Renewed «Isoxazoline Route» for the Synthesis of Densely Functionalized Ketones

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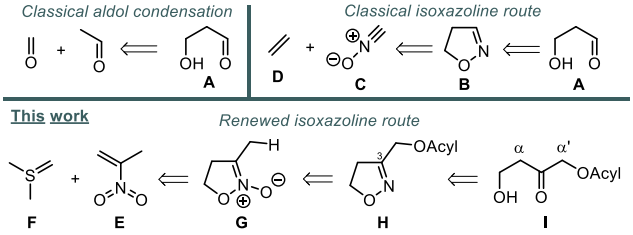
In this work, the «isoxazoline route» to aldols involving the [3+2]-cycloaddition of nitrile oxide to alkenes and hydrogenolysis of oxime group was revisited. To avoid regioselectivity issues, [4+1]-annulation of nitroalkenes with sulfonium ylides was used to construct the isoxazoline ring bearing an N-oxide moiety. Subsequent deoxygenative C-H functionalization using Boekelheide rearrangement and hydrogenolysis of the isoxazoline ring afforded α'-acyloxy-substituted aldols, which are difficult to access both by classical aldol reaction and the «isoxazoline route». The products are formed in good to high overall yields and as single diastereomers in most cases. The synthetic use of these aldols was showcased by their smooth transformation into diastereomerically pure triols and a 2,3-diaryl-4-hydroxy-substituted tetrahydrofurane derivative, which is structurally related to Cinncassin B.

Introduction

Aldol condensation is undoubtedly one of the most general and widely applied carbon-carbon bond forming transformations.[1] Despite of a great progress in developing new methods for aldol reaction,[1e-k] regio- and diastereoselective synthesis of aldols A is still challenging in many cases (Scheme 1). An alternative to a classical aldol condensation is a so-called «isoxazoline route»,[2] which consists in hydrogenolysis of isoxazolines B generated by a [3+2] cycloaddition of nitrile oxides **C** with alkenes **D** (Scheme 1). This strategy received much attention in the end of 20th century and was successfully exploited in total synthesis of numerous natural products.[3] However, «isoxazoline route» has limitations associated with regioselectivity issues at the dipolar cycloaddition stage,[4a] unless it is performed in an intramolecular fashion. In the intermolecular variant, satisfactory regioselectivity can be achieved only with mono-substituted dipolarophiles and processes involving chelation reagents.[4b-d] Reactions of nitrile oxides with non-symmetrical 1,2-disubstituted alkenes (stilbenes, chalcones, cinnamates, etc.) produce mixtures of regioisomeric isoxazolines.[4a] Thus, due to certain restrictions at the [3+2]-cycloaddition stage, the "isoxazoline route" cannot be considered as a universal methodology to access aldols with different substitution patterns.

A possible solution to this issue could be the assembly of isoxazolines by [4+1]-annulation reactions, which are more regioselective compared to the [3+2]-cycloaddition of nitrile oxides. In the past few years, our group has been actively involved in the development of [4+1]-annulation methodology to construct isoxazoline ring.[5] We have shown that isoxazolines with a functionalized alkyl group at the C-3 atom can be prepared by a [4+1]-annulation between nitroalkenes **E** and sulfonium ylides **F**



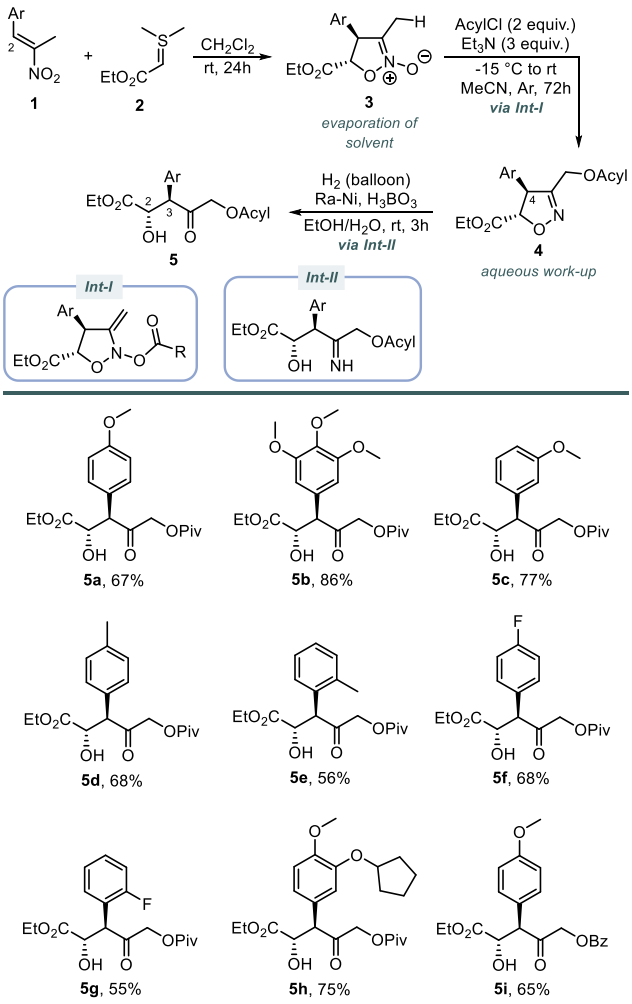
Scheme 1. Overview of the routes to aldol products and this work

followed by deoxygenative C-H functionalizations of the resulting isoxazoline *N*-oxides **G**.[5a,c,d] In this work, we aimed to demonstrate that this approach complements to the Classical «isoxazoline route» providing an expedient access to aldols bearing additional functionality at the α' carbon atom, which are difficult to access both by a classical aldol reaction and the «isoxazoline route» (Scheme 1). In particular, here we wish to report a regio- and diastereoselective method for preparation of bis-oxygenated ketones of type **I** in a 3-step sequence from nitroalkenes **E** and ylides **F**. Also, synthetically useful transformations of aldols **I** were showcased in this work.

Results and Discussion

The proposed approach to aldols **I** (Scheme 1) required C-H oxygenation of the methyl group at the C-3 position in isoxazoline *N*-oxides **G**. This was sought to be accomplished via tandem O-acylation/[3,3]-rearrangement process (Boekelheide rearrangement[6]), which was previously shown to be efficient for related 6-membered cyclic *N*-oxides (Scheme 2).[6b,d]

Thus, model isoxazoline-*N*-oxide **3a** (Ar = 4-MeO-C_6H_4) was generated in a completely stereoselective fashion by reacting nitrostyrene **1a** with stabilized sulfonium ylide **2** (Scheme 2). Treatment of *N*-oxide **3a** with pivaloyl chloride (PivCl) and Et_3N in MeCN led to a slow

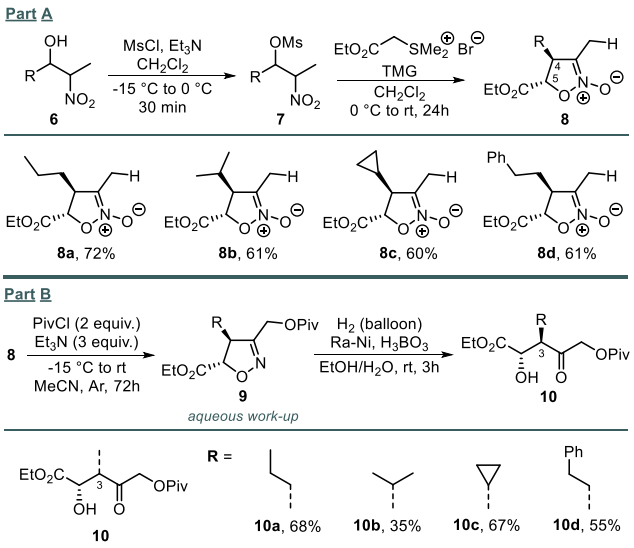


Scheme 2. Synthesis of aldol products **5** from aryl nitroalkenes **1**

conversion into 3-acyloxymethyl-substituted isoxazoline **4a**. With excess reagents (2 equiv. PivCl, 3 equiv. Et_3N), complete conversion of *N*-oxide **3a** and nearly quantitative yield of product **4a** were achieved within 72 h at ambient temperature. Since both [4+1]-annulation and Boekelheide rearrangement proceeded without any noticeable side products, intermediates **3a** and **4a** were not subjected to a chromatographic purification. Hydrogenolysis of crude isoxazoline **4a** at ca. 1 bar of H_2 (balloon) over Raney nickel (Ra-Ni) in the presence of boric acid delivered the desired hydroxyketone **5a** in 67% total yield based on nitroalkene **1a**.

Substrate scope of this method was then explored (Scheme 2). Nitrostyrenes **1** having alkyl, alkoxy groups and fluorine in the aromatic ring produced the corresponding polyfunctionalized ketones **5** in moderate to good yields over three steps. The highest yields were observed with nitrostyrenes **1** having an alkoxy group at the meta-position. Thus, ketones **5b** and **5h** bearing pharmacophore di- and trialkoxyaryl fragments[7] were obtained in 86% and 75%, respectively. The developed sequence is efficient and practical, since a single column chromatography was required over three steps. Moreover, due to an exceptionally high stereoselectivity of the [4+1]-annulation stage, final aldols **5a-h** were obtained as single diastereomers with 2,3-anti-disposition of hydroxyl and aryl groups.

We then investigated the effect of the acylating agent used in the second stage of the sequence. In a similar fashion to PivCl, benzyl chloride was successfully involved in the acylation stage leading to benzoyloxy-substituted aldol **5i** after hydrogenolysis (Scheme 2). However, acyl halides possessing a hydrogen atom in the α-position (e.g. isobutyryl chloride) were not suitable for Boekelheide rearrangement of isoxazoline-*N*-oxides **3**. This may be due to a generation of ketenes from these acyl halides under the reaction conditions. Ketenes may undergo dimerization and side reactions involving *N*-oxides **3**.[8] Unlike nitrostyrenes **1**, aliphatic nitroalkenes are labile upon isolation and storage that limits their synthetic application. Recently, we developed the synthesis of 3-alkyl substituted isoxazoline-*N*-oxides **8** from vicinal nitroalcohols **6**, in which isolation of aliphatic nitroalkenes is avoided (Scheme 3, Part A).[5a] In this method, nitroalkenes generated *in situ* from mesylates **7** are intercepted with sulfonium ylide **2** (also generated *in situ* from corresponding sulfonium salt). Using this method, several new isoxazoline-*N*-oxides **8a-d** bearing alkyl groups at the C-4 position were prepared. Due to the formation of side products, chromatographic purification of these *N*-oxides was needed. Note that switching from nitrostyrenes **1** to aliphatic nitroalkenes did not affect the stereoselectivity of the [4+1]-annulation, and *N*-oxides **8a-d** were obtained as single stereoisomers with 2,3-

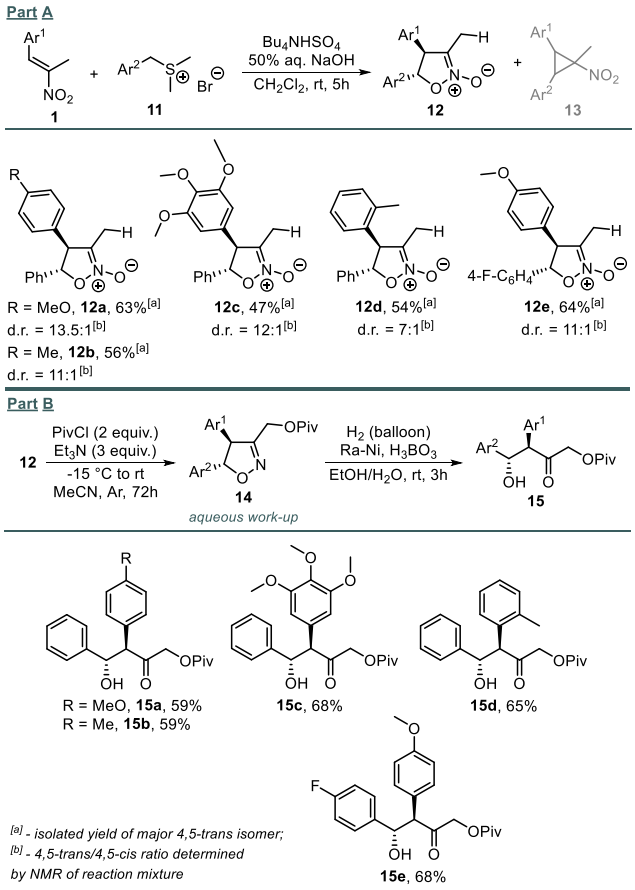


Scheme 3. Synthesis of aldol products **5** from alkyl nitroalcoholes **6**

trans-configuration. Acylation followed by hydrogenolysis of the resulting isoxazolines **9a-d** produced the desired aldols **10a-d** in moderate yields (Scheme 3, Part B).

Ketones **5** and **10** can be formally viewed as products of aldol condensation involving ethyl glyoxylate. For a variation of the "formal carbonyl component" in the structure of these aldols, aryl-substituted ylides derived from sulfonium salts **11** were used instead of ester-stabilized ylide **2** (Scheme 4, Part A). Since reaction of nitroalkenes with this type of unstabilized ylides is poorly explored,[9] a short optimization of conditions was performed on a model nitrostyrene **1a** and benzylsulfonium salt **11a** (Ar^2 = Ph, see Supporting information). The highest yield of isoxazoline-*N*-oxide **12a** (63%) was achieved when the reaction was conducted in a biphasic system CH_2Cl_2/50% aqueous NaOH with a phase-transfer catalyst (Bu_4NHSO_4). The second product was the nitrocyclopropane derivative **13a** (28%, Ar^1 = 4-$MeOC_6H_4$-, Ar^2 = Ph). *N*-Oxide **12a** was formed as a mixture of diastereomers with 4,5-trans-isomer being predominant (d.r. ca. 14 : 1). The isomers could be separated by column chromatography.

Under the same conditions, previously unknown 4,5-diaryl-substituted isoxazoline-N-oxides **12a-d** were synthesized in moderate yields from different involved in the [4+1]-annulation with nitroalkene **1a** affording product **12e** in 64% yield. Isoxazoline-*N*- nitrostyrenes **1** (47-63%, Scheme 4, Part A). Also, p-fluorobenzylsulfonium salt **11b** was successfully oxides **12a-e** were then converted into corresponding diaryl-substituted aldols **15** via Boekelheide rearrangement and catalytic hydrogenation of isoxazolines **14** (Scheme 4, Part B). Importantly, benzylic hydroxyl moiety remained intact upon catalytic hydrogenation under these conditions. Note, that transient isoxazolines **14a-e** possessing two different aryl groups at C-4 and C-5 cannot be prepared in a regioselective manner by the [3+2]-cycloaddition of nitrile-oxides with corresponding non-symmetrical stilbenes.



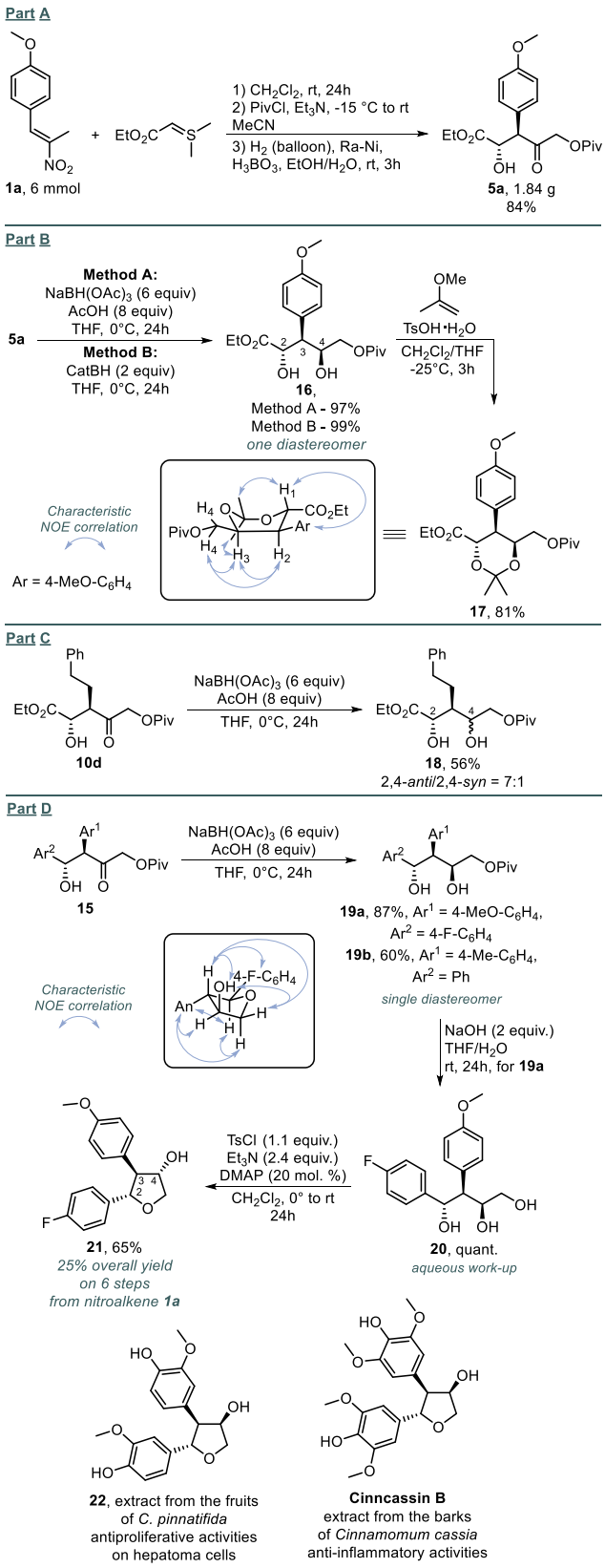
Scheme 4. Synthesis of biaryl aldol products **15** from aryl-stabilized sulfonium ylides

The synthetic potential of the obtained aldols was then explored (Scheme 5). Firstly, a scale-up study was performed. Starting from **6** mmol of nitroalkene **1a**, 1.84 grams (84 %) of the desired aldol **5a** were prepared. Interestingly, in the scale-up experiment the yield of **5a** was even higher than in a model experiment performed on 1 mmol of nitroalkene **1a** (cf. with data in Schemes 2 and 5, Part A). Thus, multi-gram quantities of aldols **5** can be prepared using this method with high efficiency.

Aldols are conventionally used as precursors of 1,3-dioles, which widely occur in the structure of natural products. This transformation is typically accomplished by stereoselective reduction with borohydride reagents.[10a] Thus, reduction of model aldol **5a** with $NaBH(OAc)_3$/AcOH system in THF produced a single diastereomer of triol derivative **16** in 97 % yield (Scheme 5, Part B). To establish the relative configuration of all three contiguous stereocenters, product **16** was converted into the cyclic acetal **17** by treatment with 2-methoxypropene and TsOH. Analysis of 2D NOESY revealed characteristic correlations H-2/H-3 and H-1/aryl from which 2,3-anti/3,4-syn configuration in product **16** was deduced. This stereochemical assignment was also supported by the fact that H-1 and H-3 hydrogens gave cross-peaks with different methyl groups.

An unexpected result was obtained in the reduction of ketone **5a** with catecholborane (Scheme 5, Part B). This method is known to produce 1,3-syn isomers of diols upon reduction of aldols.[10b] However, in the case of aldol **5a**, selective 1,3-anti-reduction took place resulting in a quantitative formation of product **16** having the same relative configuration as in the experiment with $NaBH(OAc)_3$.

Reduction of 3-alkyl-substituted aldol **10d** with $NaBH(OAc)_3$/AcOH gave the expected product **18** with



Scheme 5. Post-transformations of hydroxy ketones **5**, **10** and **15**

2,3-anti/3,4-syn configuration (Scheme 5, Part C). However, lower yield (56 %) and stereoselectivity were observed (d.r. = 7:1) as compared to aldol **5a**.

Finally, hydride reduction of bis-aryl-substituted aldols **15a,b** with $NaBH(OAc)_3$/AcOH afforded single diastereomers of triol derivatives **19a,b** in 87% and 60% yield, respectively (Scheme 5, Part D). Product **19a** was further converted into the trisubstituted tetrahydrofuran **21** by removal of pivaloyl group followed by tosylation of primary hydroxyl group and cyclization. The stereochemistry of tetrahydrofuran **21** was confirmed by 2D NOESY (characteristic correlations are depicted in Scheme 5, D). Note that tetrahydrofurans with similar substitution patterns are found in some natural products. Examples are Cinncassin B isolated from bark of Cinnamomum cassia[11] and an anti-cancer tetrahydrofuran derivative **22** found in the extract of fruit C. Pinnatifida.[12] The suggested strategy provides a straightforward access to this structural core in six-steps from nitrostyrenes **1**.

Conclusions

In conclusion, we have demonstrated the efficiency of a "renewed isoxazoline route" in a regio- and stereoselective synthesis of densely functionalized ketones. The developed synthetic methodology consists of three stages, namely: 1) [4+1]-annulation of nitroalkenes and sulfonium ylides to construct isoxazoline-N-oxides; 2) tandem acylation/[3,3]-sigmatropic rearrangement of the N-oxide moiety to accomplish deoxygenative C-H oxygenation of the C-3 position; 3) hydrogenolysis of isoxazoline ring over Raney nickel. This sequence provides a practical and diastereoselective access to α'-acyloxy-substituted aldols, which are difficult to synthesize both by a classical aldol reaction and the «isoxazoline route». The synthetic potential of these aldols was demonstrated by their reduction into valuable triol derivatives having three contiguous stereogenic centers. Moreover, a 2,3-diaryl-4-hydroxy-substituted tetrahydrofuran derivative, which is structurally related to Cinncassin B, was synthesized to showcase the use of "renewed isoxazoline route" for the assembly of stereochemically complex natural product cores. We believe this methodology will find use in the stereoselective total synthesis of pharmaceutically relevant molecules.

Experimental section

All reactions were carried out in oven-dried (150 °C) glassware. NMR spectra were recorded at 298 K (unless otherwise stated) with residual solvents peaks as an internal standard. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), dd (doublet of doublets), q (quartet), ddd (doublet of doublets of doublets), dddd (doublet of doublets of doublets of doublets), td (triplet of doublets), m (multiplet), br (broad). IR spectra were recorded at

Simex FT-801 spectrometer in thin layer with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). HRMS were measured on electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Column chromatography was performed using Kieselgel 40–60 μm 60 A with ethyl acetate (EA)/petroleum ether (PE) mixtures as eluent. Analytical thin layer chromatography was performed on silica gel plates with F 254 indicator. Visualization was accomplished with UV light and solution of anisaldehyde/H_2SO_4 in ethanol. Melting points were determined on a Koffler apparatus and are uncorrected. Brine refers to a saturated aqueous solution of NaCl. CH_2Cl_2, MeCN and Et_3N were distilled from CaH_2, TMG were distilled from CaH_2 under reduced pressure. THF was distilled from $LiAlH_4$. Petroleum ether, ethyl acetate, ethanol were distilled without drying agents. AcOH was recrystallized. Most of the chemicals were acquired from commercial sources and used as received. "An" corresponds to 4-methoxyphenyl group.

Procedures

Synthesis of sulfonium salts

(Ethoxycarbonylmethyl)dimethylsulfonium bromide[13] and sulfonium salt **11a**[14] were synthesized by literature procedure.

(4-fluorobenzyl)dimethylsulfonium bromide (11b)

Salt **11b** was prepared analogously to the literature procedure for the synthesis of **11a**.[14] 3.26 g from 20 mmol of 4-fluorobenzylbromide, yield – 65%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (dd, J = 8.7, 5.5 Hz, 2H, 2- and 6-$\underline{H}_{Ar}$), 7.31 (t, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{Ar}$), 4.90 (s, 2H, $C\underline{H}_2SMe_2$), 2.90 (s, 6H, $S\underline{Me}_2$) ppm.

^{13}C NMR (76 MHz, DMSO-d6) δ 162.69 (d, J = 246.6 Hz, 1C, 4-$\underline{C}_{Ar}$), 133.00 (d, J = 8.7 Hz, 2C, 2- and 6-$\underline{C}_{Ar}$), 124.77 (d, J = 3.1 Hz, 1C, 1-$\underline{C}_{Ar}$), 116.26 (d, J = 21.8 Hz, 2C, 3- and 5-$\underline{C}_{Ar}$), 44.34 (1C, $\underline{C}H_2SMe_2$), 23.61 (2C, $CH_2S\underline{Me}_2$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -111.67 ppm (with proton decoupling).

HRMS (ESI): m/z $[M]^+$ calcd for $C_9H_{12}FS^+$: 284.1281, found 284.1277.

Synthesis of nitroalkenes 1 and nitroalcoholes 6

Nitroalkenes **1a**,[15] **1f**,[16] **1h**[17] and **1g**[18] were synthesized according to literature protocols.

General procedure 1 (GP1): A solution of corresponding aldehyde (1 equiv., 50 mmol), nitroethane (1.4 equiv., 70 mmol, 5.25 g, d = 1.05 g/mL) and N,N-dimethylethylenediamine (5 mol. %, 2.5 mmol, 220 mg, d = 0.8 g/mL) in 10 mL of PhMe was heated to reflux with Dean-Stark trap until corresponding amount of water was collected. After that the solvent was evaporated and crude product was recrystallized from EtOH (**1b-d**) or subjected to column chromatography (**1e**) to give pure nitroalkene **1**.

(E)-1,2,3-trimethoxy-5-(2-nitroprop-1-en-1-yl)benzene (1b)

Nitroalkene **1b** was synthesized according to **GP1**. 9.1 g from 50 mmol of 3,4,5-trimethoxybenzaldehyde, yield – 72%. ^{1}H NMR was in accordance with literature data.[19]

(E)-1-methoxy-3-(2-nitroprop-1-en-1-yl)benzene (1c)

Nitroalkene **1c** was synthesized according to **GP1**. 7.28 g from 50 mmol of 3-methoxybenzaldehyde, yield – 75%. ^{1}H NMR was in accordance with literature data.[20]

(E)-1-methyl-4-(2-nitroprop-1-en-1-yl)benzene (1d)

Nitroalkene **1d** was synthesized according to **GP1**. 2.53 g from 20 mmol of 4-methylbenzaldehyde, yield – 71%. ^{1}H NMR was in accordance with literature data.[20]

(E)-1-methyl-2-(2-nitroprop-1-en-1-yl)benzene (1e)

Nitroalkene **1e** was synthesized according to **GP1**. 2.4 g from 20 mmol of 2-methylbenzaldehyde, yield – 68%. ^{1}H NMR was in accordance with literature data.[21]

Nitroalcoholes **6a-d** were synthesized according to a known method.[22]

2-nitrohexan-3-ol (6a)

2.0 g from 15 mmol of butyraldehyde, yield – 91%. ^{1}H NMR was in accordance with literature data.[23]

2-methyl-4-nitropentan-3-ol (6b)

2.6 g from 20 mmol of isobutyraldehyde, yield – 88%. ^{1}H NMR was in accordance with literature data.[22]

1-cyclopropyl-2-nitropropan-1-ol (6c)

1.68 g from 15 mmol of cyclopropanecarboxaldehyde, yield – 77%. ^{1}H NMR was in accordance with literature data.[24]

4-nitro-1-phenylpentan-3-ol (6d)

3.35 g from 20 mmol of hydrocinnamaldehyde, yield – 80%. ^{1}H NMR was in accordance with literature data.[22]

Synthesis of isoxazoline N-oxides 8

General procedure 2 (GP2): To a solution of nitroalcohol **6** (1 equiv., 3 mmol) in anhydrous CH_2Cl_2 (6 mL) MsCl (1 equiv., 3 mmol, 344 mg, d = 1.48 g/mL) and freshly distilled Et_3N (1 equiv., 3 mmol, 303 mg, d = 0.726 g/mL) were added at -15 °C under inert atmosphere. The reaction mixture was stirred for 30 min at the same temperature and then warmed to 0 °C. (Ethoxycarbonylmethyl)dimethylsulfonium bromide (1.2 equiv., 3.6 mmol, 824 mg) was added followed by TMG (3.2 equiv., 9.6 mmol, 1.1 g, d = 0.918 g/mL). The mixture was warmed to rt and stirred for additional 24h. After that the reaction mixture was diluted with 100 mL of EA and washed with 100 mL of 0.25M aqueous solution of $NaHSO_4$. Aqueous layer was back extracted with 50 mL of EA.

Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to column chromatography to give pure isoxazoline N-oxide **8**.

Rel (4S,5S)-5-(ethoxycarbonyl)-3-methyl-4-propyl-4,5-dihydroisoxazole 2-oxide (8a). Isoxazoline-*N*-oxide **8a** was synthesized by **GP2**. 0.773 g from 5 mmol of nitroalcohol **6a**, yield – 72%. Colorless oil. $\mathbf{R_f}$ = 0.50 (PE/EA 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, J = 4.1 Hz, 1H, C<u>H</u>O), 4.16 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2O$), 3.31 – 3.23 (m, 1H, C<u>H</u>Pr), 1.86 (d, J = 1.4 Hz, 3H, $C\underline{H}_3$), 1.72 – 1.43 (m, 2H, $CH_3CH_2C\underline{H}_2$), 1.44 – 1.24 (m, 2H, $CH_3C\underline{H}_2CH_2$), 1.21 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$), 0.88 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2CH_2$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 169.23 (1C, C=O), 113.42 (1C, C=N), 75.40 (1C, <u>C</u>HO), 61.92 (1C, $CH_3C\underline{H}_2O$), 49.95 (1C, <u>C</u>HPr), 33.02 and 19.07 (2C, $CH_3C\underline{H}_2CH_2$ and $CH_3CH_2C\underline{H}_2$), 13.92, 13.58 and 10.64 (3C, $\underline{C}H_3CH_2CH_2$, $\underline{C}H_3$ and $\underline{C}H_3CH_2O$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{18}NO_4^+$: 216.1230, found 216.1237.

Rel (4S,5S)-5-(ethoxycarbonyl)-4-isopropyl-3-methyl-4,5-dihydroisoxazole 2-oxide (8b). Isoxazoline-*N*-oxide **8b** was synthesized by **GP2**. 0.392 g from 3 mmol of nitroalcohol **6b**, yield – 61%. Colorless oil. $\mathbf{R_f}$ = 0.50 (PE/EA 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, J = 3.7 Hz, 1H, C<u>H</u>O), 4.26 – 7.11 (m, 2H, $CH_3C\underline{H}_2O$), 3.23 (dq, J = 3.7, 1.5 Hz, 1H, C<u>H</u>iPr), 2.13 – 1.98 (m, 1H, C<u>H</u>Me_2), 1.90 (d, J = 1.5 Hz, 3H, $C\underline{H}_3$), 1.23 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$), 0.98 (d, J = 6.9 Hz, 3H, CH$\underline{Me}_2$), 0.88 (d, J = 6.9 Hz, 3H, CH$\underline{Me}_2$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 169.75 (1C, C=O), 112.73 (1C, C=N), 72.28 (1C, <u>C</u>HO), 62.01 (1C, $CH_3C\underline{H}_2O$), 56.39 (1C, <u>C</u>HiPr), 29.16 (1C, <u>C</u>HMe_2), 19.35, 17.30, 14.01 and 11.29 (4C, $\underline{C}H_3CH_2O$, $\underline{C}H_3$ and CH$\underline{Me}_2$) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_{17}NO_4Na^+$: 238.1050, found 238.1056.

Rel (4S,5S)-4-cyclopropyl-5-(ethoxycarbonyl)-3-methyl-4,5-dihydroisoxazole 2-oxide (8c). Isoxazoline-*N*-oxide **8c** was synthesized by **GP2**. 0.381 g from 3 mmol of nitroalcohol **6c**, yield – 60%. Colorless oil. $\mathbf{R_f}$ = 0.50 (PE/EA 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, J = 4.8 Hz, 1H, C<u>H</u>O), 4.21 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2O$), 2.67 – 2.50 (m, 1H, C<u>H</u>Cyp), 1.99 (d, J = 1.5 Hz, 3H, $C\underline{H}_3$), 1.26 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2O$), 1.06 – 0.91 (m, 1H, C<u>H</u> of Cyp), 0.76 – 0.67 (m, 1H, $C\underline{H}_2$ of Cyp), 0.65 – 0.53 (m, 1H, $C\underline{H}_2$ of Cyp), 0.43 – 0.24 (m, 2H, $C\underline{H}_2$ of Cyp) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 169.19 (1C, C=O), 113.77 (1C, C=N), 76.74 (1C, <u>C</u>HO), 62.19 (1C, $CH_3C\underline{H}_2O$), 55.74 (1C, <u>C</u>HCyp), 14.08, 13.23 and 11.00 (3C, $\underline{C}H_3CH_2O$, $\underline{C}H_3$ and <u>C</u>H of Cyp), 4.48 and 2.33 (2C, $\underline{C}H_2$ of Cyp) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{16}NO_4^+$: 214.1074, found 214.1067.

Rel (4S,5S)-5-(ethoxycarbonyl)-3-methyl-4-phenethyl-4,5-dihydroisoxazole 2-oxide (8d). Isoxazoline-*N*-oxide **8d** was synthesized by **GP2**. 0.511 g from 3 mmol of nitroalcohol **6d**, yield – 61%. Colorless oil. $\mathbf{R_f}$ = 0.50 (PE/EA 1:1). ^{1}H NMR was in accordance with literature data.[5a]

General procedure 3 (GP3): To a stirred solution of nitroalkene **1** (1 equiv., 3 mmol), sulfonium salt **11** (1.3 equiv., 3.9 mmol) and Bu_4NHSO_4 (0.1 equiv., 0.3 mmol, 102 mg) in 6 mL of CH_2Cl_2 was added a solution of NaOH (17 equiv., 51 mmol, 2.04 g) in water (2.7 mL) at rt. The reaction mixture was stirred at the same temperature for 5h. After that the solution was diluted with 100 mL of EA and washed with 100 mL of water. Aqueous layer was back extracted with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to column chromatography to give pure isoxazoline N-oxide **12**. Also, nitrocyclopropanes **13** were isolated as side products in some cases.

Rel (4S,5S)-4-(4-methoxyphenyl)-3-methyl-5-phenyl-4,5-dihydroisoxazole 2-oxide (12a). Isoxazoline-*N*-oxide **12a** was synthesized by **GP3**. 0.910 g from 5 mmol of nitroalkene **1a**, yield – 63%. White solid. **Mp** = 119 – 121 °C. $\mathbf{R_f}$ = 0.35 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 5H, C<u>H</u> of Ph), 7.13 (d, J = 8.7 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 6.93 (d, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{An}$), 5.35 (d, J = 7.5 Hz, 1H, C<u>H</u>O), 4.25 (dd, J = 7.5, 1.8 Hz, 1H, C<u>H</u>An), 3.82 (s, 3H, $C\underline{H}_3O$), 1.87 (d, J = 1.8 Hz, 3H, $C\underline{H}_3$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 159.84 (1C, 4-$\underline{C}_{An}$), 138.23 (1C, 1-$\underline{C}_{Ph}$), 129.08 (1C, 1-$\underline{C}_{An}$), 129.11, 129.01, 128.84 and 125.57 (7C, 2-, 3-, 4-, 5- and 6-$\underline{C}_{Ph}$, 2- and 6-$\underline{C}_{An}$), 115.41 (1C, C=N), 114.94 (2C, 3- and 5-$\underline{C}_{An}$), 84.36 (1C, <u>C</u>HO), 60.80 (1C, <u>C</u>HAn), 55.46 (1C, $\underline{C}H_3O$), 11.03 (1C, $\underline{C}H_3$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{18}NO_3^+$: 284.1281, found 284.1277.

1-Methoxy-4-(2-methyl-2-nitro-3-phenylcyclopropyl)benzene (**13a**)

Nitrocyclopropane **13a** was isolated as a side-product in the synthesis of **12a** by **GP3**. 0.284 g from 5 mmol of nitroalkene **1a**, yield – 20%. Colorless oil. $\mathbf{R_f}$ = 0.77 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H, $\underline{H}_{Ph}$), 7.24 – 7.17 (m, 1H, $\underline{H}_{Ph}$), 7.12 – 7.05 (m, 2H, $\underline{H}_{Ph}$), 6.98 (d, J = 8.8 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 6.84 (d, J = 8.8 Hz, 2H, 3- and 5-$\underline{H}_{An}$), 3.93 – 3.70 (m, 5H, $C\underline{H}_3O$, C<u>H</u>Ph and C<u>H</u>An), 1.77 (s, 3H, $C\underline{H}_3$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 158.92 (1C, 4-$\underline{C}_{An}$), 132.74 (1C, 1-$\underline{C}_{Ph}$), 131.55, 130.48 and 128.39 (6C, 2-, 3-, 5- and 6-$\underline{C}_{Ph}$, 2- and 6-$\underline{C}_{An}$), 127.45 (1C, 4-$\underline{C}_{Ph}$), 124.43 (1C, 1-$\underline{C}_{An}$), 113.85 (2C, 3- and 5-$\underline{C}_{An}$), 70.10 (1C, <u>C</u>(Me)NO_2), 55.29

(1C, $\underline{C}H_3O$), 37.77 and 37.50 (2C, $\underline{C}$HPh and $\underline{C}$HAn), 12.75 (1C, $\underline{C}H_3$) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{17}NO_3Na^+$: 306.1101, found 306.1092.

Rel (4S,5S)-3-methyl-5-phenyl-4-(p-tolyl)-4,5-dihydroisoxazole 2-oxide (12b). Isoxazoline-*N*-oxide **12b** was synthesized by **GP3**. 0.447 g from 3 mmol of nitroalkene **1d**, yield – 56%. White solid. **Mp** = 110 – 112 °C. $\mathbf{R_f}$ = 0.50 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H, 2, 3, 4-, 5, and 6-$\underline{H}_{Ph}$), 7.21 (d, J = 8.0 Hz, 2H, 2- and 6-$\underline{H}_{Ar}$), 7.10 (d, J = 8.0 Hz, 2H, 3- and 5-$\underline{H}_{Ar}$), 5.37 (d, J = 7.4 Hz, 1H, C$\underline{H}$O), 4.26 (dd, J = 7.4, 1.9 Hz, 1H, C$\underline{H}$Ar), 2.37 (s, 3H, $C\underline{H}_3$ of Ar), 1.87 (d, J = 1.9 Hz, 3H, $C\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT135) δ 138.48 and 138.26 (2C, 1-$\underline{C}_{Ph}$ and 1-$\underline{C}_{Ar}$), 134.18 (1C, 4-$\underline{C}_{Ar}$), 128.79 (1C, 4-$\underline{C}_{Ph}$), 130.19, 128.95, 127.80 and 125.53 (8C, 2-, 3-, 5- and 6-$\underline{C}_{Ph}$, 2-, 3-, 5- and 6-$\underline{C}_{Ar}$), 115.22 (1C, C=N), 84.16 (1C, $\underline{C}$HO), 61.08 (1C, $\underline{C}$HAr), 21.19 (1C, $\underline{C}H_3$ of Ar), 10.98 (1C, $\underline{C}H_3$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{18}NO_2^+$: 268.1332, found 268.1332.

Rel (4S,5S)-3-methyl-5-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole 2-oxide (12c). Isoxazoline-*N*-oxide **12c** was synthesized by **GP3**. 0.482 g from 3 mmol of nitroalkene **1b**, yield – 47%. White solid. **Mp** = 156 – 158 °C. $\mathbf{R_f}$ = 0.58 (PE/EA 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H, 2, 3, 4-, 5, and 6-$\underline{H}_{Ph}$), 6.37 (s, 2H, 2- and 6-$\underline{H}_{Ar}$), 5.38 (d, J = 7.3 Hz, 1H, C$\underline{H}$O), 4.19 (dd, J = 7.3, 1.8 Hz, 1H, C$\underline{H}$Ar), 3.85 (s, 3H, $C\underline{H}_3O$), 3.83 (s, 6H, 2 $C\underline{H}_3O$), 1.90 (d, J = 1.8 Hz, 3H, $C\underline{H}_3$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 154.06, 138.31, 138.10 and 132.87 (5C, 1-$\underline{C}_{Ph}$, 1-, 3-, 4- and 5-$\underline{C}_{Ar}$), 129.02 and 125.52 (4C, 2-, 3-, 5- and 6-$\underline{C}_{Ph}$), 128.91 (1C, 4-$\underline{C}_{Ph}$), 115.04 (1C, C=N), 104.68 (2C, 2- and 6-$\underline{C}_{Ar}$), 83.94 (1C, $\underline{C}$HO), 61.84, 60.93 and 56.37 (4C, $\underline{C}$HAr and 3$\underline{C}H_3O$), 11.09 (1C, $\underline{C}H_3$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{22}NO_5^+$: 344.1492, found 344.1488.

Rel (4S,5S)-3-methyl-5-phenyl-4-(o-tolyl)-4,5-dihydroisoxazole 2-oxide (12d). Isoxazoline-*N*-oxide **12d** was synthesized by **GP3**. 0.431 g from 3 mmol of nitroalkene **1e**, yield – 54%. White solid. **Mp** = 118 – 120 °C. $\mathbf{R_f}$ = 0.50 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.17 (m, 9H, Ph and Ar), 5.35 (d, J = 7.3 Hz, 1H, C$\underline{H}$O), 4.65 (dd, J = 7.3, 1.8 Hz, 1H, C$\underline{H}$Ar), 2.09 (s, 3H, $C\underline{H}_3$ of Ar), 1.91 (d, J = 1.8 Hz, 3H, $C\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT135) δ 138.37, 136.23 and 135.39 (3C, 1- and 2-$\underline{C}_{Ar}$, 1-$\underline{C}_{Ph}$), 131.24, 129.07, 128.97, 128.34, 127.86, 127.35 and 125.64 (9C, $\underline{C}$ of Ph, 3-, 4-, 5- and 6-$\underline{C}_{Ar}$), 115.24 (1C, C=N), 84.25 (1C, $\underline{C}$HO), 57.43 (1C, $\underline{C}$HAr), 19.52 (1C, $\underline{C}H_3$ of Ar), 11.16 (1C, $\underline{C}H_3$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{18}NO_2^+$: 268.1332, found 268.1334.

Rel (4S,5S)-5-(4-fluorophenyl)-4-(4-methoxyphenyl)-3-methyl-4,5-dihydroisoxazole 2-oxide (12e). Isoxazoline-*N*-oxide **12e** was synthesized by **GP3**. 0.580 g from 3 mmol of nitroalkene **1a**, yield – 64%. White solid. **Mp** = 88 – 89 °C. $\mathbf{R_f}$ = 0.37 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.6, 5.2 Hz, 2H, 2- and 6-$\underline{H}_{Ar}$), 7.10 (d, J = 8.7 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 7.04 (t, J = 8.6 Hz, 2H, 3- and 5-$\underline{H}_{Ar}$), 6.91 (d, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{An}$), 5.31 (d, J = 7.9 Hz, 1H, C$\underline{H}$O), 4.22 (dd, J = 7.9, 1.9 Hz, 1H, C$\underline{H}$An), 3.80 (s, 3H, $OC\underline{H}_3$), 1.85 (d, J = 1.9 Hz, 3H, $C\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT135) δ 162.91 (d, J = 247.6 Hz, 1C, 4-$\underline{C}_{Ar}$), 159.85 (1C, 4-$\underline{C}_{An}$), 133.76 (d, J = 3.2 Hz, 1C, 1-$\underline{C}_{Ar}$), 129.06 (2C, 2- and 6-$\underline{C}_{An}$), 128.63 (1C, 1-$\underline{C}_{An}$), 127.52 (d, J = 8.4 Hz, 2C, 2- and 6-$\underline{C}_{Ar}$), 115.94 (d, J = 21.7 Hz, 2C, 3- and 5-$\underline{C}_{Ar}$), 115.31 (1C, $\underline{C}$=N), 114.93 (2C, 3- and 5-$\underline{C}_{An}$), 83.87 (1C, $\underline{C}$HO), 60.76 (1C, $O\underline{C}H_3$), 55.40 (1C, $\underline{C}$HAn), 10.96 (1C, $\underline{C}H_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -112.77 ppm (with proton decoupling).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{17}FNO_3^+$: 302.1187, found 302.1195.

Synthesis of hydroxy ketones

General procedure 4 (GP4):

Step 1 ([4+1]-annulation). To a solution of nitroalkene **1** (1 equiv., 1 mmol) in 1 mL of CH_2Cl_2 a solution of sulfonium ylide **2**[13] (1.2 equiv., 1.2 mmol, 178 mg) in 1 mL of CH_2Cl_2 was added at rt. The mixture was stirred at the same temperature for 24h. After that the solvent was evaporated and crude isoxazoline-*N*-oxide **3** was used in Step 2 without additional purification.

Step 2 (C-H functionalization). Crude product **3** from Step 1 was dissolved in 2 mL of freshly distilled MeCN. To this solution Et_3N (3 equiv., 3 mmol, 303 mg, d = 0.726 g/mL) and acyl chloride (2 equiv., 2 mmol) were added at -15 °C under inert atmosphere. The reaction mixture was stirred for 15 min at this temperature and then warmed to rt. The mixture was stirred at this temperature for additional 72h. Then, the solution was diluted with 50 mL of EA and washed with 50 mL of 0.25M aqueous solution of $NaHSO_4$. Aqueous layer was back extracted with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude isoxazoline **4** was used in Step 3 without additional purification.

Step 3 (Catalytic hydrogenolysis). The crude product **4** from Step 2 was dissolved in a mixture of EtOH (8 mL) and water (2 mL). To this solution H_3BO_3 (2 equiv., 2 mmol, 124

mg) was added. After that a suspension of Ra-Ni (ca. 50 mg, previously washed with EtOH, 3×2 mL) in 2 mL EtOH was added. Reaction vessel was evacuated and backfilled with H_2 from a balloon for 5 times. Reaction mixture was vigorously stirred for 3h under hydrogen atmosphere (balloon) at rt. Then, the solution was decanted and the residual Ra-Ni was washed with 5 mL of EA. The collected organic solution was diluted with 45 mL of EA and washed with 50 mL of water. Aqueous layer was washed with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to a column chromatography to give pure hydroxy ketone **5**.

Rel ethyl (2S,3R)-2-hydroxy-3-(4-methoxyphenyl)-4-oxo-5-(pivaloyloxy)pentanoate (5a). Hydroxyketone **5a** was synthesized by **GP4**. 0.244 g from 1 mmol of nitroalkene **1a**, yield – 67% (yield 84% for 6 mmol-scale synthesis). White solid. **Mp** = 52 – 55 °C. $\mathbf{R_f}$ = 0.36 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 6.88 (d, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{An}$), 4.61 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.54 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.51 (d, J = 5.9 Hz, 1H, C$\underline{H}$OH), 4.13 (d, J = 5.9 Hz, 1H, C$\underline{H}$An), 4.10 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2O$), 3.79 (s, 3H, $C\underline{H}_3O$), 3.20 (br s, 1H, CHO$\underline{H}$), 1.21 (s, 9H, $C\underline{H}_3$ of Piv), 1.11 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 202.51 (1C, C=O of ketone), 177.72 (1C, C=O of Piv), 172.69 (1C, C=O of CO_2Et), 159.78 (1C, 4-$\underline{C}_{An}$), 130.59 (2C, 2- and 6-$\underline{C}_{An}$), 125.47 (1C, 1-$\underline{C}_{An}$), 114.58 (2C, 3- and 5-$\underline{C}_{An}$), 72.64 (1C, $\underline{C}$HOH), 67.55 (1C, C$\underline{H}_2$OPiv), 61.83 (1C, $CH_3\underline{C}H_2O$), 58.03 (1C, $\underline{C}$HAn), 55.39 (1C, $C\underline{H}_3O$), 38.77 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.23 (3C, $\underline{C}H_3$ of Piv), 13.97 (1C, $\underline{C}H_3CH_2O$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{27}O_7^+$: 367.1751, found 367.1748.

Rel ethyl (2S,3R)-2-hydroxy-4-oxo-5-(pivaloyloxy)-3-(3,4,5-trimethoxyphenyl)pentanoate (5b). Hydroxyketone **5b** was synthesized by **GP4**. 0.367 g from 1 mmol of nitroalkene **1b**, yield – 86%. Colorless oil. $\mathbf{R_f}$ = 0.20 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 2H, 2- and 6-$\underline{H}_{Ar}$), 4.61 (s, 2H, C$\underline{H}_2$OPiv), 4.51 (d, J = 5.5 Hz, 1H, C$\underline{H}$OH), 4.16 – 4.06 (m, 3H, $CH_3C\underline{H}_2O$ and C$\underline{H}$Ar), 3.84 (s, 6H, $2CH_3O$), 3.82 (s, 3H, $C\underline{H}_3O$), 3.08 (br s, 1H, CHO$\underline{H}$), 1.21 (s, 9H, $C\underline{H}_3$ of Piv), 1.13 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 202.21 (1C, C=O of ketone), 177.69 (1C, C=O of Piv), 172.66 (1C, C=O of CO_2Et), 153.67, 138.23 and 129.07 (4C, 1-, 3-, 4- and 5-$\underline{C}_{Ar}$), 106.58 (2C, 2- and 6-$\underline{C}_{Ar}$), 72.56 (1C, $\underline{C}$HOH), 67.60 (1C, C$\underline{H}_2$OPiv), 61.93 (1C, $CH_3\underline{C}H_2O$), 60.93 (1C, $\underline{C}H_3O$), 58.87 (1C, $\underline{C}H_{Ar}$), 56.33 (2C, $2CH_3O$), 38.76 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.23 (3C, $\underline{C}H_3$ of Piv), 14.01 (1C, $\underline{C}H_3CH_2O$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{31}O_9^+$: 427.1963, found 427.1954.

Rel ethyl (2S,3R)-2-hydroxy-3-(3-methoxyphenyl)-4-oxo-5-(pivaloyloxy)pentanoate (5c). Hydroxyketone **5c** was synthesized by **GP4**. 0.281 g from 1 mmol of nitroalkene **1c**, yield – 77%. White solid. **Mp** = 63 – 65 °C. $\mathbf{R_f}$ = 0.42 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 1H, $\underline{H}_{Ar}$), 6.94 – 6.80 (m, 3H, $\underline{H}_{Ar}$), 4.66 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.57 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.57 (d, J = 5.9 Hz, 1H, C$\underline{H}$OH), 4.17 (d, J = 5.9 Hz, 1H, C$\underline{H}$Ar), 4.11 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2O$), 3.80 (s, 3H, $C\underline{H}_3O$), 3.46 (br s, 1H, CHO$\underline{H}$), 1.22 (s, 9H, $C\underline{H}_3$ of Piv), 1.12 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2O$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 202.12 (1C, C=O of ketone), 177.63 (1C, C=O of Piv), 172.60 (1C, C=O of CO_2Et), 160.04 and 134.90 (2C, 1- and 3-$\underline{C}_{Ar}$), 130.09, 121.72, 115.00 and 113.96 (4C, 2-, 4-, 5- and 6-$\underline{C}_{Ar}$), 72.49 (1C, $\underline{C}$HOH), 67.59 (1C, C$\underline{H}_2$OPiv), 61.81 (1C, $CH_3\underline{C}H_2O$), 58.78 (1C, $\underline{C}H_{Ar}$), 55.35 (1C, $\underline{C}H_3O$), 38.72 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.18 (3C, $\underline{C}H_3$ of Piv), 13.90 (1C, $\underline{C}H_3CH_2O$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{27}O_7^+$: 367.1751, found 367.1746.

Rel ethyl (2S,3R)-2-hydroxy-4-oxo-5-(pivaloyloxy)-3-(p-tolyl)pentanoate (5d). Hydroxyketone **5d** was synthesized by **GP4**. 0.239 g from 1 mmol of nitroalkene **1d**, yield – 68%. White solid. **Mp** = 57 – 60 °C. $\mathbf{R_f}$ = 0.55 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.3 Hz, 2H, 2- and 6-$\underline{H}_{Ar}$), 7.15 (d, J = 8.3 Hz, 2H, 3- and 5-$\underline{H}_{Ar}$), 4.62 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.54 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.52 (d, J = 5.9 Hz, 1H, C$\underline{H}$OH), 4.15 (d, J = 5.9 Hz, 1H, C$\underline{H}$Ar), 4.09 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2O$), 3.72 (br s, 1H, CHO$\underline{H}$), 2.33 (s, 3H, $C\underline{H}_3$ of Ar), 1.21 (s, 9H, $C\underline{H}_3$ of Piv), 1.10 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 202.48 (1C, C=O of ketone), 177.71 (1C, C=O of Piv), 172.69 (1C, C=O of CO_2Et), 138.33 and 130.47 (2C, 1- and 4-$\underline{C}_{Ar}$), 129.85 and 129.31 (4C, 2-, 3-, 5- and 6-$\underline{C}_{Ar}$), 72.63 (1C, $\underline{C}$HOH), 67.57 (1C, C$\underline{H}_2$OPiv), 61.83 (1C, $CH_3\underline{C}H_2O$), 58.51 (1C, $\underline{C}H_{Ar}$), 38.77 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.23 (3C, $\underline{C}H_3$ of Piv), 21.21 (1C, $\underline{C}H_3$ of Ar), 13.93 (1C, $\underline{C}H_3CH_2O$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{27}O_6^+$: 351.1802, found 351.1796.

Rel ethyl (2S,3R)-2-hydroxy-4-oxo-5-(pivaloyloxy)-3-(o-tolyl)pentanoate (5e). Hydroxyketone **5e** was synthesized by **GP4**. 0.196 g from 1 mmol of nitroalkene **1e**, yield – 56%. Colorless oil. $\mathbf{R_f}$ = 0.54 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H, $\underline{H}_{Ar}$), 7.23 – 7.20 (m, 3H, $\underline{H}_{Ar}$), 4.57 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.56 (d, J = 5.7 Hz, 1H, C$\underline{H}$OH), 4.48 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.44 (d, J = 5.7 Hz, 1H, C$\underline{H}$Ar), 4.10 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2O$), 3.25 (br s, 1H, CHO$\underline{H}$), 2.41 (s, 3H, $C\underline{H}_3$ of Ar),

1.21 (s, 9H, C$\underline{H}_3$ of Piv), 1.09 (t, J = 7.2 Hz, 3H, C$\underline{H}_3$CH$_2$O) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 202.53 (1C, C=O of ketone), 177.78 (1C, C=O of Piv), 172.72 (1C, C=O of CO_2Et), 136.59 and 132.03 (2C, 1- and 2-$\underline{C}_{Ar}$), 131.16, 129.21, 128.45 and 126.83 (4C, 3-, 4-, 5- and 6-$\underline{C}_{Ar}$), 71.81 (1C, $\underline{C}$HOH), 67.57 (1C, C$\underline{H}_2$OPiv), 61.91 (1C, CH$_3\underline{C}$H$_2$O), 55.01 (1C, $\underline{C}H_{Ar}$), 38.78 (1C, (CH$_3$)$_3\underline{C}$ of Piv), 27.23 (3C, $\underline{C}$H$_3$ of Piv), 20.01 (1C, $\underline{C}$H$_3$ of Ar), 13.90 (1C, $\underline{C}$H$_3$CH$_2$O) ppm.

HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{19}H_{27}O_6^+$: 351.1802, found 351.1792.

Rel ethyl (2S,3R)-3-(4-fluorophenyl)-2-hydroxy-4-oxo-5-(pivaloyloxy)pentanoate (5f). Hydroxyketone **5f** was synthesized by **GP4**. 0.241 g from 1 mmol of nitroalkene **1f**, yield – 68%. White solid. **Mp** = 42 – 44 °C. **R$_f$** = 0.54 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 8.7, 5.3 Hz, 2H, 2- and 6-$\underline{H}_{Ar}$), 7.05 (t, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{Ar}$), 4.62 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.55 – 4.49 (br m, 1H, C$\underline{H}$OH), 4.54 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.17 (d, J = 6.0 Hz, 1H, C$\underline{H}$Ar), 4.09 (q, J = 7.1 Hz, 2H, CH$_3$C$\underline{H}_2$O), 3.37 (br s, 1H, CHO$\underline{H}$), 1.21 (s, 9H, C$\underline{H}_3$ of Piv), 1.10 (t, J = 7.1 Hz, 3H, C$\underline{H}_3$CH$_2$O) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 202.01 (1C, C=O of ketone), 177.70 (1C, C=O of Piv), 172.50 (1C, C=O of CO_2Et), 162.87 (d, J = 247.8 Hz, 1C, 4-$\underline{C}_{Ar}$), 131.18 (d, J = 8.2 Hz, 2C, 2- and 6-$\underline{C}_{Ar}$), 129.40 (d, J = 3.2 Hz, 1C, 1-$\underline{C}_{Ar}$), 116.11 (d, J = 21.6 Hz, 2C, 3- and 5-$\underline{C}_{Ar}$), 72.57 (1C, $\underline{C}$HOH), 67.65 (1C, C$\underline{H}_2$OPiv), 61.95 (1C, CH$_3\underline{C}$H$_2$O), 57.86 (1C, $\underline{C}H_{Ar}$), 38.77 (1C, (CH$_3$)$_3\underline{C}$ of Piv), 27.21 (3C, $\underline{C}$H$_3$ of Piv), 13.94 (1C, $\underline{C}$H$_3$CH$_2$O) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.17 ppm.

HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{18}H_{24}FO_6^+$: 355.1551, found 355.1553.

Rel ethyl (2S,3R)-3-(2-fluorophenyl)-2-hydroxy-4-oxo-5-(pivaloyloxy)pentanoate (5g). Hydroxyketone **5g** was synthesized by **GP4**. 0.196 g from 1 mmol of nitroalkene **1g**, yield – 55%. Colorless oil. **R$_f$** = 0.50 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (td, J = 7.5, 1.8 Hz, 1H, $\underline{H}_{Ar}$), 7.35 – 7.25 (m, 1H, $\underline{H}_{Ar}$), 7.18 – 7.03 (m, 2H, $\underline{H}_{Ar}$), 4.67 – 4.47 (m, 4H, C$\underline{H}_2$OPiv, C$\underline{H}$OH and C$\underline{H}$Ar), 4.12 (q, J = 7.1 Hz, 2H, CH$_3$C$\underline{H}_2$O), 3.80 (br s, 1H, CHO$\underline{H}$), 1.19 (s, 9H, C$\underline{H}_3$ of Piv), 1.12 (t, J = 7.1 Hz, 3H, C$\underline{H}_3$CH$_2$O) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 201.74 (1C, C=O of ketone), 177.62 (1C, C=O of Piv), 172.39 (1C, C=O of CO_2Et), 160.67 (d, J = 246.6 Hz, 1C, 2-$\underline{C}_{Ar}$), 130.77 (d, J = 3.0 Hz, 1C, 6-$\underline{C}_{Ar}$), 130.20 (d, J = 8.4 Hz, 1C, 4-$\underline{C}_{Ar}$), 124.79 (d, J = 3.6 Hz, 1C, 5-$\underline{C}_{Ar}$), 120.94 (d, J = 14.7 Hz, 1C, 1-$\underline{C}_{Ar}$), 115.73 (d, J = 22.3 Hz, 1C, 3-$\underline{C}_{Ar}$), 71.55 (1C, $\underline{C}$HOH), 67.54 (1C, C$\underline{H}_2$OPiv), 62.03 (1C, CH$_3\underline{C}$H$_2$O), 50.48 (1C, $\underline{C}H_{Ar}$), 38.72 (1C, (CH$_3$)$_3\underline{C}$ of Piv), 27.13 (3C, $\underline{C}$H$_3$ of Piv), 13.86 (1C, $\underline{C}$H$_3$CH$_2$O) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -117.12 (ddd, J = 10.1, 7.5, 5.4 Hz) ppm.

HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{18}H_{23}FO_6Na^+$: 377.1371, found 377.1366.

Rel ethyl (2S,3R)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-hydroxy-4-oxo-5-(pivaloyloxy)pentanoate (5h). Hydroxyketone **5h** was synthesized by **GP4**. 0.339 g from 1 mmol of nitroalkene **1h**, yield – 75%. White solid. **Mp** = 87 – 89 °C. **R$_f$** = 0.34 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 – 6.79 (m, 3H, $\underline{H}_{Ar}$), 4.81 – 4.69 (m, 1H, OC$\underline{H}$ of cyclopentyl), 4.67 – 4.49 (m, 3H, C$\underline{H}_2$OPiv and C$\underline{H}$OH), 4.15 – 4.05 (m, 3H, C$\underline{H}$Ar and CH$_3$C$\underline{H}_2$O), 3.82 (s, 3H, C$\underline{H}_3$O), 3.19 (br s, 1H, CHO$\underline{H}$), 2.00 – 1.75 (m, 6H, C$\underline{H}_2$ of cyclopentyl), 1.68 – 1.49 (m, 2H, C$\underline{H}_2$ of cyclopentyl), 1.21 (s, 9H, C$\underline{H}_3$ of Piv), 1.12 (t, J = 7.1 Hz, 3H, C$\underline{H}_3$CH$_2$O) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 202.49 (1C, C=O of ketone), 177.66 (1C, C=O of Piv), 172.72 (1C, C=O of CO_2Et), 150.29 and 148.08 (2C, 3- and 4-$\underline{C}_{Ar}$), 125.74 (1C, 1-$\underline{C}_{Ar}$), 121.86, 115.91 and 112.28 (3C, 2-, 5- and 6-$\underline{C}_{Ar}$), 80.63 (1C, O$\underline{C}$H of cyclopentyl), 72.64 (1C, $\underline{C}$HOH), 67.52 (1C, C$\underline{H}_2$OPiv), 61.81 (1C, CH$_3\underline{C}$H$_2$O), 58.41 (1C, C$\underline{H}$Ar), 56.15 (1C, $\underline{C}$H$_3$O), 38.75 (1C, (CH$_3$)$_3\underline{C}$ of Piv), 32.83 and 24.13 (4C, $\underline{C}$H$_2$ of cyclopentyl), 27.22 (3C, $\underline{C}$H$_3$ of Piv), 13.99 (1C, $\underline{C}$H$_3$CH$_2$O) ppm.

HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{24}H_{35}O_8^+$: 451.2326, found 451.2310.

Rel (3R,4S)-5-ethoxy-4-hydroxy-3-(4-methoxyphenyl)-2,5-dioxopentyl benzoate (5i). Hydroxyketone **5i** was synthesized by **GP4**. 0.339 g from 1 mmol of nitroalkene **1a**, yield – 65%. White solid. **Mp** = 74 – 76 °C. **R$_f$** = 0.24 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.1 Hz, 2H, 2- and 6-$\underline{H}_{Bz}$), 7.57 (t, J = 7.4 Hz, 1H, 4-$\underline{H}_{Bz}$), 7.43 (t, J = 7.7 Hz, 2H, 3- and 5-$\underline{H}_{Bz}$), 7.26 (d, J = 8.7 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 6.89 (d, J = 8.7 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 4.88 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OBz), 4.81 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OBz), 4.56 (d, J = 6.0 Hz, 1H, C$\underline{H}$OH), 4.23 (d, J = 6.0 Hz, 1H, C$\underline{H}$An), 4.10 (q, J = 7.2 Hz, 2H, CH$_3$C$\underline{H}_2$O), 3.80 (s, 3H, C$\underline{H}_3$O), 3.27 (br s, 1H, CHO$\underline{H}$), 1.12 (t, J = 7.1 Hz, 3H, C$\underline{H}_3$CH$_2$O) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 202.62 (1C, C=O of ketone), 172.70 (1C, C=O of CO_2Et), 165.71 (1C, C=O of Bz), 159.84 (1C, 4-$\underline{C}_{An}$), 133.50 (1C, 4-$\underline{C}_{Bz}$), 130.64, 130.00 and 128.53 (6C, 2- and 6-$\underline{C}_{An}$, 2-, 3-, 5- and 6-$\underline{C}_{Bz}$), 129.23 and 125.35 (2C, 1-$\underline{C}_{An}$ and 1-$\underline{C}_{Bz}$), 114.64 (2C, 3- and 5-$\underline{C}_{An}$), 72.70 (1C, $\underline{C}$HOH), 68.05 (1C, C$\underline{H}_2$OBz), 61.88 (1C, CH$_3\underline{C}$H$_2$O), 58.16 (1C, C$\underline{H}$Ar), 55.41 (1C, $\underline{C}$H$_3$O), 14.00 (1C, $\underline{C}$H$_3$CH$_2$O) ppm.

HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{21}H_{23}O_7^+$: 387.1438, found 387.1421.

General procedure 5 (GP5): **Step 1 (C–H functionalization).** Isoxazoline-*N*-oxide **8** or **12** (1 equiv., 1 mmol) was dissolved in 2 mL of freshly distilled MeCN. To this solution Et_3N (3 equiv., 3 mmol., 303 mg, d = 0.726 g/mL) and acyl chloride (2 equiv., 2 mmol) were added at -15 °C under inert atmosphere. The reaction mixture was stirred for 15 min at this temperature and then warmed to rt. The mixture was stirred at this temperature for additional 72h. After that the solution was diluted with 50 mL of EA and washed with 50 mL of 0.25M aqueous solution of $NaHSO_4$. Aqueous layer was back extracted with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude isoxazoline **9** or **14** was used in Step 2 without additional purification.

Step 2 (Catalytic hydrogenolysis). Crude isoxazoline **9** or **14** from Step 1 was dissolved in mixture of EtOH (8 mL) and water (2 mL). To this solution H_3BO_3 (2 equiv., 2 mmol, 124 mg) was added. After that a suspension of Ra-Ni (ca. 50 mg, previously washed for 3 times with EtOH) in 2 mL EtOH was added. Reaction vessel was evacuated and backfilled with H_2 from balloon for 5 times. Reaction mixture was vigorously stirred for 3h under hydrogen atmosphere (balloon) at rt. Then, the solution was decanted and the residual Ra-Ni was washed with 5 mL of EA. The collected organic solution was diluted with 45 mL of EA and extracted with 50 mL of water. Aqueous layer was washed with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to a column chromatography to give pure hydroxy ketone **10** or **15**.

Rel ethyl (2S,3R)-2-hydroxy-3-(2-(pivaloyloxy)acetyl)hexanoate (10a). Hydroxyketone **10a** was synthesized by **GP5**. 0.205 g from 1 mmol of isoxazoline-*N*-oxide **8a**, yield – 68%. White solid. **Mp** = 32 – 34 °C. $\mathbf{R_f}$ = 0.50 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) 4.72 (d, J = 17.1 Hz, 1H, C$\underline{H}_2$OPiv), 4.64 (d, J = 17.1 Hz, 1H, C$\underline{H}_2$OPiv), 4.29 – 4.17 (m, 3H, C$\underline{H}$OH and $CH_3C\underline{H}_2O$), 3.20 (br s, 1H, CHO$\underline{H}$), 2.97 (td, J = 7.2, 4.9 Hz, 1H, C$\underline{H}$Pr), 1.81 – 1.55 (m, 2H, C$\underline{H}_2$ of Pr), 1.49 – 1.27 (m, 2H, C$\underline{H}_2$ of Pr), 1.27 (d, J = 7.2 Hz, 3H, $\underline{C}H_3CH_2O$), 1.24 (s, 9H, C$\underline{H}_3$ of Piv), 0.93 (t, J = 7.2 Hz, 3H, C$\underline{H}_3$ of Pr) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 205.92 (1C, C=O of ketone), 177.85 (1C, C=O of Piv), 173.19 (1C, C=O of CO_2Et), 71.22 (1C, $\underline{C}$HOH), 68.38 (1C, C$\underline{H}_2$OPiv), 62.07 (1C, $CH_3\underline{C}H_2O$), 51.37 (1C, $\underline{C}$HPr), 38.82 (1C, $(CH_3)_3\underline{C}$ of Piv), 29.86 (1C, $\underline{C}H_2$ of Pr), 27.26 (3C, $\underline{C}H_3$ of Piv), 20.65 (1C, $\underline{C}H_2$ of Pr), 14.21 and 14.11 (2C, CH_3CH_2O and $\underline{C}H_3$ of Pr) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{27}O_6^+$: 303.1802, found 303.1803.

Rel ethyl (2S,3R)-2-hydroxy-3-isopropyl-4-oxo-5-(pivaloyloxy)pentanoate (10b). Hydroxyketone **10b** was synthesized by **GP5**. 0.106 g from 1 mmol of isoxazoline-*N*-oxide **8b**, yield – 35%. Colorless oil. $\mathbf{R_f}$ = 0.68 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J = 17.4 Hz, 1H, C$\underline{H}_2$OPiv), 4.59 (d, J = 17.5 Hz, 1H, C$\underline{H}_2$OPiv), 4.35 (br s, 1H, C$\underline{H}$OH), 4.20 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2O$), 3.38 (br s, 1H, CHO$\underline{H}$), 2.68 (dd, J = 9.1, 4.0 Hz, 1H, C$\underline{H}$iPr), 2.25 – 2.11 (m, 1H, C$\underline{H}$ of iPr), 1.25 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2O$), 1.21 (s, 9H, C$\underline{H}_3$ of Piv), 1.04 (d, J = 6.7 Hz, 3H, C$\underline{H}_3$ of iPr), 1.01 (d, J = 6.7 Hz, 3H, C$\underline{H}_3$ of iPr) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 206.87 (1C, C=O of ketone), 177.65 (1C, C=O of Piv), 173.26 (1C, C=O of CO_2Et), 70.54 (1C, $\underline{C}$HOH), 69.41 (1C, C$\underline{H}_2$OPiv), 61.99 (1C, $CH_3\underline{C}H_2O$), 57.02 (1C, $\underline{C}$HiPr), 38.72 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.93 (1C, $\underline{C}$H of iPr), 27.21 (3C, $\underline{C}H_3$ of Piv), 20.77 and 20.61 (2C, $\underline{C}H_3$ of iPr), 14.13 (1C, $C\underline{H}_3CH_2O$) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{27}O_6^+$: 303.1802, found 303.1801.

Rel ethyl (2S,3R)-3-cyclopropyl-2-hydroxy-4-oxo-5-(pivaloyloxy)pentanoate (10c). Hydroxyketone **10c** was synthesized by **GP5**. 0.200 g from 1 mmol of isoxazoline-*N*-oxide **8c**, yield – 67%. Colorless oil. $\mathbf{R_f}$ = 0.39 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (d, J = 18.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.80 (d, J = 18.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.33 (d, J = 4.3 Hz, 1H, C$\underline{H}$OH), 4.22 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2O$), 3.15 (br s, 1H, CHO$\underline{H}$), 2.08 (dd, J = 10.8, 4.3 Hz, 1H, C$\underline{H}$Cyp), 1.28 – 1.11 (m, 13H, $C\underline{H}_3CH_2O$, C$\underline{H}_3$ of Piv and C$\underline{H}$ of Cyp), 0.85 – 0.58 (m, 2H, C$\underline{H}_2$ of Cyp), 0.41 (dq, J = 9.4, 4.8 Hz, 1H, C$\underline{H}_2$ of Cyp), 0.30 (dq, J = 9.7, 4.8 Hz, 1H, C$\underline{H}_2$ of Cyp) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 203.99 (1C, C=O of ketone), 177.85 (1C, C=O of Piv), 173.15 (1C, C=O of CO_2Et), 72.18 (1C, $\underline{C}$HOH), 67.97 (1C, $\underline{C}H_2$OPiv), 62.02 (1C, $CH_3\underline{C}H_2O$), 57.75 (1C, $\underline{C}$HCyp), 38.79 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.25 (3C, $\underline{C}H_3$ of Piv), 14.14 (1C, $C\underline{H}_3CH_2O$), 9.90 (1C, $\underline{C}$H of Cyp), 5.56 and 4.94 (2C, $\underline{C}H_2$ of Cyp) ppm.

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{25}O_6^+$: 301.1646, found 301.1621.

Rel ethyl (2S,3R)-2-hydroxy-4-oxo-3-phenethyl-5-(pivaloyloxy)pentanoate (10d). Hydroxyketone **10d** was synthesized by **GP5**. 0.202 g from 1 mmol of isoxazoline-*N*-oxide **8d**, yield – 55%. White solid. **Mp** = 51 – 53 °C. $\mathbf{R_f}$ = 0.59 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H, $\underline{H}_{Ph}$), 7.26 – 7.18 (m, 3H, $\underline{H}_{Ph}$), 4.72 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.64 (d, J = 17.0 Hz, 1H, C$\underline{H}_2$OPiv), 4.34 (dd, J = 7.5, 5.2 Hz, 1H, C$\underline{H}$OH), 4.30 – 4.20 (m, 2H, $CH_3C\underline{H}_2O$), 3.32 (d, J = 7.5 Hz, 1H, CHO$\underline{H}$), 3.02 (td, J = 7.2, 5.2 Hz, 1H, C$\underline{H}CH_2CH_2Ph$), 2.72 (t, J = 7.8 Hz, 2H, $CHCH_2C\underline{H}_2Ph$), 2.22 – 1.94 (m, 2H, $CHC\underline{H}_2CH_2Ph$), 1.32 – 1.27 (s and t, 12H, C$\underline{H}_3$ of Piv and $C\underline{H}_3CH_2O$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 205.37 (1C, C=O of ketone), 177.82 (1C, C=O of Piv), 172.96 (1C, C=O of CO_2Et), 140.79 (1C, 1-C_{Ph}), 128.66 and 128.49 (4C, 2-, 3-, 5- and 6-C_{Ph}), 126.36 (1C, 4-C_{Ph}), 71.04 (1C, CHOH), 68.37 (1C, CH_2OPiv), 62.14 (1C, CH_3CH_2O), 50.80 (1C, $CHCH_2CH_2Ph$), 38.78 (1C, $(CH_3)_3C$ of Piv), 33.20 (1C, $CHCH_2CH_2Ph$), 29.06 (1C, $CHCH_2CH_2Ph$), 27.23 (3C, CH_3 of Piv), 14.18 (1C, CH_3CH_2O) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{28}O_6Na^+$: 387.1778, found 387.1778.

Rel (3R,4S)-4-hydroxy-3-(4-methoxyphenyl)-2-oxo-4-phenylbutyl pivalate (15a). Hydroxyketone **15a** was synthesized by **GP5**. 0.219 g from 1 mmol of isoxazoline-*N*-oxide **12a**, yield – 59%. White solid. **Mp** = 86 – 88 °C. **R_f** = 0.27 (PE/EA 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 3H, H_{Ph}), 7.09 – 7.06 (m, 2H, H_{Ph}), 6.89 (d, J = 8.7 Hz, 2H, 2- and 6-H_{An}), 6.70 (d, J = 8.7 Hz, 2H, 3- and 5-H_{An}), 5.20 (d, J = 9.4 Hz, 1H, CHOH), 4.74 (d, J = 17.0 Hz, 1H, CH_2OPiv), 4.62 (d, J = 17.0 Hz, 1H, CH_2OPiv), 3.94 (d, J = 9.4 Hz, 1H, CHAn), 3.72 (s, 3H, CH_3O), 3.14 (s, 1H, CHOH), 1.25 (s, 9H, CH_3 of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 204.69 (1C, C=O of ketone), 177.83 (1C, C=O of Piv), 159.22 (1C, 4-C_{An}), 140.89 (1C, 1-C_{Ph}), 130.16, 128.12 and 126.75 (6C, 2- and 6-C_{An}, 2-, 3-, 5- and 6-C_{Ph}), 127.77 (1C, 4-C_{Ph}), 125.98 (1C, 1-C_{An}), 114.28 (2C, 3- and 5-C_{An}), 76.19 (1C, CHOH), 68.03 (1C, CH_2OPiv), 62.37 (1C, CHAn), 55.24 (1C, CH_3O), 38.83 (1C, $(CH_3)_3C$ of Piv), 27.29 (3C, CH_3 of Piv) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{26}O_5Na^+$: 393.1672, found 393.1666.

Rel (3R,4S)-4-hydroxy-2-oxo-4-phenyl-3-(p-tolyl)butyl pivalate (15b). Hydroxyketone **15b** was synthesized by **GP5**. 0.207 g from 1 mmol of isoxazoline-*N*-oxide **12b**, yield – 59%. White solid. **Mp** = 99 – 101 °C. **R_f** = 0.42 (PE/EA 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.10 (m, 3H, H_{Ph}), 7.11 – 7.01 (m, 2H, H_{Ph}), 6.98 (d, J = 7.9 Hz, 2H, 2- and 6-H_{Ar}), 6.87 (d, J = 7.9 Hz, 2H, 3- and 5-H_{Ar}), 5.22 (d, J = 9.4 Hz, 1H, CHOH), 4.74 (d, J = 17.0 Hz, 1H, CH_2OPiv), 4.61 (d, J = 17.0 Hz, 1H, CH_2OPiv), 3.97 (d, J = 9.4 Hz, 1H, CHAr), 3.17 (s, 1H, CHOH), 2.24 (s, 3H, CH_3), 1.26 (s, 9H, CH_3 of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 204.65 (1C, C=O of ketone), 177.82 (1C, C=O of Piv), 140.82, 137.63 and 130.87 (3C, 1- and 4-C_{Ar}, 1-C_{Ph}), 129.59, 128.93, 128.10 and 126.78 (8C, 2-, 3-, 5- and 6-C_{Ph}, 2-, 3-, 5- and 6-C_{Ar}), 127.77 (1C, 4-C_{Ph}), , 76.13 (1C, CHOH), 68.01 (1C, CH_2OPiv), 62.88 (1C, CHAr), 38.83 (1C, $(CH_3)_3C$ of Piv), 27.28 (3C, CH_3 of Piv), 21.16 (1C, CH_3) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{26}O_4Na^+$: 377.1723, found 377.1716.

Rel (3R,4S)-4-hydroxy-2-oxo-4-phenyl-3-(3,4,5-trimethoxyphenyl)butyl pivalate (15c). Hydroxyketone **15c** was synthesized by **GP5**. 0.291 g from 1 mmol of isoxazoline-*N*-oxide **12c**, yield – 68%. White solid. **Mp** = 93 – 95 °C. **R_f** = 0.37 (PE/EA 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 3H, H_{Ph}), 7.08 – 6.99 (m, 2H, H_{Ph}), 6.09 (s, 2H, 2- and 6-H_{Ar}), 5.16 (d, J = 7.7 Hz, 1H, CHOH), 4.74 (d, J = 18.0 Hz, 1H, CH_2OPiv), 4.68 (d, J = 18.0 Hz, 1H, CH_2OPiv), 3.85 (d, J = 9.5 Hz, 1H, CHAr), 3.75 (s, 3H, CH_3O), 3.65 (s, 6H, $2CH_3O$), 3.10 (s, 1H, CHOH), 1.25 (s, 9H, CH_3 of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 204.41 (1C, C=O of ketone), 177.78 (1C, C=O of Piv), 153.27, 140.82, 137.71 and 129.26 (4C, 3-, 4- and 5-C_{Ar}, 1-C_{Ph}), 128.11 and 126.66 (4C, 2-, 3-, 5- and 6-C_{Ph}), 127.83 (1C, 4-C_{Ph}), 106.28 (2C, 2- and 6-C_{Ar}), 76.23 (1C, CHOH), 68.18 (1C, CH_2OPiv), 63.30 (1C, CHAr), 60.91 and 56.19 (3C, $3CH_3O$), 38.82 (1C, $(CH_3)_3C$ of Piv), 27.27 (3C, CH_3 of Piv) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{30}O_7Na^+$: 453.1884, found 453.1878.

Rel (3R,4S)-4-hydroxy-2-oxo-4-phenyl-3-(o-tolyl)butyl pivalate (15d). Hydroxyketone **15d** was synthesized by **GP5**. 0.229 g from 1 mmol of isoxazoline-*N*-oxide **12d**, yield – 65%. White solid. **Mp** = 83 – 85 °C. **R_f** = 0.46 (PE/EA 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.08 (m, 6H, H_{Ph} and H_{Ar}), 7.07 – 6.93 (m, 3H, H_{Ph} and H_{Ar}), 5.29 (d, J = 9.2 Hz, 1H, CHOH), 4.70 (d, J = 16.8 Hz, 1H, CH_2OPiv), 4.51 (d, J = 16.8 Hz, 1H, CH_2OPiv), 4.24 (d, J = 9.2 Hz, 1H, CHAr), 3.45 (s, 1H, CHOH), 1.87 (s, 3H, CH_3), 1.28 (s, 9H, CH_3 of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 204.85 (1C, C=O of ketone), 177.88 (1C, C=O of Piv), 140.34, 137.07 and 132.41 (3C, 1- and 2-C_{Ar}, 1-C_{Ph}), 130.98, 128.24, 127.99, 127.88, 127.73, 126.59 and 126.55 (9C, C_{Ph} and C_{Ar}), 76.05 (1C, CHOH), 67.71 (1C, CH_2OPiv), 59.00 (1C, CHAr), 38.83 (1C, $(CH_3)_3C$ of Piv), 27.27 (3C, CH_3 of Piv), 19.58 (1C, CH_3) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{26}O_4Na^+$: 377.1723, found 377.1715.

Rel (3R,4S)-4-(4-fluorophenyl)-4-hydroxy-3-(4-methoxyphenyl)-2-oxobutyl pivalate (15e). Hydroxyketone **15e** was synthesized by **GP5**. 0.263 g from 1 mmol of isoxazoline-*N*-oxide **12e**, yield – 68%. White solid. **Mp** = 96 – 98 °C. **R_f** = 0.39 (PE/EA 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 – 6.94 (m, 2H, H_{Ar}), 6.89 – 6.77 (m, 4H, H_{Ar} and H_{an}), 6.71 (d, J = 8.7 Hz, 2H, 3- and 5-H_{An}), 5.18 (d, J = 9.5 Hz, 1H, CHOH), 4.72 (d, J = 17.0 Hz, 1H, CH_2OPiv), 4.60 (d, J = 17.0 Hz, 1H, CH_2OPiv), 3.86 (d, J = 9.5 Hz, 1H, CHAn), 3.72 (s, 3H, CH_3O), 3.22 (br s, 1H, CHOH), 1.25 (s, 9H, CH_3 of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135) δ 204.70 (1C, C=O of ketone), 177.90 (1C, C=O of Piv), 162.24 (d, J = 245.6 Hz, 1C, 4-C_{Ar}), 159.32 (1C, 4-C_{An}), 136.68 (d, J = 3.1 Hz, 1C, 1-C_{Ar}), 130.14 (2C, 2- and 6-C_{An}), 128.36 (d, J = 8.1 Hz, 2C, 2- and 6-C_{Ar}), 125.77 (1C, 1-C_{An}), 114.96 (d, J = 21.4 Hz, 2C, 3- and 5-C_{Ar}), 114.40 (2C, 3- and 5-C_{An}), 75.48 (1C, CHOH),

67.97 (1C, $\underline{C}H_2OPiv$), 62.65 (1C, $\underline{C}HAn$), 55.27 (1C, $\underline{C}H_3O$), 38.83 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.28 (3C, $\underline{C}H_3$ of Piv) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.67 ppm (with proton decoupling).

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{25}FO_4Na^+$: 411.1578, found 411.1573.

Post-transformations.

General procedure 6 (GP6). Reduction of hydroxy ketones.

Method A ($NaBH(OAc)_3$ with AcOH).[25]

The corresponding aldol (1 equiv., 0.5 mmol) was dissolved in 5 mL of freshly distilled THF. To this solution $NaBH(OAc)_3$ (8 equiv., 4 mmol., 848 mg) and AcOH (6 equiv., 3 mmol, 180 mg, d = 1.05 g/mL) were added at 0°C under inert atmosphere. The reaction mixture was stirred for 24h at this temperature. After that the solution was diluted with 50 mL of EA and washed with 50 mL of sat. aqueous solution of $NaHCO_3$ (**Caution!** Intensive gas evolution). Aqueous layer was back extracted with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to column chromatography to give pure triol.

Method B (CatBH).[10b]

The corresponding aldol (1 equiv., 0.5 mmol) was dissolved in 2.5 mL of freshly distilled THF. To this solution catecholborane (CatBH) (5 equiv., 2.5 mmol., 2.5 mL of 1M solution in THF) was added at -10°C under inert atmosphere. The reaction mixture was stirred for 15 min at this temperature and then warmed to 0°C. At this temperature mixture was stirred for additional 24h. After that the reaction mixture was quenched with 1 mL of EtOH and 1 mL of sat. aqueous solution of Na-K tartrate and stirred for 30 min. Then the solution was diluted with 50 mL of EA and extracted with 50 mL of sat. aqueous solution of $NaHCO_3$. Aqueous layer was back extracted with 50 mL of EA. Combined organic layers were washed with 50 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to column chromatography to give pure triol.

Rel ethyl (2S,3S,4S)-2,4-dihydroxy-3-(4-methoxyphenyl)-5-(pivaloyloxy)pentanoate (16). Triol **16** was synthesized by **GP6**. **Method A** – 0.356 g from 1 mmol of hydroxy ketone **15a**, yield – 97%; **method B** – 0.182 g from 0.5 mmol of hydroxy ketone **15a**, yield – 99%. Colorless oil. $\mathbf{R_f}$ = 0.54 (PE/EA 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H, 2- and 6-$\underline{H}_{An}$), 6.85 (d, J = 8.4 Hz, 2H, 3- and 5-$\underline{H}_{An}$), 4.59 (t, J = 7.1 Hz, 1H, $C\underline{H}(OH)CO_2Et$), 4.44 (tt, J = 6.3, 3.4 Hz, 1H, $C\underline{H}OH$), 4.06 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2O$), 3.94 – 3.86 (m, 2H, $C\underline{H}_2OPiv$), 3.80 (s, 3H, $C\underline{H}_3O$), 3.48 – 3.37 (m, 1H, $O\underline{H}$), 3.04 (dd, J = 7.1, 3.4 Hz, 1H, $C\underline{H}An$), 2.97 – 2.94 (m, 1H, $O\underline{H}$), 1.20 (s, 9H, $C\underline{H}_3$ of Piv), 1.06 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 178.63 and 174.26 (2C, 2 $\underline{C}$=O), 159.15 (1C, 4-$\underline{C}_{An}$), 130.91 (2C, 2- and 6-$\underline{C}_{An}$), 128.32 (1C, 1-$\underline{C}_{An}$), 113.87 (2C, 3- and 5-$\underline{C}_{An}$), 73.37 (1C, $\underline{C}H(OH)CO_2Et$), 69.49 (1C, $\underline{C}HOH$), 66.85 (1C, CH_2OPiv), 61.65 (1C, $CH_3\underline{C}H_2O$), 55.33 (1C, $\underline{C}H_3O$), 50.93 (1C, $\underline{C}HAn$), 38.87 (1C, $(CH_3)_3\underline{C}$ of Piv), 27.27 (3C, $\underline{C}H_3$ of Piv), 13.95 (1C, $CH_3\underline{C}H_2O$) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{28}O_7Na^+$: 391.1727, found 391.1735.

Rel ethyl (2S,3S,4S)-2,4-dihydroxy-3-phenethyl-5-(pivaloyloxy)pentanoate (18a). Triol **18a** was synthesized by **GP6, Method A**. 0.049 g of **18a** from 0.275 mmol of hydroxy ketone **10d**, yield – 49%. Also, minor diastereomer **18a'** (yield 7 %) was isolated from column chromatography in a mixture with **18a** (1:1 ratio).

Major isomer **18a**: Colorless oil. $\mathbf{R_f}$ = 0.32 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.36 – 7.14 (m, 5H, $\underline{H}_{Ph}$), 4.47 (br s, 1H, $C\underline{H}(OH)CO_2Et$), 4.37 – 4.17 (m, 2H, $CH_3C\underline{H}_2O$), 4.12 (dd, J = 12.7, 8.7 Hz, 1H, $C\underline{H}_2OPiv$), 4.05 – 3.95 (m, 2H, $C\underline{H}_2OPiv$ and $C\underline{H}OH$), 3.64 (s, 1H, $CH(O\underline{H})CO_2Et$), 3.14 (s, 1H, $CHO\underline{H}$), 2.88 (ddd, J = 13.5, 9.7, 4.6 Hz, 1H, $PhC\underline{H}_2CH_2CH$), 2.64 (dt, J = 13.5, 7.7 Hz, 1H, $PhC\underline{H}_2CH_2CH$), 2.20 – 1.99 (m, 2H, $PhCH_2C\underline{H}_2CH$ and $PhCH_2CH_2C\underline{H}$), 1.94 – 1.77 (m, 1H, $PhCH_2C\underline{H}_2CH$), 1.31 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2O$), 1.18 (s, 9H, $(CH_3)_3\underline{C}$ of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 178.52 and 174.76 (2C, 2 $\underline{C}$=O), 141.53 (1C, 1-$\underline{C}_{Ph}$), 128.54 and 128.51 (4C, 2-, 3-, 5- and 6-$\underline{C}_{Ph}$), 126.13 (1C, 4-$\underline{C}_{Ph}$), 72.34 (1C, $\underline{C}H(OH)CO_2Et$), 70.98 (1C, $\underline{C}HOH$), 65.90 (1C, $\underline{C}H_2OPiv$), 62.00 (1C, $CH_3\underline{C}H_2O$), 42.13 (1C, $PhCH_2CH_2\underline{C}H$), 38.80 (1C, $(CH_3)_3\underline{C}$ of Piv), 33.48 (1C, $Ph\underline{C}H_2CH_2CH$), 27.20 (3C, $\underline{C}H_3$ of Piv), 26.33 (1C, $PhCH_2\underline{C}H_2CH$), 14.25 (1C, $CH_3\underline{C}H_2O$) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{30}O_6Na^+$: 389.1935, found 389.1934.

Minor isomer **18a'**: $\mathbf{R_f}$ = 0.32 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$, characteristic signals) δ 4.36 – 4.32 (m, 1H), 2.58 (d, J = 5.7 Hz, 1H), 1.75 – 1.60 (m, 2H), 1.18 (s, 9H) ppm.

Rel (2S,3R,4S)-4-(4-fluorophenyl)-2,4-dihydroxy-3-(4-methoxyphenyl)butyl pivalate (19a). Triol **19a** was synthesized by **GP6, Method A**. 0.169 g from 0.5 mmol of hydroxy ketone **15e**, yield – 87%. Colorless oil. $\mathbf{R_f}$ = 0.59 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.03 (m, 4H, 2- and 6-$\underline{H}_{Ar}$, 2- and 6-$\underline{H}_{An}$), 6.87 (t, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{Ar}$), 6.71 (d, J = 8.7 Hz, 2H, 3- and 5-$\underline{H}_{An}$), 5.11 (d, J = 8.8 Hz, 1H, $C\underline{H}(OH)Ar$), 4.54 (dt, J = 7.7, 3.5 Hz, 1H, $C\underline{H}OH$), 3.89 (dd, J = 11.5, 3.5 Hz, 1H, $C\underline{H}_2OPiv$), 3.81 (dd, J = 11.5, 7.7 Hz, 1H, $C\underline{H}_2OPiv$), 3.72 (s, 3H, $C\underline{H}_3O$), 2.96 (s, 2H, 2 $O\underline{H}$), 2.89 (dd, J = 8.8, 3.5 Hz, 1H, $C\underline{H}An$), 1.16 (s, 9H, $(CH_3)_3\underline{C}$ of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 179.02 (1C, C=O), 162.09 (d, J = 245.5 Hz, 1C, 4-C_{Ar}), 158.68 (1C, 4-C_{An}), 138.92 (d, J = 3.1 Hz, 1C, 1-C_{Ar}), 130.78 (2C, 2C, 3- and 5-C_{An}), 129.30 (1C, 1-C_{An}), 128.22 (d, J = 8.1 Hz, 2C, 3- and 5-C_{Ar}), 115.11 (d, J = 21.4 Hz, 2C, 3- and 5-C_{Ar}), 113.81 (2C, 3- and 5-C_{An}), 75.42 (1C, CH(OH)An), 69.71 (1C, CHOH), 67.83 (1C, CH_2OPiv), 55.22 (1C, CH_3O), 54.64 (1C, CHAn), 38.89 (1C, $(CH_3)_3C$ of Piv), 27.27 (3C, CH_3 of Piv) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.97 ppm (with proton decoupling).

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{27}FO_4Na^+$: 413.1735, found 413.1733.

Rel (2S,3R,4S)-2,4-dihydroxy-4-phenyl-3-(p-tolyl)butyl pivalate (19b). Triol **19b** was synthesized by **GP6, Method A**. 0.050 g from 0.235 mmol of hydroxy ketone **15b**, yield – 60%. Colorless oil. $\mathbf{R_f}$ = 0.68 (PE/EA 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 4.5 Hz, 5H, H_{Ph}), 7.12 (d, J = 8.0 Hz, 2H, 2- and 6-H_{Ar}), 6.99 (d, J = 8.0 Hz, 2H, 3- and 5-H_{Ar}), 5.16 (d, J = 8.1 Hz, 1H, CH(OH)Ph), 4.54 (ddd, J = 7.5, 4.9, 2.9 Hz, 1H, CHOH), 3.88 (dd, J = 11.5, 4.9 Hz, 1H, CH_2OPiv), 3.83 (dd, J = 11.5, 7.5 Hz, 1H, CH_2OPiv), 3.04 (br s, 2H, 2OH), 2.99 (dd, J = 8.1, 2.9 Hz, 1H, CHAr), 2.25 (s, 3H, CH_3), 1.16 (s, 9H, $(CH_3)_3C$ of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 178.87 (1C, C=O), 143.07, 136.63 and 134.44 (3C, 1-C_{Ph}, 1- and 4-C_{Ar}), 129.68 (2C, 2- and 6-C_{Ar}), 129.07 (2C, 3- and 5-C_{Ar}), 128.29 and 126.59 (4C, 2-, 3-, 5- and 6-C_{Ph}), 127.57 (1C, 4-C_{Ph}), 76.19 (1C, CH(OH)Ph), 69.62 (1C, CHOH), 67.54 (1C, CH_2OPiv), 54.66 (1C, CHAr), 38.85 (1C, $(CH_3)_3C$ of Piv), 27.26 (3C, CH_3 of Piv), 21.11 (1C, CH_3) ppm.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{28}O_4Na^+$: 379.1880, found 379.1875.

Rel ethyl (4S,5S,6S)-5-(4-methoxyphenyl)-2,2-dimethyl-6-((pivaloyloxy)methyl)-1,3-dioxane-4-carboxylate (17). Triol **16** (1 equiv., 0.4 mmol, 147 mg) was dissolved in 4 mL of freshly distilled CH_2Cl_2. To this solution 2-methoxypropene (2 equiv., 0.8 mmol., 58 mg, d = 0.753 g/mL) and a solution of $TsOH·H_2O$ (0.05 equiv., 0.02 mmol, 3.8 mg) in 200 µL of freshly distilled THF were added at -25°C under inert atmosphere. The reaction mixture was stirred for 3h at this temperature. After that the solution was diluted with 25 mL of EA and washed with 25 mL of sat. aqueous solution of $NaHCO_3$. Aqueous layer was back extracted with 25 mL of EA. Combined organic layers were washed with 25 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to column chromatography to give 0.132 g of pure acetal **17**, yield – 81%. Colorless oil. $\mathbf{R_f}$ = 0.53 (PE/EA 3:1).

^{1}H NMR (300 MHz, $CDCl_3$, COSY, NOESY) δ 7.29 (d, J = 8.7 Hz, 2H, 2- and 6-H_{An}), 6.82 (d, J = 8.7 Hz, 2H, 3- and 5-H_{An}), 4.44 (d, J = 8.0 Hz, 1H, CHCO$_2$Et), 4.37 (ddd, J = 8.0, 5.3, 4.4 Hz, 1H, CHCH$_2$OPiv), 4.24 – 4.00 (m, 2H, CH_3CH_2O), 3.77 (s, 3H, CH_3O), 3.72 (d, J = 11.8, 4.4 Hz, 1H, CH_2OPiv), 3.68 (d, J = 11.8, 8.0 Hz, 1H, CH_2OPiv), 3.32 (dd, J = 8.0, 5.3 Hz, 1H, CHAn), 1.55 (s, 3H, CH_{3a}), 1.46 (s, 3H, CH_{3b}), 1.16 (t, J = 7.1 Hz, 3H, CH_3CH_2O), 1.14 (s, 9H, $(CH_3)_3C$ of Piv) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC, HMBC) δ 178.08 (1C, C=O of Piv), 170.93 (1C, C=O of CO_2Et), 159.04 (1C, 4-C_{An}), 130.12 (2C, 2- and 6-C_{An}), 129.87 (1C, 1-C_{An}), 113.99 (2C, 2- and 6-C_{An}), 101.97 (1C, CMe_2), 74.59 (1C, CHCO$_2$Et), 68.45 (1C, CHCH$_2$OPiv), 64.37 (1C, CH_2OPiv), 61.31 (1C, CH_3CH_2O), 55.26 (1C, CH_3O), 46.53 (1C, CHAn), 38.76 (1C, $(CH_3)_3C$ of Piv), 27.21 (3C, CH_3 of Piv), 24.73 (1C, CH_3), 23.91 (1C, CH_3), 14.15 (1C, CH_3CH_2O) ppm.

Characteristic NOE correlations: CHCO$_2$Et/2- and 6-H_{An}; CHCO$_2$Et/CH_{3a}; CHAn/ CHCH$_2$OPiv; CHAn/CH_2OPiv; CHCH$_2$OPiv/CH_2OPiv; CHCH$_2$OPiv/CH_{3b}.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{22}H_{32}O_7Na^+$: 431.2040, found 431.2035.

Rel (3S,4S,5S)-5-(4-fluorophenyl)-4-(4-methoxyphenyl)tetrahydrofuran-3-ol (21). Deprotection. Triol **19a** (1 equiv., 0.31 mmol, 120 mg) was dissolved in mixture of THF (0.7 mL) and MeOH (6 mL). To this solution the solution of NaOH (2 equiv., 0.62 mmol., 25 mg) in 0.7 mL of H_2O was added at rt. The reaction mixture was stirred for 24h at this temperature. After that the solution was diluted with 25 mL of EA and washed with 25 mL of H_2O. Aqueous layer was back extracted with of EA (2×25 mL). Combined organic layers were dried over anhydrous Na_2SO_4. Solvent was evaporated and crude deprotected triol **20** (95 mg, yield – quant.) was used without further purification. **Cyclization**. Deprotected triol **20** (1 equiv., 0.21 mmol, 65 mg) was dissolved 2 mL of freshly distilled CH_2Cl_2. To this solution TsCl (1.1 equiv., 0.23 mmol, 44 mg), DMAP (0.2 equiv., 0.04 mmol, 5 mg) and Et_3N (1.2 equiv., 0.25 mmol, 25 mg, d = 0.726 g/mL) were added at 0°C under inert atmosphere. The reaction mixture was stirred for 30 min at this temperature and second portion of Et_3N (1.2 equiv., 0.25 mmol, 25 mg, d = 0.726 g/mL) was added. After that the solution was warmed to rt and stirred for additional 24h. Then the mixture was diluted with 25 mL of EA and washed with 25 mL of 0.25M aqueous solution of $NaHSO_4$. Aqueous layer was back extracted with 25 mL of EA. Combined organic layers were washed with 25 mL of Brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude product was subjected to column chromatography to give pure tetrahydrofuran **21**. 0.039 g from 0.21 mmol of triol **19a**, yield – 65%. Colorless oil. $\mathbf{R_f}$ = 0.47 (PE/EA 1:1).

^{1}H NMR (300 MHz, $CDCl_3$, NOESY) δ 7.18 (dd, J = 8.5, 5.5 Hz, 2H, 2- and 6-H_{Ar}), 7.07 (d, J = 8.6 Hz, 2H, 2- and 6-H_{An}), 6.97 (d, J = 8.7 Hz, 2H, 3- and 5-H_{Ar}), 6.86 (d, J = 8.7 Hz, 2H, 3- and 5-H_{An}), 4.80 (d, J = 9.2 Hz, 1H, CH(O)Ar), 4.56 (td, J =

6.2, 4.7 Hz, 1H, CHOH), 4.26 (dd, J = 9.5, 6.2 Hz, 1H, $CH_{2\alpha}O$), 4.05 (dd, J = 9.5, 4.7 Hz, 1H, $CH_{2\beta}O$), 3.79 (s, 3H, CH_3O), 3.02 (dd, J = 9.2, 6.2 Hz, 1H, CHAn), 2.22 (br s, 1H, CHOH) ppm.

^{13}C NMR (76 MHz, $CDCl_3$, DEPT135, HSQC) δ 162.40 (d, J = 245.5 Hz, 1C, 4-C_{Ar}), 158.90 (1C, 4-C_{An}), 136.51 (d, J = 3.0 Hz, 1C, 1-C_{Ar}), 130.27 (2C, 2C, 3- and 5-C_{An}), 129.01 (1C, 1-C_{An}), 127.61 (d, J = 8.1 Hz, 2C, 3- and 5-C_{Ar}), 115.29 (d, J = 21.4 Hz, 2C, 3- and 5-C_{Ar}), 114.44 (2C, 3- and 5-C_{An}), 86.78 (1C, CH(O)Ar), 79.65 (1C, CHOH), 74.54 (1C, CH_2O), 62.95 (1C, CHAn), 55.38 (1C, CH_3O) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.83 ppm (with proton decoupling).

Characteristic NOE correlations: CH(O)Ar/2- and 6-H_{An}, CH(O)Ar/$CH_{2\alpha}O$, CHAn/2- and 6-H_{Ar}, CHAn/CHOH, CHAn/$CH_{2\beta}O$, CHOH/2- and 6-H_{An}, CHOH/$CH_{2\beta}O$, $CH_{2\alpha}O$/2- and 6-H_{An}.

HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{17}FO_3Na^+$: 311.1054, found 311.1058.

Conflicts of interest

The authors declare no conflict of interest.

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