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A Versatile Approach to Noncoded β-Hydroxy-α-amino Esters and α-Amino Acids/Esters from Morita–Baylis–Hillman Adducts

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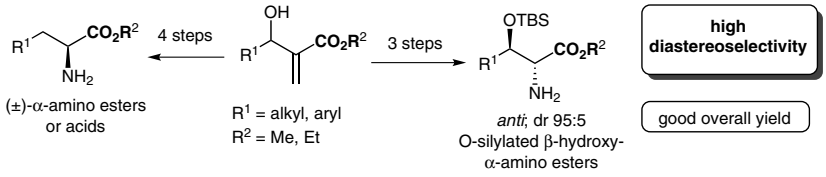

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Abstract A simple and straightforward approach to the diastereoselective synthesis of noncoded β-hydroxy-α-amino esters from Morita–Baylis–Hillman (MBH) adducts is described. The strategy is based on a one-pot sequence involving an oxidative cleavage of the double bond of silylated Morita–Baylis–Hillman adducts, followed by the reaction with hydroxylamine hydrochloride/pyridine to form oximes. The stereoselective reduction of the oximes with the mixture $MoCl_5 \cdot nH_2O/NaBH_3CN$ led to the corresponding *anti*-β-hydroxy-α-amino esters in four steps in good overall yield and with diastereoselectivity higher than 95%. A slight modification of the synthetic approach has allowed for the racemic synthesis of a set of noncoded α-amino esters/acids and DOPA.

Key words Morita–Baylis–Hillman adducts, amino acids, reduction, diastereoselectivity, DOPA

β-Hydroxy-α-amino acids/esters and their corresponding vicinal amino alcohols are essential building blocks found in a variety of pharmacologically active natural products, herbicides, and fungicides. This basic structural unit can be found in proteins (through the amino acids serine and threonine)[1] and in several biologically active natural products.[2] In Figure 1, some representative examples of natural products containing this unit are shown.

Kaitocephalin (**1**) is a pyrrolidine alkaloid, isolated from the filamentous fungus *Eupenicillium shearii* PF1191.[3] Due to the suppression of kainic acid toxicity, this compound is a candidate for use as a lead compound in the development of new medicines for the treatment of neurological diseases related to glutamate excitotoxicity.[4] Sphingofungin E (**2**) is also an example of a compound containing the β-hydroxy-α-amino acid moiety. This compound has a potent immunosuppressive activity.[5] Altemicidin (**3**) is a six-azaindene monoterpene alkaloid, which exhibits a strong acaricidal activity along with a promising inhibition activity of tumor

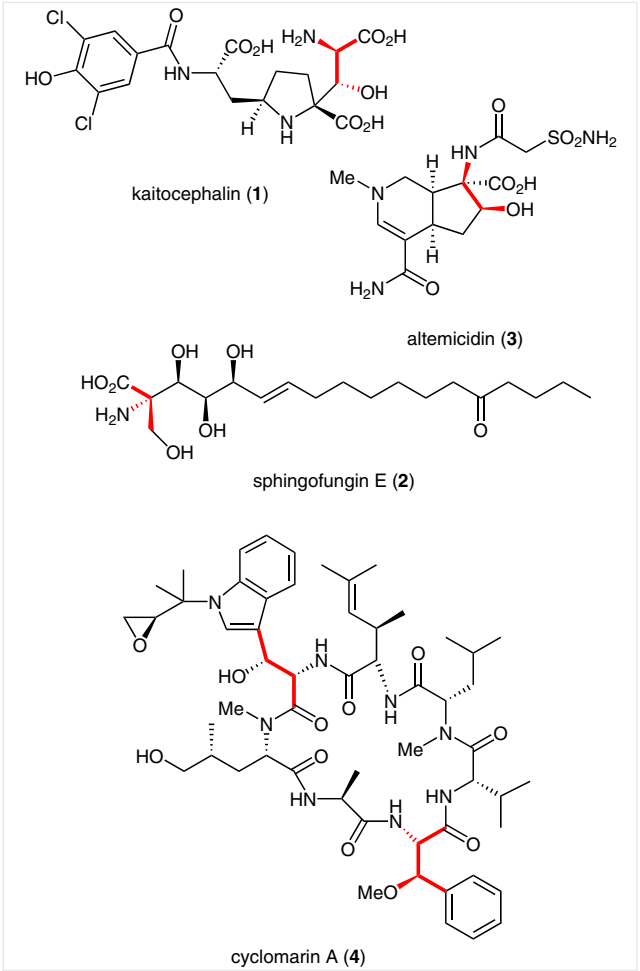


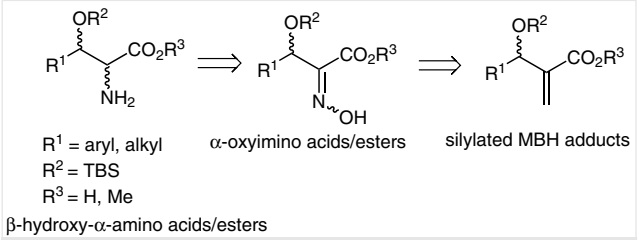
Figure 1 Some representative examples of biologically active natural products containing the β-hydroxy-α-amino acid/ester unit

cell growth.[6] The β-hydroxy-α-amino acid/ester unit can also be presented as part of a cyclic compound. The family of cyclomarins exemplifies this property. The most abundant component of this family, cyclomarin A (**4**), exhibits anticancer and anti-inflammatory activities both in vivo and in vitro.[7]

Noncoded amino acids/esters offer structural units with extensive use in the design of new protease inhibitors and in the determination of the specificity of proteases.[8] Moreover, β-hydroxy-α-amino acids/esters can be readily transformed into a variety of catalyst, ligands, chiral auxiliaries, and other valuable compounds that may serve as useful precursors in organic synthesis. For instance, β-hydroxy-α-amino carbonyl compounds are more often employed as intermediates for the syntheses of compounds such as, 2-aminopropane-1,3-diols[9] (key intermediates to the synthesis of oxazolidine-2-ones), lactams such as (+)-lactacystin (which is a strong and selective inhibitor of the proteasome),[10] parent β-hydroxy-α-amino acids, β-halo-α-amino acids, and aziridines.[11,12]

The essential role played by β-hydroxy-α-amino acid esters in biological systems, as characterized by great synthetic versatility, has attracted an interest on the part of the synthetic community in preparing these building blocks, especially in a stereoselective manner.[13] As a consequence, a number of useful enzymatic and chemical approaches for their syntheses are available. Some of these methods are the aldol reaction (including enzymatic versions),[14] the Strecker reaction,[15] dihydroxylation reactions,[16] aminohydroxylation,[17] epoxidations,[18] use of azomethine ylide,[19] hydrogenation and dynamic kinetic resolution,[20] oxy-Michael additions,[21] photocycloadditions,[22] oxazolidinones,[12a,23] sigmatropic rearrangements,[24] and the Ireland–Claisen rearrangement.[25] These methods have appealing aspects, but they also suffer from disadvantages such as low overall yields, multiple synthetic steps, and in certain cases, expensive and or drastic reaction conditions. Additionally, remarkably few efforts to synthesize these target amino acids or esters from β-hydroxy-α-oxyimino esters have been reported to date.[26] This motivated us to develop an alternative approach to α-oxyimino esters from Morita–Baylis–Hillman adducts. The stereoselective reduction of these intermediates would allow for fast and easy access to β-hydroxy-α-amino esters and noncoded amino acids.

The designed strategy is based on a one-pot synthesis of oxyimino esters through ozonolysis and oximation of silylated (TBS)-protected Morita–Baylis–Hillman (MBH) adducts. The diastereoselective reduction of oxyimino derivatives forms the desired amino acid esters, as illustrated in the retrosynthetic analysis depicted below (Scheme 1). Based on our previous results and those of others,[27] a good control of the relative stereochemistry during the reduction step was expected.

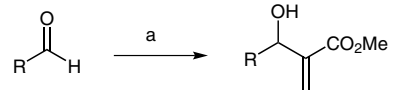


Scheme 1 Retrosynthetic analysis for the preparation of β-hydroxy-α-amino acid/esters

We describe herein a fast, simple, and alternative approach to the synthesis of β-hydroxy-α-amino esters, which is based on the stereoselective reduction of oxyiminoesters that are easily obtained from Morita–Baylis–Hillman adducts. The same approach also allowed for describing the synthesis of noncoded amino acids.

We began this work by preparing some Morita–Baylis–Hillman (MBH) adducts, using a method that was previously described by our group.[28] Specifically, a mixture of a suitable aldehyde with methyl acrylate and DABCO was sonicated for a few hours to yield the corresponding MBH adducts in good to excellent yields (Table 1).

Table 1 Preparation of the MBH Adducts[a]

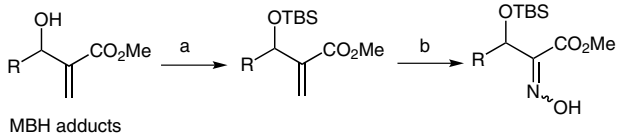


Entry	R	MBH adduct	Yield (%)[b]
1	6-bromopiperonyl	**5**	82
2	4-$MeOC_6H_4$	**6**	76
3	4-*t*-BuC_6H_4	**7**	78
4	Ph	**8**	87
5	Et	**9**	80
6	3-ClC_6H_4	**10**	82
7	4-$O_2NC_6H_4$	**11**	93
8	4-ClC_6H_4	**12**	88
9	4-BrC_6H_4	**13**	75
10	3,4,5-$(MeO)_3C_6H_2$	**14**	70
11	piperonyl	**15**	70[c]

[a] Reaction conditions: a) methyl acrylate (excess), DABCO, ultrasound, r.t., 3–144 h.
[b] Yields refer to isolated and purified products.
[c] In this particular case, the reaction was carried out in the presence of 2–3 drops of [bmim]Br.

Next, a subset of these MBH adducts **5**–**11** was treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole and anhydrous DMF (few drops when necessary) to give the corresponding silylated adducts in excellent yields in a few hours (Table 2).

Table 2 Silylation of MBH Adducts and Preparation of the Oxyimino Esters[a]



MBH adducts **5–11** | **16–22** | **23–29**

Entry	MBH adduct, R	Silylated MBH, yield (%)	Oxyimino ester, yield (%)[b]
1	**5**, 6-bromopiperonyl	**16**, 92	**23**, 89
2	**6**, 4-MeOC$_6$H$_4$	**17**, 91	**24**, 91
3	**7**, 4-*t*-BuC$_6$H$_4$	**18**, 90	**25**, >98
4	**8**, Ph	**19**, 93	**26**, 94
5	**9**, Et	**20**, 85	**27**, 90
6	**10**, 3-ClC$_6$H$_4$	**21**, 94	**28**, 96
7	**11**, 4-O$_2$NC6H$_4$	**22**, 92	**29**, 80

[a] Reaction conditions: a) TBSCl, imidazole, DMF, r.t., 4–6 h; b) i. O_3, MeOH, –78 °C, 15–30 min, ii. Me_2S, –78 °C to r.t., 1 h, iii. MeOH, NH_2OH·HCl, pyridine, reflux, 50 min.
[b] Yields refer to isolated and purified products. However, after isolation, the crude compounds exhibited a high degree of purity and no chromatographic purification proved to be necessary.

The TBS protection step is necessary for two reasons: the ozonolysis reaction of the silylated MBH adducts is more efficient and clean, and the product can be easily purified, if necessary. The bulky nature of this protecting group is the second reason that justifies its use. In previous work, we have demonstrated the influence of this protecting group in the diastereoselectivity of some reactions, such as heterogeneous hydrogenation and epoxidation.[27]

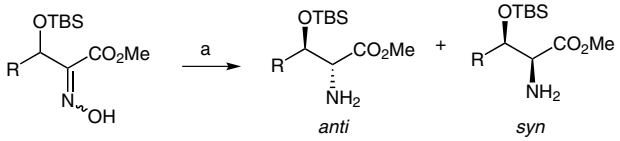
Ozonolysis of the silylated MBH adducts at –78 °C gave, after 15–50 minutes, the corresponding α-keto-β-silyloxy esters, which, in turn, were initially treated with dimethyl sulfide at the same temperature.[29] Next, hydroxylamine hydrochloride and pyridine (1 equiv each) were added to the reaction medium, and the temperature was raised to 60 °C to give the oxyimino esters **23**–**29**, in good to excellent yields after one hour (Table 2). The tiny amount of DMSO formed in the reaction after the ozonide's reductive workup probably accelerates the reaction by providing more polar organic media.

For all synthesized oximes, the formation of a mixture of isomers was observed. No efforts were made to determine the configuration of the major isomer in this step.

To complete this sequence, the oximes have to be reduced to the corresponding amino groups. Several methods are available to carry out this transformation selectively.[30] However, we were interested in using mild conditions to avoid the removal of the acid-sensitive protecting group. Recently, Kouhkan et al.[31] reported on a mild and simple method to reduce an oxime directly to an amine. This method is based on the combination of a reducing agent with a molybdenum salt and a buffer to generate the amine in good yields.

Thus, an ethanolic solution of the corresponding oxyimino esters **23**–**29** was added to a mixture of $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$ to generate the amino esters in good to excellent yields. In a careful analysis of the NMR spectra of the crude products, the presence of a mixture of diastereoisomers was not observed. In most cases, only one isomer was observed, which demonstrates the high level of diastereoselection attained in this reduction step.[32] The only exception occurred with oxyimino ester **27** (Table 3, entry 5). In this particular instance, one of the substituents was a small alkyl group, which is a possible reason for the observed decrease in the level of diastereoselection (Table 3).

Table 3 Synthesis of O-Silylated β-Hydroxy-α-amino Esters from Oxyimino Esters[a]

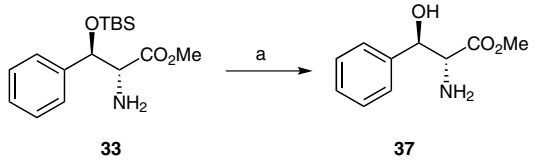


oxyimino esters **23–29** | *anti* | *syn* | O-silylated β-hydroxy-α-amino esters **30–36**

Entry	R	Product, yield (%)[b]	dr[c]
1	**23**, 6-bromopiperonyl	**30**, 88	>95:5
2	**24**, 4-MeOC$_6$H$_4$	**31**, 95	>95: 5
3	**25**, 4-*t*-BuC$_6$H$_4$	**32**, 93	>95:5
4	**26**, Ph	**33**, 93	>95: 5
5	**27**, Et	**34**, 91	78:22
6	**28**, 3-ClC$_6$H$_4$	**35**, 96	>95: 5
7	**29**, 4-O$_2$NC$_6$H$_4$	**36**, 80	>95:5

[a] Reaction conditions: a) $MoCl_5$, $NaBH_3CN$, $NaHSO_4{\cdot}H_2O$, EtOH, reflux.
[b] Yields refer to isolated and purified compounds.
[c] The diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

Seeking to determine unambiguously the relative stereochemistry of amino esters, one of the silylated amino esters was converted into a known compound. Amino ester **33** (Table 3) was therefore treated with TBAF in THF for 45 minutes to give methyl β-phenylserinate (**37**), in 92% yield. Both diastereoisomers (*anti* and *syn*) of this noncoded amino ester are well known, and the complete set of spectral data is available in the literature (Scheme 2).[33]



33 37

Scheme 2 Synthesis of the *anti* methyl β-phenylserinate (**37**). *Reagents and conditions*: a) TBAF, THF, 45 min, 0 °C, 92%.

The analysis of the ^{1}H NMR spectrum of compound **37**, which was synthesized using our sequence, shows a doublet centred at 4.9 ppm with a coupling constant (*J*) of 6.0 Hz, and a second doublet centred at 3.56 ppm with the same value of coupling constant. These data were then compared with those available in the literature for the same compound.

The data for the known *anti*-diastereoisomer show the carbinolic hydrogen (C*H*OTBS) as a doublet, centred at 4.9 ppm, with a coupling constant of 5.5 Hz, while for the known *syn*-diasteroisomer the coupling constant is 7.7 Hz.[12b] For all O-silylated β-hydroxy-α-amino esters synthesized by our group (compounds **30**–**36**, Table 3), we observed coupling constants varying from 5.5 to 6.0 Hz, which confirms the *anti* relative configuration for the major diastereoisomers. The *anti*-diastereoselectivity could be rationalized from the chelate model (Figure 2) proposed by Cram[34] and previously reported by our group for other reactions.[9]

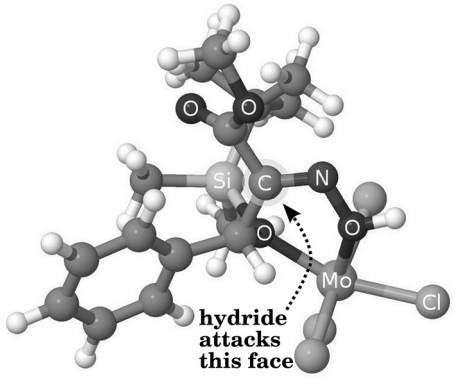


Figure 2 DFT optimized structure for a Cram-chelate complex with a $MoCl_4$ fragment coordinated to **26** (bottom view). The bulky TBS group is presented as a space-filling model. The highlighted carbon is the reaction center for hydride.

In order to evaluate the Cram-chelate model, DFT calculations were performed for compound **26** coordinated to a $[MoCl_4]^+$ fragment. Two modes of coordination were investigated, through the oxygen of the OTBS protecting group and either with the *N*(oxyimino) or with the *O*(oxymino). Several attempts were performed to obtain a N-bonded complex, but in all cases, the starting geometries with the coordination through the nitrogen atom converged to the oxygen bound complexes. Apparently, the five membered ring in these cases resulted in unstable coordination modes due to steric hindrance.

The most stable complex can be seen in Figure 2 (geometric parameters of the complex can be found as Supporting Information together with the most stable structure obtained for **26**). Coordination of the $[MoCl_4]^+$ fragment restricts rotation of OTBS around the C–O bond forcing the bulk group to be positioned over the carbon that will be attacked by the hydride. Even if the rotation around the O–Si bond is not completely restricted in the complex, coordination imposes a serious steric hindrance effect for reduction in only one side.

Analysis of the free molecule **26** reveals that the effect is indeed important since when the metal fragment is removed, the bulky group settles away from the reaction site, that is, without coordination, the OTBS group is no longer selecting the preferred site for hydride attack.

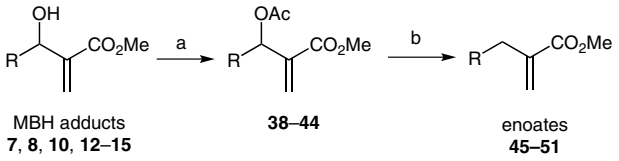
Comparison with ligand **26** structure shows that coordination increases the N–OH bond distance of the oxime group by 0.06 Å and decreases the C(sp^2)–N bond by 0.01 Å revealing that coordination has a role in weakening the N–OH bond.

The observed selectivity can be inferred from the formation of a transition state in which the hydride approach occurs only from the less-hindered side, yielding a product with relative *anti*-stereochemistry.

Moving to broaden the scope and applicability of this method, we decided to synthesize several racemic noncoded α-amino acids. For this purpose, MBH adducts **7**, **8**, **10**, and **12**–**15** (see Table 1) were treated with acetyl chloride in the presence of triethylamine to give the corresponding acetylated products **38**–**44** in good to excellent yields (Table 4). The acetylated MBH adducts **38**–**44** were then deoxygenated under mild conditions[35] to provide the enoate derivatives **45–51** in good overall yields (ranging from 63–87% over 2 steps) (Table 4).

The substituted enoates **45–51** were then subjected to the same sequence of reactions described previously for the synthesis of β-hydroxy-α-amino esters. The methanolic solutions of compounds **45**–**51** were treated with a flow of ozone at –78 °C for a few minutes (10–30 min), followed by the addition of a large excess of dimethyl sulfide. After a couple of hours, the crude α-keto esters were then reacted with hydroxylamine hydrochloride and pyridine at 60 °C to afford the corresponding oximes in good overall yields. For all cases, we were not able to observe a mixture of isomeric oximes. After chromatographic filtration, the oximes were reduced by treatment with a mixture of $MoCl_5$, $NaBH_3CN$, and $NaHSO_4{\cdot}H_2O$ to provide the corresponding racemic noncoded amino esters in good overall yields (ranging from 46 to 61% over 2 steps) (Table 5).

Table 4 Acetylation of MBH Adducts and Preparation of the Enoate Derivatives[a]

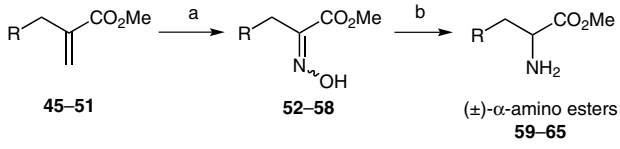


MBH adducts **7**, **8**, **10**, **12**–**15** | **38**–**44** | enoates **45**–**51**

Entry	MBH adduct, R	Acetylated MBH, yield (%)[b]	Enoate, yield (%)[b]
1	**7**, 4-*t*-BuC_6H_4	**38**, 81	**45**, 94
2	**8**, Ph	**39**, 70	**46**, 92
3	**10**, 3-ClC_6H_4	**40**, 92	**47**, 95
4	**12**, 4-ClC_6H_4	**41**, 75	**48**, >93
5	**13**, 4-BrC_6H_4	**42**, 87	**49**, 94
6	**14**, 3,4,5-$(MeO)_3C_6H_2$	**43**, 71	**50**, 90
7	**15**, piperonyl	**44**, 75	**51**, 89

[a] Reaction conditions: a) AcCl, Et_3N, CH_2Cl_2, r.t., 2 h; b) DABCO, $NaBH_4$, THF–H_2O (3:1).
[b] Yields refer to isolated and purified products.

Table 5 Synthesis of Noncoded Racemic α-Amino Esters from MBH Adducts[a]



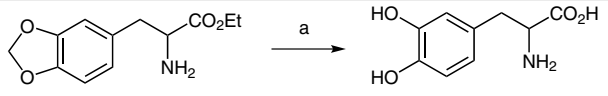
45–**51** | **52**–**58** | (±)-α-amino esters **59**–**65**

Entry	Enoate, R	Oxime, yield (%)[b]	Amino ester, yield (%)[b,c]
1	**45**, 4-*t*-BuC_6H_4	**52**, 94[b]	**59**, 64
2	**46**, Ph	**53**, 92	**60**, 59
3	**47**, 3-ClC_6H_4	**54**, 95	**61**, 65
4	**48**, 4-ClC_6H_4	**55**, 91	**62**, 61
5	**49**, 4-BrC_6H_4	**56**, 90	**63**, 63
6	**50**, 3,4,5-$(MeO)_3C_6H_2$	**57**, 94	**64**, 64
7	**51**, piperonyl[d]	**58**, 88	**65**, 52

[a] Reaction conditions: a) i. O_3, MeOH, –78 °C, 15–30 min, ii. SMe_2, 2 h, r.t., iii. $NH_2OH{\cdot}HCl$, pyridine, 60 °C, 30 min to 1 h; b) $MoCl_5$, $NaBH_3CN$, $NaHSO_4{\cdot}H_2O$, EtOH, reflux.
[b] Yields refer to isolated and purified products.
[c] We observed a small amount of hydrolysis products during the chromatographic purification. The corresponding amino acids are much more polar than the ester and likely stay retained on the silica gel column.
[d] In this particular case, the ethyl amino ester derivatives were also synthesized in 87% and 60% yield, respectively.

The entire synthetic sequence is very simple and direct. The noncoded amino esters were synthesized in their racemic versions in four steps from the MBH adducts in good overall yields, ranging from 30 to 53%. To our knowledge, this is the first report on the synthesis of α-amino esters from Morita–Baylis–Hillman adducts.

To demonstrate the feasibility of this approach, we decided to use it in the total synthesis of a useful target. DOPA is a noncoded amino acid, which is used in the treatment of degenerative diseases such as Parkinson's disease. In its racemic form, this amino acid was initially used to treat this disease.[36] Some years later, the *S*-enantiomer was identified as the eutomer.[37] Despite the existence of several chemical and biotechnological asymmetric approaches to the synthesis of this compound,[38] its chemical resolution is very easy to perform on a large scale, which justifies the development of racemic strategies. Thus, the α-amino ester **65** was treated in a mixture of glacial acetic acid and phenol in a solution of hydrochloric acid (6 mol/L) to provide racemic DOPA as a sole compound in 63% yield (Scheme 3).



(±)-α-amino ester **65** | (±)-DOPA (**66**)

Scheme 3 Preparation of racemic DOPA from Morita–Baylis–Hillman adduct. *Reagents and conditions*: a) glacial AcOH, phenol, HCl (6 mol/L), 65%.

DOPA in its racemic form was prepared in six steps from MBH adducts, with an overall yield of 19%. The sequence is very simple and straightforward. Because the commercial availability of both enantiomers of a given amino acid is always interesting and considering that the chemical resolution is as yet a valid strategy to obtain them, the method described herein could be considered as an alternative to obtain this class of compounds.

In conclusion, we have reported an efficient and highly diastereoselective approach for the synthesis of *anti*-β-hydroxy-α-amino acid esters. These *anti*-β-hydroxy-α-amino acid esters were obtained in a sequence of three steps from MBH adducts in good to excellent overall yields (ranging from 85 to 96%) with high *anti*-stereoselectivity. Additionally, this is the first report directly describing the synthesis of *anti*-β-hydroxy-α-amino acid esters from MBH adducts. Theoretical calculations have allowed the rationalization for the attained diastereoselectivity. As far as we know, this is the first report dealing with calculations involving Mo salts in the diastereoselective reduction of oximes.

A simple and easy extension of this methodology has also allowed for the synthesis of racemic noncoded α-amino esters in good overall yields. The synthetic applicability of this sequence was demonstrated through the racemic synthesis of DOPA. To the best of our knowledge, this is also the first report of the synthesis of this α-amino acid from a Morita–Baylis–Hillman adduct.

Other efforts to demonstrate the usefulness of this method in the total synthesis of pharmacologically active alkaloids are under way in our laboratory and the results will be disclosed in due time. Efforts to reduce the oxyimino intermediate in an asymmetric manner as well as to use the α-keto esters as substrates for enzymatic reductive amination (by employing transaminases) are ongoing in our laboratory, and the results will be disclosed as soon as possible.

The reaction progress was monitored by TLC on silica gel (aluminum foils) and spotted under UV light (254 nm), followed by staining with ethanolic 25% phosphomolybdic solution or aqueous $KMnO_4$. Purification by column chromatography was carried out on silica gel (70–230 or 230–400 Mesh). ^1H NMR spectra were recorded at 250 and 500 MHz and the ^{13}C NMR spectra at 62.5 and 125 MHz, in $CDCl_3$ or CD_3OD at r.t. Chemical shifts (δ) were reported in ppm and the coupling constants (*J*) in hertz (Hz). Standard abbreviations were used to assign the multiplicities of NMR signals. High-resolution mass spectra were recorded using Q-TOF Micromass equipment (Waters, UK). Compounds were named according to IUPAC rules using the program MarvinSketch 5.5.0.1.

Oxyimino Esters 23–29; General Procedure

Into a solution of the respective silylated MBH adduct **16**–**22** (2 mmol) in MeOH (30 mL), was bubbled a flow of ozone (3.5 g O_3/h), at –78 °C. The progress of the reaction was followed by TLC (eluent: (EtOAc–hexane, 20:80). After the completion of the reaction (15–30 min), to the resulting solution was added Me_2S (10 equiv) at –78 °C and reaction mixture was warmed to r.t. and stirred for 1–2 h. ***Caution***! Before adding Me_2S, the reaction medium was purged with N_2 for 15 min at –78 °C in order to remove the excess of ozone. After this time, 2 to 3 drops of pyridine and $NH_2OH{\cdot}HCl$ (1 equiv) were added and the reaction flask was fitted with a reflux condenser and the mixture was refluxed for 30 min to 1 h.[39] The progress of the reaction was monitored by TLC (eluent: EtOAc–hexane, 40:60). After completion of the reaction, the solvents were removed under vacuum and the residue was partitioned between CH_2Cl_2 and H_2O (1:1, 20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and then concentrated to yield the corresponding oximes. In the most cases, the products showed purity sufficient to be used in the next step without any further purification. If necessary, chromatographic purification on silica gel can be carried out.

Methyl (±)-3-(6-Bromo-2*H*-1,3-benzodioxol-5-yl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-(*N*-hydroxyimino)propanoate (23)

Reaction time: 60 min; yield: 395 mg (89%); colorless oil.

IR (neat): 3273, 2954, 2930, 2857, 1746, 1474, 1503, 1408, 1240 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = –0.10 (s, 3 H), 0.04 (s, 3 H), 0.83 (s, 9 H), 3.81 (s, 3 H), 5.85 (s, 1 H), 5.93 (d, *J* = 10 Hz, 2 H), 6.90 (s, 2 H), 7.02 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.0, –4.6, 18.3, 25.8, 29.9, 52.5, 72.3, 102.1, 109.5, 112.3, 112.8, 132.5, 147.7, 148.4, 151.8, 163.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{24}BrNO_6Si$ + Na : 470.0436; found: 470.0395.

(±)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)-2-(*N*-hydroxyimino)propanoate (24)

Reaction time: 70 min; yield: 640 mg (91%); viscous yellow oil.

IR (neat): 3200, 3479, 2954, 2928, 2856, 1735, 1611, 1520, 1445, 1434 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = –0.03 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 5.51 (s, 1 H), 6.87 (d, *J* = 10 Hz, 2 H), 7.27 (m, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.0, –4.8, 18.3, 25.7, 52.1, 55.3, 73.3, 113.7, 113.8, 114.4, 127.5, 127.8, 128.7, 131.9, 149.9, 153.9, 159.4, 163.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{27}NO_5Si$ + Na: 376.1556; found: 376.1548.

Methyl (±)-3-[(*tert*-Butyldimethylsilyl)oxy]-3-(4-*tert*-butylphenyl)-2-(*N*-hydroxyimino)propanoate (25)

Reaction time: 80 min; yield: 746 mg (98%); yellow viscous oil.

IR (neat): 3381, 2968, 2931, 2869, 1735, 1483, 1268, 1088 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 1.29 (s, 18 H), 3.86 (s, 3 H), 5.27 (s, 1 H), 6.16 (s, 1 H), 5.51 (s, 1 H), 7.50 (m, 4 H), 7.27.

^{13}C NMR (125 MHz, $CDCl_3$): δ = –0.9, 0.0, 29.0, 31.5, 52.25, 68.3, 73.0, 127.0, 128.5, 137.0, 151.0, 152.6, 159.4, 163.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{33}NO_4Si$ + Na: 402.2071; found: 402.2056.

Methyl (±)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-(*N*-hydroxyimino)-3-phenylpropanoate (26)

Reaction time: 60 min; yield: 608 mg (94%); colorless viscous oil.

IR (neat): 3321, 2954, 2920, 2857, 1747, 1455, 1290, 1246, 1140 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 3.76 (s, 3 H), 5.56 (s, 1 H), 7.22–7.41 (m, 5 H), 9.28 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.0, -4.9, 18.3, 25.8, 52.1, 73.6, 126.5, 128.1, 128.3, 139.7, 153.6, 162.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}NO_4Si$ + Na: 346.145; found: 346.1416.

Methyl (±)-3-[(*tert*-butyldimethylsilyl)oxy]-2-(*N*-hydroxyimino)pentanoate (27)

Reaction time: 45 min; yield: 494 mg (90%); colorless oil.

IR (neat): 3200–3400, 2955, 2931, 2859, 1742, 1463, 1438, 1310, 1257, 1159, 1106 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.86–0.89 (s, 9 H), 0.86–0.89 (m, 3 H), 1.68–1.80 (m, 3 H), 3.82 (s, 3 H), 4.27 (t, *J* = 6.7 Hz, 1 H), 9.28 (br, 1 H).

^{13}C NMR (62,5 MHz, $CDCl_3$): δ = –5.3, –5.1, 9.5, 17.9, 25.5, 28.8, 51.7, 73.1, 154.1, 162.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{26}NO_4Si$: 276.163; found: 276.1604.

Methyl (±)-3-[(*tert*-Butyldimethylsilyl)oxy]-3-(3-chlorophenyl)-2-(*N*-hydroxyimino)propanoate (28)

Reaction time: 40 min; yield: 686 mg (96%); yellow viscous oil.

IR (neat): 3200–3400, 2954, 2935, 2858, 1743, 1596, 1575, 1472, 1445, 1316 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.09 (s, 6 H), 0.89 (s, 9 H), 3.74 (s, 3 H), 5.51 (s, 1 H), 7.24–7.38 (m, 4 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.9, 18.2, 25.7, 52.4, 73.0, 124.3, 126.2, 127.9, 129.5, 134.1, 142.1, 153.1, 162.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}ClNO_4Si$: 358.124; found: 358.1244.

Methyl (±)-3-(*tert*-Butyldimethylsilyloxy)-2-(*N*-hydroxyimino)-3-(4-nitrophenyl)propanoate (29)

Reaction time: 70 min; yield: 588 mg (80%); reddish brown viscous oil.

IR (neat): 3392, 2949, 2925, 2855, 2857, 1742, 1462, 1362, 1258, 1166, 1088 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.005 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 3.73 (s, 3 H), 5.60 (s, 1 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 8.16 (d, *J* = 8.8 Hz, 2 H), 9.66 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.9, 18.3, 25.7, 52.4, 55.3, 73.1, 123.7, 127.2, 147.3, 147.8, 152.1, 128.7, 131.9, 149.9, 153.9, 159.4, 162.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}N_2O_6Si$: 369.1467; found: 369.1467.

Silylated *anti*-β-Hydroxy-α-amino Esters 30–36; General Procedure

To a stirred solution of the respective oxyimino ester (1 mmol, 1 equiv) in EtOH (2 mL for 1 mmol of starting material) was carefully added a solid mixture of $NaBH_3CN$ (4 equiv), $MoCl_5$ (1 equiv) and $NaHSO_4{\cdot}H_2O$ (3 equiv). The resultant mixture was stirred under reflux from 50 min up to 1 h. The reaction was monitored by TLC (eluent: EtOAc–hexane, 20:80), and after the end of the reaction, 5% aq $NaHCO_3$ (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: gradient of EtOAc–hexane, varying from 15:85 up to 80:20 v/v).

Methyl (±)-*anti*-2-Amino-3-(6-bromo-2*H*-1,3-benzodioxol-5-yl)-3-[(*tert*-butyldimethylsilyl)oxy]propanoate (30)

Reaction time: 55 min; yield: 380 mg (88%); yellow oil.

IR (neat): 3627, 2950, 2924, 2853, 1740, 1510, 1475, 1250 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.17 (s, 3 H), 0.05 (s, 3 H), 0.85 (s, 9 H), 3.57 (d, *J* = 7.0 Hz, 1 H), 3.70 (s, 3 H), 5.15 (d, *J* = 7.0 Hz, 1 H), 5.98 (dd, *J* = 1.0, 9.2 Hz, 2 H), 6.95 (s, 1 H), 6.96 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.4, –4.8, 17.8, 25.5, 51.6, 61.8, 75.6, 101.7, 108.2, 111.9, 113.3, 133.8, 147.5, 147.9, 173.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{27}BrNO_5Si$: 434.0824; found: 434.0831.

Methyl (±)-*anti*-2-Amino-3-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)propanoate (31)

Reaction time: 50 min; yield: 322 mg (95%); yellow oil.

IR (neat): 3371, 2955, 2929, 2856, 1741, 1683, 1611, 1525, 1463, 1439 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.18 (s, 3 H), 0.07 (s, 3 H), 0.85 (s, 9 H), 3.63 (d, *J* = 6.5 Hz, 1 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 4.76 (d, *J* = 6.3 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.1, –4.4, 18.3, 25.9, 29.93, 52.0, 55.4, 62.5, 113.8, 128.3, 132.8, 159.6, 173.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{30}NO_4Si$: 340.1944; found: 340.1945

Methyl (±)-*anti*-2-Amino-3-(*tert*-butyldimethylsilyloxy)-3-(4-*tert*-butylphenyl)propanoate (32)

Reaction time: 45 min, yield: 340 mg (93%); brown oil.

IR (neat): 3392, 2949, 2925, 2855, 1742, 1462, 1363, 1258, 1166, 1088 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.21 (s, 3 H), –0.02 (s, 3 H), 0.84 (s, 9 H), 1.28 (s, 9 H), 3.63 (d, *J* = 6.5 Hz, 1 H), 3.68 (br s, 1 H), 4.75 (d, *J* = 6.7 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.1, –4.1, 18.2, 25.9, 29.9, 31.5, 34.7, 51.9, 52.0, 62.4, 125.2, 126.8, 135.5, 151.1, 173.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{36}NO_3Si$: 366.2459; found: 366.2459.

Methyl (±)-*anti*-2-Amino-3-[(*tert*-butyldimethylsilyl)oxy]-3-phenylpropanoate (33)

Reaction time: 40 min; yield: 287 mg (93%); viscous colorless oil.

IR (neat): 3483, 2954, 2920, 2854, 1720, 1477, 1447, 1234, 1038 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.14 (s, 3 H), 0.07 (s, 3 H), 0.94 (s, 9 H), 3.41 (s, 3 H), 3.68 (d, *J* = 7.0 Hz, 1 H), 4.79 (d, *J* = 7.0 Hz, 1 H), 7.05–7.22 (m, 5 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = -5.3, –4.7, 18.0, 25.6, 51.7, 62.0, 76.5, 126.0, 126.8, 128.1, 140.3, 173.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_3Si$: 310.1838; found: 310.1826.

Methyl (±)-*anti*-2-Amino-3-[(*tert*-butyldimethylsilyl)oxy]pentanoate (34)

Reaction time: 50 min; yield: 188 mg (72%); colorless oil.

IR (neat): 3400, 2955, 2931, 2859, 1742, 1463, 1438, 1253, 1172, 1106, 1058 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.83 (s, 9 H), 1.25–1.71 (m, 5 H), 3.54 (d, *J* = 4.5 Hz, 1 H), 3.64 (s, 1 H), 3.75–3.79 (m, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.6, –4.3, 9.8, 18.1, 25.8, 51.9, 59.1, 75.7, 173.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{28}NO_3Si$: 262.1838; found: 262.1833.

Methyl (±)-*anti*-2-Amino-3-[(*tert*-butyldimethylsilyl)oxy]-3-(3-chlorophenyl)propanoate (35)

Reaction time: 40 min; yield: 330 mg (96%); viscous yellow oil.

IR (neat): 3392, 3388, 2972, 2915, 2857, 1752, 1598, 1483, 1436, 1274, 1102 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.14 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 3.51 (s, 1 H), 3.65 (s, 3 H), 3.69 (d, *J* = 6.0 Hz, 1 H), 4.81 (d, *J* = 6.3 Hz, 1 H), 7.14–7.26 (m, 4 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.1, –4.5, 18.2, 25.8, 52.0, 62.3, 125.22, 127.2, 128.3, 129.6, 134.4, 142.9, 173.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{27}ClNO_3Si$: 344.1449; found: 344.1450.

Methyl (±)-*anti*-2-Amino-3-(*tert*-butyldimethylsilyloxy)-3-(4-nitrophenyl)propanoate (36)

Reaction time: 40 min; yield: 283 mg (80%); reddish brown oil.

IR (neat): 3382, 2957 2929, 2860, 1741, 1572, 1524, 1346, 1258, 1087 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = –0.16 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 3.67 (br s, 4 H), 4.93 (s, *J* = 6.0 Hz 1 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 8.18 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.0, –4.5, 18.2, 25.8, 52.2, 62.2, 76.6, 123.5, 127.9, 147.9, 147.5, 173.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{27}N_2O_5Si$: 355.1684; found: 355.1683.

Anti-β-hydroxy-α-amino Acid Esters; General Procedure

To a solution of the appropriate β-hydroxy-α-amino ester (3.0 mmol.) in anhydrous THF (20 mL) was added a solution of TBAF (1 mol/L in THF, 3.6 mmol) at 0 °C. The resulting mixture was stirred for 30 min. The solvent was evaporated and residue was dissolved in EtOAc (15 mL). The organic layer was washed with distilled H_2O (15 mL), brine (2 × 15 mL), dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was filtered through silica gel (EtOAc–hexanes, 30:70) to provide the corresponding amino acid ester.

Methyl (±)-*anti*-2-Amino-3-hydroxy-3-phenylpropanoate (37)

Reaction time: 30 min; yield: 538 mg (92%); yellow oil.

IR (neat): 3600, 3299, 2954, 1733, 1453, 1437, 1206, 1103, 1053 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 3.66 (s, 3 H), 3.72 (d, *J* = 5.5 Hz, 1 H), 4.88 (d, *J* = 6.0 Hz, 1 H), 7.27–7.34 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.4, 61.9, 76.0, 127.9, 129.1, 129.4, 141.9, 174.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}NO_3$: 196.0974; found: 196.0987.

Deoxygenation of the MBH Adducts and Preparation of Enoates 45–51; General Procedure

To a mixture of a given acetylated MBH adduct (2.0 mmol) in THF–H_2O (3:1, 4 mL) was added DABCO (2.0 mmol). The resulting solution was stirred at r.t. for 15 min. Then, NaBH (2.0 mmol) was added at r.t. and the resulting mixture was stirred for 15 min. The solvent was removed and the crude residue was purified by flash chromatography over silica gel (hexane–5% EtOAc) to afford the corresponding enoates. Compounds **45**–**49** are known and their spectroscopic data are in agreement with the data available in the literature. For details see Supporting Information. The analytical and spectral data of the unknown compounds are given below.

Methyl 2-[(3,4,5-Trimethoxyphenyl)methyl]prop-2-enoate (50)

Yield: 479 mg (90%); colorless oil.

IR (neat): 3010, 2996, 1741, 1445, 1236 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.57 (s, 2 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 3.83 (s, 6 H), 5.50 (s, 1 H), 6.24 (s, 1 H), 6.41 (s, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 38.2, 51.7, 55.9, 60.6, 105.8, 126.1, 134.2, 136.4, 139.8, 153.0, 167.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}O_5$: 267.1232; found: 267.1199.

Ethyl 2-(2*H*-1,3-Benzodioxol-5-ylmethyl)prop-2-enoate (51)

Yield: 392 mg (89%); colorless oil.

IR (neat): 3002, 2991, 1736, 1240 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H), 3.54 (s, 2 H), 4.17 (q, *J* = 7.1 Hz 2 H), 5.45 (d, *J* = 1.2 Hz, 1 H), 5.91 (s, 2 H), 6.21 (s, 1 H), 6.59–6.74 (m, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.3, 37.9, 60.9, 101.0, 108.3, 109.6, 122.1, 125.9, 132,7, 140.7, 146.2, 147.8, 167.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}O_4$: 235.0970; found: 235.0983.

Ozonolysis and Oximation of Enoates 52–58; General Procedure

Ozonolysis of the MBH adducts **45**–**51** (2 mmol, 1 equiv) was carried out similar to the silylated MBH adducts **16**–**22** at –78 °C for 15–30 min to give the corresponding α-keto esters. To the resulting solution, hydroxylamine hydrochloride (1.5 equiv) and pyridine (1.0 mL) were added and the mixture was stirred at r.t. for 50 min. The solvent was removed and the crude residue was purified by silica gel flash chromatography (EtOAc–hexane, 20:80) to afford the corresponding non-coded α-amino esters. Compounds **53**, **55**, **57**, and **58** are known and their spectroscopic data are in agreement with the data available in the literature. For details see Supporting Information. The analytical and spectral data of the unknown compounds are given below.

Methyl 3-(4-*tert*-Butylphenyl)-2-(*N*-hydroxyimino)propanoate (52)

Yield: 442 mg (94%); white solid; mp 165–167 °C.

^1H NMR (250 MHz, CD_3OD): δ = 1.27 (s, 9 H), 3.88 (s, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (62.5 MHz, CD_3OD): δ = 28.2, 30.3, 33.7, 124.4, 129.0, 134.7, 148.7, 153.7, 162.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_3$: 236.1287; found 236.1272.

Methyl 3-(3-Chlorophenyl)-2-(*N*-hydroxyimino)propanoate (54)

Yield: 431 mg (95%); white solid; mp 90–92 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.97 (s, 2 H), 7.28–7.35 (m, 3 H), 7.67–7.76 (m, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 30.1, 52.8, 126.9, 127.3, 129.2, 129.7, 134.2, 137.5, 150.2, 163.6.

Methyl 3-(4-Bromophenyl)-2-(*N*-hydroxyimino)propanoate (56)

Yield: 488 mg (90%); colorless oil.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 3.90 (s, 2 H), 7.13–7.19 (d, *J* = 7.8 Hz, 2 H), 7.31–7.36 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 30.0, 52.7, 120.4, 130.9, 131.5, 134.9, 150.1, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}BrNO_3$: 271.9922; found: 271.8000.

α-Amino Esters/Acids 59–65; General Procedure

See Supporting Information for complete experimental details and spectral data.

Theoretical Calculations

Density functional theory (DFT) calculations were carried out using PBE0[40] gradient-corrected hybrid to solve the Kohn–Sham equations with a 10^{-5} a.u. convergence criterion for the density change. The choice of PBE0 is based on the fact that this functional gives better geometries than B3LYP for coordination compounds.[41] The LANL2DZ effective core potential[42] was used for Mo and the atomic 6-31G(d) basis set[43] for all other atoms. All calculations were performed using GAMESS software[44] (version Jan 12, 2009 R3 for 64 bit) and geometries were optimized with a convergence criterion of 10^{-4} a.u. in a conjugated gradient algorithm without constraints. Vibrational frequency analyses were performed at the same level of theory to confirm the structures as minima of the potential energy surfaces (PES) showing no imaginary frequencies. All the models and figures were plotted using Jmol.[45]

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Supporting Information

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