Diastereoselective Conjugate Addition to Chiral α,β-Unsaturated Carbonyl Systems in Aqueous Media: An Enantioselective Entry to α- and γ-Hydroxy Acids and α-Amino Acids

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Abstract: The stereoselectivity of the ultrasonically induced zinc–copper conjugate addition of iodides to chiral α,β-unsaturated carbonyl systems under aqueous conditions was studied. Alkyl iodides add diastereoselectively to methylenedioxolanone **1** and methyleneoxazolidinone **2** to afford the 1,4-addition products in good yields (38–95%) and with high diastereomeric excess (44–90% *de*). The 1,4-addition to chiral γ,δ-dioxolanyl-α,β-unsaturated esters **3**–**5** also proceeds with good yields (51–99%). The diastereoselectivity is dependent on the geometry of the olefin: the *Z* isomer **3** gives high diastereoselectivity, while the reactions with the *E* isomer **4** are nonstereoselective. The reaction proceeds with excellent chemoselectivity and allows the use of iodides bearing ester, hydroxy, and amino groups. Since the 1,4-addition products can be readily hydrolyzed, this methodology constitutes a novel entry for the enantioselective synthesis of α- and γ-hydroxy acids and α-amino acids in aqueous media. The results obtained support the radical mechanism proposed by Luche, and represent one of the few examples of a radical stereoselective conjugate addition in aqueous medium.

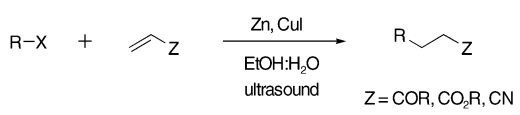
Keywords: aqueous media · asymmetric synthesis · diastereoselectivity · Michael addition · radicals

Introduction

Water is an attractive solvent for chemical reactions owing to its low cost, safety, and environmental compatibility.[1] Moreover, the study of organic reactions in water is important to gain an understanding of the basic mechanisms of life. During the past decade, fundamental organic reactions such as cyclizations, aldol reactions, allylations, oxidations, hydrogenations and others have been performed in aqueous media,[1] but aqueous stereoselective variants are still undeveloped in many cases.[2] Indeed, the majority of stereoselective processes is performed in apolar and aprotic media, which precludes the use of water-soluble compounds and requires the use of protecting groups.

The 1,4-conjugate addition reaction,[3] which is one of the most important transformations in organic chemistry, has been studied under aqueous conditions. The first breakthroughs in this area concerned Michael additions,[4] but more recently this has been extended to other stabilized nucleophiles under different reaction conditions.[5] The use of other nucleophiles such as organometallic species or radicals is of current interest, but very few examples have been reported to date.[6] Furthermore, stereoselective conjugate additions in aqueous media remain practically unknown.[7]

One of the most important methods to perform conjugate additions in aqueous media was discovered by Luche et al. in 1986.[8] Alkyl halides add regioselectively to electron-deficient olefins in the presence of a zinc–copper couple under ultrasonic irradiation (Scheme 1). This aqueous reaction combines several advantages over other methods such as simplicity, mild reaction conditions, and high chemoselectivity. Despite these interesting features, the stereoselectivity of this reaction and its utility in asymmetric synthesis has not been studied in detail.[9]



Scheme 1. Luche's conjugate addition.

The mechanism for the Zn(Cu) conjugate addition has been a subject of study and debate. Although a mechanism involving some type of organometallic species cannot be discarded, the radical pathway shown in Scheme 2 has been proposed.[8c] In the first step, a single-electron transfer (SET) occurs from the metal surface to the carbon–halogen bond, which subsequently breaks to generate an adsorbed radical. In the subsequent steps a radical 1,4-addition to the α,β-unsatu-

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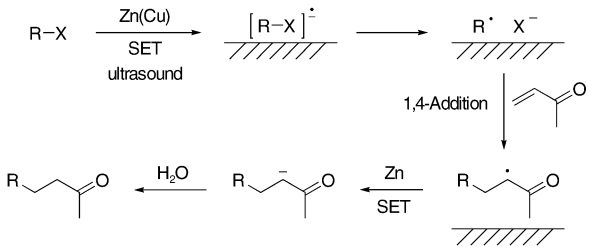


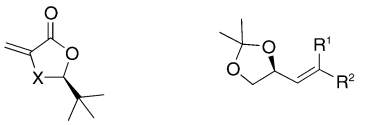
Scheme 2. Mechanism proposed for the zinc–copper conjugate addition.

rated system is followed by additional SET, which gives rise to an enolate that is protonated by the solvent. Evidence for the enolate intermediate was provided by the use of deuterated solvents, but the trapping of radical intermediates was achieved with low yields only.[8c]

Since its discovery, Luche's conjugate addition has been of great utility in organic synthesis.[10] In particular, our group soon found applications for this methodology in the synthesis of vitamin D metabolites and analogues.[11] Later, we applied this methodology for the stereoselective synthesis of 24-hydroxyvitamin D metabolites[12] and 24-aminovitamin D derivatives.[13] In a recent communication,[14] we reported the diastereoselective ultrasonically induced zinc–copper conjugate addition of achiral iodides to chiral α,β-unsaturated systems in aqueous media. Herein, we summarize our studies concerning the diastereoselectivity of this interesting reaction discovered by Luche in the 1980s.

Results and Discussion

Herein we describe the study of the stereoselectivity of the 1,4-conjugate addition reaction between organic halides and chiral Michael acceptors (**1**–**5**). In accordance with the



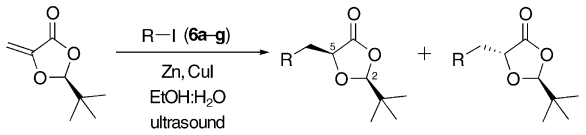
1, X = O
2, X = NBz

3, $R^1 = CO_2Me$, $R^2 = H$
4, $R^1 = H$, $R^2 = CO_2Me$
5, $R^1 = R^2 = CO_2Et$

mechanism proposed by Luche et al.(Scheme 2), stereoselectivity could be achieved either in the nucleophilic addition by using β-substituted Michael acceptors, or in the enolate protonation step, if the α,β-unsaturated carbonyl system was α-substituted. For the study of the protonation step we chose methylenedioxolanone **1** and methyleneoxazolidinone **2**, whereas we chose the γ,δ-dioxolanyl-α,β-unsaturated esters **3**–**5** for the study of the nucleophilic-addition step. The diastereoselective conjugate addition to these chiral α,β-unsaturated systems was explored under different reaction conditions using various types of nucleophiles. The results should serve to establish comparisons and give additional data about the mechanism of Luche's conjugate addition. Furthermore, the 1,4-addition products are valuable intermediates in the synthesis of important organic compounds such as α- and γ-hydroxy acids, α-amino acids, and complex natural products. The stereoselective conjugate addition of radicals in aqueous media is also a relatively unexplored methodology.[15]

Conjugate addition to methylenedioxolanone 1 and methyleneoxazolidinone 2: We started our investigation by studying the reaction of various alkyl iodides (**6a**–**g**, Table 1) with the Seebach dioxolanone **1**, which can be efficiently prepared in enantiomerically pure form from (*S*)-lactic acid.[16] The radical

Table 1. Zinc–copper-conjugate addition of iodides **6a**–**g** to methylenedioxolanone **1**.



1 **7a–g** **8a–g**

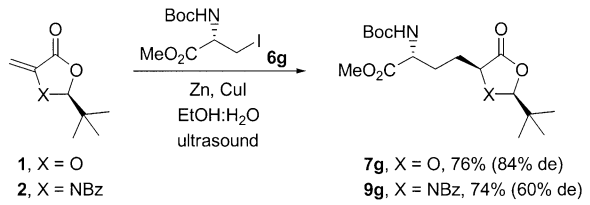
	R–I	Yield [%][a]	*cis*:*trans*[b]
1	$nC_5H_{11}I$ (**6a**)	75	93:7
2	iC_3H_7I (**6b**)	65	95:5
3	$cC_6H_{11}I$ (**6c**)	95	92:8
4	$MeO_2C(CH_2)_3I$ (**6d**)	65	92:8
5	$HO(CH_2)_3I$ (**6e**)	45	92:8
6	$HO(CH_2)_{12}I$ (**6f**)	57	92:8
7	(*S*)-$MeO_2CCH(NHBoc)CH_2I$ (**6g**)	72	92:8

[a] Yield of isolated product. [b] *cis*:*trans* ratio determined by ^1H NMR spectroscopy.

1,4-addition of alkyl iodides to methylenedioxolanone **1**, under classical reaction conditions (nBu_3SnH, azobisisobutyronitrile (AIBN), reflux), proceeds in good yield and with moderate to good diastereoselectivity (60–75% *de*).[17] Following previous experimental procedures,[11] dioxolanone **1** was treated with 1-iodopentane (**6a**, 2 equiv), copper iodide (2 equiv), and zinc (6 equiv) in $EtOH/H_2O$ (7:3). The mixture was sonicated in an ultrasonic cleaning bath at room temperature. After one hour of sonication it was found (TLC) that dioxolanone **1** had been consumed and the 1,4-conjugate addition product was isolated as a *cis*:*trans* mixture of diastereomers in good yield (75%, Table 1, entry 1) and high stereoselectivity (93:7, 86% *de*). Under the same experimental conditions, the reaction of secondary alkyl iodides such as 2-iodopropane (**6b**) and cyclohexyl iodide (**6c**) afforded the conjugate addition products in excellent yield (65–95%) and diastereoselectivity (84–90% *de*) (Table 1, entries 2 and 3). The diastereomeric ratio was determined by integration of the resonances of H2 and H5 in the ^1H NMR spectra of the crude products, and the stereochemistry of the major diastereomer was assigned on the basis of NOE experiments, as described in the literature.[17]

The chemoselectivity of the reaction was investigated by studying the reactions of iodoester **6d** and iodoalcohols **6e**,**f**. In these cases, the conjugate addition products were obtained in reasonable yields (45–65%) and high stereoselectivities (84% *de*) as the only reaction products (Table 1, entries 3–6).

We also explored the reactivity of more complex iodides such as the enantiomerically pure serine derivative **6g**,[18] which bears an α-amino ester functionality and is useful in the synthesis of α-amino acids (Scheme 3).[19] The Zn(Cu)-



Scheme 3. Conjugate addition with serine derivative **6g**.

conjugate addition of iodide **6g** (1.5 equiv) to methylenedioxolanone **1** afforded the protected 5-hydroxyhomoglutamic acid in good yield (72%, Table 1, entry 7 and Scheme 3) as a separable mixture of *cis*:*trans* diastereomers in an 92:8 ratio (**7g**:**8g**, 84% *de*). The diastereomeric excess, which is in the same range as previous examples, indicates that the origin of the stereoselectivity is the chirality of the dioxolanone.

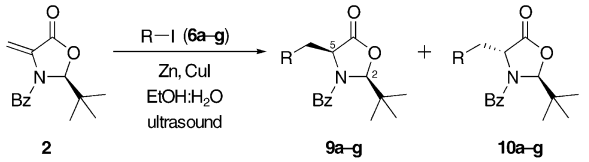
According to the reaction mechanism proposed by Luche et al. (Scheme 2), the stereochemistry of the major diastereomer can be explained by stereoselective protonation of the intermediate enolate generated in aqueous medium, and is *anti* with respect to the *tert*-butyl group. The reaction is probably under thermodynamic control; monitoring of the reaction (^{1}H NMR at different reaction times) shows that the stereoselectivity is constant during the reaction time, that is epimerization of the reaction products under the reaction conditions is improbable. The stereochemical outcome of the Zn(Cu)-conjugate addition is the same as that observed in previous radical 1,4-additions to dioxolanone **1**,[17] and that observed by Seebach et al. in the alkylation of enolates of 2-*tert*-butyl-5-alkyl-1,3-dioxolan-4-ones.[16] In comparison with other methodologies, Luche's conjugate addition, besides its experimental simplicity and the attractive characteristics associated with aqueous media, shows excellent chemoselectivity with iodides bearing functional groups such as hydroxy, amino, or ester groups (Table 1, entries 4–7). Hydrolysis of the resulting addition products should provide the corresponding enantiopure α-hydroxy acids,[20] a fact that highlights this methodology as a formal and practical enantioselective synthesis of α-hydroxy acids in aqueous media.

Encouraged by these results we decided to explore the reactivity of methyleneoxazolidinone **2**, a chiral α,β-unsaturated system that has been previously used in radical conjugate additions for the enantioselective synthesis of α-amino acids.[21] Following the experimental procedure described previously, the reaction of 1-iodopentane and cyclohexyl iodide with oxazolidinone **2** afforded, after 45 min of sonication, the conjugate addition products in good yields (72–94%) as a mixture of *cis*:*trans* diastereomers in 88:12 (76% *de*) and 91:9 (82% *de*) ratios, respectively (Table 2, entries 1 and 2). The addition of iodoester **6d** and iodoalcohols **6e**, **f** proceeded with moderate yields and with good stereoselectivities (Table 2, entries 3–5).

The Zn(Cu)-conjugate addition of serine derivative **6g** with oxazolidinone **2** afforded the conjugate addition product **9g**, a protected derivative of diaminoadipic acid,[22] in 61% yield as a separable mixture of *cis*:*trans* diastereomers in a 80:20 ratio (Table 2, entry 6 and Scheme 3).

The diastereomeric ratio of the conjugate addition products (**9**:**10**) was measured from the crude reaction mixture by integration of the resonances in the region $\delta = 6.00-6.25$ ppm of the ^{1}H NMR spectra; the assignments were made on the basis of *trans* adducts having signals at lower field than their *cis* isomers.[21] As in dioxolanone **1**, the stereochemistry of the major diastereomer was determined to be *cis* as a result of the protonation of the enolate intermediate *anti* to the *tert*-butyl group. The lower diastereoselectivity observed in the conjugate addition to oxazolidinone **2** (compare with dioxolanone **1**) can be attributed to the presence of the nitrogen atom and its protecting group.[21] Interestingly, this stereochemical outcome is opposite to that observed by Beckwith in 1,4-conjugate additions under classical radical conditions (nBu$_3$SnH/AIBN),[21] but it is consistent with results obtained by Seebach in the alkylation of enolates of 2-*tert*-butyl-5-alkyl-1,3-oxazolidin-4-ones.[20] This result can be explained in terms of the mechanism proposed by Luche (Scheme 2): a nucleophilic radical mechanism for the initial step followed by the protonation of an intermediate enolate. As in the case of dioxolanone **1**, hydrolysis of the conjugate addition products should afford the corresponding enantiopure α-amino acids. Therefore, the Zn(Cu) conjugate addition can be a useful methodology for the enantioselective synthesis of α-amino acids in aqueous media.[20]

Table 2. Zinc–copper conjugate addition of iodides **6a–g** to methyleneoxazolidinone **2**.



	R–I	Yield [%][a]	*cis*:*trans*[b]
1	nC$_5$H$_{11}$I (**6a**)	72	88:12
2	cC$_6$H$_{11}$I (**6c**)	94	91:9
3	MeO$_2$C(CH$_2$)$_3$I (**6d**)	56	72:28
4	HO(CH$_2$)$_3$I (**6e**)	38	77:23
5	HO(CH$_2$)$_{12}$I (**6f**)	74	77:23
6	(*S*)-MeO$_2$CCH(NHBoc)CH$_2$I (**6g**)	61	80:20

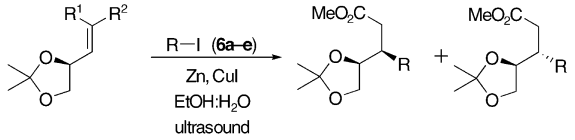
[a] Yield of isolated product. [b] *cis*:*trans* ratio determined by ^{1}H NMR spectroscopy.

Conjugate addition to γ-oxy-α,β-unsaturated ester derivatives 3–5: Having determined the diastereoselectivity in the Zn(Cu)-conjugate addition to **1** and **2** in the protonation step, we proceeded to study the stereoselectivity in the nucleophilic addition step. For this purpose we used acyclic Michael acceptors bearing a chiral center at the γ position, such as γ-oxy-α,β-unsaturated ester derivatives **3–5**, derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde.[23] The reactivity of these substrates in conjugate additions was studied with a variety of nucleophiles. The stereochemical outcome is dependent on the nature of the nucleophile and the geometry of the double bond.[24]

The first series of experiments was performed with methyl (*S*)-(2,2-dimethyl-1,3-dioxolane-4-yl)-*cis*-2-propenoate (**3**). Under the same experimental conditions as for dioxolanone **1**, we observed that the sonochemical conjugate addition of iodides **6a–e** occurs in good yields (51–86%), although

longer reaction times (3 h) and a larger excess of the iodide (up to 6 equiv) were necessary to complete the reactions (Table 3, entries 1–5). This lower reactivity is expected given the substitution of the α,β-unsaturated system at the β-carbon atom, which makes this center less reactive due to steric and electronic effects. Nevertheless, the reactions exhibit high stereoselectivity, affording a *syn*:*anti* diastereomeric mixture in ratios from 86:14 to 96:4 (72–92% *de*).

Table 3. Zinc–copper conjugate addition of iodides **6a–e** to the *cis* (**3**) and *trans* (**4**) methyl (*S*)-(2,2-dimethyl-1,3-dioxolane-4-yl)-2-propenoate.



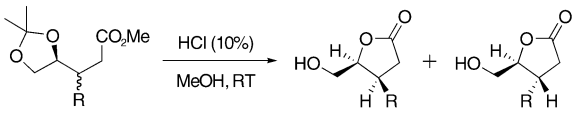
3, $R^1 = CO_2Me$, $R^2 = H$
4, $R^1 = H$, $R^2 = CO_2Me$

11a–e **12a–e**

	R–I	α,β-Unsaturated system	Yield [%][a]	*syn*:*anti*[b]
1	$nC_5H_{11}I$ (**6a**)	**3**	82	93:7
2	iC_3H_7I (**6b**)	**3**	64	88:12
3	$cC_6H_{11}I$ (**6c**)	**3**	86	96:4
4	$MeO_2C(CH_2)_3I$ (**6d**)	**3**	67	86:14
5	$HO(CH_2)_3I$ (**6e**)	**3**	51	87:13
6	$nC_5H_{11}I$ (**6a**)	**4**	47 (18)[c]	52:48
7	iC_3H_7I (**6b**)	**4**	48 (30)[c]	52:48
8	$cC_6H_{11}I$ (**6c**)	**4**	48 (35)[c]	54:46

[a] Yield of isolated product. [b] Diastereomeric ratio estimated by quantitative ^{13}C NMR spectroscopy. [c] Yields of recovered **4** in parentheses.

The diastereomeric excess was measured by integration of the γ-carbon signal ($\delta = 65.0-68.0$ ppm) in quantitative ^{13}C NMR spectra. The stereochemistries of the 1,4-addition products (**11a**,**b**, **12a**, **b**) derived from the addition of 1-iodopentane (**6a**) and isopropyl iodide (**6b**) to **3** were determined by conversion to the known lactones **13a** and **13b** (Scheme 4).[24a–c] The stereochemistries of the other conjugate addition products were determined by chemical correlation.



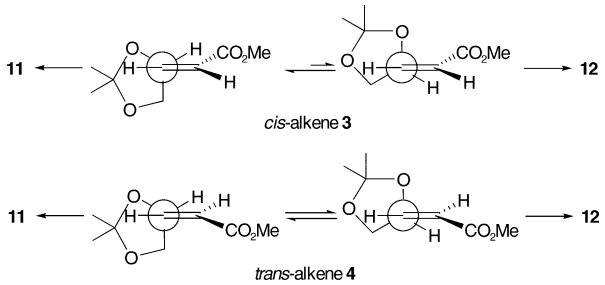
11a:12a, R = nC_5H_{11}
11b:12b, R = *i*Pr

13a, R = nC_5H_{11}
13b, R = *i*Pr

14a, R = nC_5H_{11}
14b, R = *i*Pr

Scheme 4. Lactonization of conjugate addition products obtained from **3**.

The 1,2-stereoinduction obtained, which leads to the *syn* adducts as the major diastereomers, can be explained by assuming that, in the transition state, the alkene adopts a conformation in which the 1,3-allylic strain is minimized (Scheme 5).[25] The role of the geometry of the double bond in the γ-oxy-α,β-unsaturated ester **3** was studied by performing the conjugate addition on the *trans* isomer **4**. Under the same reaction conditions, it was found that the *trans* alkene **4** has a lower reactivity than the *cis* alkene **3**. For example, after 3 h of sonication with six equivalents of alkyl iodide, the reaction was still incomplete (Table 2, entries 6–8). Additionally, we



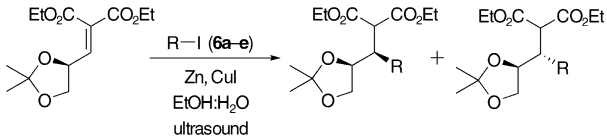
Scheme 5. Most stable conformers for *cis* alkene **3** and *trans* alkene **4**.[24b]

found that the reactions were nonstereoselective, a situation that indicates the importance of the geometry of the alkene in the stereoselectivity. Similar behavior has previously been observed in the 1,4-addition of alkyl radicals to these substrates, and attributed to the fact that the 1,3-allylic strain in the *trans* alkene **4** is very low, thus allowing the rotation of the C3–C4 bond and preventing the facial selection (Scheme 5).

The stereochemical outcome of the zinc–copper 1,4-addition to **3** and **4** is the same as that obtained under the classical radical conditions (nBu_3SnH, AIBN), which proceeded with *syn* 1,2-stereoinduction for the *Z* isomer (**2**) but a lack of stereoselectivity for the *E* isomer (**3**). Interestingly, the results are contrary to those observed in the conjugate addition of organocopper reagents (*anti* stereoselectivity),[24d, 26] a fact that supports the radical mechanism proposed by Luche and co-workers.

In an attempt to increase the reactivity of the α,β-unsaturated systems **3** and **4**, we prepared a more electron-deficient α,β-unsaturated carbonyl system bearing a diester group at the α-position (**5**). The Michael acceptor **5** was prepared by Knoevenagel condensation of (*R*)-2,3-*O*-isopropylideneglyceraldehyde with diethyl malonate.[27] In accordance with our predictions, the reaction of iodides **6a–e** (2 equiv) with **5** proceeded to completion after less than 45 min of sonication (i.e. similar reaction times as **1** and **2**) to afford the conjugate addition products **15/16a–e** in excellent

Table 4. Zinc–copper conjugate addition of iodides **6a–e** to (*S*)- γ,δ-dioxolanyl-α,β-unsaturated ester **5**.



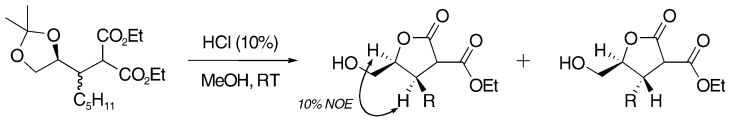
5 **15a–e** **16a–e**

	R–I	Yield [%][a]	*syn*:*anti*[b]
1	$nC_5H_{11}I$ (**6a**)	96	87:13
2	iC_3H_7I (**6b**)	70	88:12
3	$cC_6H_{11}I$ (**6c**)	99	84:16
4	$MeO_2C(CH_2)_3I$ (**6d**)	72	83:17
5	$HO(CH_2)_3I$ (**6e**)	52	83:17

[a] Yield of isolated product. [b] Diastereomeric ratio estimated by quantitative ^{13}C NMR spectroscopy.

yields (up to 99%, Table 4). The stereoselectivity was of the same order as those observed with *cis* alkene **3** (66–74% *de*).

As in the case of **3**, the major diastereomer corresponds to the product of *syn* addition. The stereochemistries of the



15a:**16a** **17a** **18a**

Scheme 6. Lactonization of conjugate addition product **15a**:**16a** derived from diester **5**.

reaction products were determined by chemical correlation or, in the case of **15a/16a**, by transformation into the corresponding lactone, analysis of the coupling constant, and NOE experiments (Scheme 6).

In summary, the ultrasonically induced zinc–copper conjugate addition of alkyl iodides to asymmetric α,β-unsaturated carbonyl systems can be performed in a stereoselective manner on methylenedioxolanone **1**, methyleneoxazolidinone **2**, and γ,δ-dioxolanyl-α,β-unsaturated esters **3** and **5**. The reaction proceeds in good yields (45–99%) and gives high stereoselectivities (44–90% *de*). The results obtained support the mechanism proposed by Luche and co-workers: the nucleophilic addition seems to be performed by a radical species and the final step is the protonation of an enolate. The stereoselectivity is similar to that obtained with other nucleophiles although the experimental simplicity, the aqueous medium and high chemoselectivity should be highlighted. Since the conjugate addition products can be readily hydrolysed, the zinc–copper conjugate addition provides a new entry for the synthesis of α-amino acids, as well as α- and γ-hydroxy acids, in aqueous media.

Experimental Section

General materials and methods: Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Absolute MeOH and EtOH were distilled from Mg turnings. For conjugate addition reactions, Milli-Q water was used and the solvent mixture EtOH:H_2O was deoxygenated by bubbling a positive pressure of argon through for 10 min. Zinc dust (325 mesh) was used without purification and copper iodide was purified by recrystallization from saturated potassium iodide solution.[28] All other reagents were commercial products and used as received. Sonications were carried out in a Selecta SE3000513 (50 kHz, 150 W) cleaning bath, filled with water and thermostated (18–20 °C) by running tap water through a stainless steel coil. Thin-layer chromatography was carried out on Merck silica gel 60 F_{254} (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh) by Still's method.[29] $[\alpha]_D$: Jasco DIP-1000. UV: Kontron Uvikon 941. IR: Matson FTIR. ^{1}H NMR: 200 MHz, Bruker AC-200F. ^{13}C NMR: 50 MHz, Bruker AC-200F (DEPT was used to assign carbon types). MS: Fisons VG-Quattro. HRMS: VG Autospec M.

General experimental procedure for conjugate addition of alkyl iodides (6a–g) to chiral α,β-unsaturated systems 1–5: CuI (2 mmol) and Zn (6 mmol) were added to a solution of the chiral Michael acceptor **1**–**5** (1 mmol) and alkyl iodide (**6a**–**g**, 2–6 mmol) in aqueous EtOH (5 mL, 70%) under ultrasonic irradiation. After few minutes, more aqueous EtOH (5 mL, 70%) was added and sonication was continued for 45–90 min. In the cases where the α,β-unsaturated system was not completely consumed (TLC test), more CuI (1 mmol) and Zn (3 mmol) were added, and the sonication was continued for 3 h. The mixture was diluted with Et_2O (25 mL), sonicated a further 10 min, and filtered through a short pad of Celite. The solids were washed with Et_2O (3 × 30 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4 anhydrous), filtered, and concentrated under reduced pressure (20–30 mm Hg). The residue was purified by flash chromatography to afford, after concentration, the desired 1,4-addition product.

(2*S*,5ξ)-2-(*tert*-Butyl)-5-hexyl-1,3-dioxolan-4-one (7a:8a): Following the general experimental procedure, a mixture containing dioxolanone **1** (65 mg, 0.416 mmol) and 1-iodopentane (163 μL, 1.248 mmol) was treated with CuI (158 mg, 0.832 mmol) and Zn (163 mg, 2.496 mmol) to give, after column chromatography (10% EtOAc/hexanes), **7a**:**8a** (71 mg, 75%, 93:7, 86% *de*) as a yellow oil. R_f = 0.6 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2960–2873, 1802, 1197–1103 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.90 (t, J = 6.8 Hz, 3H), 0.99 (s, 9H), 1.20–1.95 (m, 10H), 4.25 (ddd, J = 6.8, 4.4, 1.0 Hz, 0.93H), 4.35 (ddd, J = 6.8, 4.4, 1.0 Hz, 0.07H), 5.12 (d, J = 1.5 Hz, 0.93H) 5.27 ppm (d, J = 1.5 Hz, 0.07H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 14.0 (CH_3), 22.5 (CH_2), 23.4 (3 × CH_3), 24.9 (CH_2), 28.8 (CH_2), 30.6 (CH_2), 31.5 (CH_2), 34.2 (C), 75.1 (CH), 109.3 (CH), 173.7 ppm (C); MS (FAB): *m*/*z* (%): 229 (13) [M^++H], 228 (48) [M^+], 149 (100); HRMS (FAB): *m*/*z*: calcd for $C_{13}H_{25}O_3$: 229.1804 [M^++H]; found: 229.1797.

(2S,5ξ)-2-(*tert*-Butyl)-5-(2-methylpropyl)-1,3-dioxolan-4-one (7b:8b):[16a] Following the general experimental procedure, a mixture containing dioxolanone **1** (100 mg, 0.64 mmol) and 2-iodopropane (192 μL, 1.92 mmol) was treated with CuI (244 mg, 1.28 mmol) and Zn (251 mg, 3.84 mmol) to give, after column chromatography (10% EtOAc/hexanes), **7b**:**8b** (79 mg, 65%, 95:5, 90% *de*) as a yellow oil. R_f = 0.5 (20% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2962–2875, 1797, 1197–1104 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.98 (s, 9H), 1.00 (s, 6H), 1.55–2.00 (m, 2H), 4.28 (ddd, J = 10.3, 9.3, 4.9 Hz, 1H), 5.14 (d, J = 1.0 Hz, 0.95H), 5.26 ppm (d, J = 1.0 Hz, 0.05H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 21.9 (CH_3), 22.8 (CH_3), 23.4 (3 × CH_3), 25.1 (CH), 34.2 (C), 39.7 (CH_2), 73.7 (CH), 109.4 (CH), 174.1 ppm (C); MS (FAB): *m*/*z* (%): 201 (14) [M^++H], 200 (78) [M^+], 171 (36), 133 (100); HRMS (FAB): *m*/*z*: calcd for $C_{11}H_{21}O_3$: 201.1491 [M^++H]; found: 201.1481.

(2*S*,5ξ)-2-(*tert*-Butyl)-5-cyclohexylmethyl-1,3-dioxolan-4-one (7c:8c):[17] Following the general experimental procedure, a mixture containing dioxolanone **1** (100 mg, 0.64 mmol) and cyclohexyl iodide (248 μL, 1.92 mmol) was treated with CuI (244 mg, 1.28 mmol) and Zn (251 mg, 3.84 mmol) to give, after column chromatography (10% EtOAc/hexanes), **7c**:**8c** (146 mg, 95%, 92:8, 84% *de*) as a yellow oil. R_f = 0.6 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2925–2853, 1799, 1216–1194 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.97 (s, 9H), 1.15–1.85 (m, 13H), 4.31 (ddd, J = 7.8, 3.9, 1.0 Hz, 0.92H), 4.42 (ddd, J = 7.8, 3.9, 1.0 Hz, 0.08H), 5.12 (d, J = 1.0 Hz, 0.92H), 5.25 ppm (d, J = 1.0 Hz, 0.08H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 23.4 (3), 26.0, 26.1, 26.3, 32.6, 33.5, 34.3, 38.3, 73.4, 109.3, 174.1 ppm; MS (70 eV, EI): *m*/*z* (%): 241 (10) [M^++H], 240 (61) [M^+], 225 (8) [$M^+ - CH_3$], 149 (100); HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{25}O_3$: 241.1804 [M^++H]; found: 241.1792.

Methyl 5-[(2*S*,4ξ)-2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-yl]pentanoate (7d:8d): Following the general experimental procedure, a mixture containing dioxolanone **1** (100 mg, 0.64 mmol) and methyl 4-iodobutyrate (259 μL, 1.92 mmol) was treated with CuI (244 mg, 1.28 mmol) and Zn (251 mg, 3.84 mmol) to give, after column chromatography (10% EtOAc/hexanes), **7d**:**8d** (107 mg, 65%, 92:8, 84% *de*) as a yellow oil. R_f = 0.4 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2961–2874, 1799, 1739, 1197–1116 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.98 (s, 9H), 1.50–2.05 (m, 6H), 2.35 (dd, J = 14.6, 7.3 Hz, 2H), 4.25 (dd, J = 5.9, 4.4 Hz, 0.92H), 4.36 (dd, J = 5.9, 4.4 Hz, 0.08H), 5.12 (d, J = 1.0 Hz, 0.92H), 5.27 ppm (d, J = 1.0 Hz, 0.08H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ =

23.4 (3 × CH_3), 24.4 (CH_2), 28.7 (CH_2), 30.2 (CH_2), 33.7 (CH_2), 51.5 (CH_3), 74.8 (CH), 109.3 (CH), 173.4 (C), 173.8 ppm (C); MS (70 eV, EI): *m*/*z* (%): 258 (10) [M^+], 111 (100); HRMS (FAB): *m*/*z*: calcd for $C_{13}H_{23}O_5$: 259.1545 [M^++H]; found: 259.1545.

(2*S*,5*ξ*)-2-(*tert*-Butyl)-5-(4-hydroxybutyl)-1,3-dioxolan-4-one (7e:8e): Following the general experimental procedure, a mixture containing dioxolanone **1** (150 mg, 0.96 mmol) and 3-iodo-1-propanol (275 μL, 2.88 mmol) was treated with CuI (365 mg, 1.92 mmol) and Zn (377 mg, 5.76 mmol) to give, after column chromatography (20% EtOAc/hexanes), **7e**:**8e** (94 mg, 45%, 92:8, 84% *de*) as a yellow oil. R_f = 0.2 (40% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3391, 2962–2874, 1796, 1201–1115 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.99 (s, 9H), 1.55–1.96 (m, 6H), 3.60–3.71 (m, 2H), 4.27 (ddd, *J* = 6.8, 4.4, 1.0 Hz, 0.92H), 4.38 (ddd, *J* = 6.8, 4.4, 1.0 Hz, 0.08H), 5.15 (d, *J* = 1.5 Hz, 0.92H), 5.28 ppm (d, *J* = 1.5 Hz, 0.08H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 21.3 (CH_2), 23.4 (3 × CH_3), 30.3 (CH_2), 34.2 (C), 62.4 (CH_2), 75.0 (CH), 109.3 (CH), 173.5 ppm (C); MS (FAB): *m*/*z* (%): 217 (54) [M^++H], 147 (100); HRMS (FAB): *m*/*z*: calcd for $C_{11}H_{21}O_4$: 217.1440 [M^++H]; found: 217.1447.

(2*S*,5*ξ*)-2-(*tert*-Butyl)-5-(13-hydroxytridecyl)-1,3-dioxolan-4-one (7f:8f): Following the general experimental procedure, a mixture containing dioxolanone **1** (100 mg, 0.64 mmol) and 12-iodo-1-dodecanol (600 mg, 1.92 mmol) was treated with CuI (244 mg, 1.28 mmol) and Zn (251 mg, 3.84 mmol) to give, after column chromatography (20% EtOAc/hexanes), **7f**:**8f** (170 mg, 57%, 92:8, 84% *de*) as a yellow oil. R_f = 0.5 (50% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3363, 2925–2854, 1800, 1197 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.98 (s, 9H), 0.87–0.95 (m, 2H), 1.18–1.90 (m, 20H), 3.48 (q, *J* = 6.8 Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 4.25 (ddd, *J* = 11.7, 4.4, 1.5 Hz, 0.92H), 4.28 (ddd, *J* = 11.7, 4.4, 1.5 Hz, 0.08H), 5.12 (d, *J* = 1.5 Hz, 0.92H), 5.25 ppm (d, *J* = 1.5 Hz, 0.08H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 23.2 (CH_2), 23.4 (3 × CH_3), 24.9 (CH_2), 25.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 30.6 (CH_2), 32.8 (CH_2), 34.2 (C), 63.0 (CH_2), 75.1 (CH), 109.3 (CH), 173.7 ppm (C); MS (FAB): *m*/*z* (%): 343 (64) [M^++H], 154 (100); HRMS (FAB): *m*/*z*: calcd for $C_{20}H_{39}O_4$: 343.2848 [M^++H]; found: 343.2836.

Methyl (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-4-[(2*S*,4*S*)-2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-yl]butanoate (7g): Following the general experimental procedure, dioxolanone **1** (60 mg, 0.384 mmol) and **6g** (242 mg, 0.768 mmol) was treated with CuI (219 mg, 1.152 mmol) and Zn (176 mg, 2.688 mmol) to give, after column chromatography (20% EtOAc/hexanes), **7g** and **8g** (91 mg and 8 mg, respectively, 72%, 92:8, 84% *de*) as colorless oils. R_f = 0.30 (**7g**) and 0.35 (**8g**) (30% EtOAc/hexanes); **7g**: IR (neat): $\tilde{\nu}$ = 2974–2876, 1797, 1745, 1714, 1199–1171 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.98 (s, 9H), 1.45 (s, 9H), 1.77–2.01 (m, 4H), 3.76 (s, 3H), 4.25 (m, 1H), 4.35 (m, 1H), 5.14 ppm (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 23.4 (3 × CH_3), 26.7 (CH_2), 28.2 (CH_2), 28.2 (3 × CH_3), 34.2 (C), 52.4 (CH_3), 74.5 (CH), 109.4 (2 × CH), 172.8 ppm (C); MS (CI): *m*/*z* (%): 360 (16) [M^++H], 260 (100); HRMS (CI): *m*/*z*: calcd for $C_{17}H_{29}NO_7$: 360.2022 [M^++H]; found: 360.2025.

(2*S*,4*ξ*)-3-Benzoyl-2-(*tert*-butyl)-4-hexyl-5-oxazolidinone (9a:10a): Following the general experimental procedure, a mixture containing oxazolidinone **2** (77 mg, 0.297 mmol) and 1-iodopentane (80 μL, 0.617 mmol) was treated with CuI (117 mg, 0.617 mmol) and Zn (121 mg, 1.848 mmol) to give, after column chromatography (12% EtOAc/hexanes), **9a**:**10a** (71 mg, 72%, 88:12, 76% *de*) as a yellow solid. R_f = 0.5 (30% EtOAc/hexanes); m.p. 26–28 °C; IR (neat): $\tilde{\nu}$ = 3043–2865, 1712, 1670, 1474–1458, 1257, 1213 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.84 (t, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 0.94–2.04 (m, 10H), 3.88 (dd, *J* = 10.2, 3.4 Hz, 1H), 6.06 (s, 0.88H), 6.19 ppm (s, 0.12H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 13.9 (CH_3), 22.4 (CH_2), 25.2 (3 × CH_3), 26.4 (CH_2), 28.4 (CH_2), 31.2 (CH_2), 35.4 (CH_2), 36.9 (C), 57.8 (CH), 95.4 (CH), 126.5 (2 × CH), 128.7 (2 × CH), 130.5 (CH), 135.7 (C), 172.4 (C), 173.8 ppm (C); MS (70 eV, EI): *m*/*z* (%): 332 (2) [M^++H], 316 (20) [$M^+ - CH_3$], 274 (100); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{29}NO_3$: 331.2147 [M^+]; found: 331.2150.

(2*S*,4*ξ*)-3-Benzoyl-2-(*tert*-butyl)-4-cyclohexylmethyl-5-oxazolidinone (9c:10c):[17] Following the general experimental procedure, a mixture containing **2** (80 mg, 0.308 mmol) and cyclohexyl iodide (80 μL, 0.617 mmol) was treated with CuI (117 mg, 0.617 mmol) and Zn (121 mg, 1.848 mmol) to give, after column chromatography (10% EtOAc/hexanes), **9c**:**10c** (100 mg, 94%, 91:9, 82% *de*) as a yellow solid. R_f = 0.55 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2952–2879, 1877, 1712, 1480–1460, 1254, 1212 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.05 (s, 9H), 0.83–1.91 (m, 12H), 4.03 (dd, *J* = 10.7, 2.9 Hz, 0.91H), 4.4 (dd, *J* = 7.8, 2.4 Hz, 0.09H), 6.08 (s, 0.91H), 6.20 (s, 0.09H), 7.37–7.61 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.2 (3 × CH_3), 25.8 (CH_2), 25.9 (CH_2), 26.2 (CH_2), 31.4 (CH_2), 33.8 (CH_2), 34.3 (CH), 36.9 (C), 42.6 (CH_2), 55.7 (CH), 95.1 (CH), 126.5 (2 × CH), 128.8 (2 × CH), 130.4 (CH), 135.8 (C), 172.4 (C), 173.8 ppm (C); MS (70 eV, EI): *m*/*z* (%): 343 (2) [M^+], 328 (2) [$M^+ - CH_3$], 286 (78) [$M^+ - C_4H_9$], 105 (100); HRMS (EI): *m*/*z*: calcd for $C_{21}H_{29}NO_3$: 343.2147 [M^+]; found: 343.2147.

Methyl 5-[(2*S*,4*ξ*)-3-benzoyl-2-(*tert*-butyl)-5-oxo-4-oxazolidinyl]pentanoate (9d:10d): Following the general experimental procedure, a mixture containing **2** (80 mg, 0.308 mmol) and methyl 4-iodobutyrate (80 μL, 0.617 mmol) was treated with CuI (117 mg, 0.617 mmol) and Zn (121 mg, 1.848 mmol) to give, after column chromatography (15% EtOAc/hexanes), **9d**:**10d** (56 mg, 56%, 72:28, 44% *de*) as a yellow oil. R_f = 0.25 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3017–2890, 1760, 1720, 1670, 1474–1456, 1215, 1183, 1162 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.03 (s, 9H), 1.22–1.98 (m, 6H), 2.16 (dd, *J* = 15.6, 8.3 Hz, 2H), 3.64 (s, 3H), 3.9 (dd, *J* = 10.3, 2.9 Hz, 0.72H), 4.42 (m, 0.28H), 6.06 (s, 0.72H), 6.18 (s, 0.28H), 7.37–7.65 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 24.0 (CH_2), 25.1 (3 × CH_3), 25.9 (CH_2), 33.5 (CH_2), 34.9 (CH_2), 33.5 (CH_2), 34.9 (CH_2), 36.9 (C), 51.5 (CH_3), 57.6 (CH), 95.4 (CH), 126.5 (2 × CH), 128.8 (2 × CH), 130.6 (CH), 135.6 (C), 172.2 (C), 173.4 (C), 173.5 ppm (C); MS (70 eV, EI): *m*/*z* (%): 362 (7) [M^++H], 361 (10) [M^+], 346 (14) [$M^+ - CH_3$), 330 (5) [$M^+ - CH_3O$], 304 (17) [$M^+ - C_4H_9$], 105 (100); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{27}NO_5$: 361.1889 [M^+]; found: 361.1892; elemental analysis calcd (%) for $C_{20}H_{27}NO_5$ (361.4): C 66.46, H 7.53, N 3.88; found: C 66.17, H 7.52, N 3.71.

(2*S*,4*ξ*)-3-Benzoyl-2-(*tert*-butyl)-4-(4-hydroxybutyl)-5-oxazolidinone (9e:10e): Following the general experimental procedure, a mixture containing **2** (60 mg, 0.231 mmol) and 3-iodo-1-propanol (44 μL, 0.46 mmol) was treated with CuI (88 mg, 0.46 mmol) and Zn (91 mg, 1.39 mmol) to give, after column chromatography (40% EtOAc/hexanes), **9e**:**10e** (28 mg, 38%, 77:23, 54% *de*) as a yellow oil. R_f = 0.2 (50% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3647, 2980–2947, 1843, 1714, 1472–1456, 1253, 1213 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.03 (s, 9H), 1.43–2.02 (m, 6H), 3.50 (t, *J* = 5.8 Hz, 2H), 3.91 (dd, *J* = 10.3, 2.9 Hz, 0.77H), 4.44 (m, 0.23H), 6.07 (s, 0.77H), 6.19 (s, 0.23H), 7.38–7.65 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.8 (CH_2), 25.1 (3 × CH_3), 31.6 (CH_2), 35.0 (CH_2), 36.9 (C), 57.7 (CH), 62.2 (CH_2), 95.4 (CH), 126.5 (2 × CH), 128.8 (2 × CH), 130.6 (CH), 135.6 (C), 172.4 (C), 173.7 ppm (C); MS (70 eV, EI): *m*/*z* (%): 320 (9) [M^++H], 319 (11) [M^+], 304 (16) [$M^+ - CH_3$], 262 (7) [$M^+ - C_4H_9$), 105 (100); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{25}NO_4$: 319.1784 [M^+]; found: 319.1795.

(2*S*,4*ξ*)-3-Benzoyl-2-(*tert*-butyl)-4-(13-hydroxytridecyl)-5-oxazolidinone (9f:10f): Following the general experimental procedure, a mixture containing **2** (80 mg, 0.308 mmol) and 12-iodo-1-dodecanol (193 mg, 0.617 mmol) was treated with CuI (117 mg, 0.617 mmol) and Zn (121 mg, 1.848 mmol) to give, after column chromatography (20% EtOAc/hexanes), **9f**:**10f** (96 mg, 74%, 77:23, 54% *de*) as a yellow oil. R_f = 0.15 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3676, 2880–2850, 1780, 1675, 1485–1450, 1245, 1212 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.05 (s, 9H), 1.10–2.00 (m, 24H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.88 (dd, *J* = 9.8, 2.9 Hz, 0.77H), 4.43 (m, 0.23H), 6.07 (s, 0.77H), 6.20 (s, 0.23H), 7.40–7.64 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 24.7, 25.2, 25.7, 26.4, 28.7, 29.1, 29.3, 29.4, 29.4, 29.5, 29.6, 32.8, 35.4, 36.8, 39.8, 57.8, 63.0, 95.3, 126.5, 128.7, 129.0, 130.5, 135.7, 172.4, 173.8 ppm; MS (70 eV, EI): *m*/*z* (%): 446 (15) [M^++H], 431 (8) [$M^+ - CH_3$], 388 (12) [$M^+ - C_4H_9$], 105 (100); HRMS (EI): *m*/*z*: calcd for $C_{27}H_{43}NO_4$: 445.3192 [M^+]; found: 445.3193.

Methyl (2*R*)-4-[(2*S*,4*S*)-3-benzoyl-2-(*tert*-butyl)-5-oxo-4-oxazolidinyl]-2-[(*tert*-butoxycarbonyl)amino]butanoate (9g): Following the general experimental procedure, a mixture containing oxazolidinone **2** (95 mg, 0.374 mmol) and **6g** (200 mg, 0.634 mmol) was treated with CuI (142 mg, 0.748 mmol) and Zn (147 mg, 2.244 mmol) to give, after column chromatography (25% EtOAc/hexanes), **9g** and **10g** (85 mg and 21 mg, respectively, 61%, 80:20, 60% *de*) as pale yellow oils. **9g**: R_f = 0.2 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3060–2875, 1789, 1743, 1712, 1667, 1512–1449, 1244, 1199 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.03 (s, 9H), 1.45 (s, 9H), 1.88–2.14 (m, 4H), 3.71 (s, 3H), 4.45 (m, 1H), 5.02 (m, 1H), 6.07 (s, 1H), 7.37–7.66 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.1 (3 × CH_3), 28.3 (3 × CH_3), 30.1 (CH_2), 31.5 (CH_2), 36.8 (C), 36.9 (C), 52.4

(CH_3), 57.5 (CH), 57.6 (CH), 95.6 (CH), 126.5 (2 × CH), 128.9 (2 × CH), 130.7 (CH), 135.3 (C), 171.9 (C), 172.0 (C), 173.6 (C), 173.7 ppm (C); MS (CI): *m/z* (%): 463 (7) [M^++H], 106 (100); HRMS (CI): *m/z*: calcd for $C_{24}H_{35}N_2O_7$: 463.2444 [M^++H]; found: 463.2431.

Methyl (3ξ)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]octanoate (11a:12a): Following the general experimental procedure, a mixture containing **3** (150 μL, 0.805 mmol) and 1-iodopentane (630 μL, 4.833 mmol) was treated with CuI (460 mg, 2.416 mmol) and Zn (464 mg, 7.249 mmol) to give, after column chromatography (10% EtOAc/hexanes), **11a**:**12a** (170 mg, 82%, 93:7, 86% *de*) as a yellow oil. R_f = 0.6 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2985–2861, 1740, 1370–1065 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.27 (m, 8H), 1.32 (s, 3H), 1.38 (s, 3H), 2.23 (m, 2H), 2.45 (m, 1H), 3.63 (br t, *J* = 7.8 Hz, 1H), 3.66 (s, 3H), 3.95 (dd, *J* = 8.3, 6.3 Hz, 1H), 4.12 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 14.0, 22.5, 25.2, 26.3, 26.5, 30.6, 31.9, 34.6, 37.5, 51.5, 66.3:68.0 (93:7), 77.6, 108.7, 173.5 ppm; MS (FAB): *m/z* (%): 259 (17) [M^++H], 243 (70) [M^+ – CH_3], 201 (100); HRMS (FAB): *m/z*: calcd for $C_{14}H_{27}O_4$: 259.1909 [M^++H]; found: 259.1905.

Following the general experimental procedure, a mixture containing **4** (139 μL, 0.805 mmol) and 1-iodopentane (630 μL, 4.833 mmol) was treated with CuI (460 mg, 2.416 mmol) and Zn (474 mg, 7.249 mmol) to give, after column chromatography (15% EtOAc/hexanes), **11a**:**12a** (98 mg, 47%, 52:48, 4% *de*) as a yellow oil and **4** (28 mg, 18%).

Methyl (3ξ)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylpentanoate (11b:12b): Following the general experimental procedure, a mixture containing **3** (141 μL, 0.805 mmol) and 2-iodopropane (483 μL, 4.833 mmol) was treated with CuI (460 mg, 2.416 mmol) and Zn (474 mg, 7.249 mmol) to give, after column chromatography (20% EtOAc/hexanes), **11b**:**12b** (118 mg, 64%, 88:12, 76% *de*) as a yellow oil. R_f = 0.6 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2960–2877, 1739, 1437–1064 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.88 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H), 1.31 (s, 3H), 1.36 (s, 3H), 1.81–1.90 (m, 1H), 2.13–2.28 (m, 3H), 3.53 (dd, *J* = 8.3, 7.8 Hz, 1H), 3.64 (s, 3H), 3.91 (dd, *J* = 7.8, 5.9 Hz, 1H), 4.08–4.12 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 18.7, 20.3, 25.3, 26.4, 28.4, 31.4, 43.2, 51.5, 66.8:68.6 (88:12), 76.6, 108.2, 174.3 ppm; MS (70 eV, EI): *m/z* (%): 215 (11) [M^+ – CH_3], 69 (100); HRMS (FAB): *m/z*: calcd for $C_{12}H_{23}O_4$: 231.1596 [M^+ – H]; found: 231.1606.

Following the general experimental procedure, a mixture containing **4** (185 μL, 1.074 mmol) and 2-iodopropane (644 μL, 6.44 mmol) was treated with CuI (613 mg, 3.22 mmol) and Zn (843 mg, 9.67 mmol) to give, after column chromatography (20% EtOAc/hexanes), **11b**:**12b** (119 mg, 48%, 52:48, 4% *de*) as a yellow oil, and **4** (65 mg, 30%).

Methyl (3ξ)-3-cyclohexyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propionate (11c:12c):[24c] Following the general experimental procedure, a mixture containing **3** (141 μL, 0.80 mmol) and cyclohexyl iodide (625 μL, 4.83 mmol) was treated with CuI (460 mg, 2.42 mmol) and Zn (474 mg, 7.25 mmol) to give, after column chromatography (10% EtOAc/hexanes), **11c**:**12c** (188 mg, 86%, 96:4, 92% *de*) as a yellow oil. R_f = 0.5 (30% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2986–2854, 1738, 1370–1066 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.28 (s, 3H), 1.34 (s, 3H), 0.84–1.77 (m, 12H), 2.20 (m, 2H), 3.50 (dd, *J* = 8.3, 7.8 Hz, 1H), 3.62 (s, 3H), 3.89 (dd, *J* = 7.8, 6.3 Hz, 1H), 4.15 ppm (dq, *J* = 12.2, 6.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.2, 26.4, 29.5, 30.8, 31.9, 32.8, 39.1, 40.3, 42.8, 43.9, 66.6:68.6 (96:4), 76.6, 108.6, 174.4 ppm; MS (FAB): *m/z* (%): 271 (14) [M^++H], 255 (72) [M^+ – CH_3], 213 (100); HRMS (FAB): *m/z*: calcd for $C_{15}H_{27}O_4$: 271.1909 [M^++H]; found: 271.1900; elemental analysis calcd (%) for $C_{15}H_{26}O_4$ (270.4): C 66.64, H 9.68; found: C 66.31, H 9.73.

Following the general experimental procedure, a mixture containing **4** (139 μL, 0.80 mmol) and cyclohexyl iodide (625 μL, 4.83 mmol) was treated with CuI (460 mg, 2.42 mmol) and Zn (474 mg, 7.25 mmol) to give, after column chromatography (10% EtOAc/hexanes), **11c**:**12c** (104 mg, 48%, 54:46, 8% *de*) as a yellow oil and **4** (52 mg, 35%).

Dimethyl (3ξ)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]heptanedioate (11d:12d): Following the general experimental procedure, a mixture containing **3** (141 μL, 0.805 mmol) and methyl 4-iodobutyrate (650 μL, 4.833 mmol) was treated with CuI (460 mg, 2.416 mmol) and Zn (474 mg, 7.249 mmol) to give, after column chromatography (15% EtOAc/hexanes), **11d**:**12d** (155 mg, 67%, 86:14, 72% *de*) as a yellow oil. R_f = 0.4 (40% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2987–2952, 1738, 1371–1064 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.33 (s, 3H), 1.39 (s, 3H), 1.23–1.77 (m, 4H), 2.15–2.45 (m, 5H), 3.58 (dd, *J* = 7.8, 7.3 Hz, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 3.95 (dd, *J* = 7.8, 6.3 Hz, 1H), 4.09 ppm (dq, *J* = 7.3, 2.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.2, 25.2, 26.3, 28.7, 30.1, 34.0, 34.6, 37.5, 51.6, 66.5:67.7 (86:14), 77.4, 108.8, 173.1, 173.7 ppm; MS (FAB): *m/z* (%): 289 (38) [M^++H], 273 (41) [M^+ – CH_3], 231 (100); HRMS (FAB): *m/z*: calcd for $C_{14}H_{25}O_6$: 289.1651 [M^++H]; found: 289.1643.

Methyl (3ξ)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-hydroxyhexanoate (11e:12e): Following the general experimental procedure, a mixture containing **3** (141 μL, 0.80 mmol) and 3-iodo-1-propanol (465 μL, 4.83 mmol) was treated with CuI (460 mg, 2.42 mmol) and Zn (474 mg, 7.25 mmol) to give, after column chromatography (75% EtOAc/hexanes), **11e**:**12e** (82 mg, 51%, 87:13, 74% *de*) as a yellow oil. R_f = 0.1 (50% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2986–2876, 1731, 1372–1061 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.34 (s, 3H), 1.40 (s, 3H), 1.17–1.89 (m, 7H), 2.18–2.48 (m, 3H), 3.37–3.65 (m, 1H), 3.68 (s, 3H), 3.95–4.15 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.2 (CH_2), 26.4 (CH_2), 27.2 (CH_3), 29.6 (CH_3), 35.2 (CH), 38.3 (CH_2), 51.6 (CH_2), 62.5 (CH), 66.6 (0.87 × CH), 67.8 (0.13 × CH), 77.0 (CH_2), 108.8 (C), 173.7 ppm (C); MS (70 eV, EI): *m/z* (%): 247 (1) [M^++1], 231 (9) [M^+ – CH_3], 101 (100); HRMS (FAB): *m/z*: calcd for $C_{12}H_{23}O_5$: 247.1545 [M^++H]; found: 247.1542.

(4ξ,5*S*)-4,5-Dihydroxy-5-pentylpentanoic acid γ-lactone (13a:14a): HCl (10%, 200 μL) was added to a solution of **11a**:**12a** (40 mg, 0.15 mmol, 93:7) in MeOH (1 mL). The reaction mixture was stirred for 1 h, concentrated and purified by column chromatography (silica gel, 50% EtOAc/hexanes) stopped with a short pad of $NaHCO_3$ and Na_2SO_4, to give **13a**:**14a** (24 mg, 86%, 93:7) as a colorless oil. **13a**: R_f = 0.3 (50% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 3470, 2931–2860, 1778, 1467–1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, *J* = 6.8 Hz, 3H), 1.17–1.57 (m, 6H), 1.82 (br s, 1H), 2.15–2.85 (m, 4H), 3.48 (dd, *J* = 7.3, 6.8 Hz, 1H), 3.76–3.93 (m, 2H), 4.55 ppm (dd, *J* = 7.3, 3.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 13.9, 22.4, 27.9, 28.8, 31.7, 34.6, 38.0, 61.7, 82.7, 177.5 ppm; MS (70 eV, EI): *m/z* (%): 187 (11) [M^++1], 95 (100).

(4ξ,5*S*)-4,5-Dihydroxy-5-(1-methylethyl)pentanoic acid γ-lactone (13b:14b):[24b] HCl (10%, 310 μL) was added to a solution of **11b**:**12b** (53 mg, 0.23 mmol, 88:12) in MeOH (1 mL). The reaction mixture was stirred for 1 h, concentrated, and purified by column chromatography (silica gel, 50% EtOAc/hexanes) stopped with a short pad of $NaHCO_3$ and Na_2SO_4, to give **13b**:**14b** (27 mg, 75%, 88:12) as a yellow oil. **13b**: R_f = 0.2 (50% EtOAc/hexanes); ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.98 (m, 6H), 1.73–1.90 (m, 4H), 2.28–2.67 (m, 3H), 4.59 ppm (dt, *J* = 7.3, 4.4 Hz, 1H); MS (70 eV, EI): *m/z* (%): 159 (8) [M^++1], 158 (2) [M$^+$], 145 (9) [M^+ – CH_3], 127 (100).

Diethyl 2-{(1ξ)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]hexyl}malonate (15a:16a): Following the general experimental procedure, a mixture containing **5** (100 mg, 0.367 mmol) and 1-iodopentane (140 μL, 1.101 mmol) was treated with CuI (140 mg, 0.734 mmol) and Zn (144 mg, 2.202 mmol) to give, after column chromatography (75% EtOAc/hexanes), **15a**:**16a** (121 mg, 96%, 87:13, 74% *de*) as a yellow oil. R_f = 0.5 (50% Et_2O/hexanes); IR (neat): $\tilde{\nu}$ = 2984–2934, 1733, 1370–1157 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.27 (s, 6H), 1.28 (t, *J* = 7.3 Hz, 6H), 1.22–1.46 (m, 8H), 2.48 (m, 1H), 3.49 (d, *J* = 6.3 Hz, 1H), 3.65 (t, *J* = 7.8 Hz, 1H), 3.99 (dd, *J* = 7.8, 6.3 Hz, 2H), 4.21 ppm (q, *J* = 1.5 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 14.0 (CH_3), 22.4 (CH_2), 25.2 (CH_3), 26.2 (CH_3), 27.5 (CH_2), 28.1 (CH_2), 31.9 (CH_2), 40.2 (CH_3), 42.3 (CH_3), 52.7 (CH), 61.3 (CH_2), 66.8 (0.87 × CH_2), 68.3 (0.13 × CH_2), 76.4 (CH), 108.8 (C), 168.8 (C), 168.9 ppm (C); MS (FAB): *m/z* (%): 345 (11) [M^++H], 329 (92) [M^+ – CH_3], 287 (100); HRMS (FAB): *m/z*: calcd for $C_{18}H_{33}O_6$: 345.2277 [M^++H]; found: 345.2265.

Diethyl 2-{(1ξ)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl}-2-methylpropyl]-malonate (15b:16b): Following the general experimental procedure, a mixture containing **5** (199 mg, 0.731 mmol) and 2-iodopropane (145 μL, 1.47 mmol) was treated with CuI (420 mg, 2.203 mmol) and Zn (336 mg, 5.14 mmol) to give, after column chromatography (10% EtOAc/hexanes), **15b**:**16b** (162 mg, 70%, 88:12, 76% *de*) as a yellow oil. R_f = 0.4 (20% EtOAc/hexanes); IR (neat): $\tilde{\nu}$ = 2983, 1732, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.97 (t, *J* = 7.3 Hz, 6H), 1.26 (d, *J* = 7.3 Hz, 3H), 1.29 (d, *J* = 7.3 Hz, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 2.09–2.21 (m, 1H), 2.44–2.52 (m, 1H), 3.54 (d, *J* = 4.9 Hz, 1H), 3.63 (t, *J* = 7.8 Hz, 1H), 4.01 (dd, *J* = 7.8, 5.8 Hz, 1H), 4.19 (m, 4H), 4.32 ppm (m, 1H); ^{13}C NMR

(50 MHz, $CDCl_3$, 25 °C): $\delta = 14.0$ (CH_3), 20.4 (CH_3), 20.8 (CH_3), 26.1 (CH_3), 27.6 (CH_3), 28.2 (CH_3), 41.6 (CH_2), 46.3 (CH), 50.5 (CH), 61.3 (CH_2), 67.4 ($0.88 \times CH_2$), 69.5 ($0.12 \times CH_2$), 75.2 (CH), 108.0 (C), 169.0 (C), 169.4 ppm (C); MS (FAB): *m*/*z* (%): 317 (10) [M^++H], 301 (51) [$M^+ - CH_3$], 259 (100); HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{29}O_6$: 317.1964 [M^++H]; found: 317.1963.

Diethyl 2-{(1ξ)-1-cyclohexyl-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}malonate (15c:16c): Following the general experimental procedure, a mixture containing **5** (75 mg, 0.275 mmol) and cyclohexyl iodide (110 μL, 0.825 mmol) was treated with CuI (108 mg, 0.55 mmol) and Zn (110 mg, 1.65 mmol) to give, after column chromatography (15% EtOAc/hexanes), **15c**:**16c** (100 mg, 99%, 84:16, 68% *de*) as a yellow oil. $R_f = 0.5$ (30% EtOAc/hexanes); IR (neat): $\tilde{\nu} = 2983 - 2854$, 1732, 1369 – 1060 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.22$ (t, $J = 6.8$ Hz, 6H), 1.27 (s, 3H), 1.32 (s, 3H), 1.38 (s, 3H), 0.96 – 1.42 (m, 2H), 1.55 – 1.75 (m, 8H), 2.48 (m, 1H), 3.58 (d, $J = 5.4$ Hz, 1H), 3.65 (q, $J = 6.8$ Hz, 1H), 4.00 (dd, $J = 14.2$, 5.9 Hz, 1H), 4.20 (q, $J = 6.8$ Hz, 2H), 4.35 ppm (q, $J = 7.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.9$, 14.0, 25.4, 26.4, 26.5, 26.7, 26.8, 30.6, 30.9, 38.4, 46.0, 50.9, 61.3, 61.4, 67.3:69.5 (84:16), 75.1, 108.0, 169.1, 169.4 ppm; MS (70 eV, EI): *m*/*z* (%): 341 (19) [$M^+ - CH_3$], 101 (100); HRMS (FAB): *m*/*z*: calcd for $C_{19}H_{33}O_6$: 357.2277 [M^++H]; found: 357.2277; elemental analysis calcd (%) for $C_{19}H_{32}O_6$ (356.5): C 64.02, H 9.05; found: C 63.87, H 8.80.

1-Ethyl 7-methyl (3ξ)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(ethoxycarbonyl)heptanedioate (15d:16d): Following the general experimental procedure, a mixture containing **5** (100 mg, 0.367 mmol) and methyl 4-iodobutyrate (99 μL, 0.734 mmol) was treated with CuI (140 mg, 0.734 mmol) and Zn (144 mg, 2.202 mmol) to give, after column chromatography (15% EtOAc/hexanes), **15d**:**16d** (97 mg, 72%, 83:17, 66% *de*) as a yellow oil. $R_f = 0.4$ (40% EtOAc/hexanes); IR (neat): $\tilde{\nu} = 2984 - 2939$, 1739, 1371 – 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.23$ (t, $J = 6.8$ Hz, 6H), 1.33 (s, 3H), 1.35 (s, 3H), 1.41 – 1.72 (m, 6H), 2.32 (m, 2H), 2.44 (m, 1H), 3.44 (d, $J = 6.3$ Hz, 1H), 3.67 (s, 3H), 4.01 (dd, $J = 8.3$, 6.4 Hz, 1H), 4.22 ppm (q, $J = 2.0$ Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 14.0$ (CH_3), 23.3 (CH_2), 25.2 (CH_3), 26.2 (CH_3), 27.8 (CH_2), 34.1 (CH_2), 40.2 (CH_3), 41.9 (CH_3), 51.4 (CH), 52.6 (CH), 61.4 (CH_2), 67.0 ($0.83 \times CH_2$), 67.6 ($0.17 \times CH_2$), 68.1 (CH_2), 76.3 (CH), 108.9 (C), 168.6 (C), 168.7 (C), 173.7 ppm (C); MS (FAB): *m*/*z* (%): 375 (26) [M^++H], 359 (76) [$M^+ - CH_3$], 317 (100); HRMS (FAB): *m*/*z*: calcd for $C_{18}H_{31}O_8$: 375.2019 [M^++H]; found: 375.2009.

Diethyl 2-{(1ξ)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-hydroxybutyl}malonate (15e:16e): Following the general experimental procedure, a mixture containing **5** (100 mg, 0.367 mmol) and 3-iodo-1-propanol (105 μL, 1.101 mmol) was treated with CuI (140 mg, 0.734 mmol) and Zn (144 mg, 2.202 mmol) to give, after column chromatography (25% EtOAc/hexanes), **15e**:**16e** (64 mg, 52%, 83:17, 66% *de*) as a yellow oil. $R_f = 0.2$ (EtOAc); IR (neat): $\tilde{\nu} = 3443$, 2985 – 2939, 1729, 1371 – 1059 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.21$ (s, 3H), 1.26 (s, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.50 – 1.72 (m, 5H), 1.97 (br s, 1H), 2.42 (m, 1H), 3.44 (d, $J = 5.9$ Hz, 1H), 3.63 (m, 3H), 3.99 (dd, $J = 7.8$, 5.9 Hz, 1H), 4.17 ppm (q, $J = 5.9$ Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.9$ (CH), 14.0 (CH_3), 24.6 (CH_2), 25.2 (CH_3), 26.2 (CH_3), 30.8 (CH_2), 39.8 (CH), 41.3 (CH_3), 52.8 (CH), 61.4 (CH_2), 62.3 (CH_2), 67.2 (CH_2), 68.1 (CH_2), 76.9 (CH), 108.9 (C), 168.7 ppm (C); MS (FAB): *m*/*z* (%): 333 (30) [M^++H], 275 (100); HRMS (FAB): *m*/*z*: calcd for $C_{16}H_{29}O_7$: 333.1913 [M^++H]; found: 333.1924.

Ethyl (4ξ,5*S*)-tetrahydro-5-(hydroxymethyl)-4-pentyl-2-oxo-3-furancarboxylate (17a:18a): HCl (10%, 250 μL) was added to a solution of **15a**:**16a** (65 mg, 0.189 mmol, 87:13) in MeOH (1 mL) at room temperature. After stirring for 1 h, the reaction mixture was concentrated and purified by column chromatography (silica gel, 50% EtOAc/hexanes) stopped with a short pad of $NaHCO_3$ and Na_2SO_4, to give **17a**:**18a** (39 mg, 80%, 87:13) as a yellow oil. **18a:** $R_f = 0.2$ (30% EtOAc/hexanes); ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.88$ (t, $J = 6.3$ Hz, 3H), 1.31 (m, 6H), 1.63 (m, 2H), 1.77 (br s, 1H), 2.48 (m, 1H), 3.12 (dq, $J = 11.2$, 7.8 Hz, 1H), 3.61 (d, $J = 11.7$ Hz, 1H), 3.87 (qq, $J = 18.5$, 2.4 Hz, 2H), 4.25 (q, $J = 7.3$ Hz, 4H), 4.59 ppm (dt, $J = 7.8$, 2.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.9$, 14.0, 22.4, 27.5, 28.7, 31.6, 42.3, 52.4, 61.4, 62.0, 81.2, 168.6, 172.9 ppm; MS (FAB): *m*/*z* (%): 259 (100) [M^++H].

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