Synthesis of *N*-Cbz-Substituted β^3-Amino Ketones Utilizing 4-Substituted 1,3-Oxazinan-6-ones

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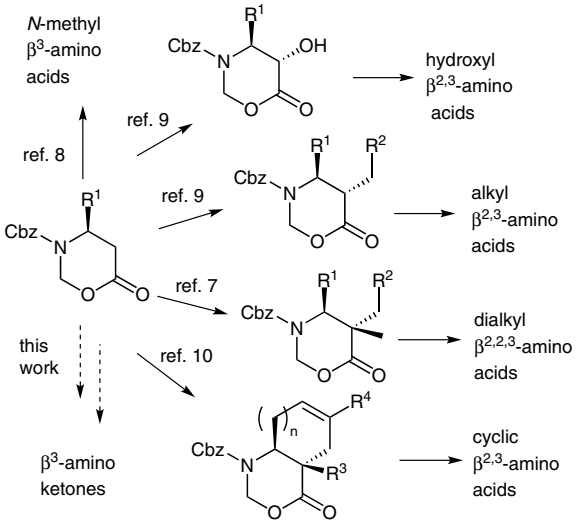
Abstract: Stereoselective synthesis of *N*-Cbz-substituted β-amino ketones exploiting the versatile 1,3-oxazin-6-one scaffold is reported. The 4-substituted 1,3-oxazinan-6-ones were enolized and acylated diastereoselectively by addition of various acyl halides. Acidic decarboxylation was then employed to smoothly transform the 5-acylated products to chiral β-amino ketones. This methodology further highlights the utility of the 1,3-oxazinan-6-one as a scaffold to access valuable synthons that are used in the peptidomimetic field.

Key words: ketones, amino acids, acylation, ring opening, oxazinanones

β-Amino ketones are important synthetic precursors for many syntheses[1,2] and also have demonstrated biological activity.[3] There are numerous methods to gain access to β-amino ketones, such as Michael addition of an amine surrogate to an α,β-unsaturated ketone,[4] via a Mannich reaction,[2,5] or by reduction of α,β-unsaturated ketones.[6] However, many of these methods are limited in their use and a large proportion do not produce chiral β-amino ketones. To overcome the shortcomings of previous syntheses, a stereoselective synthesis of β-amino ketones was devised, starting from 1,3-oxazinan-6-ones.

1,3-Oxazinan-6-ones have previously been utilized to produce a variety of different β-amino acid derivatives.[7–10] The versatility of the 1,3-oxazinan-6-one scaffold has been shown to produce *N*-methyl β^3-amino acids, 2-hydroxy,[9] 2-alkyl,[9] and 2,2-dialkyl β^3-amino acids,[7] and recently β^{2,3}-cyclic amino acids[10] (Scheme 1). Ring opening of the 1,3-oxazinan-6-one has also been shown to produce a variety of carboxylic acids, esters, and amides.[7–10] Herein the versatility of the 1,3-oxazinan-6-one is further exploited to produce chiral substituted β^3-amino ketones.

It was proposed to produce the N-protected β^3-amino ketones in two steps from the 1,3-oxazinan-6-one. Firstly, the 1,3-oxazinan-6-one would be enolized and then acylated by addition of an acyl halide. The 5-acylated oxazinanone would then be subjected to an acid-mediated ring opening followed by an in situ decarboxylation to produce the N-protected β-amino ketone (Scheme 2).



Scheme 1 Transformations of the 1,3-oxazinan-6-one to produce stereopure β-amino acid derivatives

The starting 1,3-oxazinan-6-ones **1**–**4** were easily prepared in three steps from the parent N-protected α-amino acids via the Arndt–Eistert homologation to produce the corresponding β-amino acids. The β-amino acids were then cyclized using a previously described method[7–10] to afford the N-protected 4-substituted 1,3-oxazinan-6-ones **1**–**4**.

The 5-position of the 1,3-oxazinan-6-one was then acylated using enolate chemistry.[11] Enolization of the 1,3-oxazinan-6-ones **1**–**4** was performed using LiHMDS as the base at –78 °C. The acyl halide was then added at –78 °C. The reaction was maintained at –78 °C for three hours before warming to –50 °C and quenching with an ammonium chloride solution (Table 1).[11] A combination of the 4-substituted 1,3-oxazinan-6-ones **1**–**4** and various acyl halides were subjected to these conditions, and the results are shown in Table 1. Moderate to good yields were obtained across a range of different substrates, however, the pivaloyl chloride used in entries 3, 6, and 9 consistently gave the lowest yields (30%, 43%, and 28%, respectively). Although the stereoselectivity of the 5-acylation reaction is not of relevance, because the stereocenter is removed in the next transformation to give the β-amino ketone, in all cases the *trans* isomer was produced with high diastereoselectivity (>95% dr, Table 1). The *trans* se-

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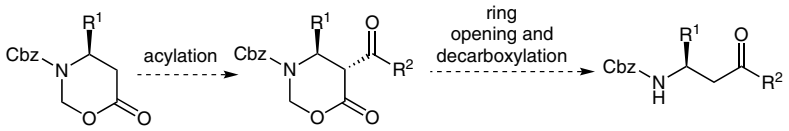


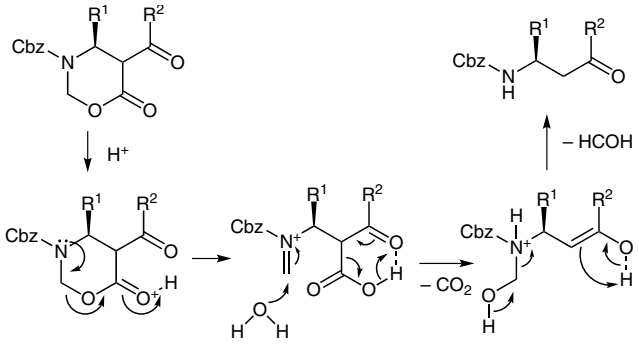
Scheme 2 Proposed route to access β-amino ketones from 1,3-oxazinan-6-ones

lectivity was determined using coupling constants observed in the ^{1}H NMR spectra. The *trans* selectivity has also been observed with both 5-alkylations and 5-hydroxylations of numerous 4-substituted 1,3-oxazinan-6-ones.[7,9,10]

The 5-acylated 1,3-oxazinan-6-ones **5**–**14** were then transformed into the β-amino ketones under mild acidic conditions (Table 1).[12] The 5-acylated 1,3-oxazinan-6-ones **5**–**14** were dissolved in a mixture of THF and 2 M HCl, and the mixture was heated at 50 °C for 4–6 h. Under the acidic conditions the 1,3-oxazinan-6-one ring opens to produce the corresponding carboxylic acid. In situ decarboxylation of the β-keto carboxylic acid and hydrolysis of the iminium species then occurs to produce the β-amino ketone (Scheme 3). The substituted β^3-amino ketones **15**–**24** were all prepared in high yields (Table 1).[12,13]

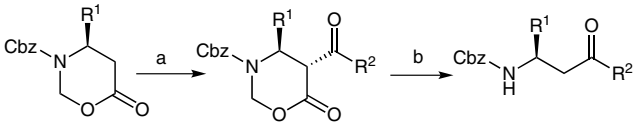
In an extension of this work, it was proposed that an *N*-methyl β-amino ketone could also be produced using acidic conditions. It has been established that reductive cleavage of the 1,3-oxazinan-6-one ring employing $BF_3{\cdot}OEt_2$ or TFA and triethylsilane produces *N*-methyl β-amino acids.[7–10] It was proposed to use the same acidic reductive cleavage conditions to transform the 5-acylated 1,3-oxazinan-6-one **5** into the *N*-methyl β-amino ketone **25** (Scheme 4). However, when this reaction was attempted the desired *N*-methyl β-amino ketone **25** was not obtained. The only product observed was the Cbz derivative of a secondary amine **27**. This was formed via an iminium species **26** which is intercepted by a hydride anion from triethylsilane. Possible uses of this unexpected reaction are now being investigated.

To further elaborate the methodology demonstrated here to produce β-amino ketones, a 5-methylated 1,3-oxazinan-6-one **28** would be 5-acylated and then subsequently subjected to acidic conditions to produce a disubstituted β^{2,3}-amino ketone. The previously synthesized 5-methyl 1,3-oxazinan-6-one **28** was produced using enolate chem-



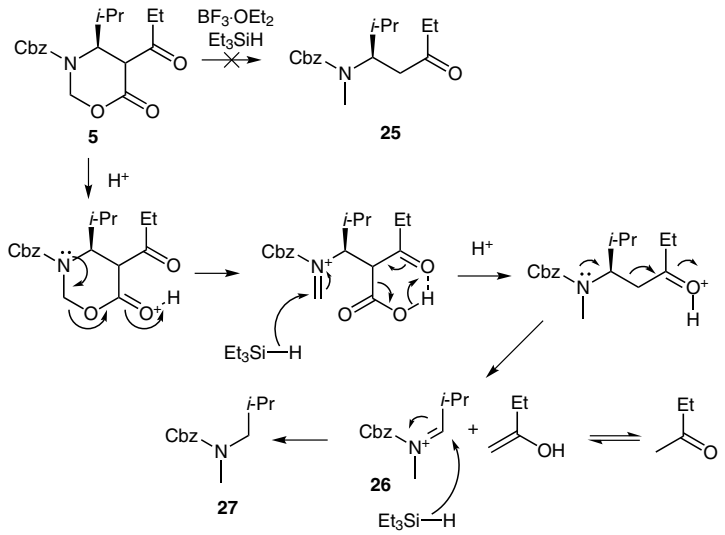
Scheme 3 Mechanism of the β-amino ketone formation

Table 1 Acylation of the 1,3-Oxazinan-6-ones **1**–**4** and β-Amino Ketone Formation **15**–**24**



Entry	Oxazinanone	R^1	R^2	Product (yield, %)	Product (yield, %)	ee (%)
1	**1**	*i*-Pr	Et	**5** (80)	**15** (91)	97
2	**1**	*i*-Pr	Ph	**6** (71)	**16** (89)	100
3	**1**	*i*-Pr	*t*-Bu	**7** (30)	**17** (70)	99
4	**2**	*n*-Bu	Et	**8** (79)	**18** (82)	97
5	**2**	*n*-Bu	Ph	**9** (65)	**19** (66)	99
6	**2**	*n*-Bu	*t*-Bu	**10** (43)	**20** (90)	100
7	**3**	*s*-Bu	Et	**11** (79)	**21** (63)	98
8	**3**	*s*-Bu	Ph	**12** (78)	**22** (75)	100
9	**3**	*s*-Bu	*t*-Bu	**13** (28)	**23** (87)	98
10	**4**	Bn	Et	**14** (66)	**24** (85)	100

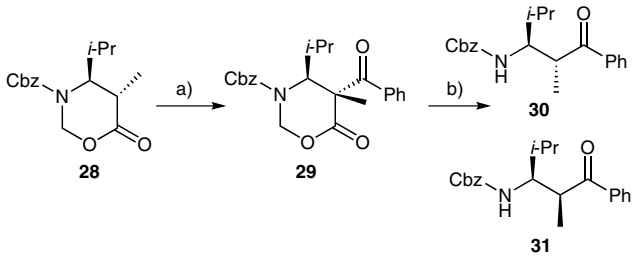
[a] Reaction conditions: (a) 1. LiHMDS, THF, –78 °C, 40 min; 2. R^2COCl, –78 °C to –50 °C, 3 h; 3. NH_4Cl; (b) 2 M HCl, THF, 50 °C, 4–6 h.



Scheme 4 Attempted formation of the *N*-methyl β-amino ketone **25** and the mechanism of formation of the unexpected byproduct **27**

istry and quenching with methyl triflate using established conditions.[7,9,10] The 5-methyl 1,3-oxazinan-6-one **28** was then enolized and 5-acylated using benzoyl chloride to afford **29** in moderate yield (40%). The 5,5-disubstituted 1,3-oxazinan-6-one **29** was then subjected to acidic conditions to produce the β-amino ketone as a mixture of diastereoisomers **30** and **31** in a good yield (82%, Scheme 5). Although the stereochemistry was not the focus of this transformation, because the stereocenter is epimerized under the decarboxylation conditions, a sample of the *trans* isomer was obtained during purification. This transformation further demonstrates the capacity of this methodology to produce highly functionalized substituted β[2,3]-amino ketones.

In summary, the synthesis of chiral substituted β³-amino ketones **15**–**24** has been described starting from 4-substituted 1,3-oxazinan-6-ones **1**–**4**. The 1,3-oxazinan-6-ones **1**–**4** were acylated using enolate chemistry to afford the 5-acylated 1,3-oxazinan-6-ones **5**–**14** in moderate to high yields. The 5-acylated products **5**–**14** were then smoothly transformed into the corresponding β-amino ketones **15**–**24**, under acidic conditions. This methodology was further expanded to demonstrate that a disubstituted β[2,3]-amino ketone (**30** and **31**) could also be produced starting from the 5-methyl 4-substituted 1,3-oxazinan-6-one **28**.



Scheme 5 Acylation of the 1,3-oxazinan-6-one **28** and β-amino ketone (**30** and **31**) formation. *Reagents and conditions*: (a) 1. LiHMDS, THF, –78 °C, 40 min; 2. PhCOCl, –78 °C to –50 °C, 3 h; 3. NH_4Cl (40%); (b) 2 M HCl, THF, 50 °C, 4–6 h (82%).

The methodology described again highlights the versatility of the 1,3-oxazinan-6-one as a useful scaffold to access a diverse assortment of β-amino acids and β-amino ketones for use in the peptidomimetic field.

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References and Notes

(1) (a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052. (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Sistaré, J. *J. Heterocycl. Chem.* **1981**, *18*, 47. (c) Brough, P.; Pécaut, J.; Rassat, A.; Rey, P. *Chem. Eur. J.* **2006**, *12*, 5134. (d) Fisyuk, A. S.; Poendaev, N. V. *Chem. Heterocycl. Compd.* **2003**, *39*, 895. (e) Fisyuk, A. S.; Ryzhova, E. A.; Unkovskii, B. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 597. (f) Hansen, C. P.; Jensen, A. A.; Balle, T.; Bitsch-Jensen, K.; Hassan, M. M.; Liljefors, T.; Fralund, B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 87. (g) Holzgrabe, U. *Arch. Pharm. (Weinheim)* **1988**, *321*, 767. (h) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131. (i) King, F. D. *Tetrahedron Lett.* **1983**, *24*, 3281. (j) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905. (k) Richards, J. J.; Ballard, T. E.; Huigens, R. W.; Melander, C. *ChemBioChem* **2008**, *9*, 1267. (l) Son, P.-N.; Lai, J. T. *J. Org. Chem.* **1981**, *46*, 323. (m) Winter, A.; Risch, N. *Synthesis* **2003**, 2667. (n) Yagi, T.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, 1063.

(2) Webster, S. P.; Binnie, M.; McConnell, K. M. M.; Sooy, K.; Ward, P.; Greaney, M. F.; Vinter, A.; Pallin, T. D.; Dyke, H. J.; Gill, M. I. A.; Warner, I.; Seckl, J. R.; Walker, B. R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3265.

(3) (a) Du, Y.; Li, Q.; Xiong, B.; Hui, X.; Wang, X.; Feng, Y.; Meng, T.; Hu, D.; Zhang, D.; Wang, M.; Shen, J. *Bioorg. Med. Chem.* **2010**, *18*, 4255. (b) Makarova, N.; Boreko, E.; Moiseev, I.; Pavlova, N.; Zemtsova, M.; Nikolaeva, S.; Vladyko, G. *Pharm. Chem. J.* **2001**, *35*, 480.

(c) Schönenberger, H.; Bastug, T.; Bindl, L.; Adelheid, A.; Adam, D.; Petter, A.; Zwez, W. *Pharm. Acta Helv.* **1969**, *44*, 691.
(4) (a) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, *7*, 700. (b) Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011. (c) Gomtsyan, A. *Org. Lett.* **1999**, *2*, 11. (d) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891.
(5) (a) Cardova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (b) Das, B.; Reddy, K. R.; Ramu, R.; Thirupathi, P.; Ravikanth, B. *Synlett* **2006**, 1756. (c) Das, B.; Srilatha, M.; Veeranjaneyulu, B.; Rama, Rao. B. *Synthesis* **2010**, 803. (d) Davis, F. A.; Yang, B.; Deng, J.; Zhang, J. *ARKIVOC* **2006**, *(viii)*, 120. (e) Eftekhari-Sis, B.; Abdollahifar, A.; Hashemi, M. M.; Zirak, M. *Eur. J. Org. Chem.* **2006**, 5152. (f) Hartman, A. E.; Brophy, C. L.; Cupp, J. A.; Hodge, D. K.; Peelen, T. J. *J. Org. Chem.* **2009**, *74*, 3952. (g) Jia, X.-D.; Wang, X.-E.; Yang, C.-X.; Huo, C.-D.; Wang, W.-J.; Ren, Y.; Wang, X.-C. *Org. Lett.* **2010**, *12*, 732. (h) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (i) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (j) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (k) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998. (l) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (m) Mei, H.; Xiong, Y.; Han, J.; Pan, Y. *Org. Biomol.Chem.* **2010**, *9*, 1402. (n) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F. III. *Tetrahedron Lett.* **2001**, *42*, 199. (o) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292. (p) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *Tetrahedron* **2002**, *58*, 983. (q) Schunk, S.; Enders, D. *Org. Lett.* **2001**, *3*, 3177. (r) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2005**, *128*, 74. (s) Syu, S.-e.; Lee, Y.-T.; Jang, Y.-J.; Lin, W. *J. Org. Chem.* **2011**, *76*, 2888. (t) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2254. (u) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature (London)* **2008**, *452*, 453. (v) Yang, J.-W.; Stadler, M.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 609.
(6) Geng, H.; Huang, K.; Sun, T.; Li, W.; Zhang, X.; Zhou, L.; Wu, W.; Zhang, X. *J. Org. Chem.* **2011**, *76*, 332.
(7) Nguyen, N. H.; Sleebs, B. E.; Hughes, A. B. *Tetrahedron* **2012**, *68*, 4745.
(8) (a) Sleebs, B. E.; Hughes, A. B. *Helv. Chim. Acta* **2006**, *89*, 2611. (b) Sleebs, B. E.; Hughes, A. B. *Aust. J. Chem.* **2006**, *58*, 778.
(9) Sleebs, B. E.; Hughes, A. B. *J. Org. Chem.* **2007**, *72*, 3340.
(10) Sleebs, B. E.; Nguyen, N. H.; Hughes, A. B. *Tetrahedron* **2013**, *69*, in press.

(11) **General Procedure 1**
5-Acylation of 1,3-Oxazinan-6-ones
A solution of the 1,3-oxazinan-6-one **1**–**4** (0.1 M in dry freshly distilled THF) was cooled to –78 °C under an argon atmosphere. Then LiHMDS (1.1 equiv of a 1.0 M solution in THF) was added dropwise, and the solution was left to stir at –78 °C for 40 min. The acylating agent (3.0 equiv) was then added dropwise and stirring was continued for 3 h at –78 °C. The solution was then allowed to warm to –50 °C, and the reaction was then quenched with sat. NH_4Cl solution (5 mL). The solution was diluted with EtOAc (20 mL) and washed with H_2O (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oil. The oil was subjected to flash column chromatography, eluting with 5–30% EtOAc–hexane.

Data for (4*S*,5*R*)-*N*-Benzyloxycarbonyl-4-isopropyl-5-propionyl-1,3-oxazinan-6-one (5)
General Procedure 1 was followed for the acylation of oxazinanone **1** (63 mg, 0.23 mmol) with propionyl chloride (59.8 μL, 0.68 mmol), to afford the desired 5-substituted 1,3-oxazinan-6-one **5** as a clear oil (crystallized on standing; 60 mg, 80% yield); mp 82–84 °C; R_f = 0.23 (20% EtOAc–hexane); $[\alpha]_D^{25}$ +116 (*c* 2.17, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (s, 5 H), 5.93 (d, 1 H, *J* = 9.9 Hz), 5.17 (s, 2 H), 4.93 (d, 1 H, *J* = 9.9 Hz), 4.59 (t, 1 H, *J* = 7.2 Hz), 3.73 (d, 1 H, *J* = 7.2 Hz), 2.84–2.73 (m, 1 H), 2.58–2.47 (m, 1 H), 1.88–1.77 (m, 1 H), 1.09 (t, 3 H, *J* = 7.2 Hz), 0.89 (d, 3 H, *J* = 7.2 Hz), 0.85 (d, 3 H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.7 167.3, 154.5, 134.9, 128.3, 128.1, 127.8, 72.9, 68.2, 55.9, 55.1, 36.5, 31.0, 18.3, 18.1, 7.2. IR (film): ν_{max} = 2967, 2940, 1748, 1717, 1458, 1412, 1258, 1123, 979 cm^{-1}. HRMS (ESI$^-$): *m/z* calcd for $C_{18}H_{23}NO_5$ $[M - H]^-$: 332.1503; found: 332.1496.

(12) **General Procedure 2**
Formation of the β^3-Amino Ketones
The oxazinanone **15**–**24** was dissolved in a mixture of THF–2 M HCl (1:1, 0.013 M solution), and the reaction mixture was gently heated to 50 °C for 4–6 h. The THF was then removed under reduced pressure. The aqueous solution was taken up EtOAc and washed with H_2O (3 × 10 mL) followed by brine (1 × 10 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give an oil. The oil was subjected to flash column chromatography, eluting with 5–20% EtOAc–hexane.

(13) **Data for (5*R*)-(*N*-Benzyloxylcarbonyl-5-amino)-6-methyl-heptan-2-one (15)**
General Procedure 2 was followed for the hydrolysis of the 1,3-oxazinan-6-one **5** (31 mg, 0.09 mmol), and afforded the β-amino ketone **15** as a white solid (24 mg, 92% yield); mp 75–77 °C; R_f = 0.50 (30% EtOAc–hexane); $[\alpha]_D^{25}$ –3.6 (*c* 1.09, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 5 H), 5.14 (d, 1 H, *J* = 8.9 Hz), 5.06 (s, 2 H), 3.83–3.76 (m, 1 H), 2.61 (br d, 2 H, *J* = 5.7 Hz), 2.47–2.33 (m, 2 H), 1.89–1.80 (m, 1 H), 1.00 (t, 3 H, *J* = 7.2 Hz), 0.89 (d, 3 H, *J* = 4.2 Hz), 0.87 (d, 3 H, *J* = 4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.0, 155.7, 136.3, 128.1, 127.6, 127.5, 66.2, 53.2, 43.9, 35.8, 31.2, 19.1, 18.2, 7.3. IR (film): ν_{max} = 3325, 2940, 2878, 1709, 1682, 2539, 1454, 1416, 1308. HRMS (ESI$^+$): *m/z* calcd for $C_{16}H_{23}NO_3$ $[M + H]^+$: 278.1751; found: 278.1756. HPLC [Chiralpak AD-H, PE–2-PrOH (90:10), 25 °C, 254 nm]: t_R (major) = 7.1 min; t_R (minor) = 6.1 min, 97% ee.

