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Domino Primary Alcohol Oxidation-Wittig Reaction: Total Synthesis of ABT-418 and (*E*)-4-Oxonon-2-enoic Acid

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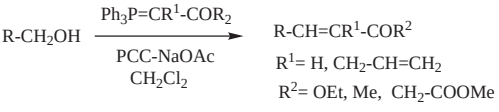
Abstract: Domino oxidation of primary alcohols to α,β-unsaturated compounds using the combination of PCC-NaOAc and stabilized Wittig reagent and its application towards total synthesis of ABT-418 and 4-oxonon-2-enoic acid is described.

Keywords: primary alcohols, oxidation, PCC, olefination, domino reaction

Domino reactions[1] have attracted considerable attention as they lead to reduction in the amount of byproducts, solvents, eluents, time and energy, thereby contributing to the protection of the environment. The sequence of oxidation of a primary alcohol and its condensation with a stable Wittig reagent is a routinely used step in organic synthesis. The most common problem associated with this sequence is the handling of intermediate aldehydes. The isolation of intermediate aldehyde is difficult due to volatility, toxicity or high reactivity. This problem has been overcome to a great extent by the 'one pot' oxidation approach[2] or by more convenient way via the recently reported excellent 'in situ' procedures.[3] One of these procedures uses[3a,b] Dess–Martin periodinane reagent as an oxidant with a stable Wittig reagent in the presence of benzoic acid to expedite the reaction in DMSO–CH_2Cl_2 (1:6) solvent mixture. The second procedure[3c] uses IBX in DMSO for 21 hours to give homologated nucleosides. The third procedure uses MnO_2 as an oxidant to oxidize activated alcohols[3d–f] such as allylic, benzylic and propargylic alcohols in presence of a carbonyl stabilized Wittig reagent for 5 hours to 3.5 days or *N*-protected β-amino alcohols[3g] with the Wittig reagent by refluxing in MeCN for 15 hours. In another similar procedure,[3h] allylic alcohols were converted to dienyl esters by using barium permanganate as an oxidant in presence of stable Wittig reagent. These authors reported failure of PDC and Dess–Martin periodinane reagent for such conversions.

Our main objective of looking towards synthesis of α,β-unsaturated compounds in a domino approach was to obtain large amount of 1-[1-methyl-2(*S*)-pyrrolidinyl]-1-butene-3-one for extending our method[4] of synthesis of 3,5-disubstitued isoxazole to synthesize 3-methyl-5-[1-methyl-2(*S*)-pyrrolidinyl]isoxazole (ABT-418) (**1**), a potent cholinergic agent[5] and also the difficulties faced in the handling of intermediate aldehyde during the synthesis. It appeared that we could easily achieve the synthesis of this compound by Wittig condensation of 1-triphenylphosphorylidine-2-propanone with *N*-substituted prolinol using the above 'in situ' procedures. However, application of the above two procedures[3a–c] as well as use of PDC as an oxidant did not give the desired product of the reaction of 1-triphenylphosphorylidine-2-propanone with *N*-methyl, *N*-ethoxycarbonyl or *N*-BOC-prolinol in our hand. The third procedure available[3g] was not used, since we thought that its harsh conditions may result in racemization.

Pyridinium chlorochromate[6] (PCC) is one of the most easily available reagents for the oxidation of primary alcohol to aldehydes. However, this reagent along with stable Wittig reagent has, to our knowledge, not been used for 'in situ' homologation. This prompted us to investigate its possible application toward this end. In order to check the feasibility of this domino approach, we took benzyl alcohol as the substrate and treated it with PCC and stable Wittig reagent [(carboethoxymethylene) triphenylphosphorane] in molar ratios and stirred in CH_2Cl_2. No homologated product was observed. Pyridinium chlorochromate, being an acidic reagent has been buffered with NaOAc effectively. Using the buffered PCC (1.5 molar ratio) along with one mole of stable Wittig reagent [(carboethoxymethylene) triphenylphosphorane] and benzyl alcohol, we got ethyl cinnamate in excellent yield of 96% (Scheme 1). Further studies using long chain as well as branched aliphatic alcohols (Table 1) with different Wittig reagents revealed the usefulness of this method. Reaction of ethylene glycol using the same one-pot approach gave the corresponding, α,β-unsaturated diester[3h] in 39% yield. Interestingly, the product obtained from diethylene glycol was also the same as that for ethylene glycol. The reaction with sensitive alcohols such as 2-phenylethanol and 3-chloropropanol (entries 2 and 10) gave the desired products.



Scheme 1

ABT-418 (**1**) is a potent and selective ligand for the neuronal nicotinic acetylcholine receptor and used effectively for the treatment of Alzheimer's disease.[8] There are five

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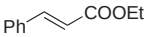
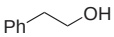
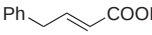
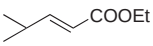
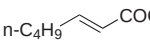
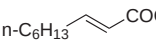
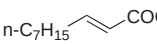
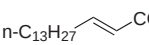
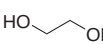
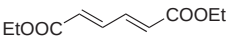
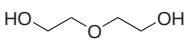
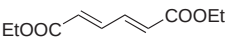
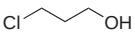
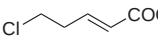
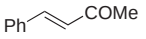
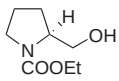
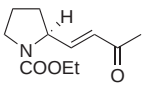
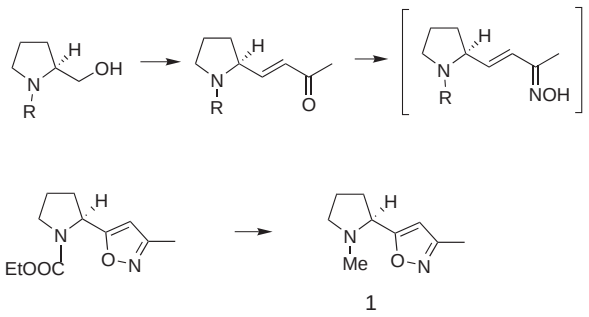
Table 1 In situ PCC-NaOAc Oxidation-Wittig Reaction in CH_2Cl_2

Entry	Alcohol	Product	Time, Yield (%)
1[7a]			1 h, 96 (*E*:*Z* = 9:1)
2[7b]			2 h, 70
3[7c]			4 h, 55
4[7d]	n-C_4H_9-CH_2OH		4 h, 85
5[7a]	n-C_6H_{13}-CH_2OH		3 h, 70
6[7e]	n-C_7H_{15}-CH_2OH		3.5 h, 70
7[7f]	n-$C_{13}H_{27}$-CH_2OH		5 h, 60
8[3h]			3 h, 39
9[3h]			4 h, 30
10[7g]			4 h, 65
11[7h]			1 h, 90
12			5 h, 72
13[7i]			1 h, 50

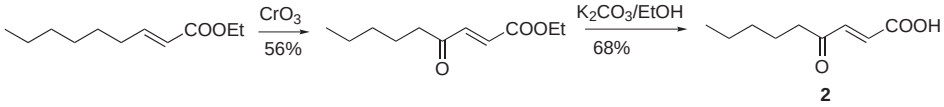
reports[5] available for the synthesis of ABT-418. All these approaches require strongly basic conditions, which require cryogenic conditions to avoid the problem of racemization or side product formation. Keeping this in mind, following Scheme 2 was visualized for the synthesis of ABT-418 (**1**). As depicted in the scheme, we use 1-triphenylphosphorylidine-2-propanone for our projected synthesis of ABT-418. Therefore, we initially checked the reactivity of this Wittig reagent with benzyl alcohol. Herein, we got the corresponding condensation product benzalacetone in 90% yield (entry 11).[7h] This was then converted to its oxime which without isolation was converted to 3-methyl-5-phenylisoxazole in 75% yield by oxidative cyclization method using DDQ as reagent reported in our laboratory.[4]



Scheme 2

After having successfully carried out model studies, we subjected *N*-methylprolinol and *N*-BOC-prolinol to the same set of experiments but unfortunately, we could not isolate the expected product. When *N*-ethoxycarbonyl prolinol, prepared from L-proline in two steps was used, it gave the corresponding product ethyl (2*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate in 72% yield. Ethyl (2*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate was then converted to oxime and the crude oxime when subjected to our oxidative cyclization method[4] failed to get converted to isoxazole. Ethyl (2*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate was then directly converted to 3-methyl-5-(carboethoxy)-pyrrolidine isoxazole by one pot experiment of the reported two step method[9] of preparing isoxazoles in 69% yield. The conversion to ABT-418 was achieved by $LiAlH_4$ reduction of 3-methyl-5-(carboethoxy)-(*S*)-pyrrolidine isoxazole in 62% yield. The salient features of this synthesis are: i) direct conversion of *N*-ethoxycarbonyl prolinol to ethyl (2*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate without isolation of the sensitive aldehyde, ii) no cryogenic conditions required at any step, and iii) the one-pot conversion of α,β-unsaturated ketones to isoxazole.

After the successful synthesis of ABT-418, we decided to use the product ethyl-(*E*)-non-2-enoate (entry 5) obtained via one-pot approach towards synthesis of (*E*)-4-oxonon-2-enoic acid (**2**), a natural antibiotic isolated from *Streptomyces olivaceus*. There are only two reported methods for the preparation of this compound and both these approaches require drastic conditions as well as costlier reagents.[10,11] Our approach from *n*-heptanol in three steps gave the (*E*)-4-oxonon-2-enoic acid (**2**) in 68% yield (Scheme 3).



2

Scheme 3

This protocol can also be used with other stable Wittig reagents for such homologations (entries 11–13). In all cases except for one (entry 1), the products obtained have exclusively *E*-geometry.

In conclusion, we have developed a mild and general method for domino primary alcohol oxidation-Wittig reaction for the synthesis of α,β-unsaturated compounds. The easy availability of PCC and comparatively milder Wittig reaction conditions of this protocol should provide a powerful alternative for the preparation of fuctionalized α,β-unsaturated compounds and may find widespread use in organic synthesis. The synthesis of enantiopure[12] ABT-418 (**1**) and (*E*)-4-oxonon-2-enoic acid (**2**) illustrates the usefulness of this method. We are presently exploring this reaction and its intramolecular version for the synthesis of pyrrolizidine alkaloids.

All melting points are uncorrected and measured by normal thiels tube (paraffin) method. Column chromatography was performed on silica gel 60–120 mesh size and TLC on silica gel G (13% $CaSO_4$ as binder). IR spectra were recorded on a Shimadzu FT-IR spectrophometer (KBr pellet or neat sample). ^{1}H NMR and ^{13}C NMR were recorded on a Brucker-300 MHz instrument. The multiplicities of carbon signals were obtained from DEPT experiments.

Synthesis of 3-Methyl-5-phenylisoxazole; Typical Procedure
Benzalacetone oxime (0.5 g, 3.1 mmol) and DDQ (1.4 g, 6.2 mmol) mixture was stirred for 5 h in MeOH (5mL). The reaction mixture was then concentrated and adsorbed on silica gel. The column chromatographic separation using EtOAc–hexanes (1:9) as eluent gave the product as a colourless solid (0.372 g, 75%); mp 67 °C.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 2.32 (s, 3 H, CH_3), 6.35 (s, 1 H, 4-H), 7.41 (m, 3 H, Ar-H), 7.75 (m, 2 H, ArH).

Domino Primary Alcohol Oxidation–Wittig Reaction; General Procedure (Table 1, Entries 1–13)
To a magnetically stirred suspension of pyridinium chlorochromate (1.5 mmol) and sodium acetate (1.5 mmol) in anhyd CH_2Cl_2 (10 mL), alcohol (1 mmol) in anhyd CH_2Cl_2 (5 mL) was added, followed by the Wittig reagent (1 mmol) in one portion. Et_2O (5 mL) was added after the completion of the reaction and the supernatant solution was decanted from the black granular solid. The combined organic solutions were filtered through a short pad celite and the filtrate obtained was evaporated to give a residue. Purification of the residue by column chromatography using hexanes as eluent gave the product.

Ethyl Cinnamate (Entry 1, *E* and *Z*)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.26 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.33 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 4.17 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.26 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 5.93, 6.43 (2 d, *J* = 12.0, 15.9 Hz, 1 H, CH=C*H*CO), 6.95, 7.90 (2 d, *J* = 12.0, 15.9 Hz, 1 H, C*H*=CHCO).

Ethyl-2(*E*)-4-phenylbutenoate (Entry 2)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 3.54 (br d, *J* = 6.8 Hz, 2 H, CH_2), 4.18 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.80 (d, *J* = 15.0 Hz, 1 H, CH=C*H*CO), 7.00–7.50 (m, 6 H, ArH, C*H*=CHCO).

Ethyl-2(*E*)-4-methylpentenoate (Entry 3)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.00 (t, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 1.05 (t, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.22 (m, 1 H, CH_3CHCH_3), 4.20 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.78 (dt, *J* = 16.0, 1.5 Hz, 1 H, CH=C*H*CO), 6.95 (td, *J* = 16.0, 7.0, 1.5 Hz, 1 H, C*H*=CHCO).

Ethyl-2(*E*)-heptenoate (Entry 4)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.29 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.33–1.50 (m, 4 H, 2 × CH_2), 2.02 (m, 2 H, CH_2CH=CH), 4.20 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 5.82 (dt, *J* = 15.6, 1.5 Hz, 1 H, CH=C*H*CO), 6.97 (td, *J* = 15.6, 6.7, 1.5 Hz, 1 H, C*H*=CHCO).

Ethyl-2(*E*)-nonenoate (Entry 5)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3), 1.29 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.23–1.50 (m, 8 H, 4 × CH_2), 2.20 (m, 2 H, CH_2CH=CH), 4.19 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 5.81 (dt, *J* = 15.6, 1.4 Hz, 1 H, CH=C*H*CO), 6.97 (td, *J* = 15.6, 6.7, 1.4 Hz, 1 H, C*H*=CHCO).

Ethyl-2(*E*)-decenoate (Entry 6)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.90 (t, *J* = 6.7 Hz, 3 H, CH_2CH_3), 1.10–1.65 (m, 10 H, 5 × CH_2), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.18 (m, 2 H, CH_2CH=CH), 4.20 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.80 (dt, *J* = 17.1, 1.6 Hz, 1 H, CH=C*H*CO), 6.97 (td, *J* = 17.1, 7.0, 1.6 Hz, 1 H, C*H*=CHCO).

Ethyl-2(*E*)-hexadecenoate (Entry 7)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.95 (t, *J* = 6.7 Hz, 3 H, CH_2CH_3), 1.20–1.70 (m, 22 H, 11 × CH_2), 1.22 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.19 (m, 2 H, CH_2CH=CH), 4.20 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.80 (dt, *J* = 15.9, 1.8 Hz, 1 H, CH=C*H*CO), 6.97 (td, *J* = 15.9, 7.3, 1.8 Hz, 1 H, C*H*=CHCO).

Diethylhexa-2(*E*),4(*E*)-diene-1,6-dioate (Entries 8 and 9)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.29 (t, *J* = 7.2 Hz, 6 H, 2 × OCH_2CH_3), 4.22 (q, *J* = 7.1 Hz, 4 H, 2 × OCH_2CH_3), 6.16–6.21 (m, 2 H, 2 × CH=C*H*CO), 7.26–7.33 (m, 2 H, 2 × C*H*=CHCO).

Ethyl-2(*E*)-5-chloropentenoate (Entry 10)
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.63 (q, *J* = 6.7 Hz, 2 H, $ClCH_2CH_2$), 3.57 (t, *J* = 6.7 Hz, 2 H, $ClCH_2CH_2$), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.87 (dt, *J* = 15.7, 1.7 Hz, 1 H, CH=C*H*CO), 6.83 (td, *J* = 15.7, 6.8, 1.7 Hz, 1 H, C*H*=CHCO).

Ethyl (2*S*)-2-[(1*E*)-3-Oxobut-1-enyl]pyrrolidine-1-carboxylate (Entry 12)
$[\alpha]_D^{25}$ –89.78 (*c* = 2.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.26 (t, *J* = 6.9 Hz, 3 H, $COOCH_2CH_3$), 1.85–1.93 (m, 3 H), 2.13–2.2 (m, 2 H), 2.26 (s, 3 H, $COCH_3$), 3.47 (t, *J* = 7.5 Hz, 1 H), 4.11 (q, *J* = 6.9 Hz, 2 H,

COOCH_2CH$_3$), 4.5 (m, 1 H, CH), 6.07 (d, J = 15.9 Hz, 1 H, CH=CHCO), 6.69 (d, J = 15.9 Hz, 1 H, CH=CHCO).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 14.7, 23.18, 27.28, 31.07, 46.61, 57.99, 61.13, 129.75, 140.87, 155.0, 198.04.

EIMS: m/z (%) = 212 (8.7) [M + 1], 169 (22.5), 142 (100), 96 (20), 70 (83.7), 29 (100).

Methyl (4*E*)-3-Oxo-5-phenylpent-4-enoate (Entry 13)

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.67, 5.14, 11.87 (3 s, 2 H, CH_2, HC=COH, HC=COH), 3.71, 3.72 (2 s, 3 H, OCH_3), 6.37 (dd, J = 15.9, 1.2 Hz, 1 H, CH=CHCO), 6.42 (d, J = 16.2 Hz, 1 H, CH=CHCO). 7.27–7.57 (m, 5 H, ArH).

Synthesis of 3-Methyl-5-(carboethoxy)pyrrolidinylisoxazole; Typical Procedure

To ethyl (2*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate (0.718 g, 3.4 mmol) was added hydroxylamine hydrochloride (0.284 g, 4.1 mmol) in THF–H_2O (9:1) and the reaction mixture was stirred for 2 h. Then, KI (1.97 g, 11.9 mmol), iodine (0.863 g, 3.4 mmol), and $NaHCO_3$ (1.13 g, 13.6 mmol) was added and refluxed for 16 h. The mixture was then cooled to r.t. and diluted with 1.7 M sodium bisulphite solution (10 mL) and extracted with Et_2O (3 × 15 mL). The combined Et_2O extracts were washed with brine solution and dried with anhyd Na_2SO_4. The solvent was evaporated off and the product obtained was further purified by column chromatography using EtOAc–hexanes (1:9) as eluent, which gave the product (0.525 g, 69%) as a colourless oil; $[\alpha]_D^{25}$ –123.92 (c = 1.19, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.24 (t, J = 6.9 Hz, 3 H, COOCH_2CH_3), 1.86–2.12 (m, 3 H), 2.12–2.18 (m, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 3.48 (t, J = 7.5 Hz, 1 H), 4.10 (q, J = 6.9 Hz, 2 H, COOCH_2CH$_3$), 4.9 (m, 1 H, CH), 5.98 (s, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 11.50, 14.47, 24.34, 31.78, 46.00, 62.00, 102, 154, 160.

EIMS: m/z (%) = 223 (12.5) [M + 1], 151 (25), 123 (12.5), 110 (10), 82 (30), 41 (41.2), 29 (100).

Synthesis of 3-Methyl-5-[1-methyl-2(*S*)-pyrrolidinyl]isoxazole (1) (ABT-418); Typical Procedure

To a stirred solution of 3-methyl-5-(carboethoxy)-pyrrolidinyl isoxazole (0.2 g, 0.89 mmol) in anhyd THF (20 mL) cooled at 0 °C, was added $LiAlH_4$ (1.78 mmol) in small portions and the mixture was stirred for 15 min. The reaction was quenched by adding few drops of EtOAc followed by aq sat. Na_2SO_4 (10 mL) and extracted with EtOAc (3 × 10 mL) and the solvent concentrated. The crude residue was dissolved in dilute HCl acid (1 N, 30mL) and washed with EtOAc (2 × 10 mL). The aq layer was then neutralized with sat. $NaHCO_3$ solution (10 mL) and then further extracted with EtOAc (3 × 10 mL). The organic extracts were dried over anhyd Na_2SO_4. Concentration under vacuum gave the compound (0.076 g) as a light yellow oil (0.11 g, 62%); $[\alpha]_D^{25}$ –111.80 (c = 1.57, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.76–2.04 (m, 3 H,), 2.11–2.34 (m, 2 H, CH_2), 2.22 (s, 3 H, CCH_3), 2.26 (s, 3 H, NCH_3), 3.07–3.12 (m, 1 H), 3.36 (t, J = 7.5 Hz, 1 H, CH), 6.00 (s, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 11.03, 22.51, 31.38, 40.30, 56.22, 61.88, 101.12, 159.17, 173.83.

Synthesis of Ethyl-(*E*)-4-oxonon-2-enoate; Typical Procedure

A mixture of an oxidizing solution of chromium trioxide (100 mmol) in acetic anhydride (1 mL) and glacial HOAc (2 mL) was added dropwise with cooling to a stirred solution of ethyl-2-(*E*)-nonate (0.5 g, 2.7 mmol) in benzene (5 mL). The reaction mixture was stirred for 2 h at ambient temperature. Benzene (5 mL) was added and the mixture cooled in an ice-bath and cautiously neutralized with concd KOH solution. The two-phase mixture was then poured into water (20 mL) and extracted with Et_2O (4 × 15 mL). The combined Et_2O extracts were washed with sat. $NaHCO_3$ (3 × 5 mL) and then with brine solution. The organic extracts were dried over anhyd Na_2SO_4 and evaporated. The residue obtained was further purified by column chromatography using EtOAc–hexanes (1:9) as an eluent, which gave the product as colourless oil (0.3 g, 1.5 mmol, 56.60%).

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.88 (t, J = 6.7 Hz, 3 H, COOCH_2CH_3), 1.23–1.47 [m, 6 H, $(CH_2)_3$], 1.29 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.62 (t, J = 7.5 Hz, 2 H, CH_2C=O), 4.26 (q, J = 7.3 Hz, 2 H, COOCH_2CH$_3$), 6.62 (d, J = 16.07 Hz, 1 H, CH=CHCO), 7.06 (d, J = 16.07 Hz, 1 H, CH=CHCO).

Synthesis of (*E*)-4-Oxonon-2-enoic Acid (2); Typical Procedure

To a solution of ethyl-2-(*E*)-4-oxononate (0.1 g, 0.5 mmol) in EtOH (5 mL) was added K_2CO_3 (1 mmol) and stirred for 2 h. The reaction mixture was concentrated under vacuum. Water (5 mL) was added followed by acidification with dilute HCl acid. The aq layer was extracted with Et_2O (3 × 10 mL). The crude solid product obtained after drying and evaporation of the solvent was purified by column chromatography using EtOAc–hexanes (1:4) as an eluent to give the white solid (0.058 g, 68.23%); mp 104 °C.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.9 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.25–1.66 (m, 6 H, 3 × CH_2), 2.66 (t, J = 7.3 Hz, 2 H, CH_2CO), 6.66 (d, J = 16.0 Hz, 1 H, CH=CHCO), 7.12 (d, J = 16.0 Hz, 1 H, CH=CHCO), 10.60 (br s, 1 H, exchangeable with D_2O, COOH).

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(12) Enantiomeric purity of the products ethyl (2*S*)-2-[(1*E*)-3-oxobut-1-enyl]pyrrolidine-1-carboxylate, 3-methyl-5-(carboethoxy)pyrrolidinyl isoxazole, 3-methyl-5-[1-methyl-2-(*S*)-pyrrolidinyl] isoxazole (ABT-418) were determined on chiral AD-column as reported in an earlier synthesis (see reference 5b).