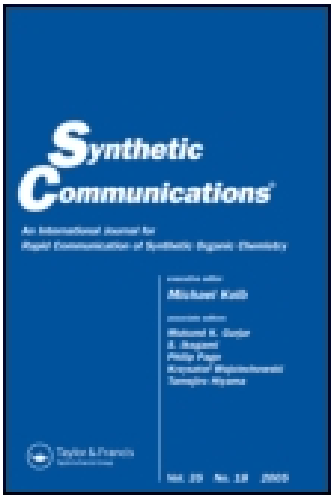


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Novel Oxime Functionalized Aldol Products via Michael Addition of Oximes Onto Baylis-Hillman Adducts

Debnath Bhuniya [a] , Srinivas Gujjary [a] & Sujata Sengupta [a]
[a] Metabolic Disorder (Chemistry) Group , Dr. Reddy's Laboratories Ltd.—Discovery Research , Miyapur, Bollaram Road, Hyderabad, India
Published online: 15 Aug 2006.

To cite this article: Debnath Bhuniya , Srinivas Gujjary & Sujata Sengupta (2006) Synthesis of Novel Oxime Functionalized Aldol Products via Michael Addition of Oximes Onto Baylis-Hillman Adducts, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:2, 151-164, DOI: 10.1080/00397910500334132

To link to this article: http://dx.doi.org/10.1080/00397910500334132

Synthetic Communications®, 36: 151–164, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500334132

Synthesis of Novel Oxime Functionalized Aldol Products via Michael Addition of Oximes Onto Baylis–Hillman Adducts

Debnath Bhuniya, Srinivas Gujjary, and Sujata Sengupta
Metabolic Disorder (Chemistry) Group, Dr. Reddy's Laboratories Ltd.—Discovery Research, Miyapur, Hyderabad, India

Abstract: Triphenylphosphine-catalyzed Michael addition of oximes **2** onto Baylis–Hillman (B-H) adducts **1** led to an easy access to a novel class of oxime functionalized aldol products **3**. This demonstrates the first use of an oxygen-centered nucleophile in Michael addition to B-H adducts, without touching any other functional group. Deprotection of oxime in **3** was further demonstrated using molecular hydrogen (1 atm) and 10% Pd/C (cat.) to furnish functionalized 1,3-diols **4** as potentially useful synthons with optional backbone choice (R^3 and EWG).

Keywords: Aldol products, Baylis–Hillman adducts, deprotection of oximes, 1,3-diols, Michael addition, oximes, triphenylphosphine

INTRODUCTION

Recently our group has shown triphenylphosphine to be an effective catalyst for the Michael addition reaction between oximes and commonly used activated olefins.[1] Baylis–Hillman (B-H) adducts **1** are also very attractive Michael acceptors, particularly because of their structural diversity.

Received in India July 14, 2005
DRL Publication No. 354. Part of these results was presented at Pharmacophore 2004, January 16–17, 2004, an international symposium organized by Dr. Reddy's Laboratories Ltd. on the occasion of its achievement in drug discovery.

Address correspondence to Debnath Bhuniya, Metabolic Disorder (Chemistry) Group, Dr. Reddy's Laboratories Ltd.—Discovery Research, Miyapur, Bollaram Road, Hyderabad 500 049, India. Tel.: (+91) 402 304 5439; Fax: (+91) 402 304 5438; E-mail: debnathbhuniya@drreddys.com

Therefore, we opted to employ triphenylphosphine as a milder catalyst for the Michael addition of oximes **2** onto B-H adducts **1**. This, as one anticipates, will lead to a novel class of highly functionalized aldol products **3**. (Fig. 1, Eq. 1).

The challenge was also to see whether dehydration of the B-H skeleton could be avoided because the present catalyst is considered to be very mild. It is worth mentioning here that there are many reports where attempts of Michael addition to B-H adducts led to destruction of hydroxyl functionality via an elimination or dehydration process (Fig. 1, Eq. 2).[2] (For many such instances, nicely captured in a recent review, please see Ref. 2(a). For a recent related reference, see Ref. 2(b)).

Among the handful of literature reports where Michael additions onto B-H adducts have been shown to produce functionalized aldol products as very useful synthons,[3–5] we did not find examples with oxygen-centered nucleophiles. (For examples with sulfur as nucleophile, see, Ref. 3. For carbon-centered nucleophile, see Ref. 4. For nitrogen-based nucleophile, see Ref. 5). Thus, the proposed idea will also serve as the first example of Michael addition of oxygen-centered nucleophile onto B-H adducts to access a variety of oxime-functionalized aldol products. These oxime derivatives may potentially be deprotected using a suitable reagent to access 1,3-diols with choice of substitution at C1 and C2 positions. It is also worth mentioning here that nitrile oxides, although not in a Michael fashion, generated in situ from the respective oximes using NaOCl, have been

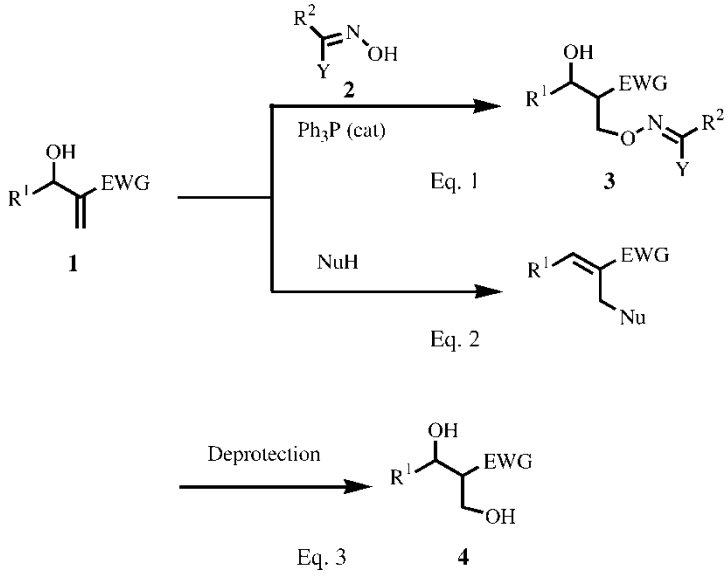


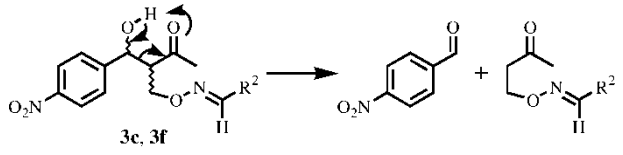
Figure 1. Proposed Michael Addition of **2** into **1**; and deprotection of oxime in **3**.

reacted with B-H adducts in a 1,3-dipolar cycloaddition fashion to obtain highly substituted isoxazolines.[6]

RESULTS AND DISCUSSION

Initial results of triphenylphosphine-catalyzed Michael addition of oximes onto B-H adducts are shown in Table 1. The model B-H adducts **1a–f**, which are the Michael acceptors here, have three different electron-withdrawing groups (EWG) and were synthesized following the literature procedure.[7] Using representative aldoximes **2a–b** and ketoxime **2c**, the Michael reactions were studied following an optimized reaction condition[1] described in the Experimental section. In most of the cases the novel oxime-derivatized aldol products **3** were obtained in good to very good isolated yield. In cases of **3a**, **3d**, **3i**, **3l**, and **3n** the expected *syn* and *anti* products separated on TLC, hence they were characterized independently. However, the other products were isolated as a mixture of *syn*/*anti* isomers. Interestingly, for entries 3 and 6 (Table 1) the expected aldol products **3c** and **3f** could not be obtained; instead, the corresponding retro-aldol products were isolated in 30–40% yields.

We explain the formation of retro-aldol products in the following way:



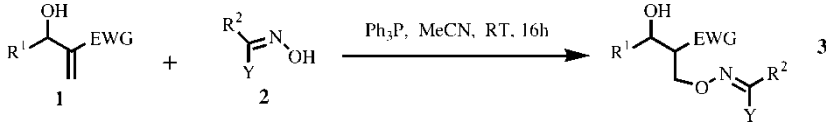
3c, 3f

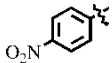
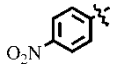
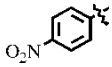
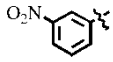
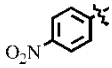
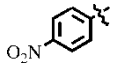
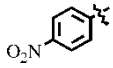
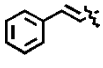
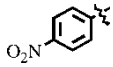
Based on 400-MHz ^{1}H NMR analysis, there was no significant stereoselectivity (to be precise, in the range of 40 : 60) observed for these aldol products **3**. The relative stereochemistry (*syn* and *anti* isomers) were tentatively assigned based on a literature precedence for similarly substituted aldol products.[8a] Thus, in ^{1}H NMR analysis, a coupling constant (*J* value) of 6 Hz and above between C2–H and C3–H were assigned for *anti*-aldol. Aldol products that had a relatively lower *J* value of ca. 5 Hz were assigned as *syn*. A proposed stereochemical course of these reactions are presented in Fig. 2.

To enquire about further generality in this reaction, selected oximes from aliphatic aldehydes (e.g., *iso* butyraldehyde and cyclohexane carboxaldehyde) were used for Michael addition with **1a**. We observed that reactions were bit slow and although 10–15% of products were obtainable, most of the starting material **1a** remained unreacted. This result supports our previous observation that in general oximes derived from aliphatic carbonyl compounds are less reactive.[1]

Obtained oxime-protected aldol derivatives as well as their corresponding oxime-deprotected chiral 1,3-diols with optional R^1 and EWG (Fig. 1, Eq. 3)

Table 1. Triphenylphosphine-catalyzed Michael addition of oximes **2** onto B-H adducts **1**



Entry no.	EWG	R^1	1	R^2	Y	2	3[a]	% Yield[b]
1	CO_2Et		**1a**		H	**2a**	**3a**[c]	60
2	CN		**1b**		H	**2a**	**3b**	82
3	C(O)Me		**1c**		H	**2a**	**3c**	—[d]
4	CO_2Et		**1a**		H	**2b**	**3d**[c]	66
5	CN		**1b**		H	**2b**	**3e**	75
6	C(O)Me		**1c**		H	**2b**	**3f**	—[d]
7	CO_2Et		**1a**		Me	**2c**	**3g**[c]	65
8	CN		**1b**		Me	**2c**	**3h**	78
9	C(O)Me		**1c**		Me	**2c**	**3i**[c]	45
10	CO_2Et		**1d**		H	**2a**	**3j**	56
11	CO_2Et		**1d**		Me	**2c**	**3k**	68
12	CO_2Et		**1e**		H	**2a**	**3l**[c]	58
13	CO_2Et		**1e**		Me	**2c**	**3m**	65
14	CO_2Et		**1f**		H	**2a**	**3n**[c]	68
15	CO_2Et		**1f**		Me	**2c**	**3o**	72

[a]Unless mentioned products were characterized after column chromatography as a mixture of *syn* and *anti* isomers because they did not separete on TLC.

[b]Isolated yield as a mixture of diastereomers or combined of isolated diastereomers.

[c]*Syn* and *anti* products separated on TLC and hence they were purified and characterized independently.

[d]Instead of the expected aldol product, retro-aldol products were obtained.

would find various potential applications in organic synthesis.[1,8] For an example of potential analoging of antibiotics Bu-2313, please see Ref. 8(a). Also on analoging on carbapenem intermediates, please see Ref. 8(b). Analoging of the methyl group (marked by star in the below structures)

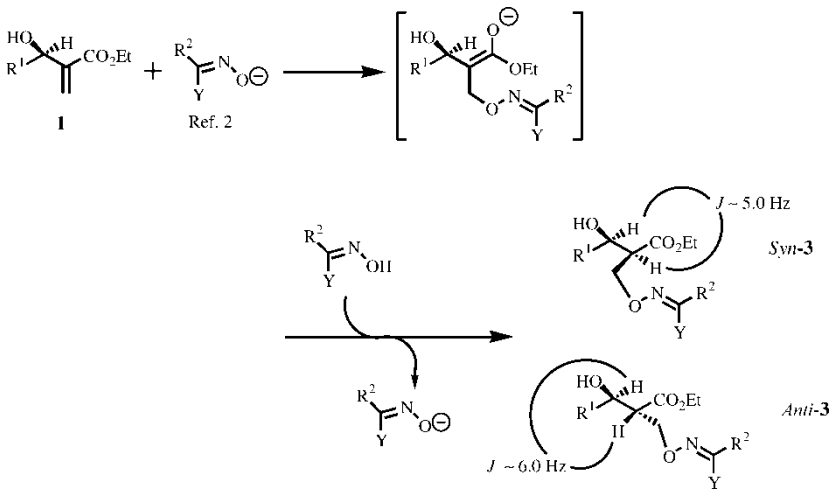
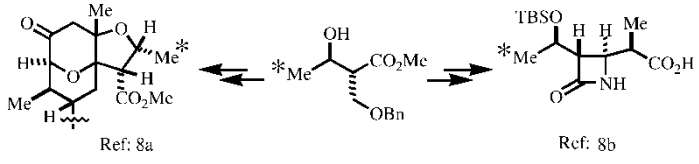


Figure 2. Proposed mechanism of formation and stereochemistry assignment for **3**

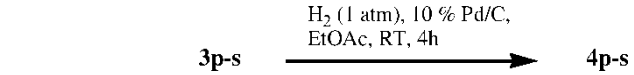
with optional substitution (R^1 in present study coming from B-H component) is a potential application of the present methodology.

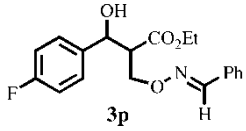
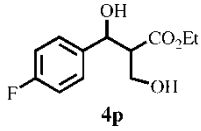
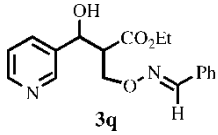
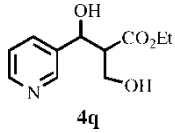
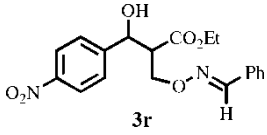
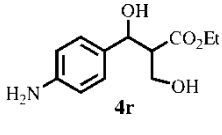
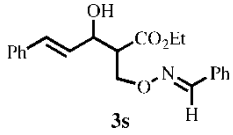
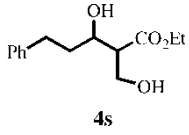


Deprotection of oxime in **3** to obtain 1,3-diol **4** is therefore demonstrated here using Pd/C-catalyzed hydrogenation.[9] (We did not see a literature report, as a methodology, for conversion of *O*-alkyl derivatives of oximes into corresponding alcohols using Pd/C-catalyzed hydrogenation way. However, for a similar philosophy, please see Ref. 9(a)). Representative Michael adducts **3p–s**, obtained from respective B-H products, were synthesized following the typical procedure described for **3d** (see the Experimental section). Except for the **3q**, others were able to be isolated as pure diatereomers and hence diatereomerically pure isomers were used for hydrogenation reaction. Expected products 1,3-diols **4p–s** were obtained in 75–95% isolated yield (Table 2).

After realizing the potential use of this strategy of Michael addition of oximes onto B-H adducts followed by deprotection of oximes to obtain varieties of 1,3-diols, we opted to see whether unsubstituted hydroxylamine could be used instead of aldoximes for making the Michael adducts. Interestingly we observed that hydroxylamine reacted very smoothly with ethyl acrylate, a representative activated olefin, through its nitrogen site, giving quantitative yield of the dimmer **5** and not the desired product **6**

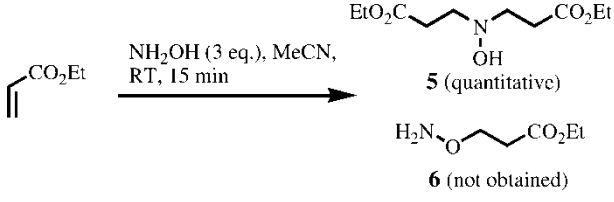
Table 2. Deprotection of oximes in **3** into 1,3-diols **4** using Pd-catalyzed hydrogenation



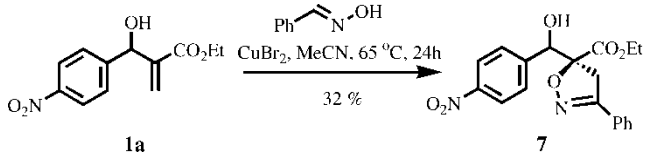
3	4	% Yield
 **3p**	 **4p**	75
 **3q**	 **4q**	90
 **3r**	 **4r**	82
 **3s**	 **4s**	95

(Scheme 1). However, hydroxyl amine failed to react with B-H adducts **1a** and **1d** (chosen arbitrarily) even under heating conditions. Interestingly, triphenylphosphine had no effect on these reactions.

Out of curiosity we wanted to see what happens when an oxime is allowed to react with a B-H adducts in the presence of Lewis acids. As an outcome of that screening, we were surprised to notice that in the presence of 0.5 equivalent of Cu(II)Br_2, benzaldehyde oxime reacted with the B-H adduct **1a** to give 32% yield of isooxazoline **7** in two diastereomers, which were isolated and characterized separately (Scheme 2). This result was otherwise



Scheme 1.



1a 7

Scheme 2.

expected using NaOCl as described before.[6] This new reaction condition is being investigated in detail presently at our group.

CONCLUSION

In conclusion, Michael addition to B-H adducts, which is a sensitive reaction with respect to 2,3 elimination reaction on the B-H backbone, has been demonstrated here using a triphenylphosphine-catalyzed method. The present methodology, in addition to our previous report, although specific to oximes, thus shows further generality on Michael acceptors. This study also demonstrates the first Michael addition reaction of an oxygen-centered nucleophile onto B-H adducts. The oxime-functionalized aldol products (**3a**–**s**) and their synthesis revealed in this communication are novel. In addition, we have demonstrated a very convenient method for deprotection of these oxime derivatives into their corresponding 1,3-diols (**4p**–**s**) using Pd-catalyzed hydrogenation. Here also, we have not seen any direct literature report where oxime-protected alcohols in general are being deprotected to the corresponding alcohols. Knowing that the area of asymmetric B-H reactions is advancing rapidly, the described protocol can be an option to access homochiral 1,3-diols carrying an optional backbone (1-R^3 and 2-EWG) coming from B-H adducts. As reported in the past for similar cases, this new class of oxime-functionalized aldols and 1,3-diols may find some potential application in the area of medicinal chemistry.

EXPERIMENTAL

General

The melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Mercury Plus (Varian 400 MHz), Unity Inova (Varian 500 MHz), and Gemini-2000 (Varian 200 MHz) spectrometer in $CDCl_3$ or DMSO-d6 with TMS as internal standard: chemical shifts and *J* values are given in ppm and Hz respectively. IR spectra were recorded on FT-IR spectrophotometer from the Perkin Elmer 1600 series. The CI-mass spectra were recorded on Hewlett Packard 5989 A using isobutane as chemical ionization gas (source

temp. 250°C and quadruple temp. 100°C). The ES-mass data were generated using a triple quadruple mass spectrometer (Perkin Elmer Sciex Model API 3000) with capillary voltage at +5000 V. Elemental analysis was done on a Perkin Elmer II series.

Ethyl 2-(3-Nitrobenzylideneaminoxymethyl)-3-hydroxy-3-(4-nitrophenyl)propanoate (3d); Typical Procedure for Synthesis of 3

A mixture of B-H adduct **1a** (301 mg, 1.2 mmol), aldoxime **2b** (200 mg, 1.2 mmol), and triphenylphosphine (63 mg, 0.24 mmol) was stirred in dry acetonitrile (600 L) at rt for 16 h. The reaction was guided by TLC. The solvent was removed (rotavapor) and the crude was purified by column chromatography (silica gel 100–200, ethyl acetate/hexanes) to obtain *syn* isomer of the aldol product **3d** as a faster eluting compound (150 mg). Further elution gave the *anti*-**3d** (180 mg).

Characterization of *Syn*-**3d**

R_f: 0.25 (30% ethyl acetate in hexanes). Mp: 99–100°C. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.20 (t, $J = 7.2$ Hz, 3H); 3.27 (dt, $J = 7$, 5.4 Hz, 1H); 3.35 (d, $J = 3.4$ Hz, –OH); 4.16 (q, $J = 7.2$ Hz, 2H); 4.46 (dd, $J = 11.2$, 5.4 Hz, 1H); 4.63 (dd, $J = 11.2$, 7 Hz, 1H); 5.27 (dd, $J = 5.4$, 3.4 Hz, 1H); 7.56 (t, $J = 8$ Hz, 1H); 7.60 (d, $J = 8.8$ Hz, 2H); 7.79 (dt, $J = 8$, 2 Hz, 1H); 7.96 (s, 1H); 8.19–8.23 (aromatics, 1H); 8.21 (d, $J = 8.8$ Hz, 2H); 8.38 (t, $J = 2$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 13.97, 52.34, 61.31, 71.32, 71.58, 121.46, 123.44 (2C), 124.38, 127.15 (2C), 129.76, 132.58, 133.33, 147.01, 147.21, 148.47, 148.65, 172.37. IR (neat, cm^{-1}): 3505 (br), 2925, 1728 (ester), 1528, 1349. Mass m/z (ES): 400.1 [M-OH], 418.1 [M + 1], 435.4 [$M + NH_4^+$], 440.1 [M + Na], 857.5 [M_2 + Na]. Anal. calcd. for $C_{19}H_{19}N_3O_8$: C, 54.68; H, 4.59; N, 10.07. Found C, 54.64; H, 4.61; N, 10.03.

Characterization of *Anti*-**3d**

R_f: 0.20 (30% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.19 (t, $J = 7.2$ Hz, 3H); 3.21 (q, $J = 6$ Hz, 1H); 3.67 (bs, –OH); 4.18 (q, $J = 7.2$ Hz, 2H); 4.35 (dd, $J = 11.2$, 6.4 Hz, 1H); 4.52 (dd, $J = 11.2$, 5.6 Hz, 1H); 5.20 (d, $J = 6$ Hz, 1H); 7.55–7.61 (aromatics, 1H); 7.58 (d, $J = 8.8$ Hz, 2H); 7.86 (dt, $J = 7.6$, 2 Hz, 1H); 8.13 (s, 1H); 8.21–8.26 (aromatics, 1H); 8.23 (d, $J = 8.8$ Hz, 2H); 8.44 (t, $J = 2$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 13.97, 52.34, 61.36, 71.10, 72.40, 121.52, 123.57 (2C), 124.42, 127.12 (2C), 129.79, 132.66, 133.41, 147.26, 147.44, 148.45, 148.65, 172.37. IR (neat, cm^{-1}): 3476 (br), 2925, 1727 (ester), 1528, 1349. Mass m/z (ES): 400.3 [M-OH], 418.1 [M + 1], 435.4 [$M + NH_4^+$], 440.1 [M + Na], 857.5 [M_2 + Na].

Characterization of Ethyl 2-(4-Nitrobenzylideneaminoxymethyl)-3-hydroxy-3-(4-nitrophenyl)propanoate (**3a**)

Syn-**3a**: R_f: 0.4 (30% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.19 (t, $J = 7.1$ Hz, 3H); 3.25 (dt, $J = 6$, 5.3 Hz, 1H); 3.33 (d, $J = 3.3$ Hz, –OH); 4.15 (q, $J = 7.1$ Hz, 2H); 4.47 (dd, $J = 11.6$, 5.4 Hz, 1H); 4.64 (dd, $J = 11.6$, 7 Hz, 1H); 5.27 (dd, $J = 5.3$, 3.3 Hz, 1H); 7.59 (d, $J = 8.3$ Hz, 2H); 7.67 (d, $J = 8.8$ Hz, 2H); 7.94 (s, 1H); 8.20 (d, $J = 8.8$ Hz, 2H); 8.22 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 14.07, 52.31, 61.42, 71.37, 71.67, 123.56 (2C), 124.05 (2C), 127.15 (2C), 127.65 (2C), 138.00, 147.25 (2C), 148.35, 172.18. IR (neat, cm^{-1}): 3476 (br), 2926, 1728 (ester), 1520, 1347. Mass m/z (ES): 400.4 [M-OH], 418.3 [M + 1], 435.3 [$M + NH_4^+$], 440.5 [M + Na], 852.7 [$M_2 + NH_4^+$], 857.5 [M_2 + Na].

Anti-**3a**: R_f: 0.35 (30% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.17 (t, $J = 7.2$ Hz, 3H); 3.21 (apparent q, $J = 6$ Hz, 1H); 3.65 (d, $J = 6.4$ Hz, –OH); 4.16(q, $J = 7.2$ Hz, 2H); 4.37 (dd, $J = 11.3$, 6.2 Hz, 1H); 4.53 (dd, $J = 11.2$, 5.6 Hz, 1H); 5.19 (apparent t, $J = 6.3$ Hz, 1H); 7.57 (d, $J = 8.6$ Hz, 2H); 7.73 (d, $J = 8.8$ Hz, 2H); 8.12 (s, 1H); 8.22 (d, $J = 8.6$ Hz, 2H); 8.24 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz)_: 14.05, 52.34, 61.45, 71.19, 72.62, 123.67 (2C), 124.06 (2C), 127.12 (2C), 127.72 (2C), 137.68, 147.49 (2C), 148.59, 172.36. IR (neat, cm^{-1}): 3476 (br), 2926, 1728 (ester), 1520, 1347. Mass m/z (ES): 400.4 [M-OH], 418.3 [M + 1], 435.3 [$M + NH_4^+$], 440.4 [M + Na], 852.7 [$M_2 + NH_4^+$], 857.5 [M_2 + Na].

Characterization of 2-(1-Phenylethylideneaminoxymethyl)-3-hydroxy-3-(4-nitrophenyl)propanoate (**3i**)

Syn-**3i**: R_f: 0.70 (30% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.11 (s, 3H); 2.22 (s, 3H); 3.35 (dt, $J = 6.5$, 4.9 Hz, 1H); 3.75 (d, $J = 3$ Hz, –OH); 4.43 (dd, $J = 11.6$, 4.9 Hz, 1H); 4.56 (dd, $J = 11.8$, 6.4 Hz, 1H); 5.28 (dd, $J = 5.1$, 3 Hz, 1H); 7.35–7.38 (aromatics, 3H); 7.54–7.60 (aromatics, 4H); 8.21 (d, $J = 8.6$ Hz, 2H). IR (neat, cm^{-1}): 3391 (br), 2924, 1709 (carbonyl), 1520, 1347. Mass m/z (ES): 357.0 [M + 1], 379.0 [M + Na], 735.5 [M_2 + Na].

Anti-**3i**: R_f: 0.65 (30% ethyl acetate in hexanes) ^{1}H NMR ($CDCl_3$, 400 MHz): 2.19 (s, 3H); 2.21 (s, 3H); 3.33 (dt, $J = 6.6$, 5.0 Hz, 1H); 3.67 (d, $J = 5.6$ Hz, –OH); 4.29 (dd, $J = 11.6$, 6.3 Hz, 1H); 4.41 (dd, $J = 11.3$, 4.9 Hz, 1H); 5.17 (apparent, $J = 5.9$ Hz, 1H); 7.35–7.40 (aromatics, 3H); 7.55–7.60 (aromatics, 4H); 8.22 (d, $J = 8.8$ Hz, 2H). IR (neat, cm^{-1}): 3454 (br), 2924, 1710 (carbonyl), 1520, 1346. Mass m/z (ES): 357.0 [M + 1], 379.0 [M + Na], 735.5 [M_2 + Na].

Characterization of Ethyl 2-(4-Nitrobenzylideneaminoxymethyl)-3-hydroxy-3-(thiophen-3-yl)propanoate (**3l**)

Anti-**3l**: R_f: 0.30 (20% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.15 (t, $J = 7.2$ Hz, 3H); 2.96 (d, $J = 3$ Hz, 1H, –OH); 3.24–3.29 (m, 1H, 2C-H); 4.12 (q, $J = 7.2$ Hz, 2H); 4.53 (dd, $J = 11.2$, 4.8 Hz, 1H); 4.67 (dd, $J = 11.2$, 7.6 Hz, 1H); 5.19 (dd, $J = 6$, 3 Hz, 1H); 7.09 (dd, $J = 5.2$, 1.6 Hz, 1H); 7.27–7.32 (aromatics, 2H); 7.71 (d, $J = 8.8$ Hz, 2H); 8.07 (s, 1H); 8.22 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 14.02, 52.47, 61.00, 69.17, 72.52, 121.84, 123.98 (2C), 125.61, 126.16, 127.64 (2C), 138.04, 142.46, 147.00, 148.47, 172.42. IR (neat, cm^{-1}): 3431 (br), 2927, 1726 (ester), 1519, 1345. Mass m/z (CI): 361 [M − 17], 379 [M + 1].

Syn-**3l**: R_f: 0.25 (20% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.20 (t, $J = 7.2$ Hz, 3H); 3.23–3.28 (m, 2H, 2C-H and –OH); 4.13–4.21 (m, 2H); 4.43 (d, $J = 6.4$ Hz, 2H); 5.13 (d, $J = 4.8$ Hz, 1H); 7.10 (dd, $J = 5.2$, 1.6 Hz, 1H); 7.25–7.27 (aromatics, 1H); 7.33 (dd, $J = 5.1$, 3 Hz, 1H); 7.72 (d, $J = 8.8$ Hz, 2H); 8.10 (s, 1H); 8.23 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 14.07, 52.34, 61.12, 68.75, 73.10, 121.84, 123.99 (2C), 125.54, 126.46, 127.66 (2C), 137.95, 142.75, 147.11, 148.20, 172.93. IR (neat, cm^{-1}): 3477 (br), 2927, 1727 (ester), 1520, 1345. Mass m/z (CI): 361 [M − 17], 379 [M + 1].

General Procedure for Hydrogenation; Conversion of 3p–s to 4p–s

3p–s (1 mmol) were hydrogenated under molecular hydrogen (1 atm) in presence of 10% Pd/C (300 mg) in solvents of choice (10 mL of AcOH for **3p–q**, alternatively 30 mL AcOEt for **3p–s**) at rt for 4–5 h (TLC guided). Reaction mixture was filtered through celite and washed with ethyl acetate. Filtrate was condensed (for AcOH solvent, a base workup was done), and the crude mass was purified by column chromatography (silica gel 100–200, ethyl acetate and hexanes) to obtain the 1,3-diols **4p–s**. Originally AcOH was used as solvent. However, it was observed later that EtOAc was a more convenient solvent.

Characterization of *Anti*-Ethyl 2-(hydroxymethyl)-3-hydroxy-3-(4-fluorophenyl)propanoate (*Anti*-**4p**)

R_f: 0.2 (40% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.24 (t, $J = 7.1$ Hz, 3H); 2.18 (dd, $J = 7$, 5.1 Hz, –OH); 2.87 (dt, $J = 6.7$, 4.7 Hz, 1H); 3.24 (d, $J = 5.4$ Hz, –OH); 3.64–3.72 (m, 1H); 3.83–3.89 (m, 1H); 4.20 (q, $J = 7.1$ Hz, 2H); 5.10 (t, $J = 5.9$ Hz, 1H); 7.05 (t, $J = 8.6$ Hz, 2H); 7.36 (dd, $J = 8.6$, 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 14.05, 54.35, 61.19, 61.54, 72.34, 115.35 (d, $J = 21$ Hz, 2C),

127.84 (d, $J = 8$ Hz, 2C), 137.14, 162.4 (d, $J = 245$Hz), 173.55. IR (neat, cm^{-1}): 3419 (br), 2938, 1717 (carbonyl), 1605. Mass m/z (ES): 260.3 [M + 18], 265.1 [M + 23], 507.1 [M_2 + 23].

Characterization of Ethyl 2-(Hydroxymethyl)-3-hydroxy-3-(pyridin-3-yl)-propanoate (**4q**)

Isolated as a 60 : 40 mixture of *anti* and *syn* diastereomers. For clarity, NMR data are given for the major diastereomer. R_f: 0.4 (80% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.14 (t, $J = 7.1$ Hz, 3H); 2.87 (dt, $J = 6.2$, 4.7 Hz, 1H); 3.71 (dd, $J = 11.3$, 5 Hz, 1H); 3.90 (dd, $J = 11.3$, 4.8 Hz, 1H); 4.10 (q, $J = 7.1$ Hz, 2H); 5.28 (d, $J = 6.4$ Hz, 1H); 7.30 (dd, $J = 8$, 5.1 Hz, 1H); 7.75 (dt, $J = 5.6$, 1.8 Hz, 1H); 8.47 (d, $J = 5$ Hz, 1H); 8.53 (d, $J = 1.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 13.92, 53.81, 61.06, 61.17, 71.76, 123.51, 134.38, 137.68, 147.67, 148.68, 172.26. Mass m/z (CI): 226 [M + 1].

Characterization of *Anti*-ethyl 2-(hydroxymethyl)-3-hydroxy-3-(4-aminoophenyl)propanoate (*Anti*-**4r**)

Mp: 114°C. R_f: 0.2 (50% ethyl acetate in hexanes). ^{1}H NMR (DMSO-d_6, 400 MHz): 1.26 (t, $J = 7.1$ Hz, 3H); 2.86 (dt, $J = 8.3$, 4.9 Hz, 1H); 3.40–3.46 (m, 1H); 3.53–3.60 (m, 1H); 3.99 (t, $J = 5.3$ Hz, –OH); 4.12 (bs, –NH2); 4.17 (q, $J = 7.1$ Hz, 2H); 4.55 (d, $J = 4.5$ Hz, –OH); 4.73 (dd, $J = 8.3$, 4.3 Hz, 1H); 6.62 (d, $J = 8.3$ Hz, 2H); 7.08 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (DMSO-d_6, 50 MHz): 13.43, 55.44, 59.35, 60.05, 71.54, 113.64 (2C), 126.58 (2C), 130.82, 145.95, 172.89. IR (neat, cm^{-1}): 3375 (br), 2926, 1715 (carbonyl), 1615. Mass m/z (ES): 222.1 [M − 17], 240.1 [M + 1], 262.3 [M + 23], 501.4 [M_2 + 23]. Anal. calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found C, 60.21; H, 7.21; N, 5.82.

Characterization of *Anti*-ethyl 2-(hydroxymethyl)-3-hydroxy-3-(2-phenethyl)propanoate (*Anti*-**4s**)

R_f: 0.2 (30% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.28 (t, $J = 7.1$ Hz, 3H); 1.74–1.84 (m, 1H); 1.90–2.00 (m, 1H); 2.55 (q, $J = 4.3$ Hz, 1H); 2.65–2.74 (m, 1H); 2.85–2.94 (m, 1H); 4.00 (dd, $J = 11.5$, 4 Hz, 1H); 4.06 (dd, $J = 11.5$, 4.3 Hz, 1H); 4.13–4.18 (m, 1H); 4.21 (q, $J = 7.1$ Hz, 2H); 7.17–7.23 (aromatics, 3H); 7.26–7.32 (aromatics, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 14.09, 32.05, 36.76, 51.70, 60.91, 61.00, 70.95, 125.87, 128.36 (4C), 141.53, 173.60. IR (neat, cm^{-1}): 3418 (br), 2938, 1722 (carbonyl), 1195. Mass m/z (ES): 253.3 [M + 1], 275.1 [M + 23], 527.3 [M_2 + 23].

Synthesis and Characterization of N,N-bis-[2-(Ethylcarboxylato)ethyl]hydroxylamine (5)

A mixture of hydroxylamine (1.0 g, 30 mmol), ethyl acrylate (1 mL, 10 mmol), and triphenylphosphine (500 mg, 2.0 mmol) in acetonitrile (5 mL) was stirred at rt for 15 min. The reaction mixture was condensed and the pure product **5** was isolated as thick oil (quantitative yield) from the crude mass using column chromatography (silica gel 100–200, ethyl acetate and hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.25 (t, $J = 7.1$ Hz, 6H); 2.59 (t, $J = 6.9$ Hz, 4H); 2.99 (t, $J = 6.9$ Hz, 4H); 4.14 (t, $J = 7.1$ Hz, 4H); 5.80 (bs, –OH). ^{13}C NMR ($CDCl_3$, 50 MHz): 13.77, 31.65, 55.14, 60.23, 171.93. IR (neat, cm^{-1}): 3426 (br), 2984, 1735 (carbonyl), 1183. Mass m/z (CI): 234 [M + 1].

Synthesis and Characterization of Ethyl 5-[1-Hydroxy-2-(4-nitrophenyl)ethyl]-3-phenyl-4,5-dihydroisoxazolo-5-carboxylate (7)

A mixture of **1a** (600 mg, 2.39 mmol), benzaldehyde oxime (290 mg, 2.39 mmol), and anhydrous $CuBr_2$ (266 mg, 1.19 mmol, 0.5 eq.) in dry acetonitrile solvent (2.4 mL) was heated at 60–65°C for 24 h. The reaction mixture was condensed to obtain the crude mass, which on column chromatography (silica gel 100–200, ethyl acetate and hexanes) yielded two the diastereomers of **7**. Combined yield: 32%. (200 and 120 mg for faster and slower eluting diastereomers respectively).

R_f: 0.4 (20% ethyl acetate in hexanes, double run). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.33 (t, $J = 7.2$ Hz, 3H); 3.40 (bs, 1H, –OH); 3.94 (d, $J = 10.5$ Hz, 1H); 3.99 (d, $J = 10.5$ Hz, 1H); 4.27–4.37 (m, 2H); 5.52 (s, 1H); 7.48 (t, $J = 7.6$ Hz, 2H); 7.62 (t, $J = 7.4$ Hz, 1H); 7.81 (d, $J = 8.9$ Hz, 2H); 8.12 (d, $J = 8.1$ Hz, 2H); 8.22 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 13.83, 33.80, 63.42, 65.39, 75.34, 122.92 (2C), 128.47 (2C), 129.26, 129.69 (2C), 130.19 (2C), 133.76, 144.84, 148.03, 167.61, 171.59. Mass m/z (ES): 371.3 [M + 1], 393.3 [M + 23], 758.3 [M_2 + 18].

R_f: 0.2 (20% ethyl acetate in hexanes, double run). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.29 (t, $J = 7.2$ Hz, 3H); 3.21 (d, $J = 4$ Hz, 1H, –OH); 3.65 (d, $J = 3.2$ Hz, 2H); 4.26 (q, $J = 7.2$ Hz, 2H); 5.41 (d, $J = 4$ Hz, 1H); 7.38–7.44 (aromatics, 3H); 7.60–7.70 (aromatics, 4H); 8.22 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 14.00, 38.15, 62.71, 73.54, 91.97, 123.56 (2C), 126.90 (2C), 127.75 (2C), 128.74, 128.84 (2C), 130.82, 144.30, 147.96, 157.31, 169.67. Mass m/z (ES): 371.3 [M + 1], 393.3 [M + 23], 758.3 [M_2 + 18].

ACKNOWLEDGMENTS

We are thankful to the management of Discovery Research, DRL, for overall support. Analytical Research Department of Discovery Research SBU is especially acknowledged for providing us with the data to characterize all the compounds.

REFERENCES

1. Bhuniya, D.; Mohan, S.; Narayanan, S. Triphenylphosphine-catalyzed Michael addition of oximes onto activated olefins. *Synthesis* **2003**, 1018–1024.
2. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Recent advances in the Baylis-Hillman reaction and applications. *Chem Rev.* **2003**, *103*, 811–891; (b) Hong, W. P.; Lee, K.-J. Synthesis of methyl (E)-2-nitromethylcinnamates derived from Baylis–Hillman acetates and conversion into several coumarin derivatives. *Synthesis* **2005**, 33–38 and the references cited herein.
3. (a) Deane, P. O.; Guthrie-Strachan, J. J.; Kaye, P. T.; Whittaker, R. E. Regio- and diastereoselectivity in the thiomethylation of α-(1-hydroxyalkyl)acrylate derivatives. *Synth. Commun.* **1998**, *28*, 2601–2611; (b) Kamimura, A.; Morita, R.; Matsuura, K.; Omata, Y.; Shirai, M. Simple preparation of β-hydroxy-α-thiomethyl carbonyl compounds via stereoselective conjugate addition of thiol to Baylis–Hillman adducts. *Tetrahedron Lett.* **2002**, *43*, 6189–6191; (c) Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. Chemistry of *O*-silylated ketene acetals: A stereoselective synthesis of optically active carbapenem antibiotics, (+)-thienamycin (+)-PS-5. *Chem. Pharm. Bull.* **1992**, *40*, 12–20.
4. (a) Mase, N.; Watanabe, Y.; Toru, T. Discrimination of diastereotopic sulfonyl oxygens by intramolecular hydrogen bonding: Stereoselective hydrogenation of α-sulfonyl radicals. *Tetrahedron Lett.* **1999**, *40*, 2797–2800; (b) Richter, H.; Walk, T.; Holtzel, A.; Jung, G. Polymer bound 3-hydroxy-2-methylidenepropionic acids. A template for multiple core structure libraries. *J. Org. Chem.* **1999**, *64*, 1362–1365; (c) Wang, W.; Yu, M. One-pot sequential Baylis–Hillman and Michael reactions. *Tetrahedron Lett.* **2004**, *45*, 7141–7143.
5. (a) Rastogi, S. K.; Gupta, P.; Srinivasan, T.; Kundu, B. Combinatorial synthesis of unsymmetrical secondary amines. Application to arylethanolamines, arylpropanolamines and aryloxypropanolamines. *Mol. Diversity* **2000**, *5*, 91–104; (b) Azizi, N.; Saidi, M. R. A new protocol for Baylis–Hillman reaction: The reaction of iminium salts prepared in situ with methyl acrylate. *Tetrahedron Lett.* **2002**, *43*, 4305–4308; (c) Batra, S.; Srinivasan, T.; Rastogi, S. K.; Kundu, B.; Patra, A.; Bhaduri, A. P.; Dixit, M. Combinatorial synthesis and biological evaluation of isoxazole-based libraries as antithrombotic agents. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1905–1908; (d) Kundu, M. K.; Sundar, N.; Kumar, S. K.; Bhat, S. V.; Biswas, S.; Valecha, N. Antimalarial activity of 3-hydroxyalkyl-2-methylenepropionic acid derivatives. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 731–736.
6. Sammelson, R. E.; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M.; Kurth, M. J. Synthesis of spiro-fused (C5)-isoxazolino-(C4)-pyrazolones (1-oxa-2,7,8-triazaspiro[4,4]-2,8-dien-6-ones) via 1,3-dipolar cycloaddition and cycloelimination. *J. Org. Chem.* **2002**, *67*, 876–882.

7. Bhuniya, D.; Narayanan, S.; Lamba, T. S.; Krishna Reddy, K. V. S. R. Porcine liver esterase catalyzed kinetic resolution of Baylis–Hillman (B-H) adducts. *Synth. Commun.* **2003**, *33*, 3711–3720.
8. (a) Ireland, R. E.; Wardle, R. B. 3-Acyltetramic acid antibiotics. 3. An approach to the synthesis of Bu-2313. *J. Org. Chem.* **1987**, *52*, 1780–1789; (b) Oh, C.-Y.; Ham, W.-H. A new diastereoselective synthesis of a 1β-methylcarbapenem intermediate. *Chem. Commun.* **1999**, 2365–2366; (c) Banfi, L.; Guanti, G.; Narisano, E. Chemoenzymatic preparation of a key intermediate for carbapenem synthesis starting from asymmetrized *bis*(hydroxymethyl)acetaldehyde (BHYMA*). *Tetrahedron* **1993**, *49*, 7385–7392.
9. (a) Jeon, G.-H.; Yoon, J.-Y.; Kim, S.; Kim, S. S. Radical reaction of phenylsulfonyl oxime ethers on solid support: Application to the synthesis of α-amino esters. *Synlett* **2000**, 128–130; (b) Anbazhagan, M.; Boykin, D. W.; Stephens, C. E. Direct conversion of amidoximes to amidines via transfer hydrogenation. *Synthesis* **2003**, 2467–2469; (c) Chandrasekhar, S.; Babu, B. N.; Ahmed, M.; Reddy, M. V.; Srihari, P.; Jagadeesh, B.; Prabhakar, A. Safe and convenient reduction of Δ^2-isoxazolines with PMHS–$Pd(OH)_2$/C. *Synlett* **2004**, 1303–1305 and references cited therein; (d) Kozikowski, A. P.; Stein, P. D. INOC route to carbocyclics: A formal total synthesis of ($\pm$)-sarkomycin. *J. Am. Chem. Soc.* **1982**, *104*, 4023–4024.