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A Direct Approach to Enantiopure Propionate Derivatives from Ethyl Lactate

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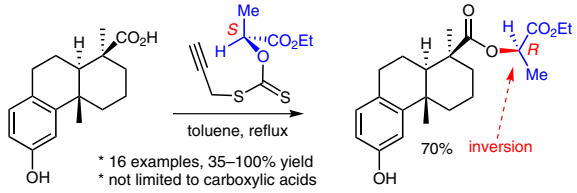
This paper is dedicated with respect and affection to the memory of Professor Jean Normant.



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Abstract The *S*-propargyl xanthate derived from ethyl (*S*)-lactate reacts upon heating with various acidic substances to give the propionate transfer product in high yield and with complete inversion of configuration.

Key words *S*-propargyl xanthate, sigmatropic rearrangement, esters, inversion, propionates

The propionate side chain is arguably one of the most important pharmacophores. It is a key element of the widely used nonsteroidal anti-inflammatory drugs (NSAIDs), such as compounds **1**–**3** (Figure 1).[2a] These are the more popular representatives and are produced on a scale of thousands of tons. The propionate motif is also central to the so-called aryloxyphenoxypropionate (AOPP or fop) class of herbicides, as illustrated by compounds **4**–**9** displayed in Figure 1. These substances act by inhibiting a particular enzyme in the plant, namely acetyl-CoA carboxylase (ACCase).[2b] It is presumed that the free carboxylic acid is the active entity, but the ester precursors (e.g., **8** and **9**) are sometimes better absorbed by the leaf and then hydrolyzed into the corresponding acid in vivo.

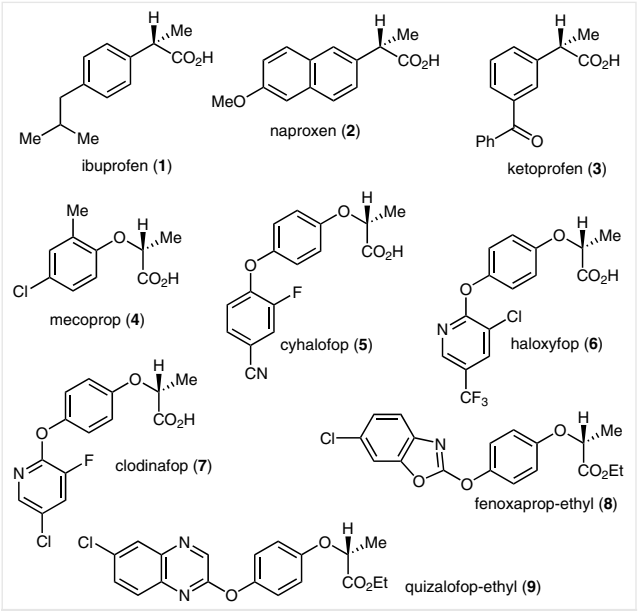
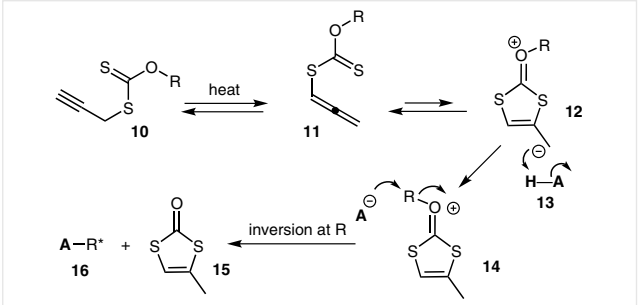


Figure 1 Examples of biologically active propionate derivatives

In view of the importance of this motif, numerous methods have been devised for its introduction. Essentially all known techniques have been exploited to obtain the optically active form, ranging from classical resolution to enantioselective protonation of ketene intermediates, to the use of asymmetric catalytic hydrogenation and enzymatic resolution based approaches.[3] Optically active alkylating agents derived from chloropropionates and lactates have played a prominent role in this respect.[4] The now classical Mitsunobu reaction, allowing the direct use of lactate esters as partners in alkylations with inversion, has logically also been used in this context.[5] Indeed, the synthesis of AOPP herbicides, which have an *R* absolute configuration, from abundant and cheap (*S*)-lactic acid derivatives by alkylation of a suitable phenol with inversion of configuration is particularly attractive. We now describe an alternative approach relying on a novel method for creating a powerful leaving group on the alcohol function of ethyl (*S*)-lactate.

In the course of our studies on various aspects of the chemistry of xanthates, in particular related to radical transformations,[6] we found that moderate heating (≥80 °C) of an *S*-propargyl xanthate **10** causes its isomerization into

the corresponding *S*-allenyl isomer **11**, which is in equilibrium with the betaine **12** (Scheme 1).[7] The latter represents a new reactive species for which only indirect evidence could be obtained. The equilibrium largely favors allene **11** and the concentration of betaine **12** is too small to allow its direct spectroscopic observation. When the thermal rearrangement is conducted in the presence of a weak acid HA, **13**, an irreversible protonation of the betaine occurs to give an ion pair **14**, which rapidly collapses into dithiolone **15** and alkylated species **16**.[8] Thus, protonation transforms the betaine motif into a powerful leaving group with the counter-anion being the nucleophile itself.

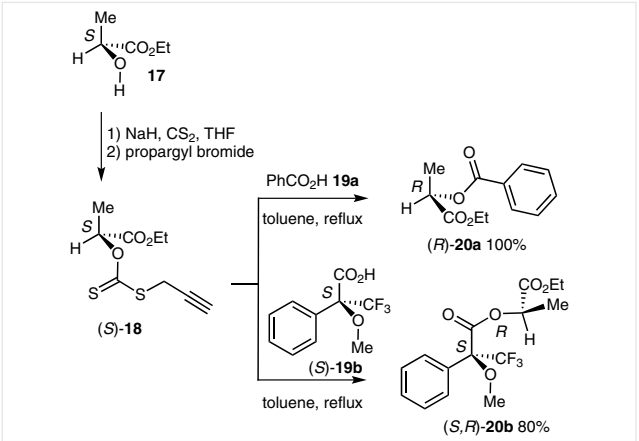


Scheme 1 Formation and capture of a betaine from an *S*-propargyl xanthate

The overall process represents an alkylation with inversion of configuration under quite mild conditions. It was therefore tempting to extend this chemistry to a lactic acid derivative, since this would allow the direct introduction of the chiral propionate group.

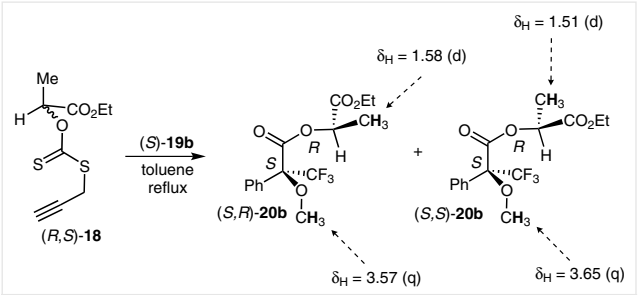
Our main concern from the outset was that the synthesis of the required reagent **10**, which entails the treatment of (*S*)-ethyl lactate with base followed by carbon disulfide and propargyl bromide, and which may not proceed without some degree of racemization. In the event, our worries were unfounded and the preparation of **10** proceeded without any noticeable erosion of the original optical purity of the lactate (Scheme 2). Thus, upon heating of xanthate **18** with benzoic acid (**19a**), the expected known benzoate of ethyl (*R*)-lactate **20a** was obtained in quantitative yield. The optical rotation of the product corresponded to the reported literature value and indicated that clean inversion had indeed taken place {$[\alpha]_D^{25}$ –13.2 (*c* 1.2, $CHCl_3$); Lit.[9] $[\alpha]_D^{17}$ –14.9 (*c* = 1.2, $CHCl_3$)}.

A more accurate method for measuring the enantiomeric purity involved making the corresponding Mosher ester (*S*,*R*)-20b from commercial Mosher acid (*S*)-**19b** (Scheme 2) and comparing its NMR spectrum with those of the two diastereoisomers (*S*,*R*)-**20b** and (*S*,*S*)-**20b** obtained by reaction of the same Mosher acid (*S*)-**19b** with racemic ethyl lactate (see relevant chemical shifts in Scheme 3). Not a trace of diastereoisomer (*S*,*S*)-**20b** was observed in the high-field NMR spectrum of the Mosher ester obtained by



Scheme 2 Formation of a benzoate and a Mosher ester from natural (*S*)-ethyl lactate

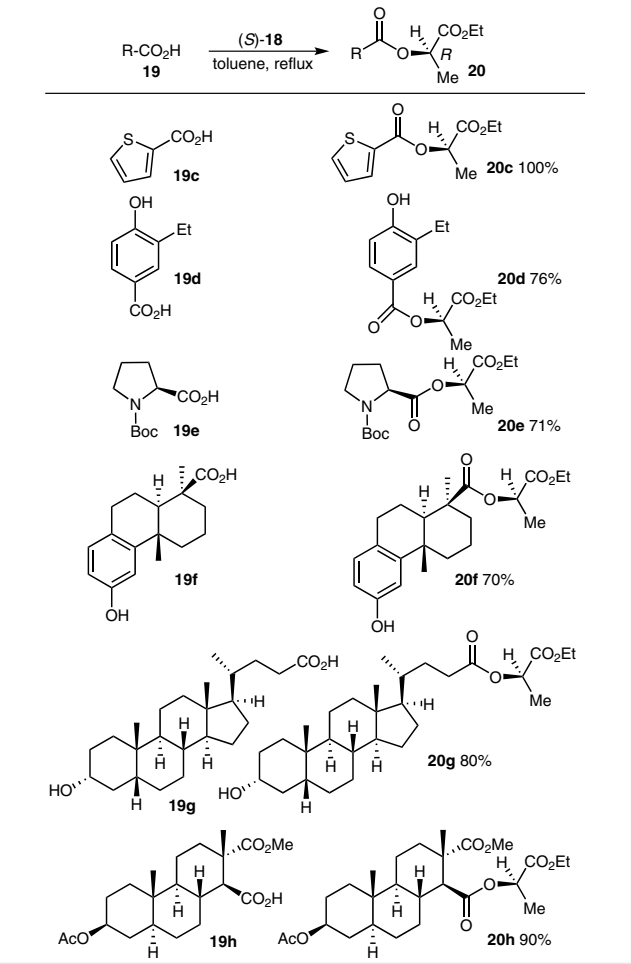
the reaction in Scheme 2. The transformation had therefore occurred with complete inversion and no racemization had taken place during the preparation of the xanthate reagent (*S*)-**18**.



Scheme 3 Formation of Mosher esters from racemic ethyl lactate

A series of esters **20** of the ethyl (*R*)-lactate esters were prepared in the same manner in generally high yield (Scheme 4). The formation of Boc-protected proline ester **20e** is especially interesting. Equally noteworthy is the clean formation of esters **20d** and **20f**, despite the presence of an unprotected phenol. The large difference in acidity between the two functional groups ensures that intermediate betaine **12** (Scheme 1) is protonated to give species **14** with a carboxylate and not a phenolate counter-anion. There is thus no need to protect phenols (or alcohols) if they are part of the substrate. Phenols and other functional groups can nevertheless react with intermediate betaine **12** if they are sufficiently acidic to protonate it. This is demonstrated by the examples in Scheme 5. Phenols **13a** and **13b** and hydroxypyridine **13c** reacted smoothly under the usual conditions to give aryl ethers **21a**, **21b**, and **21c**, respectively. Disappointingly, the somewhat less acidic phenol **13h** furnished quizalofop-ethyl (**9**) only in modest yield. This transformation was complicated by the very low solubility

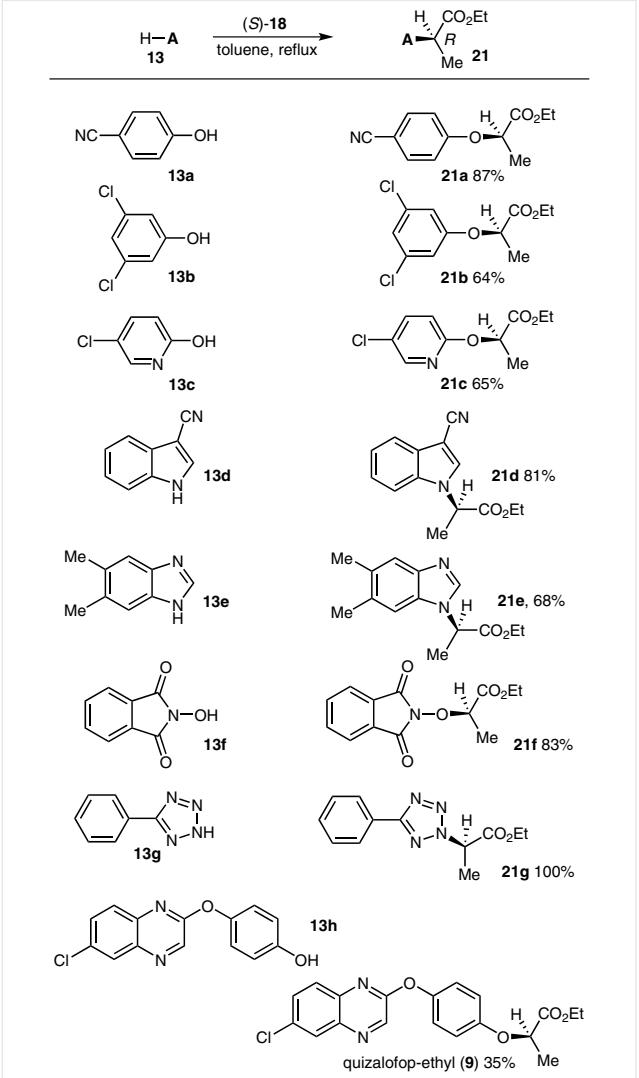
of phenol **13h**, and toluene had to be replaced by benzonitrile and the temperature had to be raised to 130 °C, which caused slow decomposition of reagent **18**. Phenols substituted with alkyl groups, such as estrone, did not react cleanly.



Scheme 4 Examples of ester formation with inversion from ethyl lactate

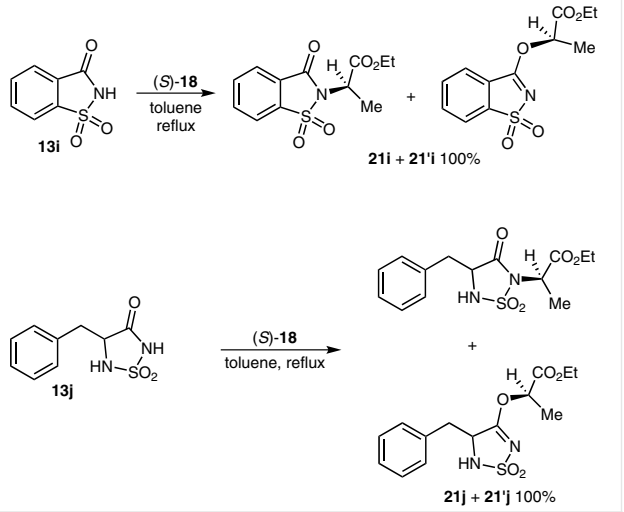
No difficulties were encountered with *N*-hydroxyphthalimide (**13f**) or with 'acidic' nitrogen derivatives: 3-cyanoindole (**13d**), benzimidazole **13e**, and phenyltetrazole **13g** (Scheme 5). The last three may be considered as aza analogues of the nonsteroidal anti-inflammatory drugs **1**–**4** in Figure 1 and could exhibit useful biological activities.[10]

Interestingly, we observed the formation of only one regioisomer in the reaction of hydroxypyridine **13c** and phenyltetrazole **13g**. This was not the case with saccharin (**13i**) and sulfonimide **13j** (Scheme 6). The reaction in both cases furnished a quantitative yield of a 1:1 mixture of *N*- and *O*-alkylated regioisomers **21i**/**21'i** and **21j**/**21'j**, respectively.



Scheme 5 Reaction of propargylic xanthate (*S*)-18 with various acidic derivatives

In summary, we have described a simple method for producing optically pure propionate derivatives from natural ethyl lactate. In the present context, this approach compares very favorably with the more traditional Mitsunobu reaction: it is more atom economical, since only one trivial shelf-stable reagent (*S*)-**18** is needed and much less waste is generated; no hazardous and expensive diazo coupling agent is involved; the experimental procedure is very simple and calls for mere heating of the acidic substance with xanthate (*S*)-**18** in refluxing toluene or other solvents with a similar boiling point; and the purification of the products is often very easy since the co-product, dithiolone **15**, is fairly volatile and the majority is in fact eliminated upon evaporation of the solvent. Numerous propionate derivatives can thus be prepared quickly and conveniently. Last,



Scheme 6 Formation of regioisomers from sulfonimides

but not least, this transformation reveals yet another fascinating mechanistic facet of the chemistry of *S*-propargyl xanthates.

Solvents were used as received. Merck Geduran SI 60 Å silica gel (35–70 µm) was used for column chromatography. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using 400 MHz ARX 400 Bruker spectrometers. Chemical shifts are given in ppm, referenced to the residual proton resonances of the solvents.

Ethyl (*S*)-2-{[(Prop-2-yn-1-ylthio)carbonothioyl]oxy}propanoate [(*S*)-18]

Ethyl (*S*)-(–)-lactate (**17**; 4 mL, 35.3 mmol) and CS_2 (21.22 mL, 352.94 mmol) were dissolved in anhyd THF (120 mL). The solution was cooled to 0 °C in an ice bath and NaH (1.016 g, 42.36 mmol) was added portionwise. The mixture was stirred for 30 min at r.t. and, after this time, again cooled to 0 °C in an ice bath. Then, propargyl bromide (9.43 mL, 105.9 mmol) was added dropwise. The reaction mixture was stirred at r.t. and followed by TLC until total absence of starting ethyl lactate. H_2O was carefully added, the solution was stirred for 20 min, and the solvent was removed under reduced pressure. The residue was extracted with Et_2O, dried ($MgSO_4$), and purified by flash column chromatography (silica gel, PE–EtOAc, 9:1).

Yield: 5.74 g, 24.7 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77–5.61 (q, *J* = 7 Hz, 1 H), 4.23 (q, *J* = 7 Hz, 2 H), 3.91 (dd, *J* = 4.4, 2.8 Hz, 2 H), 2.24 (t, *J* = 2.8 Hz, 1 H), 1.65 (d, *J* = 7 Hz, 3 H), 1.28 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.8, 169.3, 76.8, 76.7, 72.0, 61.6, 24.2, 17.0, 14.1.

MS (IC, NH_3): 233 [M + H$^+$].

Propionates 9, 20, and 21 Derived from the Propargyl Xanthate of (*S*)-(–)-Ethyl Lactate; General Procedure

Propargyl xanthate (*S*)-**18** (1 equiv) and the acidic substrate HA (2 equiv) were dissolved in toluene, unless stated otherwise (10 mL/mmol of propargyl xanthate). The mixture was refluxed under an argon atmosphere and followed by TLC until total conversion of the starting material (2–6 h). Then, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography. Due to the low solubility of compounds **13d**, **13e**, **19d**, and **19f** in toluene, chlorobenzene was used as a solvent in the reactions. In the experiment involving **13h**, benzonitrile was used as a solvent and the reaction was carried out at 130 °C. Finally, a few of the experiments were also carried out using the acid partner HA as the limiting reagent. No significant changes in yields were observed.

Ethyl (*R*)-2-{4-[(6-Chloroquinoxalin-2-yl)oxy]phenoxy}propanoate (Quizalofop-p-Ethyl; 9)

According to the general procedure, (*S*)-**18** (0.34 mmol) and **13h** (0.68 mmol) were dissolved in benzonitrile. After purification, the product was isolated as a grey solid.

Yield: 45 mg (0.12 mmol, 35%); mp 87–88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 7.96 (d, *J* = 2.4 Hz, 1 H), 7.60 (d, *J* = 8 Hz, 1 H), 7.52 (dd, *J* = 8, 2.4 Hz, 1 H), 7.10 (d, *J* = 8 Hz, 2 H), 6.88 (d, *J* = 8 Hz, 2 H), 4.68 (q, *J* = 8 Hz, 1 H), 4.18 (q, *J* = 8 Hz, 2 H), 1.57 (d, *J* = 8 Hz, 3 H), 1.21 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 157.2, 155.1, 146.5, 140.1, 139.7, 138.5, 132.8, 131.1, 128.8, 127.9, 123.0, 122.4, 116.0, 73.1, 61.3, 18.6, 14.1.

HRMS: *m*/*z* calcd: 372.0877; found: 372.0865, 299.0342 [M – CO_2Et].

(*R*)-1-Ethoxy-1-oxopropan-2-yl Benzoate [(*R*)-20a]

According to the general procedure, (*S*)-**18** (1.8 mmol) and **19a** (0.9 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 378 mg (0.91 mmol, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (m, 2 H), 7.59 (m, 1 H), 7.46 (m, 2 H), 5.32 (q, *J* = 7 Hz, 1 H), 4.24 (q, *J* = 7 Hz, 2 H), 1.64 (d, *J* = 7 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 166.0, 133.3, 129.9, 129.5, 128.4, 69.2, 61.4, 17.1, 14.1.

MS (IC, NH_3): 223 [M + H$^+$].

(*R*)-1-Ethoxy-1-oxopropan-2-yl (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate [(*S*,*R*)-20b]

According to the general procedure, (*S*)-**18** (0.5 mmol) and (*S*)-**19b** (1 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 130 mg (0.39 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (m, 2 H), 7.42 (m, 3 H), 5.28 (q, *J* =8 Hz, 1 H), 4.21 (q, *J* = 8 Hz, 2 H), 3.57 (d, *J* = 1.2 Hz, 3 H), 1.58 (d, *J* = 8 Hz, 3 H), 1.25 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 166.0, 131.6, 129.7, 128.3 (2C), 127.7, 124.5, 121.7, 84.6 (q), 70.4, 61.7, 55.4, 16.7, 14.0.

^{19}F NMR (300 MHz, $CDCl_3$): δ = 67.41 (s).

HRMS: *m*/*z* calcd: 334.1028; found: 265.1076 [M – CF_3].

(*R*)-1-Ethoxy-1-oxopropan-2-yl Thiophene-2-carboxylate (20c)

According to the general procedure, (*S*)-**18** (1.56 mmol) and **19c** (0.78 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 178 mg (0.78 mmol, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 5.2, 3.5 Hz, 1 H), 7.61 (dd, *J* = 6, 2 Hz, 1 H), 7.13 (dd, *J* = 5.2, 3.5 Hz, 1 H), 5.28 (q, *J* = 7 Hz, 1 H), 4.25 (q, *J* = 7 Hz, 2 H), 1.62 (d, *J* = 7 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 160.4, 123.7, 121.9, 116.4, 110.6, 68.6, 61.4, 17.2, 14.1.

MS (IC, NH_3): 229 [M + H$^+$].

(*R*)-1-Ethoxy-1-oxopropan-2-yl 3-Ethyl-4-hydroxybenzoate (20d)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **19d** (1 mmol) were dissolved in chlorobenzene. After purification, the product was isolated as a thick yellow oil.

Yield: 100 mg (0.38 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 4 Hz, 1 H), 7.71 (dd, *J* = 8, 2 Hz, 1 H), 6.86 (br s, 1 H), 6.71 (d, *J* = 8 Hz, 1 H), 5.28 (q, *J* = 8 Hz, 1 H), 4.25 (q, *J* = 8 Hz, 2 H), 2.61 (q, *J* = 8 Hz, 1 H), 1.63 (d, *J* = 8 Hz, 3 H), 1.29 (t, *J* = 8 Hz, 3 H), 1.20 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 166.4, 158.8, 131.3, 130.3, 129.5, 120.9, 114.9, 68.9, 61.7, 22.8, 17.1, 14.0, 13.6.

HRMS: *m*/*z* calcd: 266.1154; found: 266.1145.

1-*tert*-Butyl 2-[(*R*)-1-Ethoxy-1-oxopropan-2-yl] (*S*)-Pyrrolidine-1,2-dicarboxylate (20e)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **19e** (1 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 111 mg (0.35 mmol, 71%). The main rotamer is described.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (q, *J* = 8 Hz, 1 H), 4.26 (dd, *J* = 8, 4 Hz, 1 H), 4.16 (q, *J* = 8 Hz, 2 H), 3.49 (m, 2 H), 2.20 (m, 1 H), 2.04 (m, 2 H), 1.86 (m, 1 H), 1.45 (d, *J* = 8 Hz, 3 H), 1.39 (s, 3 H), 1.24 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 170.3, 153.7, 79.9, 68.8, 61.3, 59.2, 46.3, 30.7, 28.3, 23.4, 16.9, 14.0.

HRMS: *m*/*z* calcd: 315.1682; found: 315.1678.

(*R*)-1-Ethoxy-1-oxopropan-2-yl (1*S*,4a*S*,10a*R*)-6-Hydroxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate (20f)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **19f** (1 mmol) were dissolved in chlorobenzene. After purification, the product was isolated as a pale yellow solid.

Yield: 129 mg (0.35 mmol, 70%); mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 8 Hz, 1 H), 6.73 (d, *J* = 4 Hz, 1 H), 6.58, (dd, *J* = 8, 4 Hz, 1 H), 5.06 (q, *J* = 8 Hz, 1 H), 4.56 (br s, 1 H), 4.20 (q, *J* = 8 Hz, 2 H), 2.84 (dd, *J* = 16, 4 Hz, 1 H), 2.71 (m, 1 H), 2.30 (m, 1 H), 2.20 (m, 2 H), 2.00 (m, 2 H), 1.62 (m, 1 H), 1.57 (dd, *J* = 12, 4 Hz, 1 H), 1.48 (d, *J* = 8 Hz, 3 H), 1.36 (s, 3 H), 1.27 (t, *J* = 8, 8 Hz, 3 H), 1.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 171.1, 153.8, 149.3, 130.0, 127.3, 113.1, 112.1, 68.4, 61.4, 52.7, 44.0, 39.4, 38.7, 37.7, 31.4, 28.3, 23.2, 21.2, 19.8, 16.9, 14.0.

HRMS: *m*/*z* calcd: 374.2093; found: 374.2103.

(*R*)-1-Ethoxy-1-oxopropan-2-yl (4*R*)-4-[(3*R*,5*R*,10*S*,13*R*,17*R*)-3-Hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[α]phenanthren-17-yl]pentanoate (20g)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **19g** (1 mmol) were dissolved in toluene. After purification, the product was isolated as a pale white-yellow solid.

Yield: 191 mg (0.40 mmol, 80%); mp 59–60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (q, *J* = 8 Hz, 1 H), 4.19 (q, *J* = 8 Hz, 2 H), 3.60 (m, 1 H), 2.60 (d, *J* = 12 Hz, 1 H), 1.99 (s, 3 H), 1.39 (d, *J* = 8 Hz, 3 H), 1.22 (t, *J* = 8 Hz, 3 H), 1.18 (s, 3 H), 0.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 172.6, 170.7, 170.6, 73.4, 68.5, 61.2, 54.2, 51.9, 51.9, 45.3, 44.3, 36.3, 35.7, 35.6, 33.7, 33.5, 31.8, 28.1, 27.2, 21.4, 19.5, 16.8, 16.6, 14.0, 11.9.

HRMS: *m*/*z* calcd: 480.2723; found: 480.2729.

1-[(*R*)-1-Ethoxy-1-oxopropan-2-yl] 2-Methyl (1*S*,2*S*,4β*S*,7*S*,8α*S*)-7-Acetoxy-2,4β-dimethyltetradecahydrophenanthrene-1,2-dicarboxylate (20h)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **19h** (1 mmol) were dissolved in toluene. After purification, the product was isolated as a white-pink solid.

Yield: 214 mg (0.45 mmol, 90%); mp 81–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (q, *J* = 8 Hz, 1 H), 4.66 (m, 1 H), 4.14 (q, *J* = 8 Hz, 2 H), 3.64 (s, 3 H), 2.42 (m, 1 H), 2.30–2.22 (m, 2 H), 1.93 (d, *J* = 12 Hz, 1 H), 1.46 (d, *J* = 8 Hz, 3 H), 1.25 (t, *J* = 8 Hz, 3 H), 0.90 (d, *J* = 12 Hz, 3 H), 0.90 (s, 3 H), 0.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 170.9, 71.8, 68.4, 61.3, 56.4, 55.9, 42.7, 42.0, 40.4, 40.1, 36.3, 35.8, 35.4, 35.3, 34.5, 30.9, 30.7, 30.4, 28.1, 27.1, 26.4, 24.2, 23.3, 20.8, 18.2, 16.9, 14.1, 12.0.

HRMS: *m*/*z* calcd: 476.3502; found: 458.3386 [M – H_2O].

Ethyl (*R*)-2-(4-Cyanophenoxy)propanoate (21a)

According to the general procedure, (*S*)-**18** (5 mmol) and **13a** (2.5 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 480 mg (2.19 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 4.80 (q, *J* = 7 Hz, 1 H), 4.21 (q, *J* = 7 Hz, 2 H), 1.66 (d, *J* = 7 Hz, 3 H), 1.25 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 160.8, 118.9, 115.6, 104.7, 72.5, 61.6, 18.3, 14.0.

MS (IC, NH_3): 220 [M + H$^+$].

Ethyl (*R*)-2-(3,5-Dichlorophenoxy)propanoate (21b)

According to the general procedure, (*S*)-**18** (1.2 mmol) and **13b** (0.60 mmol) were dissolved in toluene. After purification, the product was isolated as a colorless oil.

Yield: 103 mg (0.39 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 2 Hz, 1 H), 6.77 (d, *J* = 2 Hz, 2 H), 4.72 (q, *J* = 7 Hz, 1 H), 4.25 (q, *J* = 7 Hz, 2 H), 1.62 (d, *J* = 7 Hz, 3 H), 1.28 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 158.6, 135.5, 121.9, 114.2, 73.0, 61.6, 18.4, 14.2.

MS (IC, NH_3): 263 [M + H$^+$].

Ethyl (*R*)-2-[(5-Chloropyridin-2-yl)oxy]propanoate (21c)

According to the general procedure, (*S*)-**18** (4.6 mmol) and **13c** (2.3 mmol) were dissolved in toluene. After purification, the product was isolated as a brown oil.

Yield: 343 mg (1.49 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 9.98 Hz, 1 H), 7.29 (dd, *J* = 9.98, 2.93 Hz, 1 H), 6.56 (d, *J* = 9.98 Hz, 1 H), 5.53 (q, *J* = 7.6 Hz, 1 H), 4.23 (q, *J* = 7 Hz, 2 H), 1.65 (d, *J* = 7.6 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 161.0, 140.6, 132.6, 121.5, 99.8, 64.1, 54.0, 16.7, 14.4.

MS (IC, NH_3): 230 [M + H$^+$].

Ethyl (*R*)-2-(3-Cyano-1*H*-indol-1-yl)propanoate (21d)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **13d** (1 mmol) were dissolved in chlorobenzene. After purification, the product was isolated as a brown oil.

Yield: 96 mg (0.405 mmol, 81%). Only one rotamer is described.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.71–7.64 (m, 2 H), 7.25 (m, 2 H), 4.64 (q, *J* = 8 Hz, 1 H), 4.25 (q, *J* = 8 Hz, 2 H), 1.52 (d, *J* = 8 Hz, 3 H), 1.23 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 134.2, 133.8, 124.0, 123.0, 120.3, 119.7, 115.3, 114.9, 88.3, 72.0, 61.5, 18.8, 14.1.

HRMS: *m*/*z* calcd: 242.1055; found: 242.1045.

Ethyl (*R*)-2-(5,6-Dimethyl-1*H*-benzo[δ]imidazol-1-yl)propanoate (21e)

According to the general procedure, (*S*)-**18** (0.5 mmol) and **13e** (1 mmol) were dissolved in chlorobenzene. After purification, the product was isolated as a brown solid.

Yield: 83 mg (0.34 mmol, 68%); mp 80–84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 8.04 (s, 1 H), 7.52 (s, 1 H), 5.86 (q, *J* = 8 Hz, 1 H), 4.29 (q, *J* = 8 Hz, 2 H), 2.39 (s, 3 H), 2.36 (s, 3 H), 1.81 (d, *J* = 8 Hz, 3 H), 1.32 (t, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.0, 169.3, 143.2, 135.0, 134.1, 129.7, 121.0, 116.2, 75.8, 61.9, 20.8, 20.2, 17.1, 14.1.

HRMS: *m*/*z* calcd: 246.1368; found: 246.1358.

Ethyl (*R*)-2-[(1,3-Dioxoisoindolin-2-yl)oxy]propanoate (21f)

According to the general procedure, (*S*)-**18** (3.6 mmol) and **13f** (1.8 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 404 mg (1.534 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (m, 2 H), 7.77 (m, 2 H), 4.87 (q, *J* = 7 Hz, 1 H), 4.23 (q, *J* = 7 Hz, 2 H), 1.65 (d, *J* = 7 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 163.3, 134.6, 128.8, 123.7, 81.3, 61.7, 16.4, 14.0.

MS (IC, NH_3): 264 [M + H$^+$].

Ethyl (*R*)-2-(5-Phenyl-2*H*-tetrazol-2-yl)propanoate (21g)

According to the general procedure, (*S*)-**18** (0.4 mmol) and **13g** (0.2 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 49 mg (0.198 mmol, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (m, 2 H), 7.52 (m, 3 H), 5.67 (q, *J* = 7.2 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 2.04 (d, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 130.4, 128.9, 127.3, 127.0, 62.2, 61.2, 16.7, 14.0.

MS (IC, NH_3): 247 [M + H$^+$].

Ethyl (*R*)-2-[1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl]propanoate (21i)

According to the general procedure, (*S*)-**18** (2 mmol) and **13i** (1 mmol) were dissolved in toluene. After purification, the product was isolated as a brown solid.

Yield: 140 mg (0.49 mmol, 50%); mp 90–93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 1 H), 7.94–7.83 (m, 3 H), 4.86–4.30 (q, *J* = 7.6 Hz, 1 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 1.87 (d, *J* = 7.6 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 154.8, 135.0, 134.4, 125.4, 121.0, 62.3, 49.9, 14.8, 14.1.

MS (IC, NH_3): 283 [M + H$^+$].

Ethyl (*R*)-2-[(1,1-Dioxidobenzo[*d*]isothiazol-3-yl)oxy]propanoate (21'i)

According to the general procedure, (*S*)-**18** (2 mmol) and **13i** (1 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 142 mg (0.50 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.71 (m, 4 H), 5.53 (q, *J* = 7.2 Hz, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 1.75 (d, *J* = 7.2 Hz, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 161.6, 143.6, 134.4, 133.6, 126.4, 123.6, 122.1, 75.2, 65.1, 17.2, 14.1.

MS (IC, NH_3): 283 [M + H$^+$].

Ethyl (2*R*)-2-(4-Benzyl-1,1-dioxido-3-oxo-1,2,5-thiadiazolidin-2-yl)propanoate (21j)

According to the general procedure, (*S*)-**18** (0.9 mmol) and **13j** (0.44 mmol) were dissolved in toluene. After purification, the product was isolated as a white solid.

Yield: 72 mg (0.22 mmol, 50%); mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 4.91 (d, *J* = 7.0 Hz, 1 H), 4.66 (q, *J* = 7 Hz, 1 H), 4.39 (m, 1 H), 4.21 (q, *J* = 7 Hz, 2 H), 3.33–3.13 (m, 2 H), 1.73 (d, *J* = 7 Hz, 3 H), 1.26 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 168.1, 134.8, 129.6, 129.1, 127.8, 62.4, 61.3, 51.3, 36.6, 14.1, 14.0.

MS (IC, NH_3): 327 [M + H$^+$].

Ethyl (2*R*)-2-[(4-Benzyl-1,1-dioxido-4,5-dihydro-1,2,5-thiadiazol-3-yl)oxy]propanoate (21'j)

According to the general procedure, (*S*)-**18** (0.9 mmol) and **13j** (0.44 mmol) were dissolved in toluene. After purification, the product was isolated as a yellow oil.

Yield: 71 mg (0.22 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 5.29 (d, *J* = 7.0 Hz, 1 H), 4.99 (q, *J* = 7 Hz, 1 H), 4.71–4.63 (m, 1 H), 4.27 (q, *J* = 7 Hz, 2 H), 3.29–2.95 (m, 2 H), 1.65 (d, *J* = 7 Hz, 3 H), 1.30 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 168.8, 135.1, 129.3, 129.0, 127.7, 76.2, 67.7, 62.3, 37.9, 17.1, 14.1.

MS (IC, NH_3): 327 [M + H^+].

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Supporting Information

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References

(1) Current address: Sintenovo S.A de C.v., Calle 13 este no 3, 62578 Civac Jiutepec, Estado de Morelos, México.
(2) (a) Rainsford, K. D. *Inflammopharmacology* **2009**, *17*, 275. (b) Wenger, J.; Niderman, T.; Mathews, C. In *Modern Crop Protection Compounds. Volume 1: Herbicides*; Krämer, W.; Schirmer, U.; Jeschke, P.; Witschel, M., Eds.; Wiley-VCH: Weinheim, **2012**, 447–478.
(3) For reviews, see: (a) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095. (b) Sonawane, R.; Bellur, S. N.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163.
(4) See, for example: (a) Barrett, A. G. M.; Braddock, C. D.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273. (b) King, J. F.; Loosmore, S. M.; Aslam, M.; Lock, J. D.; McGarrity, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 7108.
(5) (a) Dirlam, N. L.; Moore, B. S.; Urban, F. J. *J. Org. Chem.* **1987**, *52*, 3587. (b) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301. (c) For a review of the Mitsunobu reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(6) For recent reviews, see: (a) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519. (b) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002. (d) For an account of the discovery of this process, see: Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663.
(7) (a) Boivin, J.; Tailhan, C.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*, 5874. (b) Boivin, J.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 7853. (c) Boivin, J.; Henriet, E.; Tailhan, C.; Zard, S. Z. *Tetrahedron Lett.* **1993**, *34*, 2763. (d) Boivin, J.; Henriet, E. B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 5171. (e) Poelert, M. A.; Zard, S. Z. *Synlett* **1995**, 325. (f) Poelert, M.; Roger, W.; Zard, S. Z. *Chem. Commun.* **1996**, 743. (g) Tromeur-Fauré, M.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 1305. (h) Harrington, R.; Wright, D.; Zard, S. Z. *Heterocycles* **2012**, *86*, 965.
(8) (a) Boivin, J.; Henriet, E. B.; Zard, S. Z. *J. Am. Chem. Soc.* **1994**, *116*, 9739. (b) Tromeur-Fauré, M.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7301.
(9) Otera, J.; Nakazawa, K.; Secoguchi, K.; Orita, A. *Tetrahedron* **1997**, *40*, 13633.
(10) See, for example: (a) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. *J. Med. Chem.* **2014**, *57*, 1299. (b) Tomczuk, B. E.; Taylor, C. R. Jr.; Moses, L. M.; Sutherland, D. B.; Lo, Y. S.; Johnson, D. N.; Kinnier, W. B.; Kilpatrick, B. F. *J. Med. Chem.* **1991**, *34*, 2993.