A CONVENIENT SYNTHESIS OF HOMOCHIRAL δ-ALKYLATED α,β-UNSATURATED δ-LACTONES

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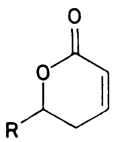
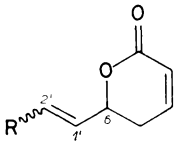
Dedicated to the memory of Professor František Šorm.

The tert-butyl propiolate ion serves as a convenient and efficient nucleophile in boron trifluoride-catalyzed openings of homochiral, mono-substituted epoxides. The resulting tert-butyl 5-hydroxy-2-alkynoates are converted into the title compounds upon semihydrogenation followed by acid hydrolysis. Specific examples include the synthesis of parasorbic acid and massoilactone, two naturally derived lactones of the present type. The scope of the synthetic protocol is discussed.

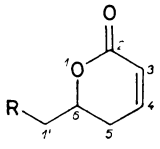
δ-Substituted α,β-unsaturated δ-valerolactones (6-substituted 5,6-dihydro-2*H*-pyran-2-ones) are widely distributed in plants and fungi, as such or as glycosidic progenitors[1]. They exhibit a range of biological activities, often providing a rationale for the established use in traditional medicine of the taxons whence they derive.[1] A major group of such naturally derived lactones conforms to structure *I*, in which R represents linear alkyl or 1-alkenyl groups, including variously oxidized derivatives hereof. Much interest has recently been devoted to the synthesis of such lactones. Thus, 6-(1′-alkenyl)-lactones *II* are approached mainly through formation of the exocyclic C(1′)—C(2′) double bond,[2-7] whereas members of the 6-alkyl series *III*, with which we shall here be concerned, are accessible primarily through bond-formation between C(5) and C(6), or, alternatively, C(4) and C(5). We have subjected the latter assemblage mode, not involving the chiral centre, to a closer study and present our results.



I



II



III

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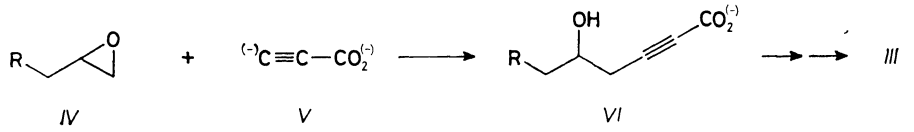
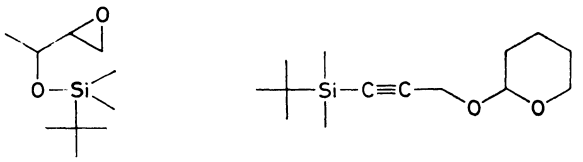
Early attempts to establish the C(4)—C(5) linkage involve epoxide openings by acetylide ion, followed by anion formation, carbonisation, partial hydrogenation, and acid-induced lactone formation[8]. The multistep approach was simplified by Carlson et al.[9] who demonstrated that the intermediate 5-hydroxyalkynoic acids *VI* were accessible through opening of simple oxiranes *IV* by the stable dianion of propiolic acid *V* (Scheme 1). A few naturally occurring lactones, or their antipodes, have been synthesized in low to moderate yields by this approach.[10–13] More recently, alternative, but less straightforward procedures for establishing the C(4)—C(5) linkage have been proposed[14,15].



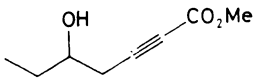
SCHEME 1

We first encountered difficulties with the Carlson-procedure when we failed to obtain yields in excess of a few per cent employing a diastereomer mixture of silylated oxiranes *VII*. Lithio derivatives of simple alkyl propiolates are precluded as alternatives to the dianion *V* due to their thermolability[9,16]. Our attempts to utilize the much more stable lithio derivative of tert-butyl propiolate[17] proved of no avail. We therefore turned to the lithio derivative of propargyl alcohol tetrahydropyranyl ether,[18] known to bring about ring opening of simple oxiranes.[19,20] Whereas epoxybutane *IV* (R = Me), as expected, reacted smoothly under ring-opening, the silylated oxirane mixture *VII* behaved differently, chiefly undergoing intermolecular O → C exchange of the silyl-grouping to give the alkynylsilane *VIII* as the major product.

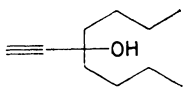


Under identical conditions the corresponding silyl ether, derived from 2-propanol, afforded the same silane *VIII* as the sole product. Although intramolecular O → C silyl group migrations are known to occur under the influence of strong bases,[21,22] the corresponding intermolecular shift, taking place, as here, under moderately basic conditions, seems to be without precedent.

In 1983, Yamaguchi and Hirao demonstrated that oxirane openings at −78°C with lithio derivatives of simple alkynes, not including propiolic acid nor esters hereof, were greatly facilitated by equimolecular amounts of boron trifluoride etherate.[23] The authors attributed the effect to the intermediacy of alkynyldifluoroboranes, an assumption that seems untenable in view of more recent studies.[24,25] Our attempts to open epoxybutane *IV* (R = Me) with the Carlson dianion *V* under these conditions failed, probably due to the formation of a stable complex between boron trifluoride and hexamethylphosphortriamide,[26] used in generating the dianion.[9] Replacement of the dianion *V* with the lithio derivative of methyl propiolate in the Yamaguchi reaction gave an almost equimolecular mixture of the desired ester *IX* and the carbinol *X*. In order to avoid 1,2-addition of butyllithium to the

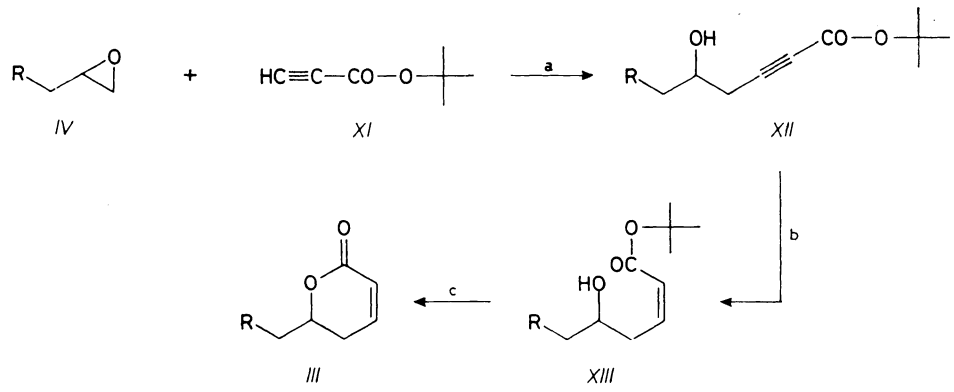


IX



X

ester grouping, tert-butyl propiolate[17] (*XI*) was tested as an alternative to the methyl ester in its reaction with epoxypropane and indeed found to afford the desired tert-butyl 5-hydroxyalkynoate (*XII*, R = H) in high yield after 10 min at −78°C (Scheme 2). Although lithium diisopropylamide serves well as a base for quantitative deprotonation of tert-butyl propiolate (*XI*) it cannot be employed in combination with boron trifluoride etherate, probably due to the reverse reaction taking place under these circumstances. It became obvious that boron trifluoride-promoted ring-openings of oxiranes with the lithio derivative of tert-butyl propiolate provide an



IV *XI* *XII* *III* *XIII*

a) 1. BuLi, THF; 2. BF_3, Et_2O, THF; 3. aq. KH_2PO_4 b) Lindlar catalyst c) TsOH, C_6H_6

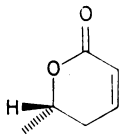
SCHEME 2

efficient route to δ-substituted, α,β-unsaturated δ-valerolactones *III* in as much as the ensuing partial reduction of the alkynoates *XII* to the *Z*-alkenoates *XIII* and the final, acid-induced transformation of the latter into the lactones *III* both proceed in virtually quantitative yields (Scheme 2).

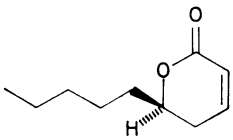
Thus, the hexenolactone *III* (R = H) was conveniently prepared in three steps from tert-butyl propiolate (*XI*) and epoxypropane *IV* (R = H) in an overall yield of 60%, comparing favourably with previous synthetic routes (cf. ref.[27]). Applying the commercially available (*S*)-propylene oxide to the reaction opens up an easy access to parasorbic acid (*XIV*), the long-known, major constituent of the volatile fraction of berries of mountain ash, *Sorbus aucuparia*.[1] A four-step synthesis of *XIV*, starting from L-rhamnose, has recently been reported.[27]

Massoilactone (*XV*), a compound with a long and interesting history,[28] was chosen as our second synthetic target. It is a major constituent of the bark oil of *Cryptocaria massoy* (OKEN) KOSTERMANS (Lauraceae)*, a species endemic to New Guinea, but handled and cherished notably on the Indonesian drug market. Several other natural sources of massoilactone have been reported, comprising plant as well as animal species.[1] About a dozen syntheses of the racemic decenolactone *III* (R = Bu) have been described but only a few of these lend themselves to the preparation of pure enantiomers. In 1976, Mori[10] reported the conversion of (*S*)-1,2-epoxyheptane into the antipode of *XV* by the Carlson method. The yield was 10% and the enantiomeric purity about 75% as shown by Pirkle and Adams[29] who synthesized both enantiomers in supposedly pure form. From their rotation values it follows that massoilactone (*XV*), derived from the bark-oil of *C. massoy*,[30] possesses an enantiomeric purity not exceeding 88%.

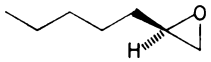
According to Scheme 2, (*R*, *S*)-1,2-epoxyheptane (*IV*, R = Bu) was converted into tert-butyl 5-hydroxy-2-decynoate (*XII*, R = Bu) in 75% yield, followed by quantitative semihydrogenation to give tert-butyl (*Z*)-5-hydroxy-2-decenoate (*XIII*, R = Bu) which, upon acid treatment, afforded an 86% yield of the racemic decenolactone *III* (R = Bu). This efficient sequence was subsequently utilized for the synthesis of massoilactone (*XV*).



XIV



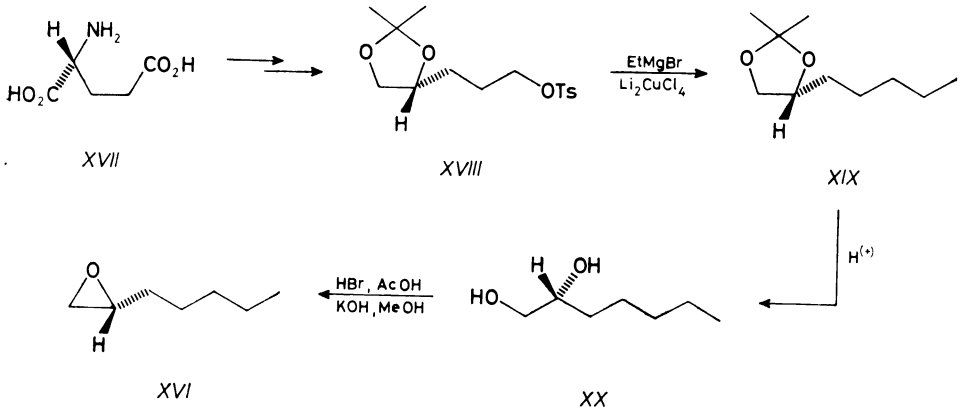
XV



XVI

* Considerable confusion exists as to the botanical source of the bark, and hence of *XV*. This source name is presented on the authority of Dr A. J. Kostermans, *Herbarium Bogoriense*, Bogor, Indonesia, a reputed expert on Lauraceae.[28]

The requisite (*R*)-1,2-epoxyheptane (*XVI*) was produced from D-glutamic acid (*XVII*) through the series of steps outlined in Scheme 3. Conversion of the amino acid* into the tosylate *XVIII*, performed as described by Larcheveque and Lalande,[32]



SCHEME 3

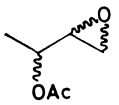
was followed by Cu-catalyzed coupling with ethylmagnesium bromide, according to the general instructions of Fouquet and Schlosser,[33] to give the acetal *XIX* which was hydrolyzed, without purification, to (*R*)-1,2-heptanediol (*XX*). Further conversion into (*R*)-1,2-epoxyheptane (*XVI*) was accomplished with hydrobromic acid in acetic acid, followed by methanolic base, as described for similar cases by Golding et al.[34] The synthetic material exhibited the rotation $[\alpha]_D^{20}$ +14·1°, to be compared with the reported rotations $[\alpha]_D^{21}$ −14·0° (ref.[10]) and $[\alpha]_D^{21}$ −15·6° (ref.[35]) for the (*S*)-enantiomer, prepared through different routes. Further conversion of oxirane *XVI* into massoilactone (*XV*) was performed as outlined in Scheme 2 (R = Bu). The synthetic end-product exhibited the rotation $[\alpha]_D^{20}$ −113·3°, to be compared with the rotation values $[\alpha]_D^{25}$ −97° for a lactone of natural derivation,[30] −110·5° (ref.[29]), +82·5° (ref.[10]), and −82·4° (76% ee)[36] for synthetic specimens of the two series.

Repetition of the above sequence, starting from L-glutamic acid, afforded the (*S*)-enantiomer of massoilactone, displaying a rotation $[\alpha]_D^{20}$ of +115°.

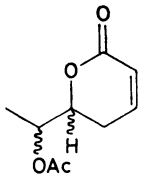
Though probably generally useful for the synthesis of simple homochiral δ-alkylated lactones *III* (R = alkyl), epoxide openings with tert-butyl propiolate ion, in their

* Chemical inversion of (*S*)-γ-hydroxymethyl-γ-butyrolactone, derivable from L-glutamic acid, to the here desired (*R*)-enantiomer, as described by Ho and Davies,[31] was accompanied by extensive racemization in our hands.

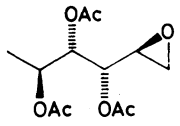
present execution, have some obvious and poorly understood limitations. Thus, whereas 1,2-epoxy-3-acetoxybutane (*XXI*, mixture of diastereomers) opens satisfactorily, easily providing the *O*-acetylated 1'-hydroxyethyllactone mixture *XXII* by the steps outlined in Scheme 2, no ring-opening was observed when the higher-substituted epoxide acetate *XXIII* (ref.[37]) was subjected to the reaction. Likewise, attempts to open the sugar epoxide *XXIV* (ref.[38]) were of no avail.



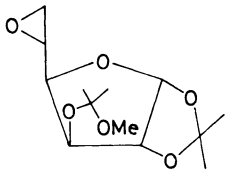
XXI



XXII



XXIII



XXIV

However, a better understanding of the BF_3-activation of these highly oxygenated substrates may well result in modified conditions under which the scope of the reaction becomes broader.

EXPERIMENTAL

^1H NMR spectra are recorded at 90 MHz or 250 MHz, ^{13}C NMR spectra at 22·6 MHz or 125 MHz, all on Bruker instruments, in deuteriochloroform, and with tetramethylsilane as an internal reference. Rotations are measured on a Perkin–Elmer 141 polarimeter. All reactions involving anions were conducted under rigorously anhydrous conditions in an argon atmosphere.

O → C Silyl Migrations

α-{[(1,1-*Dimethylethyl*)*dimethylsilyl*]*oxy*}-*ethyloxirane* (VII). α-Methallyl alcohol (1·6 g, 22 mmol) and imidazole (3·1 g, 46 mmol) were added to a solution of tert-butyldimethylchlorosilane (3·0 g, 20 mmol) in dimethylformamide (8 ml). After 0·5 h, ether and water were added. The organic phase was washed with ice-cold, diluted HCl, water, 3% sodium bicarbonate, and brine. After drying and evaporation the silyl ether remained as a colourless oil (2·9 g, 79%).

It was dissolved in dichloromethane (5 ml) and added to a solution of *m*-chloroperbenzoic acid (4·3 g, 17 mmol) in the same solvent (35 ml). After standing for 16 h at 20°C and filtration, the solution was washed with sodium sulfite, diluted alkali, diluted HCl, sodium bicarbonate,

and brine. After drying and evaporation, the crude product was distilled (Kugelrohr, 140°C, 1·6 kPa) to give the epoxide *VII* as a colourless oil which, according to the NMR spectra, consisted of an approximately 1 : 1 mixture of two diastereomers.

1-[(1,1-*Dimethylethyl*)*dimethylsilyl*]-3-[(*tetrahydropyran-2-yl*)*oxy*]*propyne* (VIII). Propargyl alcohol tetrahydropyranyl ether[18] (2·5 g, 18 mmol), dissolved in tetrahydrofuran (20 ml) was converted into its lithio derivative on adding butyllithium (1·55M solution in hexane, 12 ml, 19 mmol) at −10°C. After 15 min and cooling to −78°C, a solution of the above mixture of diastereomeric oxiranes *VII* (2·4 g, 12 mmol) in tetrahydrofuran (5 ml) and hexamethylphosphortriamide (9 ml) was added, and the temperature allowed to rise to 20°C. After 24 h the reaction mixture was quenched with 5M ammonium chloride and extracted with ethyl acetate. Chromatography on silica gel (ethyl acetate–hexane 1 : 9) of the mixture afforded, besides unreacted reactants, a fraction, which, after distillation (Kugelrohr, ~100°C, 133 Pa), was identified as the silylated alkyne *VIII* upon comparison with a synthetic specimen, produced by treating propargyl alcohol tetrahydropyranyl ether[18] (1·54 g, 11 mmol) with butyllithium, as described above, followed by tert-butyldimethylchlorosilane (1·5 g, 10 mmol) in tetrahydrofuran. After quenching, work-up, and distillation as above, the silylated alkyne *VIII* was obtained in pure form. For $C_{14}H_{26}O_2Si$ (254·4) calculated: 66·14% C, 10·24% H; found: 66·10% C, 10·29% H. ^{1}H NMR: 4·9 t, 1 H (O—CH—O); 4·3 s, 2 H (C≡C—CH_2—O); 3·8 m, 1 H, and 3·6 m, 1 H (ring CH_2—O); 1·6–1·8 m, 6 H (ring C—CH_2—C); 0·95 s, 9 H (tert-butyl); 0·15 s, 6 H (CH_3).

2-{[(1,1-*Dimethylethyl*)*dimethylsilyl*]*oxy*}*propane*. 2-Propanol was subjected to silylation with tert-butyldimethylchlorosilane as described above for α-methallyl alcohol. The pure silyl ether was obtained after distillation (Kugelrohr, 120°C, 19 kPa), 75% yield. For $C_9H_{22}OSi$ (174·4) calculated: 62·07% C, 12·64% H; found: 62·12% C, 12·65% H. ^{1}H NMR: 3·95 septet, 1 H (CH); 1·11 d, 6 H (2 × C—CH_3); 0·86 s, 9 H (tert-butyl); 0·03 s, 6 H (Si—CH_3).

On standing for 48 h at 20°C with the lithio derivative of propargyl alcohol tetrahydropyranyl ether,[18] as described above for the silylated oxirane alcohol *VII*, the silylated 2-propanol produced a 44% yield of the silylated alkyne *VIII*.

Reaction of Oxiranes with Alkyl Propiolates

Epoxybutane and methyl propiolate. Methyl propiolate (2·5 g, 30 mmol), dissolved in tetrahydrofuran (40 ml), was cooled to −78°C. Butyllithium (1·6M solution in hexane, 20 ml, 32 mmol) was added, followed by epoxybutane (2·2 g, 30 mmol) and boron triffuoride etherate (4·0 ml, 32 mmol). The reaction mixture was quenched with 5M ammonium chloride after 30 min and worked up in the usual way. The resulting oil was subjected to chromatography on silica gel, with a gradient of ethyl acetate–hexane as the mobile phase. The two major compounds were individually purified by distillation (Kugelrohr, 150°C, 80 Pa).

The fastest moving fraction (1·0 g, 30%) was identified as 3-*butyl*-1-*heptyn*-3-*ol* (X) by spectroscopic means (^{1}H, ^{13}C and MS).

The slower moving fraction (0·9 g, 27%) consisted of the expected *methyl* 5-*hydroxy*-2-*heptynoate*[9] (IX). For $C_8H_{12}O_3$ (156·2) calculated: 61·5% C, 7·75% H; found: 61·1% C, 7·8% H. ^{13}C NMR: 154·0 (C=O), 86·9 and 74·5 (C≡C), 70·8 (CHOH), 52·7 (O—CH_3), 29·3 and 27·1 (CH_2), and 9·9 (CH_3).

Epoxypropane and tert-butyl propiolate. Butyllithium (1·6M solution in hexane, 12·5 ml, 20 mmol) was added slowly to a solution of tert-butyl propiolate[17] (*XI*) (2·5 g, 20 mmol) in tetrahydrofuran (40 ml) at −78°C. After stirring for 15 min, epoxypropane (2·3 g, 40 mmol), dissolved in tetrahydrofuran (15 ml), was added, followed by dropwise addition of boron trifluoride etherate (5·1 ml, 40 mmol), dissolved in tetrahydrofuran (15 ml). After 1·5 h stirring,

potassium dihydrogen phosphate (10%, 15 ml) was added, and the mixture was allowed to come to room temperature. The organic solvent was removed in vacuo and the residue extracted with ether–pentane (1 : 1). The crude product was flash-chromatographed on silica (ethyl acetate–hexane, 1 : 4) to give gas-chromatographically homogeneous *tert-butyl 5-hydroxy-2-hexynoate* (XII, R = H) (1·5 g, 71%). ^{1}H NMR: 4·0 m, 1 H (CH—O); 2·76 br s, 1 H (OH); 2·48 d, 2 H (CH_2); 1·51 s, 9 H (tert-butyl); 1·32 d, 3 H (CH_3). ^{13}C NMR: 152·9, 83·6, 83·4, 76·2, 65·2, 29·1, 28·0, 22·5.

6-Methyl-5,6-dihydro-2*H*-pyran-2-one (*III*, R = H)

Tert-butyl 5-hydroxy-2-hexynoate (1·4 g, 7·6 mmol) was dissolved in ethyl acetate (50 ml) and subjected to hydrogenation in the presence of a Lindlar catalyst (230 mg). After the uptake of 7·6 mmol of hydrogen, the suspension was filtered and the solvent removed to give *tert-butyl* (Z)-5-*hydroxy*-2-*hexenoate* (XIII, R = H) (1·35 g, 96%).

The ester (1·2 g, 6·5 mmol) was dissolved in water-saturated toluene containing *p*-toluenesulfonic acid hydrate (0·12 g, 0·65 mmol) and heated to reflux for 1 h. The solution was washed with sodium bicarbonate, concentrated, and the residue distilled (Kugelrohr, 140°C, 400 Pa) to give 6-*methyl*-5,6-*dihydro*-2H-*pyran*-2-*one* (III, R = H) (0·54 g, 74%) as a colourless oil. ^{1}H NMR: 6·91 m, 1 H (H-4); 6·02 m, 1 H (H-3); 4·60 m, 1 H (H-6); 2·38 m, 2 H (H-5); 1·45 d, 3 H (CH_3). ^{13}C NMR: 164·2, 144·9, 120·8, 74·1, 30·7, 20·4. MS, *m/e*: 112, 97, 69, 68, 43, 42, 41, 40, 39, a pattern in accordance with literature data.[39]

6-Pentyl-5,6-dihydro-2*H*-pyran-2-one (*III*, R = Bu)

Tert-butyl propiolate (*XI*) (1·5 g, 12 mmol) was converted into its lithio derivative and reacted with 1,2-epoxyheptane (*IV*, R = Bu) (1·2 g, 10·5 mmol), produced by oxidation of 1-heptene with *m*-chloroperbenzoic acid, and boron trifluoride etherate (3·2 ml, 24 mmol) in tetrahydrofuran, as described above for the epoxypropane. Chromatography on silica afforded the pure *tert-butyl 5-hydroxy-2-decynoate* (XII, R = Bu) (1·9 g, 75%). For $C_{14}H_{24}O_3$ (240·3) calculated: 69·9% C, 10·1% H; found: 69·9% C, 10·1% H.

Semihydrogenation, conducted as described above, gave a quantitative yield of *tert-butyl* (Z)-5-*hydroxy*-2-*decenoate* (XIII, R = Bu) as a colourless oil. For $C_{14}H_{26}O_3$ (242·3) calculated: 69·4% C, 10·8% H; found: 69·3% C, 10·8% H.

The olefinic ester was subjected to acid hydrolysis as described above for the analogous hexenoate to give, after distillation (Kugelrohr), a pure specimen of 6-*pentyl*-5,6-*dihydro*-2H-*pyran*-2-*one* (III, R = Bu) (86%). ^{1}H NMR: 6·9 m, 1 H (H-4); 6·0 dt, 1 H (H-3); 4·4 m, 1 H (H-6); 2·3—2·4 m, 2 H (H-5); 1·0—1·8 m, 8 H (CH_2); 0·9 t, 3 H (CH_3). ^{13}C NMR: 164·3, 144·9, 121·1, 77·8, 34·6, 31·3, 29·2, 24·3, 22·2, 13·7. MS: identical with literature.[39]

Massoilactone [(*R*)-6-Pentyl-5,6-dihydro-2*H*-pyran-2-one] (*XV*)

D-Glutamic acid was converted into (*R*)-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonylpentan-1,2,5-triol (*XVIII*), essentially following the directions given by Larcheveque and Lalande[32] for the enantiomeric series.

To magnesium turnings (1 g, 42 mmol), covered with anhydrous ether (30 ml) in an evacuated, septum-closed flask, a solution of ethyl bromide (4·3 g, 32 mmol) in tetrahydrofuran (30 ml) was added. After ended reaction, the flask was cooled to −78°C and the tosylate *XVIII* (6·7 g, 21 mmol), dissolved in tetrahydrofuran (20 ml), added, along with a lithium cupric chloride solution in the same solvent[33] (1·0 ml). The temperature was raised to −55°C, and, after 1 h,

slowly to 30°C. Next day, the reaction mixture was quenched with ammonium chloride solution and the crude product *XIX* isolated by ether extraction. Without further purification the acetal was dissolved in methanol (50 ml); conc. HCl (2·7 ml) and water (6 ml) were added and the mixture kept at 20°C for 48 h. The methanol was removed in vacuo and the aqueous phase continuously extracted with ether. Chromatographic purification of the extract yielded pure (R)-*heptan*-1,2-*diol* (XX) (1·53 g, 55%), $[\alpha]_D^{20}$ +17·1° (*c* 2, ethanol) (reported[10] −15·2° for the enantiomer), exhibiting spectroscopic properties identical with those reported for the enantiomer.[10]

The diol (1·5 g, 11·4 mmol) was added to glacial acetic acid, saturated with hydrogen bromide (9·2 g, 6·6 ml), and kept at 0°C. After 5 min, the mixture was placed at room temperature for 30 min. Water was added (25 ml) and the solution was neutralized with sodium carbonate and extracted with ether. After evaporation of the solvent the residue was dissolved in methanol (5 ml) containing potassium hydroxide (0·6 g). After 15 min, water was added to dissolve the potassium bromide, and the solution thoroughly extracted with ether. After drying and careful removal of the ether by column distillation, a colourless oil remained (0·75 g, 58%) consisting of (R)-1,2-*epoxyheptane* (XVI), $[\alpha]_D^{20}$ +14·1° (*c* 2·6, ethanol); reported: −14·0° (ref.[10]), −15·6° (ref.[35]) for the enantiomer.

Following the procedure described above for the racemic series, the (*R*)-1,2-epoxyheptane (*XVI*) was converted into (R)-*tert-butyl*-5-*hydroxy*-2-*decynoate*, obtained as a colourless oil, $[\alpha]_D^{20}$ −6·0° (*c* 0·7, dichloromethane). For $C_{14}H_{24}O_3$ (240·3) calculated: 69·9% C, 10·1% H; found: 69·6% C, 10·2% H. ^{1}H NMR: 3·85 quintet, 1 H (CH); 2·5 ddd, 2 H (CH_2—C≡C); 2·05 br s, 1 H (OH); 1·5 s, 9 H (tert-butyl); 1·3—1·6 m, 8 H (4 × CH_2); 0·9 t, 3 H (CH_3). ^{13}C NMR: 152·7, 83·4, 83·3, 76·3, 69·6, 36·4, 31·7, 28·0, 27·6, 25·2, 22·6, 14·0. Semihydrogenation converted the alkyne ester into (R)-*tert-butyl*-(Z)-5-*hydroxy*-2-*decenoate*, a colourless oil, $[\alpha]_D^{20}$ +8·7° (*c* 0·8, dichloromethane). For $C_{14}H_{26}O_3$ (242·3) calculated: 69·4% C, 10·9% H; found: 69·3% C, 10·9% H. ^{1}H NMR: 6·3 dt, 1 H (H-3); 5·85 dt, 1 H (H-2); 3·75 quintet. 1 H (H-5); 2·75 m, 2 H (2 × H-4); 2·3 br s, 1 H (OH); 1·5 s, 9 H (tert-butyl); 1·3—1·5 m, 8 H (4 × CH_2); 0·9 t, 3 H (CH_3). ^{13}C NMR: 166·5, 144·5, 123·8, 80·6, 71·3, 37·6, 31·6, 28·2, 25·3, 22·6, 14·1. Finally, acid treatment of the α,β-unsaturated ester, as described in the racemic series, produced massoilactone (*XV*) as a colourless oil, after distillation in vacuo, $[\alpha]_D^{20}$ −113° (*c* 1·7, chloroform) (reported[29] −110·5°).

The whole sequence was repeated, starting from L-glutamic acid, to give the (*S*)-enantiomer of massoilactone, $[\alpha]_D^{20}$ +115° (*c* 0·8, chloroform), reported +82·5° (ref.[10]), +109° (ref.[29]).

1′-Acetoxy-6-ethyl-5,6-dihydro-2*H*-pyran-2-one (*XXII*)

α-Methallyl acetate (4·5 g, 39 mmol) was dissolved in dichloromethane (100 ml) together with *m*-chloroperbenzoic acid (10·0 g, 47 mmol). After 4 days at 20°C, the solution was washed with sodium sulfite and sodium bicarbonate. The residue was distilled (Kugelrohr, 170°C) to give a mixture (3·7 g, 72%) of erythro- and threo-1,2-*epoxy*-3-*acetoxybutane* (XXI) in a ratio of about 1 : 2 according to gas-chromatographic analysis of the mixture and a synthetic specimen of the pure *erythro*-isomer, produced in this laboratory in connection with other work.

The mixture (195 mg, 1·5 mmol) was reacted with tert-butyl propiolate (189 mg, 1·5 mmol), butyllithium (1·5 mmol), and boron triffuoride etherate (1·5 mmol) in tetrahydrofuran and worked up by the standard procedure described above. A mixture of the diastereomeric *tert-butyl* 6-*acetoxy*-5-*hydroxy*-2-*heptynoates* (344 mg, 90%) was obtained and subjected to semihydrogenation without further purification. The resulting mixture of diastereomeric *tert-butyl* (Z)-6-*acetoxy*-5-*hydroxy*-2-*heptenoates* was finally converted into the corresponding mixture of diastereomeric 1′-*acetoxy*-6-*ethyl*-5,6-*dihydro*-2H-*pyran*-2-*ones* (XXII), purified by distillation

(Kugelrohr, 110°C, 53 Pa). ^{1}H NMR, *threo*(*erythro*): 6·95 m, 1 H (H-4); 6·08 dd, 1 H (H-3); 5·08 (5·11) dq, 1 H (H-1'); 4·45 m, 1 H (H-6); 2·3—2·5 m, 2 H (2 × H-5); 2·10 (2·12) s, 3 H (CH_3CO); 1·35 (1·36) d, 3 H (CH_3).

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