Regio- and Stereoselective Synthesis of *Nor*-Nonactinic Acid Derivatives—Kinetic Reaction Control in the Lewis Acid Mediated Domino Reaction of 1,3-Dicarbonyl Dianions with 1-Bromo-2,3-epoxypropanes

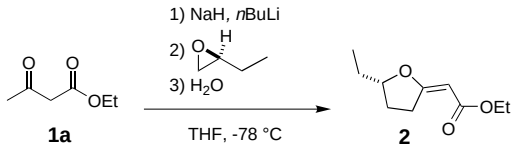
Peter Langer* and Ilia Freifeld[a]

Abstract: Reaction of 1,3-dicarbonyl dianions with epibromohydrin derivatives results in formation of functionalized 2-alkylidene-5-hydroxymethyltetrahydrofurans. These reactions proceed by chemoselective attack of the dianion onto the carbon attached to the bromine atom and subsequent nucleophilic attack of the resultant monoanion onto the epoxide. The cyclization products, which were formed with very good regio- and stereoselectivities, are of pharmacological relevance and represent versatile building blocks for the synthesis of natural products.

Keywords: cyclization · dianions · Lewis acids · regioselectivity · stereoselective synthesis · tetrahydrofurans

Introduction

The ring opening of an epoxide with functionalized carbon nucleophiles, such as enolates or cuprates, is a process of great synthetic importance,[1] especially since there is a range of methods for the preparation of substituted epoxides in optically active form.[2] Previously, attention in epoxide chemistry has been mainly focused on reactions with monofunctional nucleophiles after which the resultant open-chain product is simply quenched with water following the initial reaction. For example, a protected seco acid, an open-chain precursor to (*R*,*R*)-(−)-pyrenophorin, has been enantiospecifically prepared by reaction of the dianion of *tert*-butyl acetoacetate with (*R*)-(+)-propylene oxide and subsequent quenching of the resultant open-chain product with water.[3] Much less interest has been focused on reactions where two reactive centers of the epoxides were involved rather than only one. One such example is the reaction of epoxides with 1,3-dicarbonyl dianions, which has been reported to proceed by attack of the terminal carbon atom of the dianion onto the sterically less hindered atom of the epoxide (Scheme 1).[4] This reaction has been used for the synthesis of (±)-methyl homononactate and methyl 8-*epi*-homononactate.[5] These compounds are subunits of the nactins, a biologically important class of macrotetrolide antibiotics isolated from a variety of *Streptomyces* cultures.[6, 7]



Scheme 1. An example of the reaction of epoxides with 1,3-dicarbonyl dianions.

Despite the simplicity of the idea, only small attention has been given to cyclization reactions[8] of dianion equivalents with epoxides containing an additional electrophilic functional group. Several drawbacks are possible for these reactions: on the one hand, dianions are highly reactive compounds which can react both as nucleophiles and as bases; on the other hand, functionalized epoxides are rather labile and can undergo decomposition or side reactions. An interesting cyclization reaction of epoxyaldehydes with 3-iodo-2-[(trimethylsilyl)methyl]propene/SnF_2, a trimethylenemethane dianion equivalent, has been reported by Molander and coworkers.[9] Due to the use of a symmetrical dianion equivalent no issue of regioselectivity regarding the dianion arose. However, the reaction proceeded regioselectively with respect to the dielectrophile and involved attack of the dianion onto the aldehyde and subsequent cyclization via the *terminal* carbon of the epoxide to give a six-membered ring.

In the course of our studies[10, 11] related to domino reactions[12] of dianion equivalents,[13] we have recently reported the first cyclization reactions of 1,3-dianions with epibromohydrin derivatives.[14] These reactions proceed by chemoselective attack of the dianion onto the carbon attached to the bromine atom and subsequent nucleophilic attack of the resultant monoanion onto the *central* carbon atom giving

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rise to formation of five-membered rings. The products, 2-alkylidene-5-hydroxymethyltetrahydrofurans, were formed with very good regio- and stereoselectivities. Herein we shall report full details of our new cyclization reaction and studies related to the preparative scope of the reaction.

The cyclization products can be considered as *nor*-nonactinic acid derivatives and are versatile building blocks for the synthesis of biologically important natural products (Figure 1). Because of their hydroxyester functionality, they

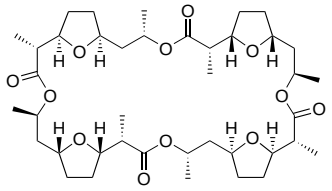


Figure 1. Biologically important macrotetrolide nonactin.

represent direct precursors for the synthesis of *nor*-nactins and related macrotetrolides[6, 7] and of tetrahydrofurylamino acids. These target molecules are of interest both for biological reasons and for applications as potential ion channels.[15] In addition, the unique functionality of 2-alkylidene-5-hydroxymethyltetrahydrofurans has been used during synthetic studies[16] on the natural products sarcodictyin A and B[17, 18] and eleutherobin.[19, 20] These marine diterpenoids have been extracted in small quantities from the soft corals *Sarcodictyon roseum* and *Eleutherobia albiflora*, and show outstanding biological activity including potent in vitro cytotoxicity against diverse tumor cell lines[19b, 21] and competition with paclitaxel to bind at the microtubuli, inhibiting their depolymerisation.[21b, 22] This tubulin-stabilizing activity adds these natural products to the restricted family of taxol-like cytotoxic agents (together with the epothilones[23] and discodermolide[24]).

Abstract in German: *Funktionalisierte 2-Alkyliden-5-hydroxymethyltetrahydrofurane können effizient und hochselektiv durch Lewis Säure vermittelte Cyclisierung von 1,3-Dicarbonyldianionen mit Epibromhydrinderivaten hergestellt werden. Die Bildung der Produkte kann durch chemoselektiven Angriff des terminalen Kohlenstoffatoms des Dianions auf die Alkylbromidfunktion des Epibromhydrins und anschließende Cyclisierung durch regioselektiven Angriff des Sauerstoffatoms des gebildeten Monoanions auf das benachbarte Kohlenstoffatom des Epoxids erklärt werden. Der Einsatz des Natrium-Lithium-Salzes der Dicarbonylverbindung sowie die Anwesenheit der Lewis Säure Lithiumperchlorat erwiesen sich als besonders wichtig bei der Optimierung der neuen Dominoreaktion. Die Cyclisierungsprodukte, die mit sehr guter Regio- und Stereoselektivität gebildet werden, sind von pharmakologischer Relevanz und stellen vielseitige Bausteine zur Synthese von Naturstoffen dar.*

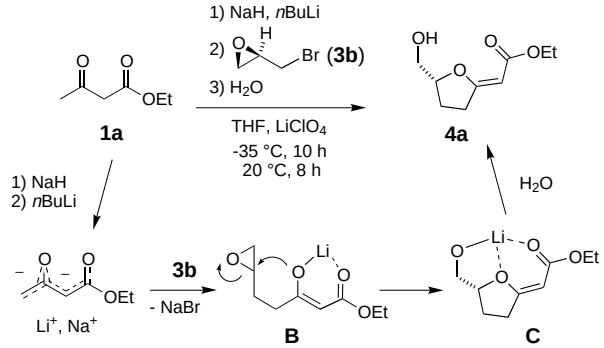
Results and Discussion

Selectivity: Our first attempts to induce a cyclization reaction of the dianion of ethyl acetoacetate (**1a**) with 1-tosyloxy-2,3-epoxypropane (**3a**) resulted in formation of a complex mixture. Employment of the corresponding mesylate and triflate was equally disappointing.[25] Reaction of the dianion of **1a** with 1-bromo-2,3-epoxypropane (**3b**) resulted in formation of the 2-alkylidenetetrahydrofuran **4a** in low yield. After much experimentation (Table 1), we found that maximum yields (up to 74%) were obtained when the reaction was carried out in the presence of 2.7 equivalents of the Lewis acids lithium chloride or, better, lithium perchlorate and when 2.5 equivalents of the dianion (rather than only one) were used (Scheme 2). The Lewis acid is necessary to activate the epoxide.[26]

Table 1. Conditions and yields of the reaction of the dianion of **1a** with substituted epoxypropanes.

Entry	X	Lewis acid [equiv]	**1a** [equiv]	t [h][a]	[%][b]
1	OTos	–	2.5	10+8	0
2	OTos	$BF_3 \cdot Et_2O$ (2.7)	1	10+8	0
3	Br	–	1	10+8	19
4	Br	–	2.5	10+8	31
5	Br	$BF_3 \cdot Et_2O$ (2.7)	2.5	10+8	0
6	Br	LiCl (2.7)	2.5	10+8	74
7	Br	$LiClO_4$ (2.7)	2.5	10+8	74
8	Br	LiCl (2.7)	1	10+8	46
9	Br	LiCl (2.7)	2.5	0+12	12

[a] Reaction time at $-35\,^{\circ}C$ + reaction time at $20\,^{\circ}C$. [b] Isolated yields.



Scheme 2. Optimized reaction conditions for cyclization of the dianion of **1a** with **3b**.

The formation of 2-alkylidenetetrahydrofuran **4a** can be explained by chemo- and regioselective attack of the terminal carbon atom of the dianion onto the carbon attached to the bromine atom and subsequent Lewis acid mediated attack of the oxygen atom onto the epoxide (Scheme 2). Since epoxides are known to be cleaved by nucleophilic attack of 1,3-dicarbonyl dianions (see above)[4] the problem of chemoselectivity was critical. After much experimentation we have found that a thorough optimization of the reaction temper-

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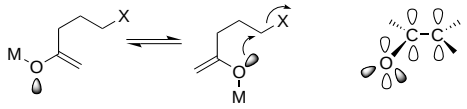
ature was crucial to obtain high chemoselectivities: the dianion could be selectively coupled with the alkyl bromide moiety by stirring of the reaction mixture at −35 °C for 10 h (TLC monitoring). To induce the cyclization step, the mixture was warmed to ambient temperature and stirred for 8 h at 20 °C.

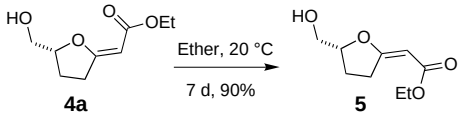
The regioselectivity for the dianion can be explained based on stereoelectronic considerations.[27] The formation of a five-membered ring by carbon alkylation of an enolate requires approach of the electrophile perpendicular to the plane of the enolate, whereas oxygen alkylation requires approach in the plane of the enolate. Consequently, in the case of the five-membered ring, approach of the alkylating center to the carbon site in the *O*-metalated enolate is sterically difficult compared with its approach in the plane to the oxygen site yielding the observed enol ether moiety (Scheme 3).



Scheme 3. Stereoelectronic explanation for the regioselectivity of five-membered-ring formation.

Regarding the epoxide, the cyclization proceeded regioselectively via the sterically more hindered central carbon atom, forming a five-membered rather than a six-membered ring. This is noteworthy, since six-membered rings were formed in the cyclization of the trimethylenemethane dianion equivalent with epoxyaldehydes.[9a] The different selectivities can again be explained by stereoelectronic considerations: in case of the trimethylenemethane dianion, no *5-exo-tet* cyclization is posssible since only carbon but no oxygen atoms are available as nucleophilic centers.

An important feature of our cyclization reaction is the fact that the exocyclic double bond of **4a** was formed with very good *Z*-selectivity. Upon standing at room temperature, 2-alkylidenetetrahydrofuran **4a** (neat or dissolved in ether or dichloromethane) isomerized within one week into the corresponding *E*-configured product (Scheme 4). This isomerization is drastically accelerated by the addition of a few drops

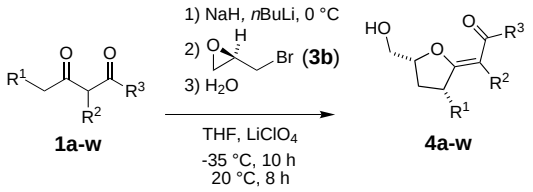


Scheme 4. Isomerization of 2-alkylidene-5-hydroxymethyltetrahydrofuran **4a**.

of TFA (trifluoroacetic acid). The isomerization shows that the thermodynamically less stable *Z* isomer is formed under kinetic reaction control. This was surprising since we and others have previously observed very good *E* selectivities in the reaction of dilithiated 1,3-dicarbonyl compounds with other 1,2-dielectrophiles (e.g. unfunctionalized epoxides,[4, 5] oxalic acid dielectrophiles,[10a] 1-bromo-2-chloroethane[11i]). Interestingly, much better yields were obtained for **4a** when the sodium–lithium rather than the dilithium salt of **1a** was employed (76 vs. 18%). In addition, the stereoselectivity was low in the latter case.

Our working hypothesis to explain the stereoselectivity is based on the assumption that the enolate in intermediate **B** possesses *Z* geometry owing to chelation with a Li^+ ion. This complexation is facilitated by the high concentration of lithium ions in solution (due to the use of 2.7 equiv of $LiClO_4$).[28] In addition, the *Z* selectivity can be explained by complexation of a lithium ion by three oxygen atoms in intermediate **C** (Scheme 2). Addition of water results in decomplexation to give the free *Z*-configured 2-alkylidenetetrahydrofuran. Although these compounds undergo slow conversion into the *E*-configured isomers (see above), they are sufficiently stable to be fully characterized and to be used in organic transformations (see below).

Preparative scope: In order to study the preparative scope of the new cyclization reaction we varied the substituents of the dicarbonyl compound and of the epoxide systematically (Scheme 5, Table 2). Reaction of 1-bromo-2,3-epoxypropane

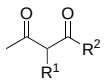
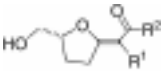
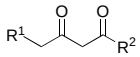
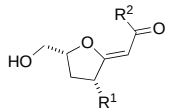
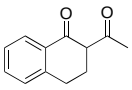
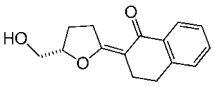
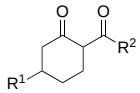
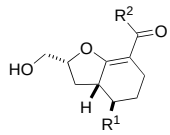
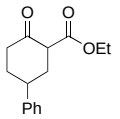
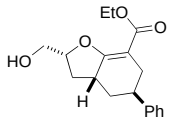
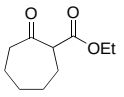
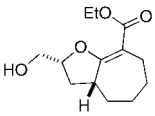


Scheme 5. Synthesis of 2-alkylidene-5-hydroxymethyltetrahydrofurans.

(**3b**) with the dianions of ethyl and methyl acetoacetate afforded the *Z*-configured 2-alkylidene-5-hydroxymethyltetrahydrofurans **4a–b** in good yields and with very good chemo-, regio-, and stereoselectivities. Cyclization of **3b** with the dianions of *tert*-butyl, isobutyl, isopropyl, methoxyethyl, and benzyl acetoacetate afforded the *Z*-configured 2-alkylidene-5-hydroxymethyltetrahydrofurans **4c–g** in good yields and with very good chemo-, regio-, and stereoselectivities. Cyclization of 1-bromo-2,3-epoxypropane (**3b**) with the dianions of *N*,*N*-diethylacetylacetic acid amide, acetylacetone, 5,5-dimethyl-2,4-hexanedione, and benzoylacetone afforded the 2-alkylidenetetrahydrofurans **4h–k** in good yields and with very good chemo- and regioselectivities and (except for **4i**) with very good stereoselectivities. In the case of **4j–k** the *E*-configured isomers were selectively formed. Reaction of 1-bromo-2,3-epoxypropane with 2-methylacetylacetone, ethyl 2-methylacetoacetate, ethyl 2-ethylacetoacetate, and ethyl 2-butylacetoacetate afforded the 2-alkylidenetetrahydrofurans **4l–o** in good yields, with very good regio- and stereoselectivities and (except for **4l**) with very good stereoselectivities.

Reaction of 1-bromo-2,3-epoxypropane with the dianions of methyl 3-oxopentanoate, ethyl 3-oxohexanoate, and ethyl 3-oxo-6-heptenoate regioselectively afforded the *Z*-configured 2-alkylidenetetrahydrofurans **4p–r** with moderate to good 1,3-diastereoselectivities. Starting with the dianion of α-acetyltetralone afforded the interesting *E*-configured 2-alkylidenetetrahydrofuran **4s**. Cyclization of **3b** with the dianion of

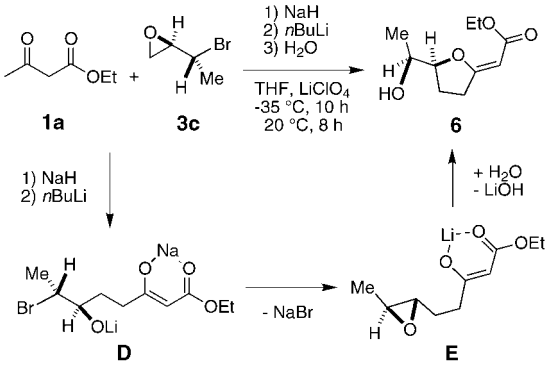
Table 2. Synthesis of 2-alkylidene-5-hydroxymethyltetrahydrofurans **4**.

Entry	**1**	**4**	R^1	R^2	Yield [%] [a]	$Z:E$	ds [b]
a			H	OEt	74	>98:2	–
b			H	OMe	74	>98:2	–
c			H	O(*t*Bu)	71	>98:2	–
d			H	O(*i*Bu)	68	>98:2	–
e			H	O(*i*Pr)	92	10:1	–
f			H	$O(CH_2)_2OMe$	57	>98:2	–
g			H	OCH_2Ph	78	>98:2	–
h			H	NEt_2	96	>98:2	–
i			H	Me	73	4:3	–
j			H	*t*Bu	70	<2:98	–
k			H	Ph	61	<2:98	–
l			Me	Me	72	4:3	–
m			Me	OEt	71	>98:2	–
n			Et	OEt	75	>98:2	–
o			Bu	OEt	72	>98:2	–
p			Me	OMe	62	>98:2	45:55
q			Et	OEt	65	>98:2	65:35
r			Allyl	OEt	78	>98:2	4:3
s			–	–	71	<2:98	–
t			H	OEt	72	–	4:1
u			Me	OMe	30	–	4:1
v			–	–	42	–	4:1
w			–	–	21	–	3:1

[a] Yields of isolated product. [b] Diastereoselectivity in favor of the drawn isomer. For **4p**–**r** the diastereomers could not be unambiguously assigned.

ethyl cyclohexanone-2-carboxylate afforded the 5,6-bicyclic 2-alkylidenetetrahydrofuran **4t** with very good chemo- and regioselectivity and with good 1,3-diasteroselectivity. The major diastereomer could be cleanly separated and isolated in good yield. From the dianion of methyl 5-methylcyclohexanone-2-carboxylate, the 5,6-bicyclic 2-alkylidenetetrahydrofuran **4u** was formed with very good chemo-, regio-, and 1,2-diastereoselectivity and with good 1,3-diasteroselectivity. In this reaction three stereocenters were formed with high selectivity. Reaction of 1-bromo-2,3-epoxypropane (**3b**) with the dianion of methyl 4-phenylcyclohexanone-2-carboxylate afforded the 5,6-bicyclic 2-alkylidenetetrahydrofuran **4v** with very good chemo- and regioselectivity and with good 1,3-diasteroselectivity. From the dianion of ethyl cycloheptanone-2-carboxylate, the 5,7-bicyclic 2-alkylidenetetrahydrofuran **4w** was formed with very good chemo- and regioselectivity and with good 1,3-diasteroselectivity.

Reaction of the dianion of ethyl acetoacetate with *threo*-3-bromo-1,2-epoxybutane (**3c**) afforded the 2-alkylidenetetrahydrofuran **6** (Scheme 6) in 38% yield with complete *Z* selectivity and with very good stereoselectivity (9:1). The formation of **6** can be explained by initial attack of the dianion onto the sterically less hindered carbon atom of the epoxide (intermediate **D**), nucleophilic displacement of the bromine atom by the alcoholate to give intermediate **E**, and subse-



Scheme 6. Route of the reaction of the ethyl acetoacetate dianion with *threo*-3-bromo-1,2-epoxybutane to give tetrahydrofuran **6**.

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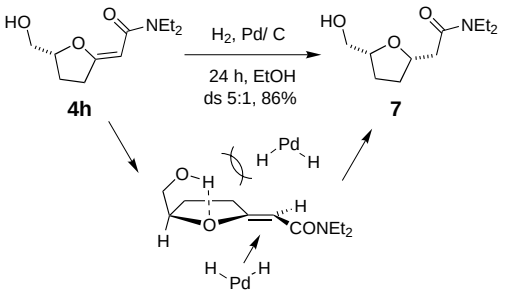
quent attack of the enolate oxygen atom onto the epoxide to give the five-membered ring **6**.

In order to demonstrate the preparative usefulness of our cyclization products, we studied the hydrogenation of the exocyclic double bond (Scheme 7). Hydrogenation of 2-alkylidenetetrahydrofuran **4h** using Pd/C as the catalyst afforded the *syn*-configured functionalized tetrahydrofuran **7** in 86% yield with good diastereoselectivity (5:1).[6f] For steric reasons, the hydrogenation occurred from the sterically less encumbered side of the molecule.



Scheme 7. Hydrogenation of an exocyclic double bond.

In summary, we have reported a new and convenient synthesis of functionalized 2-alkylidene-5-hydroxymethyltetrahydrofurans which can be regarded as *nor*-nonactinic acid derivatives. The products are of pharmacological relevance and of interest for the synthesis of a wide range of natural products. The reactions are easy to carry out and proceed with very good chemo- and regioselectivities. Interestingly, the thermodynamically less stable *Z*-configured isomers are stereoselectively formed under kinetic reaction control.

Experimental Section

General comments: All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR: 250 and 300 MHz, ^{13}C NMR: 62.5 and 75 MHz) the deuterated solvents indicated were used. The multiplicity of the ^{13}C NMR signals was determined with the DEPT 135 technique and quoted as: CH_3, CH_2, CH, and C for primary, secondary, tertiary and quaternary carbon atoms. Mass spectral data (MS) were obtained by means of the electron ionization (70 eV) or the chemical ionization technique (CI, H_2O). For the preparative chromatography, silica gel (60–200 mesh) was used. Elemental analyses were performed at the microanalytical laboratories of the Universities of Göttingen and Jena. The geometry of the exocyclic double bond of the products was determined by NOE measurements and based on comparison of the chemical shifts of the CH hydrogens of the exocyclic double bond with those of compounds with known configuration. For **4a** and **5**, a direct comparison of chemical shifts was possible. It has been previously noted for related butenolides and 2-alkylidenetetrahydrofurans that the chemical shift of the CH hydrogen is shifted further downfield for *E*-configured than for *Z*-configured products.[25, 29] The relative configuration of product **7** was determined by comparison of the NMR data of a related product to those reported for an independently prepared product with known configuration.[30] Epoxide **3c** was prepared according to a literature procedure.[31]

General procedure for the synthesis of 2-alkylidene-5-hydroxymethyltetrahydrofurans (4) exemplified by the synthesis of 4a: Ethyl acetoacetate (**1a**, 650 mg, 5.0 mmol), or the appropriate compound **1**, was added to a THF suspension (25 mL) of NaH (140 mg, 5.95 mmol) under Ar at 0 °C. After the mixture had been stirred for 60 min at 20 °C, *n*BuLi (5.00 mmol, solution in hexane) was added at 0 °C. After stirring for 30 min at 0 °C, the solution was cooled to −78 °C and a THF solution (20 mL) of lithium perchlorate (580 mg, 5.4 mmol) was added. To this solution was added a THF solution (5 mL) of **3b** (185 mg, 2.0 mmol). The solution was warmed to −35 °C over 1 h and was stirred for 10 h at this temperature; it was then allowed to warm to ambient temperature over 1 h. After stirring of the solution for 8 h, a saturated aqueous NH_4Cl solution (70 mL) was added. The aqueous layer was extracted twice with ether and twice with CH_2Cl_2, and the combined organic fractions were dried ($MgSO_4$) and filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, ether:petroleum ether = 1:3 → 3:1) to give 275 mg of **4a** (74%) as a colorless oil.

Data for 4a: ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.20$ (t, $J = 6$ Hz, 3H; CH_3), 1.92, 2.05 (2m, 2 × 1H; CH_2), 2.70 (m, 2H; CH_2), 3.63, 3.80 (2dd, $J = 4$ Hz, $J = 10$ Hz, 2 × 1H; CH_2OH), 4.07 (m, 2H; CH_2O), 4.68 (m, 1H; O–CH), 4.82 (t, $J = 1$ Hz, 1H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.25$, 24.24, 32.07, 59.17, 63.49, 87.12, 87.63, 166.38, 172.43; MS (EI, 70 eV): *m*/*z*: 186 (72) $[M]^+$, 156 (36), 141 (100), 99 (40), 69 (41); the exact molecular mass *m*/*z* 186.0892 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_9H_{14}O_4$: C 58.05, H 7.58; found: C 57.76, H 7.37.

Data for 4b: From the starting material methyl acetoacetate (1.08 mL, 10.0 mmol), **4b** was isolated as a yellow oil (0.508 g, 74%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.92$, 2.06 (2m, 2 × 1H; CH_2), 2.76 (m, 2H; CH_2), 3.63 (s, 3H; CH_3), 3.68, 3.84 (2m, 2 × 1H; CH_2OH), 4.17 (br, 1H; OH), 4.70 (m, 1H; O–CH), 4.84 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta =$ 24.24, 32.14 (CH_2), 50.66 (CH_3), 63.56 (CH_2OH), 87.15, 87.39 (CH), 166.76, 172.49 (C); MS (EI, 70 eV): *m*/*z*: 172 (84) $[M]^+$, 141 (100), 109 (36), 69 (50); the exact molecular mass *m*/*z* 172.0736 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_8H_{12}O_4$ (172.18): C 55.80, H 7.02; found: C 55.32, H 6.84.

Data for 4c: From the starting material *tert*-butyl acetoacetate (0.79 g, 5.00 mmol), **4c** was isolated as a yellow oil (0.303 g, 71%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.42$ (s, 9H; $C(CH_3)_3$), 1.88, 2.02 (2m, 2 × 1H; CH_2), 2.69 (m, 2H; CH_2), 3.68, 3.81 (2dd, $J = 4$ Hz, $J = 10$ Hz, 2 × 1H; CH_2OH), 4.67 (m, 1H; O–CH), 4.79 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 24.26$ (CH_2), 28.29 (CH_3), 32.08 (CH_2), 63.55 (CH_2OH), 79.18 ($C(CH_3)_3$), 86.98 (O–CH), 89.40 (=CH), 166.17 (C=C–O), 171.67 (C=O); MS (EI, 70 eV): *m*/*z*: 214 (14) $[M]^+$, 158 (100), 141 (94), 128 (86); the exact molecular mass *m*/*z* 214.1205 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4d: From the starting material isobutyl acetoacetate (0.81 mL, 5.0 mmol), **4d** was isolated as a yellow oil (0.291 g, 68%); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.84$ (d, $J = 5$ Hz, 6H; $(CH_3)_2$CH), 1.65–2.10 (m, 3H; CH_2, $(CH_3)_2$C*H*), 2.67 (m, 2H; CH_2), 3.51–3.90 (m, 4H; 2 × CH_2), 4.61 (m, 1H; O–CH), 4.80 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 18.88 (CH_3), 24.09 (CH_2), 27.49 ($CH(CH_3)_2$), 31.95 (CH_2), 63.29 (CH_2OH), 69.27 (CH_2O), 87.15, 87.32 (CH), 166.47, 172.46 (C); MS (EI, 70 eV): *m*/*z*: 214 (18) $[M]^+$; the exact molecular mass *m*/*z* 214.1205 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{11}H_{18}O_4$ (214.25): C 61.66, H 8.46; found: C 61.45, H 8.32.

Data for 4e: From the starting material isopropyl acetoacetate (0.72 g, 5.00 mmol), **4e** was isolated as a yellow oil (0.368 g, 92%). Isomeric ratio of the essentially pure crude product: *Z*:*E* = 10:1. Isomeric ratio after chromatography: *Z*:*E* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.18$ (d, $J = 7$ Hz, 6H; $CH(CH_3)_2$), 1.80, 2.05 (2m, 2 × 1H; CH_2), 2.68 (m, 2H; CH_2), 3.60, 3.75 (2dd, $J = 4$ Hz, $J = 10$ Hz, 2 × 1H; CH_2OH), 4.63 (m, 1H; O–CH), 4.77 (s, 1H; =CH), 4.93 (sept, $J = 7$ Hz, 1H; $OCH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 21.44$ (CH_3), 23.90 (CH_2), 31.67 (CH_2), 63.02 (CH_2OH), 65.70 (O–C*H*(CH_3)$_2$), 86.90 (O–CH), 87.45 (=CH), 165.61 (C=C–O), 172.18 (C=O); MS (EI, 70 eV): *m*/*z*: 200 (22) $[M]^+$; the exact molecular mass *m*/*z* 200.1049 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{10}H_{16}O_4$ (200.24): C 59.98, H 8.05; found: C 59.60, H 8.24.

Data for 4f: From the starting material methoxyethyl acetoacetate (0.73 mL, 5.0 mmol), **4f** was isolated as a yellow oil (0.246 g, 57%); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 1.84$, 2.02 (2m, 2 × 1H; CH_2), 2.71 (m, 2H; CH_2), 3.33 (s, 3H; CH_3), 3.54 (m, 2H; CH_2), 3.63, 3.77 (2m, 2 × 1H; CH_2OH), 4.15 (m, 2H; CH_2), 4.64 (m, 1H; O–CH), 4.88 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 24.12$, 32.10 (CH_2), 58.75 (CH_3), 62.25,

63.49, 70.52 (OCH_2), 87.24, 87.29 (CH), 166.17, 172.94 (C); MS (EI, 70 eV): m/z: 216 (20) $[M]^+$; the exact molecular mass m/z 216.09888 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4g: From the starting material benzyl acetoacetate (0.86 mL, 5.0 mmol), **4g** was isolated as a yellow oil (0.387 g, 78%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.83, 2.01 (2m, 2 × 1H; CH_2), 2.72 (m, 2H; CH_2), 3.68, 3.82 (2m, 2 × H, CH_2OH), 4.67 (m, 1H; O−CH), 4.91 (s, 1H; =CH), 5.10 (m, 2H; CH_2O), 7.27 (m, 5H; Ph); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.97, 32.10, 63.26 (CH_2), 64.80 (CH_2OH), 86.94, 87.23 (CH), 127.53, 127.63, 128.09 (Ph), 136.40, 165.97, 173.17 (C); MS (EI, 70 eV): m/z: 248 (16) $[M]^+$; the exact molecular mass m/z 248.1049 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4h: From the starting material *N*,*N*-diethylacetoacetamide (0.78 g, 5.00 mmol), **4h** was isolated as a yellow oil (0.410 g, 96%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.07 (m, 6H; 2 × CH_3), 1.96 (m, 2H; CH_2), 2.68 (m, 2H; CH_2), 3.29 (m, 4H; 2 × C$H_2$$CH_3$), 3.86 (m, 2H; CH_2OH), 4.57 (m, 1H; O−CH), 4.92 (s, 1H; C=CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 12.49, 13.63 (CH_3), 23.87, 31.21 (CH_2), 39.21 (C$H_2$$CH_3$), 41.69 (C$H_2$$CH_3$), 62.51 ($CH_2$OH), 85.52, 86.66 (CH), 165.24 (ring C), 167.59 (C); MS (EI, 70 eV): m/z: 213 (43) $[M]^+$, 141 (100), 99 (33), 71 (28); the exact molecular mass m/z 213.1365 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4i: From the starting material 2,4-pentanedione (0.50 g, 5.00 mmol), **4i** was isolated as a yellow oil (0.228 g, 73%, *Z*:*E* = 4:3); *E* isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.93 (m, 2H; CH_2), 2.14 (s, 3H; CH_3), 3.02, 3.30 (2m, 2 × 1H; CH_2), 3.65, 3.84 (2m, 2 × 1H; CH_2OH), 4.54 (m, 1H; O−CH), 5.80 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 24.67 (CH_2), 30.95 (CH_3), 31.22 (CH_2), 63.78 (CH_2OH), 84.09 (O−CH), 98.53 (=CH), 176.90 (C=), 197.91 (C=O); *Z* isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.84, 2.02 (2m, 2 × 1H; CH_2), 2.17 (s, 3H; CH_3), 2.70 (m, 2H; CH_2), 3.63, 3.80 (2m, 2 × 1H; CH_2OH), 4.64 (m, 1H; O−CH), 5.09 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.92 (CH_2), 30.45 (CH_3), 32.32 (CH_2), 63.42 (CH_2OH), 87.73 (O−CH), 99.31 (=CH), 172.15 (C=), 197.39 (C=O); MS (EI, 70 eV): m/z: 156 (100) $[M]^+$, 141 (70), 99 (51), 85 (70), 43 (63); the exact molecular mass m/z 156.0786 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_8H_{12}O_3$ (156.18): C 61.52, H 7.74; found: C 61.18, H 7.45.

Data for 4j: From the starting material 5,5-dimethyl-2,4-hexanedione (0.71 g, 5.00 mmol), **4j** was isolated as a yellow oil (0.280 g, 70%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.05 (s, 9H; C(CH_3)$_3$), 1.84, 2.09 (2m, 2 × 1H; CH_2), 2.98, 3.22 (2m, 2 × 1H; CH_2), 3.59, 3.76 (2m, 2 × 1H; CH_2OH), 4.45 (m, 1H; O−CH), 5.97 (s, 1H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 24.79 (CH_2), 26.80 (CH_3), 31.132 (CH_2), 42.91 (C(CH_3)$_3$), 63.90 (CH_2OH), 83.75 (CH−O), 94.19 (=CH), 177.45 (C=CH), 205.79 (C=O); MS (EI, 70 eV): m/z: 198 (4) $[M]^+$, 141 (100), 99 (33); elemental analysis (%) calcd for $C_{11}H_{18}O_3$ (198.26): C 66.64, H 8.39; found: C 66.31, 8.95.

Data for 4k: From the starting material benzoylacetone (0.81 g, 5.00 mmol), **4k** was isolated as a yellow oil (0.268 g, 61%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.95, 2.14 (2m, 2 × 1H; CH_2), 3.15, 3.42 (2m, 2 × 1H; CH_2), 3.63, 3.83 (2m, 2 × 1H; CH_2), 4.58 (m, 1H; O−CH), 6.49 (m, 1H; =CH), 7.40 (m, 3H; 3 × Ar−CH), 7.83 (m, 2H; 2 × Ar−CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 24.66, 31.69 (CH_2), 63.86 (CH_2OH), 84.42 (ring CH), 95.06 (CH), 127.39 (CH, Ar), 128. 23 (CH, Ar), 131.70 (CH, Ar), 139.49 (C, Ar), 179.22 (ring C), 190.52 (C); MS (EI, 70 eV): m/z: 218 (100) $[M]^+$, 147 (43), 105 (94), 77 (47); the exact molecular mass m/z 218.0943 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{13}H_{14}O_3$ (218.25): C 71.54, H 6.46; found: C 71.08, H 6.20.

Data for 4l: From the starting material 3-methyl-2,4-pentanedione (0.58 mL, 5.00 mmol), **4l** was isolated as a yellow oil (0.245 g, 72%, *E*:*Z* = 4:3); *E* isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3H; CH_3), 1.80–2.10 (m, 2H; CH_2), 2.29 (s, 3H; $COCH_3$), 2.74 (m, 2H; CH_2), 3.61 (dd, *J* = 4 Hz, *J* = 10 Hz, 1H; CH_2), 3.82 (dd, *J* = 4 Hz, *J* = 10 Hz, 1H; CH_2), 4.63 (m, 1H; CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 13.40 (CH_3), 23.91 (CH_2), 31.23 (CH_2), 31.47 (O=C−CH_3), 63.77 (CH_2OH), 86.11 (CH), 105.89 (CCH_3), 169.40 (ring C), 198.41 (C); *Z* isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.88 (m, 3H; CH_3), 1.92–2.15 (m, 2H; CH_2), 2.14 (s, 3H; $COCH_3$), 2.94 (m, 2H; CH_2), 3.16 (m, 2H; CH_2), 3.61, 3.68 (2dd, *J* = 4 Hz, *J* = 10 Hz, 2 × 1H; CH_2OH), 4.48 (m, 1H; CH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.64 (CH_3), 25.45 (CH_2), 29.13 (CH_2), 31.66 (O=C−CH_3), 63.99 (CH_2OH), 83.21 (CH, 106.15 (CCH_3), 170.64 (ring C), 199.77 (C); MS (EI, 70 eV): m/z: 170 (75) $[M]^+$, 155 (57), 99 (60), 43 (100); the exact molecular mass m/z 170.0943 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_9H_{14}O_3$ (170.20): C 63.51, H 8.29; found: C 63.11, H 8.17.

Data for 4m: From the starting material ethyl 2-methylacetoacetate (0.7 mL, 5.00 mmol), **4m** was isolated as a yellow oil (0.270 g, 68%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.26 (t, *J* = 7 Hz, 3H; CH_2CH_3), 1.75 (s, 3H; CH_3), 1.92, 2.07 (2m, 2 × 1H; CH_2), 2.74 (m, 2H; CH_2), 3.63, 3.80 (2dd, *J* = 4 Hz, *J* = 10 Hz, 2 × 1H; CH_2OH), 4.15 (m, 2H; CH_2O), 4.64 (m, 1H; O−CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.16, 14.33 (CH_3), 24.33 (CH_2), 30.83 (CH_2), 59.59 (CH_3CH_2), 63.78 (CH_2OH), 85.91 (CH), 94.96 (=CCH_3), 167.53 (ring C), 167.68 (C); MS (EI, 70 eV): m/z: 200 (63) $[M]^+$, 154 (85), 98 (58), 59 (75), 43 (100); the exact molecular mass m/z 200.1049 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{10}H_{16}O_4$ (200.23): C 59.98, H 8.05; found: C 59.60, H 7.80.

Data for 4n: From the starting material ethyl 2-ethylacetoacetate (0.79 g, 5.00 mmol), **4n** was isolated as a yellow oil (0.320 g, 75%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.99 (t, *J* = 7 Hz, 3H; chain CH_3), 1.28 (t, *J* = 7 Hz, 3H; CH_3), 1.92, 2.07 (2m, 2 × 1H; CH_2), 2.18 (m, 2H; CH_2), 2.77 (m, 2H; CH_2), 3.64, 3.85 (2m, 2 × 1H; CH_2OH), 4.16 (m, 2H; C$H_2$$CH_3$), 4.64 (m, 1H; CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 13.41, 13.68 (CH_3), 21.71, 23.90, 29.49, 58.74, 63.03 (CH_2), 85.36 (CH), 100.81 (C=), 166.63 (C=), 167.59 (C=O); MS (EI, 70 eV): m/z: 214 (100) $[M]^+$, 199 (64), 169 (75), 99 (57); the exact molecular mass m/z 214.1205 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{11}H_{18}O_4$ (214.25): C 61.66, H 8.46; found: C 61.70, H 8.16.

Data for 4o: From the starting material ethyl 2-butylacetoacetate (0.93 g, 5.00 mmol), **4o** was isolated as a yellow oil (0.242 g, 50%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.72 (t, *J* = 7 Hz, 3H; $CH_2$$CH_2$$CH_3$), 1.09 (t, *J* = 8 Hz, 3H; CH_3), 1.18 (m, 4H; CH_2), 1.81 (2m, 2 × 1H; CH_2), 2.00 (m, 2 × 1H; CH_2), 2.61 (m, 2H; C=C−CH_2, ring), 3.57 (s, 2H; CH_2OH), 3.98 (q, *J* = 8 Hz, C$H_2$$CH_3$), 4.43 (m, 1H; O−CH), 4.72 (br, 1H; OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 13.48, 13.86 (CH_3), 22.06, 24.17, 28.30, 29.86, 31.39 (CH_2), 58.98 (C$H_2$$CH_3$), 63.26 ($CH_2$OH), 85.36 (ring CH), 99.92 (C−Bu), 166.99, 167.69 (C); MS (EI, 70 eV): m/z: 242 (38) $[M]^+$, 199 (100), 153 (57), 99 (59), 85 (55), 55 (54); the exact molecular mass m/z 242.1518 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4p: From the starting material methyl 3-oxopentanoate (0.6 mL, 5.00 mmol), **4p** was isolated as a yellow oil (0.230 g, 62%, *cis*:*trans* = 45:55); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.24 (m, 3H; CH_3), 1.43–1.82 (m, 1H; CH_2), 2.19 (m, 1H; CH_2), 3.02 (m, 1H; CH), 3.67 (s, 3H; OCH_3), 3.81, 3.96 (2m, 2 × 1H; CH_2OH), 4.57 (m, 1H; O-CH), 4.83 (m, 1H; CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 16.59, 18.83 (CH_3), 32.37, 33.01 (CH_2), 38.64, 38.89 (CHCH_3), 50.64, 50.69 (O-CH_3), 63.40, 63.65 (CH_2OH), 84.88, 85.16 (O-CH), 86.33, 86.66 (=CH), 166.95, 167.12, 176.72, 177.22 (C); MS (EI, 70 eV): m/z: 186 (83) $[M]^+$, 155 (100), 101 (39), 69 (37); the exact molecular mass m/z 186.0892 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_9H_{14}O_4$ (186.20): C 58.05, H 7.58; found: C 58.22, H 7.45.

Data for 4q: From the starting material ethyl butyrylacetate (0.79 g, 5.00 mmol), **4q** was isolated as a yellow oil (0.278 g, 65%, *cis*:*trans* = 65:35); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.92 (t, *J* = 6 Hz, 3H; $CHCH_2CH_3$), 1.20 (t, *J* = 6 Hz, 3H; CH_3), 1.40, 1.77 (2m, 2 × 1H; $CHCH_2CH_3$), 2.13, 2.78 (2m, 2 × 1H; CH_2), 3.64, 3.80 (2m, 2 × 1H; CH_2), 4.04 (m, 2H; C$H_2$$CH_3$), 4.48 (m, 1H; C$H$$CH_2CH_3$), 4.68 (m, 1H; OCH), 4.74 (m, 1H; C=CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 11.45, 11.52, 14.21 (CH_3), 24.63, 26.43, 29.83, 30.36 (CH_2), 45.23, 45.49 (C$H$$CH_2CH_3$), 59.13, 59.20 (O$CH_2CH_3$), 63.43, 63.64 ($CH_2$OH), 85.11, 85.18, 86.83, 87.49 (CH), 166.47, 166.66, 175.43, 175.82 (C); MS (EI, 70 eV): m/z: 214 (62) $[M]^+$, 169 (100), 153 (41), 81 (76), 69 (46), 43 (47); elemental analysis (%) calcd for $C_{11}H_{18}O_4$ (214.26): C 61.66, H 8.47; found: C 61.70, H 8.71.

Data for 4r: From the starting material ethyl 3-oxo-6-heptenoate (0.77 g, 5.00 mmol), **4r** was isolated as a yellow oil (0.354 g, 78%, *cis*:*trans* = 4:3); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.12 (t, *J* = 6 Hz, 3H; CH_3), 1.39, 1.70 (2m, 1H; CH_2), 1.95–2.40 (m, 2H; CH_2), 2.84 (m, CH_2), 3.61 (m, 2H; CH_2OH), 3.97 (m, 2H; CH_2CH_3), 4.39, 4.52 (2m, 1H; OCH), 4.70 (s, 1H; =CH−), 4.92 (m, 2H; CH=CH_2), 5.61 (m, 1H, CH=CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 13.90 (CH_3), 29.34, 30.33, 35.64, 37.43 (CH_2), 42.89, 43.02 (CH), 58.79, 58.88 (CH_2CH_3), 63.03, 63.20 (CH_2OH), 84.90, 84.99

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(O–CH), 86.69, 87.17 (=*C*H–C=O), 117.05, 117.22 (=CH_2), 134.18, 134.27 (=CH), 166.05, 166.22, 174.47, 174.98 (C); MS (EI, 70 eV): *m/z*: 226 (54) $[M]^+$, 181 (100), 81 (70), 69 (62), 41 (49); the exact molecular mass *m/z* 226.1205 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{12}H_{18}O_4$ (226.27): C 63.70, H 8.02; found: C 63.27, 8.11.

Data for 4s: From the starting material 2-acetyl-α-tetralone (0.94 g, 5.00 mmol), **4s** was isolated as a red oil (0.346 g, 71%); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.98-2.24$ (2 m, 2 × 1 H; CH_2), 2.40 (br, 1 H; OH), 2.83 (s, 4 H; CH_2, tetralone), 3.16, 3.27 (2 m, 2 × 1 H; C=C–CH_2), 3.70, 3.88 (2 m, 2 × 1 H; CH_2OH), 4.60 (m, 1 H; O–CH), 7.29–8.03 (m, 4 H; Ar–CH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 23.84$ (CH_2), 25.33 (CH_2), 28.48 (CH_2), 31.85 (CH_2), 64.29 (CH_2OH), 83.76 (CH), 106.61 (C), 126.54 (CH, Ar), 126.99 (CH, Ar), 127.81 (CH, Ar), 131.96 (CH, Ar), 134.93 (C), 142.90 (C), 171.20 (C), 187.90 (C); MS (EI, 70 eV): *m/z*: 244 (100) $[M]^+$, 199 (66), 173 (55), 153 (33), 99 (30); the exact molecular mass *m/z* 244.1099 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4t: From the starting material ethyl cyclohexanone-2-carboxylate (0.85 g, 5.00 mmol), **4t** was isolated as a yellow oil (0.325 g, 72%, ds = 4:1). The major isomer could be cleanly separated: ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.05-2.35$ (m, 11 H; CH_3, CH_2), 2.76 (m, 1 H; C=C–C*H*), 3.68 (d, *J* = 5 Hz, 2 H; CH_2OH), 3.87 (br, 1 H; OH), 4.14 (q, *J* = 6 Hz, 2 H; CH_3CH_2), 4.65 (m, 1 H; O–CH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 14.34$ (CH_3), 22.28, 23.68, 27.77, 31.33 (CH_2), 39.75 (CH), 59.55 (CH_2CH_3), 64.27 (CH_2OH), 83.47 (O–CH), 97.07 (O=C–C=), 167.22 (ring C), 168.67 (C); MS (EI, 70 eV): *m/z*: 226 (42) $[M]^+$, 186 (100), 122 (62); the exact molecular mass *m/z* 226.1205 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{12}H_{18}O_4$ (226.27): C 63.70, H 8.02; found: C 63.44, H 8.10.

Data for 4u: From the starting material ethyl 5-methylcyclohexanone-2-carboxylate (0.92 g, 5.00 mmol), **4u** was isolated as a yellow oil (0.145 g, 30%, ds = 4:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.90-1.80$ (m, 11 H, CH, CH_2, CH_3), 2.05–2.45 (m, 3 H; C=C–CH_2, C=C–CH), 3.56, 3.74 (2 m, 2 × 1 H; CH_2OH), 4.05 (m, 2 H; O–CH_2CH_3), 4.41, 4.58 (2 m, 1 H; O–CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.13$, 14.17 ($CHCH_3$), 19.98 (CH_3), 23.74, 23.90, 30.00, 30.70, 30.79, 30.96 (CH_2), 33.75, 34.22 (CH), 46.19, 48.43 (CH), 59.28, 59.36, 63.52, 63.61 (CH_2), 83.39, 84.47 (CH), 96.07, 96.36 (=C), 166.93, 167.06 (O–C=), 168.03, 168.12 (C); MS (EI, 70 eV): *m/z*: 240 (58) $[M]^+$, 195 (60), 182 (87), 167 (100), 136 (56), 41 (60); the exact molecular mass *m/z* 240.1362 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4v: From the starting material ethyl 4-phenylcyclohexanone-2-carboxylate (1.23 g, 5.00 mmol), **4v** was isolated as a yellow oil (0.254 g, 42%, ds = 4:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.24$ (t, *J* = 6 Hz, 3 H; CH_3), 1.67 (m, 2 H; CH_2), 2.24 (m, 2 H; CH_2), 2.38 (m, 1 H; CH), 2.73 (m, 1 H; CH), 2.91 (m, 2 H; CH_2), 3.73, 3.94 (2 dd, *J* = 4 Hz, *J* = 10 Hz, 2 × 1 H; CH_2OH), 4.15 (m, 2 H; CH_2CH_3), 4.62 (m, 1 H; OCH), 7.28 (m, 5 H; Ph); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.27$ (CH_3), 31.92, 32.92, 33.85 (CH_2), 40.59 (CH), 42.56 (CH–Ph), 59.57 (CH_2CH_3), 63.51 (CH_2OH), 84.65 (O–CH), 96.68 (O=C–C=), 126.35 (CH, Ph), 126.72 (CH, Ph), 128.44 (CH, Ph), 145.39 (C, Ph), 166.76 (ring C), 168.18 (C); MS (EI, 70 eV): *m/z*: 302 (15) $[M]^+$, 198 (21), 180 (18); the exact molecular mass *m/z* 302.1518 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Data for 4w: From the starting material ethyl cycloheptanone-2-carboxylate (0.85 g, 5.00 mmol), **4w** was isolated as a yellow oil (0.100 g, 21%, ds = 3:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.24$ (t, *J* = 7 Hz, 3 H; CH_3), 1.40–2.10 (m, 8 × H, CH_2), 2.29 (m, 1 H; C=C–CH_2), 2.79 (m, 1 H; C=C–CH_2), 3.08 (m, 1 H; C=C–CH), 3.60, 3.75 (2 m, 2 × 1 H; CH_2OH), 4.12 (m, 2 H; CH_2CH_3), 4.43, 4.68 (2 m, 1 H; O–C*H*); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.28$ (CH_3), 26.62, 26.81, 26.95, 30.23, 31.29, 32.43, 32.81, 33.03, 33.18 (CH_2), 44.59, 44.66 (CH), 59.75, 59.78 (CH_2), 64.05, 64.08 (CH_2OH, 84.15, 84.47 (O–CH), 102.25, 102.35 (C), 167.80, 168.01 (=C), 173.30, 173.94 (=C); MS (EI, 70 eV): *m/z*: 240 (42) $[M]^+$, 195 (50), 182 (66), 136 (100); the exact molecular mass *m/z* 240.1362 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{13}H_{20}O_4$ (240.29): C 64.98, H 8.39; found: C 64.60, H 8.18.

2-Alkylidenetetrahydrofuran 6: From the starting materials ethyl acetoacetate (0.64 mL, 5.00 mmol) and 3-bromo-1,2-epoxybutane, **6** was isolated as a yellow oil (0.152 g, 38%, ds = 9:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta =$ 1.23 (m, 6 H; CH_3), 1.80, 2.07 (2 m, 2 × 1 H; CH_2), 2.75 (m, 2 H; CH_2), 3.81 (m, 1 H; CHOH), 4.10 (m, 2 H; OCH_2CH_3), 4.22 (m, 1 H; O–CH), 4.85 (s, 1 H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.32$, 18.22 (CH_3), 24.65, 32.30 (CH_2), 59.19 (OCH_2), 69.19 (CHOH), 87.97, 90.58 (CH), 166.14, 171.87 (C); MS (EI, 70 eV): *m/z*: 200 (8) $[M]^+$, 156 (100), 113 (26); the exact molecular mass *m/z* 200.1049 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV).

Isomerization of 4a into 5: Upon standing, an ether solution of **4a** rearranged into **5** within one week. Complete isomerization was observed within three weeks even when neat **4a** was stored in the refrigerator at −30 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.22$ (t, *J* = 6 Hz, 3 H; CH_3), 1.92, 2.10 (2 m, 2 × 1 H; CH_2), 2.98 (dddd, 1 H; CH_2), 3.28 (dddd, 1 H; CH_2), 3.61, 3.82 (2 dd, *J* = 4 Hz, *J* = 10 Hz, 2 × 1 H; CH_2OH), 4.10 (q, 2 H; CH_2O), 4.52 (m, 1 H; O–CH), 5.30 (t, *J* = 2 Hz, 1 H; =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 14.42$, 24.80, 30.45, 59.28, 64.14, 84.01, 89.94, 168.51, 176.14; MS (EI, 70 eV): *m/z*: 186 (80) $[M]^+$, 156 (38), 141 (100); the exact molecular mass *m/z* 186.0892 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_9H_{14}O_4$: C 58.05, H 7.58; found: C 57.84, H 7.40.

Hydrogenation of 4h: A suspension of tetrahydrofuran **4h** (200 mg, 0.94 mmol) and Pd/C (20 mol%) in EtOH (5 mL) was stirred under a hydrogen atmosphere for 24 h. The catalyst was filtered off and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, ether:petrol ether = 1:3) to give **7** as a colorless oil (174 mg, 86%, *syn*:*anti* = 5:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.05$ (2 t, *J* = 7 Hz, 2 × 3 H; 2 × CH_3), 1.55 (m, 1 H; CH_2), 1.82 (m, 2 H; CH_2), 2.08 (m, 1 H; CH_2), 2.42, 2.58 (2 dd, 2 × 1 H; CH_2), 3.20 (m, 4 H; 2 × CH_2CH_3), 3.35, 3.60 (2 m, 2 × 1 H; CH_2OH), 3.98 (m, 1 H; O–CH), 4.25 (quintet, *J* = 5.5 Hz, 1 H; O–CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 12.83$, 14.16 (CH_3), 26.24, 31.48, 39.39.14, 41.92 (CH_2), 64.36 (CH_2OH), 76.13, 79.80 (CH–O), 169.79 (CO); MS (EI, 70 eV): *m/z*: 215 (48) $[M]^+$; the exact molecular mass *m/z* 215.1521 ± 2 mD $[M^+]$ was confirmed by HRMS (EI, 70 eV); elemental analysis (%) calcd for $C_{11}H_{21}O_3N$ (215.29): C 61.37, H 9.83; found: C 61.10, H 9.62.

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