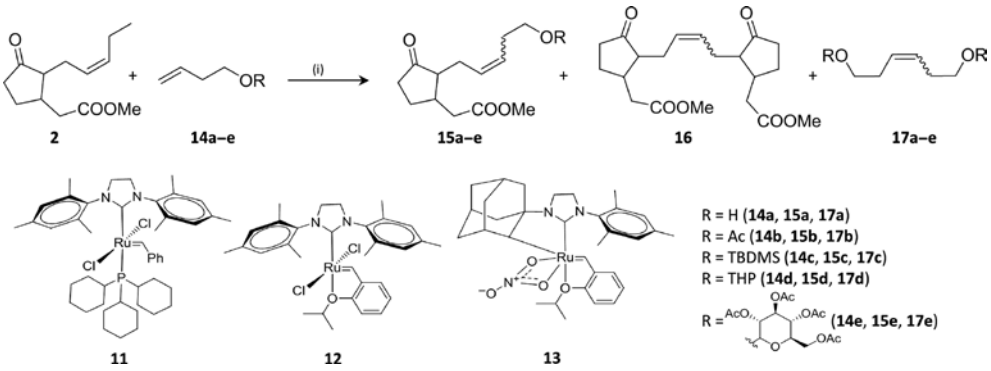
Scheme 1: Simplified scheme of jasmonate biosynthesis.
LOX, Lipoxygenase; AOS, allene oxide synthase; AOC, allene oxide cyclase; OPR3, 12-oxophytodienoate reductase 3; JMT, JA carboxyl methyltransferase; MJE, methyljasmonate esterase; JAR1, JA-amino synthetase; ILL6/IAR3, JA-Ile amidohydrolases; CYP94B1/B3/C1, cytochromes P450; LFE, lactone forming enzyme. Red squares depict ω modifications. A dashed arrow represents a proposed transformation. Nomenclature and numbering commonly used for jasmonates is employed for clarity. Epimerization at C7 may occur, lactone JKL (7) exists in nature. For comprehensive reviews on jasmonate biosynthesis, signaling and activity, please see reference [1].

jasmonates [17, 18]. However, because the procedures for synthesis are lengthy and provide low overall yield, access to these compounds for both bioassays and agricultural applications may be limited [19]. To circumvent these limitations, a synthetic route to ω-modified jasmonates based on the cross-metathesis (CM) of alkenes was explored (Scheme 2). The preferential formation of the more stable *E* over the *Z* isomer and the generation of complex mixtures disadvantaged CM for years. Nowadays, at least the stereoselectivity in favor of the *Z* isomer is no longer an issue, thanks to the recent development of molybdenum- [20, 21], tungsten- [20], and ruthenium-based (commercially available, inexpensive, and versatile) *Z*-selective catalysts [22, 23].

Jasmonates (commercially available or synthetic) are commonly employed in bioassays as mixtures of all possible diastereoisomers – in particular, with respect to the stereocenters at the cyclopentanone ring [16, 24, 25]. This is not at all disadvantageous, as cross-inhibition by the non-natural isomers or by the natural but less active (3*R*,7*R*) form does not occur. Therefore, inexpensive, commercially available MeJA (**2**) [a mixture of the (3*R*,7*R*), (3*S*,7*S*), (3*S*,7*R*), and (3*R*,7*S*) isomers in a ratio of approximately 45:45:5:5, respectively] was employed



Scheme 2: Alternative routes to 12-modified jasmonates via CM metathesis.
(ia, iib) CM of **2** with different terminal alkenes; (ib, iia) saponification/conjugation to selected amino acids (aa).



Scheme 3: CM reactions explored in this study and catalysts used.
(i) Screening of catalysts **11, 12** and **13**; catalyst loadings; solvents (THF, CH_2Cl_2 and C_6H_6); ratio of reactants; temperatures (27, 40, 60 and 80 °C).

throughout this study in order to develop and optimize the CM method. And hence, all ω-modified jasmonates were prepared as a diastereomeric mixture unless otherwise stated.

2 Results and discussion

2.1 Optimization of the reaction conditions for CM

First, the CM reaction of MeJA (**2**) with **14a** was investigated employing the Grubbs second-generation catalyst **11** (Scheme 3). Despite the broad functional group tolerance of **11** [26], the alcohol **14a** barely reacted with **2**, which meant that **2** could be recovered almost completely from the reaction mixture. This result may be explained by the reported low reactivity of homoallylic free alcohols in metathesis reactions [27]. Therefore, the protected alcohol **14b** was evaluated in the CM with **2** (Scheme 3). Catalyst **11** was active at loadings as low as 0.5 mol% (relative to **2**) in the CM. Product **15b** was obtained in 61% yield after 1 h using 1 mol% of **11** (Table 1, entry 2). To further optimize the reaction, solvents commonly employed in metathesis were screened (Table 1, entries 2, 4, and 5). All tested solvents performed similarly, but THF gave higher yields of **15b** (Table 1, entry 2). Conveniently, the reaction slowly proceeded under solvent-free conditions, so the process was environmentally friendly (Table 1, entry 6). The performance of catalysts **12** (Hoveyda–Grubbs second generation) and **13** (Grubbs *Z*-selective) was also evaluated. Reactions were run in THF at 27 °C with substrates at a concentration of approximately 0.2 M and 1 mol% catalyst loading in order to better assess differences between catalysts [23]. Catalysts **11** and **12** produced similar yield towards **15b** after 1 h of reaction (Table 1, entries 2 and 7). However, the *Z*-selective catalyst **13** needed a longer induction time (compared to **11** and **12**), and for up to 1 h, no CM product was detected. This was unexpected, as **13** has been reported active in the homodimerization of monosubstituted alkenes at catalyst loadings as low as 0.1 mol% [23]. The low reactivity of **13** may be explained by the nature of both substrate **2** and catalyst **13**. MeJA (**2**) is a 1,2-disubstituted olefin with a bulky cyclopentanone ring that could favor the homodimerization of **14b** over the CM product due to steric hindrance with the bulky adamantyl group of **13**. Following this reasoning, both catalyst loadings of **13** and different ratios of the starting substrates **2** and **14b** were screened (Table 2). It must be noted that under solvent-free conditions and at room temperature, **13** was active from a catalyst loading of 5 mol%, giving an excellent 95% of *Z*-selectivity (Table 2, entry 2). On the other hand, a six-molar excess of the terminal alkene **14b** improved the yield toward **15b** significantly, while the amount of **16** (homodimerization product of **2**) did not exceed 5% (Table 2, entry 6). While increasing the temperature may speed up a CM reaction, it may also negatively influence the yield and/or the *Z*-selectivity of the

Table 1: CM of **2** and **14b**: screening of catalysts, catalyst loading and solvents.

Entry	Catalyst	Catalyst loading (mol%)	Solvent	15b (%)[a]
1	**11**	0.5	THF	21
2	**11**	1	THF	61
3	**11**	2	THF	60
4	**11**	1	Benzene	44
5	**11**	1	CH_2Cl_2	24
6	**11**	1	No solvent	4
7	**12**	1	THF	50
8	**13**	1	THF	n.d.[b]

[a]Yield determined by GC-MS. [b]n.d., not detected.

Table 2: CM of **2** and **14b** using catalyst **13**: screening of catalyst loading, ratio of substrates and temperature.

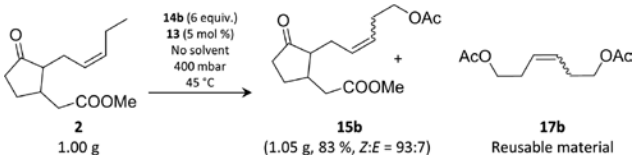
Entry	Catalyst loading (mol%)	14b:2 (mol/mol)	t (h)	T (°C)	15b (%)[a]	*Z*-15b (%)[b]	16 (%)[a,c]
1	1	1:1	24	27	~1	–	–
2	5	1:1	24	27	25	95	3
3	10	1:1	24	27	34	95	7
4	5	1:2	24	27	25	94	5
5	5	2:1	24	27	24	94	3
6	5	6:1	24	27	64	93	5
7	5	6:1	1	27	n.d.[d]	–	–
8	5	6:1	1	40	15	97	n.d.
9	5	6:1	1	60	14	97	n.d.
10	5	6:1	1	80	21	96	n.d.

[a]Yield determined by GC-MS. [b]Percentage of the *Z*-isomer of **15b**. [c]Response factor assumed as for**15b**. [d]n.d., not detected.

Table 3: CM of **2** and **14b–d** using catalyst **11** or **12**.

Entry	Substrate	Catalyst	*Z*-15 (%)[a,b]
1	**14b**	**11**	17
2	**14c**	**11**	20
3	**14d**	**11**	29
4	**14b**	**12**	18
5	**14c**	**12**	19
6	**14d**	**12**	24

[a]Percentage of *Z*-CM product **15** determined by GC-MS. [b]Average of two separate runs.



2 1.00 g — **15b** (1.05 g, 83 %, *Z*:*E* = 93:7) — **17b** Reusable material

Scheme 4: Gram-scale preparation of **15b** employing catalyst **13**.

desired CM product [23]. Strikingly, increasing the temperature in the CM of **2** with **14b** shortened reaction times from 24 h to 1 h and slightly improved the *Z*-selectivity for **15b** (Table 2, entries 8–10). It is worth mentioning that at short reaction times, the self-metathesis product **16** was not observed.

2.2 Influence of the -R group of 14

The reaction of **2** with substrates **14b–d** was studied with complexes **11** and **12** in order to generalize the method for these unselective but widely employed catalysts. As expected, **11** and **12** preferentially afforded the *E*-**15b–d** alkene (Table 3). Interestingly, the *Z*/*E* ratio of the CM product **15** was influenced by the nature of the protecting group. The amount of *Z*-**15** increased about two-fold with **14d** as the substrate (THP as the protecting group; Table 3, entry 3) compared to **14b** (Table 3, entry 1). Therefore, the *E*/*Z* ratio of the CM-product **15** can be fine-tuned by choosing the best protective group in substrate **14**. This observation may be useful in other CM reactions when the protection of alcohol groups is needed. Envisioning the possibility of directly installing more complex substituents at C12 (e.g. a sugar moiety as in jasmonate **5**, Scheme 1), the CM of **2** and the more challenging substrate **14e** (sterically hindered and more likely to chelate Ru) was explored. Under the employed conditions [**13** (20 mol%), not optimized], the CM product **15e** was obtained in 40% yield after purification and 60% of *Z*-selectivity. This result suggests that it is possible to install complex moieties at C12, such as a glycoside, by employing CM. Nonetheless, the preparation of a glycoside such as 12-OGlc-JA (**5**) might be made more efficient by the glycosylation of *Z*-**3**, which can be readily obtained from *Z*-**15b** (more than 90% *Z*-selectivity). Furthermore, it is reasonable to speculate that the CM of **2** and terminal alkenes bearing a protected sulfonic acid, aldehyde, or carboxylic acid group may offer an efficient way to prepare compounds **6**, **9**, or **10**, respectively.

2.3 Gram scale preparation of *Z*-15b

Previous reports have shown that CM reactions perform better under a static vacuum, which helps to remove undesired volatile olefins from the reaction mixture [28]. Following this idea, the CM of **2** and **14b** was carried out under a dynamic vacuum in order to remove both 1-butene and ethylene formed during the CM (Scheme 4). The versatile jasmonate **15b** (1.05 g, >80% after column purification) was obtained with more than 90% *Z*-selectivity. It is worth mentioning that **17b** (a valuable 1,2-disubstituted,

structurally symmetric alkene, as no ethylene is produced in self-metathesis [29]) was recovered and may be employed in further reactions. This CM allows for the gram-scale preparation of the valuable scaffold **15b**, a scaffold which could be used as the substrate to prepare many other 12-modified jasmonates.

2.4 Preparation of 12-modified derivatives of JA-Ile (4)

Several 12-modified jasmonates exist in nature as conjugates with amino acids [30, 31], for example, compound **8** (Scheme 1). Therefore, it was briefly explored whether the preparation of such derivatives would be more efficient with the CM reaction preceding the conjugation to the amino acid (Scheme 2, ia–iia) or vice versa (Scheme 2, ib–iib). The *Z*-selective catalyst **13** (catalyst loading up to 7 mol%) failed to promote the CM reaction of JA-Ile (**4**) [mixture of diastereoisomers] and **14b**. This result is consistent with the low activity reported for **13** catalyzing the CM of substrates bearing aldehyde or carboxylic acid groups [29]. However, catalyst **11** promoted CM at a catalyst loading of 3 mol% (Figure S1). These results indicate that the CM reaction should precede the conjugation to amino acids when aiming the synthesis of *Z*-enriched 12-modified JA-amino acid conjugates.

3 Conclusions

The CM reaction described here can be conducted on the lab bench employing inexpensive, commercially available catalysts **11**, **12**, or **13**, and the substrates MeJA (**2**) and **14b**. The *Z*-selective catalyst **13** should be used to prepare the (*Z*)-jasmonates resembling the natural signals. In addition, (*E*)-enriched 12-modified derivatives can be prepared by employing catalyst **11** or **12**. This feature may be of interest when conducting structure activity relationship (SAR) studies. The MeJA (**2**) employed in this study was a mixture of all possible diastereoisomers containing the (3*R*,7*R*)- and (3*S*,7*S*)-diastereoisomers (both *trans*- relative to the cyclopentanone ring) in a roughly 1:1 ratio. A similar 1:1 ratio of (3*R*,7*R*)- and (3*S*,7*S*)-diastereoisomers was found for two diastereomeric macrolactones prepared by using the CM method presented here as a key step [13]. This result indicates that the CM reaction of substrates **2** and **14b** is not stereocontrolled by the preexisting stereocenters on MeJA (**2**). Epimerization at C7 may occur both in vivo and when handling solutions of synthetic jasmonates [3]; therefore, our synthetic approach starting with inexpensive MeJA (**2**) is extremely useful.

In conclusion, an efficient synthetic approach which allows for the preparation of many 12-modified jasmonates has been developed based on olefin CM. Due to its efficiency and versatility, this method will likely be widely employed to prepare both naturally occurring and rationally designed 12-modified jasmonates of biological interest. The availability of such compounds (grams if needed) makes it possible to study their biological properties and, eventually, to apply them in agriculture. Additionally, the described method allows for the preparation of molecular probes in order to better understand a major signaling pathway in plants.

4 Experimental section

4.1 General experimental methods and materials

Reactions were carried out in oven-dried glassware. Flash-column chromatography was performed on silica gel 60 (230–400 mesh). Plates of silica gel 60 F^{254} were used for thin-layer chromatography. Compounds were visualized by soaking the plates in a potassium permanganate staining agent. All solvents, catalysts, and substrates **2**, **14a**, and **14b** were commercially available and were used as received. Compounds **1** [25], **4** [25], **14c** [32], **14d** [33], and **14e** [34] were prepared according to procedures described in the literature. Spectroscopic data from **15c** and **15d** matched those previously described [17, 35]. Nuclear magnetic resonance (NMR) spectra were acquired at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts were assigned relative to the residual solvent peak, which served as an internal standard. Gas chromatography-mass spectrometry (GC-MS) spectra were measured using electron impact (70 eV) as the ionization method in positive mode (EI^{+}). High-resolution mass spectrometry (HRMS) electrospray ionization in positive mode (ESI^{+}) was performed on high-resolution time-of-flight (TOF) equipment.

4.2 General procedure for CM reactions

CM reactions were carried out following the methodology described in [36]. Briefly, the desired amount of catalyst was added to a 4 mL vial. The vial was sealed with a screw cap to which a rubber septum was attached and purged with argon for 5 min. A syringe was used to add first the

solvent, then a mixture of the substrates. The reaction was allowed to stir in a heating block at the desired temperature. Aliquots of the reaction mixture were taken at the specified time periods. Samples for GC-MS analysis were obtained by adding 20 µL of the reaction to 0.5 mL of a solution of ethyl vinyl ether (3 mol L^{-1} in CH_2Cl_2); reactions under solvent-free conditions were stopped in a similar manner, but 1 µL aliquots were taken unless otherwise stated. The sample was shaken for 5 min and then analyzed via GC-MS. All reactions were performed in duplicate. Conditions for each particular experiment were as follows:

- Screening catalyst loadings of **11**, Table 1: **11** (0.9, 1.8, 3.7, or 9.0 mg; 1.1, 2.2, 4.4, or 11 µmol, respectively); THF (1 mL); **2** (50.6 mg; 0.22 mmol); **14b** (24.9 mg; 0.22 mmol); 27 °C.
- Screening solvents, Table 1: **11** (1.8 mg; 2.2 µmol, 1 mol%); benzene, THF, toluene, or dichloromethane (1 mL); **2** (50.6 mg; 0.22 mmol); **14b** (24.9 mg; 0.22 mmol); 27 °C. For solvent free; **2** (101.2 mg; 0.44 mmol); **14b** (49.8 mg; 0.44 mmol).
- Screening catalysts **11**, **12**, and **13** at 1 mol%, Table 1: **11**, **12**, or **13** (2.2 µmol; 1 mol%; 1.8, 1.4, or 1.4 mg, respectively); THF (1 mL); **2** (50.6 mg; 0.22 mmol); **14b** (24.9 mg; 0.22 mmol); 27 °C.
- Screening catalyst loadings of **13**, Table 2: **13** (2.8, 13.9, or 27.8 mg; 4.4, 22, or 44 µmol, respectively); **2** (101.2 mg; 0.44 mmol); **14b** (49.8 mg; 0.44 mmol); Neat; 27 °C.
- Screening substrate ratios, Table 2: **13** (6.0 mg, 9.5 µmol, 5 mol%); **14b/2** (0.1/0.2, 0.2/0.2, 0.4/0.2, or 1.2/0.2, mmol/mmol); Neat; 27 °C. Experiments were conducted in 1.5 mL vials.
- Screening temperatures, Table 2: **13** (6 mg, 9.5 µmol, 5 mol%); **2** (46.0 mg; 0.2 mmol); **14b** (135.6 mg; 1.2 mmol); Neat; 27, 40, 60, or 80 °C. Experiments were conducted in 1.5 mL vials.
- Screening protecting groups, Table 3: **11** (2.0 mg, 2.4 µmol, 1 mol%); **2** (55.2 mg; 0.24 mmol); **14b**, **14c**, or **14d** (27.1, 44.0, or 37.5 mg, respectively; 0.24 mmol). **12** (2.0 mg, 3.2 µmol); **2** (73.6 mg; 0.32 mmol); **14b**, **14c**, or **14d** (36.2, 59.6, or 50.5 mg, respectively; 0.32 mmol). Reactions were carried out under solvent-free conditions in 1.5 mL vials. Aliquots of 2 µL were taken after 1 h for GC-MS analysis.
- CM of JA-Ile (**4**) and **14b**, Figure S1: **11** (6.0 mg, 7 µmol, 3 mol% relative to **4**) or **13** (17 mg, 27 µmol, 7 mol% relative to **4**); **4** (74.4 mg, 0.23 mmol); **14b** (259.0 mg, 2.3 mmol); Neat; 60 °C. The reaction was followed by thin-layer chromatography. Samples for GC-MS analysis were obtained by adding 2 µL of the reaction mixture to 500 µL of ethyl vinyl ether (3 mol L^{-1} in CH_2Cl_2), shaking for 5 min and derivatizing with trimethylsilyldiazomethane.

4.3 Synthetic procedures

4.3.1 Methyl (Z)-2-(2-(5-acetoxypent-2-en-1-yl)-3-oxocyclopentyl)acetate (Z-15b); gram-scale

A 10 mL Schlenk flask was charged with **2** (1.02 g, 4.5 mmol), **14b** (3.05 g, 27 mmol, 6.0 equiv.) and catalyst **13** (0.14 g, 0.23 mmol, 5 mol%). The flask was connected to a vacuum line (400 mbar, dynamic vacuum), and gentle warming (45 °C) was applied while the contents were being stirred. After 3 h, the reaction was quenched by the addition of 5 mL of a solution of ethyl vinyl ether (3 mol L^{-1} in CH_2Cl_2). Stirring continued for 30 min, at which time $Pb(AcO)_4$ (1.5 equivalents relative to the catalyst) was added and the mixture stirred overnight. The reaction mixture was then filtered through a short pad of silica (approximately 10 g/0.05 mmol of catalyst) and eluted with four times 55 mL of CH_2Cl_2:AcOEt (10:1, v/v). The combined organic fractions were concentrated at reduced pressure and purified by flash chromatography on SiO_2 (150 g) eluted with AcOEt:*n*-pentane (3:7, v/v). Product **15b** (1.05 g; 83%, *Z*:*E* = 93:7) was obtained as a pale yellow oil. GC-MS (EI^+): *m*/*z* (%): 43 (100), 67 (43), 83 (52), 130 (57), 149 (83), 193 (20), 282 (3) $[M]^+$; HRMS (ESI^+-TOF): *m*/*z* = 305.1354 $[M + Na]^+$ (calc. for $C_{15}H_{22}NaO_5$ = 305.1359); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.39 (m; 2H), 4.00 (td; *J* = 6.9, 6.9, 1.3 Hz; 2H), 3.63 (s; 3H), 2.63 (m; 1H), 2.40–2.12 (m; 8H), 2.12–1.9 (m; 1H), 1.98 (s; 3H), 1.86 (dt; *J* = 10.3, 5.4, 5.4 Hz; 1H), 1.45 ppm (m; 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.7, 172.5, 171.1, 128.6, 127.0, 63.7, 53.9, 51.7, 38.7, 38.0, 37.7, 27.2, 26.9, 25.5, 20.9 ppm.

4.3.2 (2R,3R,4S,5R)-2-(acetoxymethyl)-6-(((Z)-5-(2-(2-methoxy-2-oxoethyl)-5-oxocyclopentyl)pent-3-en-1-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (15e)

A two-neck flask fitted with a condenser was charged with **2** (59 mg, 0.26 mmol, 2 equiv.), **14e** (53 mg, 0.13 mmol, α:β = 1:1), THF (1 mL) and catalyst **13** (16.6 mg, 0.03 mmol, 20 mol% relative to **14e**). A gentle stream of argon was passed through the solution, and the mixture was warmed to 45 °C. The reaction was stirred overnight (approximately 18 h) and worked up as described for **15b** [flash chromatography using AcOEt:*n*-hexane (1:1, (v/v)]. Product **15e** (30 mg; 40%, *Z*:*E* = 60:40) was obtained as a viscous

oil. HRMS (ESI$^+$-TOF): $m/z = 593.2181$ $[M + Na]^+$ (calc. for $C_{27}H_{38}NaO_{13} = 593.2205$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.44 (m; 2H), 5.19 (m; 1H), 5.03 (m; 2H),4.50 (d; $J = 2.9$ Hz; 1H), 4.26 (m; 1H), 4.05 (m; 2H), 3.87 (m; 1H), 3.70 (m; 4H), 3.46 (m; 1H), 2.66 (m; 1H), 2.32 (m; 7H), 2.07 (m; 13H), 1.91 (m; 1H), 1.66 ppm (m; 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.9, 172.6, 170.8, 170.4, 169.6, 169.5, 128.4, 127.5, 100.9, 73.0, 71.9, 71.4, 69.6, 68.6, 62.1, 54.1, 51.8, 38.6, 38.1, 37.9, 27.4, 25.7, 25.7, 20.9, 20.8, 20.8, 20.8 ppm (β-anomer).

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