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

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Received: 09.07.2014
Accepted after revision: 26.08.2014
Published online: 02.10.2014
DOI: 10.1055/s-0034-1379168; Art ID: ss-2014-m0435-op

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$_5$·nH$_2$O/NaBH$_3$CN 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)\textsuperscript{1} and in several biologically active natural products.\textsuperscript{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 \textit{Eupenicillium shearii} PF1191.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} Altemicidin (3) is a six-azaindene monoterpenic 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. 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.

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. 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-amino propane-1,3-diols (key intermediates to the synthesis of oxazolidine-2-ones), lactams such as (+)-lactacystin (which is a strong and selective inhibitor of the proteasome), parantoxazolidine-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 oxo-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 β-oxyimino esters from Morita–Baylis–Hillman adducts. The stereoselective reduction of oxyimino esters 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>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>MBH adduct</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-bromo piperonyl</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC6H4</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>4-t-ButC6H4</td>
<td>7</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>9</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>3-CIC6H4</td>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>4-NC6H4</td>
<td>11</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>4-CIC6H4</td>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>4-BrC6H4</td>
<td>13</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>3,4,5-(MeO)C6H2</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>Piperonyl</td>
<td>15</td>
<td>70c</td>
</tr>
</tbody>
</table>

*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).
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 NaBH₃CN/MoCl₅/NaHSO₄·H₂O 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 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>MBH adduct, R</th>
<th>Silylated MBH, yield (%)</th>
<th>Oxyimino ester, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5, 6-bromopiperonyl</td>
<td>16, 92</td>
<td>23, 89</td>
</tr>
<tr>
<td>2</td>
<td>6, 4-MeOC₆H₄</td>
<td>17, 91</td>
<td>24, 91</td>
</tr>
<tr>
<td>3</td>
<td>7, 4-t-BuC₆H₄</td>
<td>18, 90</td>
<td>25, &gt;98</td>
</tr>
<tr>
<td>4</td>
<td>8, Ph</td>
<td>19, 93</td>
<td>26, 94</td>
</tr>
<tr>
<td>5</td>
<td>9, Et</td>
<td>20, 85</td>
<td>27, 90</td>
</tr>
<tr>
<td>6</td>
<td>10, 3-ClC₆H₄</td>
<td>21, 94</td>
<td>28, 96</td>
</tr>
<tr>
<td>7</td>
<td>11, 4-O₂NC₆H₄</td>
<td>22, 92</td>
<td>29, 80</td>
</tr>
</tbody>
</table>

* Reaction conditions: a) TBSCl, imidazole, DMF, r.t., 4–6 h: b) i. O₃, MeOH, –78 °C, 15–30 min, ii. Me₂S, –78 °C to r.t., 1 h, iii. MeOH, NH₂OH·HCl, pyridine, reflux, 50 min.

### Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R Product, yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23, 6-bromopiperonyl</td>
<td>30, 88</td>
</tr>
<tr>
<td>2</td>
<td>24, 4-MeOC₆H₄</td>
<td>31, 95</td>
</tr>
<tr>
<td>3</td>
<td>25, 4-t-BuC₆H₄</td>
<td>32, 93</td>
</tr>
<tr>
<td>4</td>
<td>26, Ph</td>
<td>33, 93</td>
</tr>
<tr>
<td>5</td>
<td>27, Et</td>
<td>34, 91</td>
</tr>
<tr>
<td>6</td>
<td>28, 3-ClC₆H₄</td>
<td>35, 96</td>
</tr>
<tr>
<td>7</td>
<td>29, 4-O₂NC₆H₄</td>
<td>36, 80</td>
</tr>
</tbody>
</table>

* Reaction conditions: a) MoCl₅, NaBH₃CN, NaHSO₄·H₂O, EtOH, reflux.

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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 (CHOTBS) as a doublet, centred at 4.9 ppm, with a coupling constant of 5.5 Hz, while for the known syn-diastereoisomer the coupling constant is 7.7 Hz.† For all O-silylated $\beta$-hydroxy-$\alpha$-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 and previously reported by our group for other reactions.9

In order to evaluate the Cram-chelate model, DFT calculations were performed for compound 26 coordinated to a $[\text{MoCl}_4]^+$ fragment. Two modes of coordination were investigated, through the oxygen of the OTBS protecting group and either with the $N$(oxyimino) or with the $O$(oxyimino). 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 $[\text{MoCl}_4]^+$ 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 $\alpha$-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 enolate 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 $\beta$-hydroxy-$\alpha$-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 $\alpha$-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$_3$CN, and NaHSO$_4$·H$_2$O to provide the corresponding racemic noncoded amino esters in good overall yields (ranging from 46 to 61% over 2 steps) (Table 5).
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. Some years later, the S-enantiomer was identified as the eutomer. Despite the existence of several chemical and biotechnological asymmetric approaches to the synthesis of this compound, its chemical resolution is very easy to perform on a large scale, which justifies the development of racemic strategies. Thus, the α-amino ester 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).

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.

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### Table 4  Acetylation of MBH Adducts and Preparation of the Enoate Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>MBH adduct, R</th>
<th>Acetylated MBH, yield (%)</th>
<th>Enoate, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7, 4-t-BuC₆H₄</td>
<td>38, 81</td>
<td>45, 94</td>
</tr>
<tr>
<td>2</td>
<td>8, Ph</td>
<td>39, 70</td>
<td>46, 92</td>
</tr>
<tr>
<td>3</td>
<td>10, 3-C₆H₄</td>
<td>40, 92</td>
<td>47, 95</td>
</tr>
<tr>
<td>4</td>
<td>12, 4-C₆H₄</td>
<td>41, 75</td>
<td>48, &gt;93</td>
</tr>
<tr>
<td>5</td>
<td>13, 4-BrC₆H₄</td>
<td>42, 87</td>
<td>49, 94</td>
</tr>
<tr>
<td>6</td>
<td>14, 3,4,5-(MeO)₂C₆H₂</td>
<td>43, 71</td>
<td>50, 90</td>
</tr>
<tr>
<td>7</td>
<td>15, piperyl</td>
<td>44, 75</td>
<td>51, 89</td>
</tr>
</tbody>
</table>

* Reaction conditions: a) AcCl, Et₃N, CH₂Cl₂, r.t., 2 h; b) DABCO, NaBH₄, THF–H₂O (3:1).

*Yields refer to isolated and purified products.

### Table 5  Synthesis of Noncoded Racemic α-Amino Esters from MBH Adducts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enoate, R</th>
<th>Oxime, yield (%)</th>
<th>α-amino ester, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45, 4-t-BuC₆H₄</td>
<td>52, 94*</td>
<td>59, 64</td>
</tr>
<tr>
<td>2</td>
<td>46, Ph</td>
<td>53, 92</td>
<td>60, 59</td>
</tr>
<tr>
<td>3</td>
<td>47, 3-C₆H₄</td>
<td>54, 95</td>
<td>61, 65</td>
</tr>
<tr>
<td>4</td>
<td>48, 4-C₆H₄</td>
<td>55, 91</td>
<td>62, 61</td>
</tr>
<tr>
<td>5</td>
<td>49, 4-BrC₆H₄</td>
<td>56, 90</td>
<td>63, 63</td>
</tr>
<tr>
<td>6</td>
<td>50, 3,4,5-(MeO)₂C₆H₂</td>
<td>57, 94</td>
<td>64, 64</td>
</tr>
<tr>
<td>7</td>
<td>51, piperyl</td>
<td>58, 88</td>
<td>65, 52</td>
</tr>
</tbody>
</table>

* Reaction conditions: a) i. O₃, MeOH, –78 °C, 15–30 min, ii. SMe₂, 2 h, r.t., iii. NH₂OH·HCl, pyridine, 60 °C, 30 min to 1 h; b) MoCl₅, NaBH₃CN, NaHSO₄·H₂O, EtOH, reflux.

*Yields refer to isolated and purified products.

*We observed a small amount of hydrolys 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.

*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.
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 KMnO₄. Puriﬁcation by column chromatography was carried out on silica gel (70–230 or 230–400 Mesh).¹ H NMR spectra were recorded at 250 and 500 MHz and the ¹³C NMR spectra at 62.5 and 125 MHz, in CDCl₃ or CD₂OD 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 O₃/h), at −78 °C for 15 min before adding Me₂S, the reaction medium was purged with N₂ and reaction mixture was warmed to r.t. and stirred for 1–2 h. Caution! Before adding Me₂S, the reaction medium was purged with N₂ for 15 min at −78 °C in order to remove the excess of ozone. After this time, 2 to 3 drops of pyridine and NH₂OH·HCl (1 equiv) were added for 15 min at −78 °C in order to remove the excess of ozone. After this, reaction mixture was warmed to r.t. and stirred for 1–2 h.

This 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 CH₂Cl₂ and H₂O (1:1, 20 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The organic phases were combined, dried (Na₂SO₄), 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-[(tert-Butyldimethylsilyloxy)-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⁻¹.¹

¹H NMR (250 MHz, CDCl₃): 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).

¹³C NMR (62.5 MHz, CDCl₃): 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.


Methyl (±)-3-[(tert-Butyldimethylsilyloxy)-3-(4-tert-butyphenyl)-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, CDCl₃): 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), 6.51 (s, 1 H), 7.50 (m, 4 H), 7.27 (m, 4 H).

¹³C NMR (125 MHz, CDCl₃): δ = –9.0, 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.


Methyl (±)-3-[(tert-Butyldimethylsilyloxy)-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, CDCl₃): 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).

¹³C NMR (62.5 MHz, CDCl₃): δ = –5.0, –4.9, 18.3, 25.8, 52.1, 73.6, 126.5, 128.1, 137.0, 151.0, 153.6, 162.8.

Methyl (\(\pm\))-3-\((\text{tert-Butyldimethylsilyl}oxy)\)-2-\((\text{N-hydroxyimino})\)-3-(4-nitrophenyl)propanoate (31)

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

IR (neat): 123.7, 127.2, 147.3, 147.8, 152.1, 128.7, 131.9, 149.9, 153.9, 159.4, 101.7, 108.2, 111.9, 113.3, 133.8, 147.5, 147.9, 173.5.

HRMS (ESI): \(m/z\) [M + H]\(^+\) calcld for C\(_{16}\)H\(_{25}\)NO\(_6\)Si: 369.1467; found: 369.1467.

Silylated anti-\(\beta\)-Hydroxy-\(\alpha\)-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 added a solid mixture of NaBH\(_3\)CN (4 equiv), MoCl\(_5\) (1 equiv) and NaHSO\(_4\)·H\(_2\)O (3 equiv). The resultant mixture was stirred under reflux from 50 min up to 1 h. The reaction was monitored by TLC (eluent: gradient of EtOAc–hexane, varying from 15:85 up to 80:20 v/v).

Methyl (\(\pm\))-anti-2-Amino-3-\((6-bromo-2\text{-}1,3\text{-}benzodioxol-5-yl}-5\text{-yl)\)-3-(tert-butylphenyl)propanoate (32)

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

IR (neat): 126.0, 126.8, 128.1, 140.3, 173.3.

HRMS (ESI): \(m/z\) [M + H]\(^+\) calcld for C\(_{17}\)H\(_{30}\)NO\(_4\)Si: 340.1838; found: 340.1837.

Methyl (\(\pm\))-anti-2-Amino-3-\([(tert-butyldimethylsilyl)oxy]\)-3-phenoxypropanoate (33)

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

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

HRMS (ESI): \(m/z\) [M + H]\(^+\) calcld for C\(_{20}\)H\(_{36}\)NO\(_3\)Si: 366.2459; found: 366.2459.

Methyl (\(\pm\))-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, 2949, 2925, 2855, 1742, 1462, 1363, 1258, 1166, 1088 cm\(^{-1}\).

HRMS (ESI): \(m/z\) [M + H]\(^+\) calcld for C\(_{16}\)H\(_{27}\)ClNO\(_3\)Si: 344.1449; found: 344.1450.
Methyl (±)-anti-2-Amino-3-(3-tert-butylidimethylsilyloxy)-3-(4-nitrophenyl)propanoate (36)

Reaction time: 40 min; yield: 283 mg (80%); reddish brown oil.
IR (neat): 3600, 3299, 2954, 1733, 1453, 1437, 1206, 1103, 1053 cm⁻¹.

1H NMR (250 MHz, CDCl₃): 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).

13C NMR (62.5 MHz, CDCl₃): δ = –50.0, –4.5, 18.2, 25.8, 52.2, 62.6, 76.6, 123.5, 127.9, 147.9, 147.5, 173.2.


Ethyl 2-(2H-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, CDCl₃): 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).

13C NMR (62.5 MHz, CDCl₃): δ = 143.3, 137.9, 60.9, 101.0, 109.6, 122.1, 125.9, 132.7, 147.0, 147.8, 167.0.


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 flash chromatography (EtOAc–hexanes, 20:80) to afford the corresponding non-codified 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-hydroxymimo)propanoate (52)

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

1H NMR (250 MHz, CDCl₃): 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).

13C NMR (62.5 MHz, CDCl₃): δ = 137.1, 130.3, 133.7, 124.4, 129.0, 134.7, 148.7, 153.7, 162.8.

HRMS (ESI): m/z [M + H]+ calcd for C₁₃H₁ₐNO₅: 236.1287; found 236.1272.

Methyl 3-(3-Chlorophenyl)-2-(N-hydroxymimo)propanoate (54)

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

1H NMR (250 MHz, CDCl₃): 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).

13C NMR (62.5 MHz, CDCl₃): 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-hydroxymimo)propanoate (56)

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

1H NMR (250 MHz, CDCl₃): 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).

13C NMR (62.5 MHz, CDCl₃): δ = 30.0, 52.7, 120.4, 130.9, 131.5, 134.9, 150.1, 163.9.


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 PBE040 gradient-corrected hybrid to solve the Kohn–Sham equations with a $10^{-4}$ 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 potential42 was used for Mo and the atomic 6-31G(d) basis set43 for all other atoms. All calculations were performed using GAMESS software44 (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

Acknowledgment

The authors thank (FAPESP) and the CNPq for the financial support and CENAPAD-SP for computing time. M.T.R. Jr. thanks CNPq for the fellowship. F.C. and A.L.B.F. thank CNPq for the research fellowship. H.U. thanks TWAS/CNPq for the fellowship.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378168.

References


Paper © Georg Thieme Verlag Stuttgart · New York — Synthesis 2015, 47, 113–123

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