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Claisen Condensation as a Facile Route to an α-Alkoxy-cinnamate: Synthesis of Ethyl (2*S*)-2-Ethoxy-3-(4-hydroxyphenyl)propanoate

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Abstract:

The title compound was prepared from *p*-anisaldehyde and ethyl ethoxyacetate via a racemic synthetic route. The synthesis involves a Claisen-type condensation in which the elimination was unexpectedly promoted by an excess of the ester. The process has been successfully performed on a 2000-L scale with a total yield over seven steps of 19%.

Background

The chiral ester ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (**EEHP**) is a key intermediate for one of AstraZeneca's development projects. In the original medicinal chemistry synthesis[1] of EEHP, the key intermediate, an α-alkoxy-cinnamate ester, was prepared using Wittig chemistry[2] and resolution via chromatographic separation of the corresponding diastereomeric amides.

A number of procedures for the preparation of α-alkoxy- and α-aryloxy-cinnamate esters reported in the literature are condensation reactions between aromatic aldehydes and α-alkoxy- or α-aryloxy esters using bases such as sodium metal,[3,4] alkoxides,[5−7] or lithiumdialkylamides.[8] Several examples of syntheses involving Wittig−[9] or Wadsworth−Horner−Emmons methodology[10−13] have been reported. Other syntheses of these compounds involve Heck coupling[14,15] or rhodium-catalyzed carbenoid-mediated *O*-insertion on α-diazopropanoic acid derivatives.[16,17] Another route to 2-alkoxy-3-phenylpropanoic acid derivatives[18] starts with *O*-benzyltyrosine which is diazotised to the 2-hydroxy compound followed by alkylation using NaH in DMF as base.

As our aim was to develop an inexpensive and robust method suitable for a large-scale production of EEHP, condensation of an aromatic aldehyde with an ester using an alkoxide as base was selected as synthetic strategy.

Initial Large-Scale Synthesis of EEHP. A new synthetic method[19] starting from 4-methoxybenzaldehyde (MBA) and ethyl ethoxyacetate (EEA) was developed and rapidly scaled-up to 1000-L (Scheme 1).

Ethyl ethoxyacetate, (EEA) was initially prepared from chloroacetic acid (**1**).[20] The acid was treated with NaOEt in EtOH and then esterified by bubbling HCl gas into the reaction mixture. After filtration and removal of EtOH, the ester was obtained in 71% yield (95% conversion). The condensation between EEA and anisaldehyde in THF at −10 °C using ^{t}BuOK as the base gave a mixture of the three compounds **2**, **3**, and **4** in variable amounts. After quenching the reaction with HOAc, the solvent was changed from THF to toluene. Acid-catalyzed dehydration, using methanesulfonic acid in toluene at 100 °C, then resulted in conversion of the main component ethyl 2-ethoxy-3-hydroxy-3-(4-methoxyphenyl)propanoate (**2**) to the unsaturated analogue, ethyl (*Z*)-2-ethoxy-3-(4-methoxyphenyl)propenoate (**4**) and disappearance of 2-ethoxy-3-hydroxy-3-(4-methoxyphenyl)-propionic acid (**3**). Ester hydrolysis and crystallisation from toluene afforded pure (*Z*)-2-ethoxy-3-(4-methoxyphenyl)-propenoic acid (**5**) in 58% isolated yield based on MBA. Despite a high conversion of MBA (95% by LC), the isolated yield of **5** was relatively low. The main cause of this was the formation of 16−30% of a byproduct, **3**, during the condensation step (area % by LC, not corrected for response factors). The 3-hydroxyacid (**3**) was decomposed rather than dehydrated to **5** during the following elimination reaction. A model experiment with pure **3** and MsOH gave a mixture of (4-methoxy-phenyl)acetaldehyde (**10**) and a self-condensation product of **10**, (2*Z*)-2,4-bis(4-methoxyphenyl)-2-butenal (**11**) (GC−MS: $M^+ = 150$ and 282 respectively). The formation of **10** can be rationalized through decarboxylation and elimination of H_2O from **3** to the vinyl ether **9**

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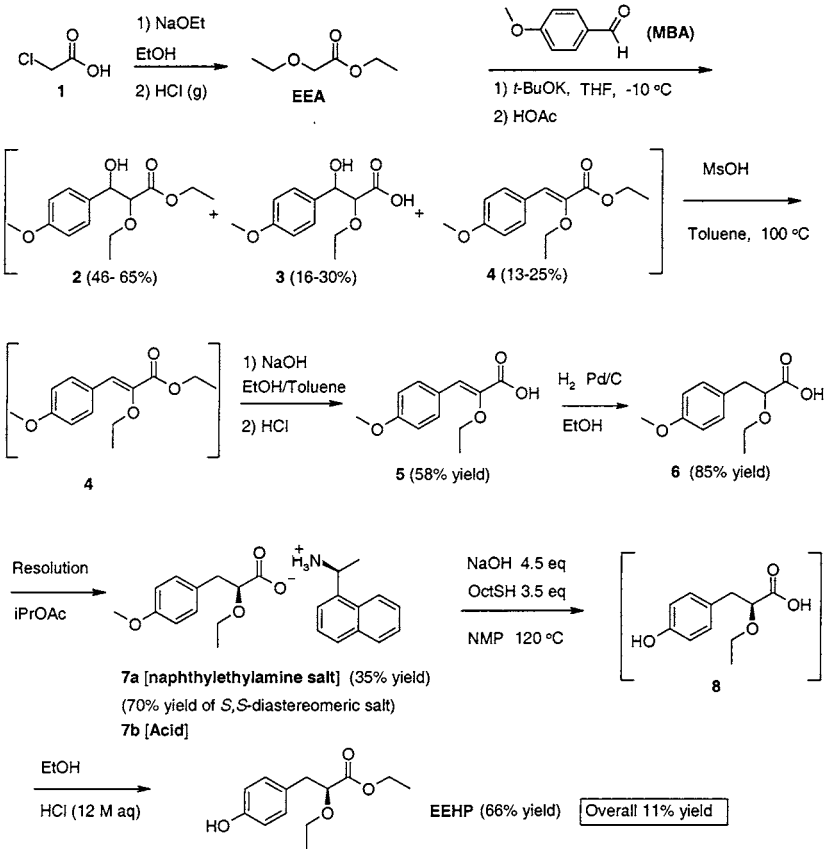
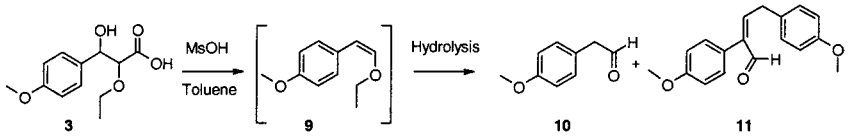
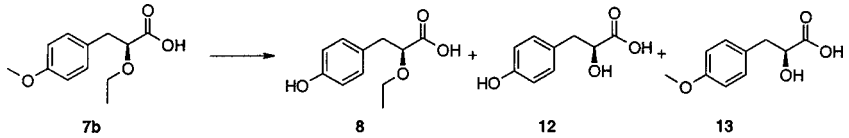
Scheme 1. **Initial large-scale synthesis of EEHP**



Scheme 2. **Decomposition of 2-ethoxy-3-hydroxy-3-(4-methoxyphenyl)propanoic acid (3)**



Scheme 3. **Demethylation of 7b**



a) BBr_3/ CH_2Cl_2 -10°C	-	(7%)	(90%)
b) HI (57%,aq)	(80%)	(10%)	(2%)
c) RSNa/NMP 120- 170°C	(95-99%)	-	-

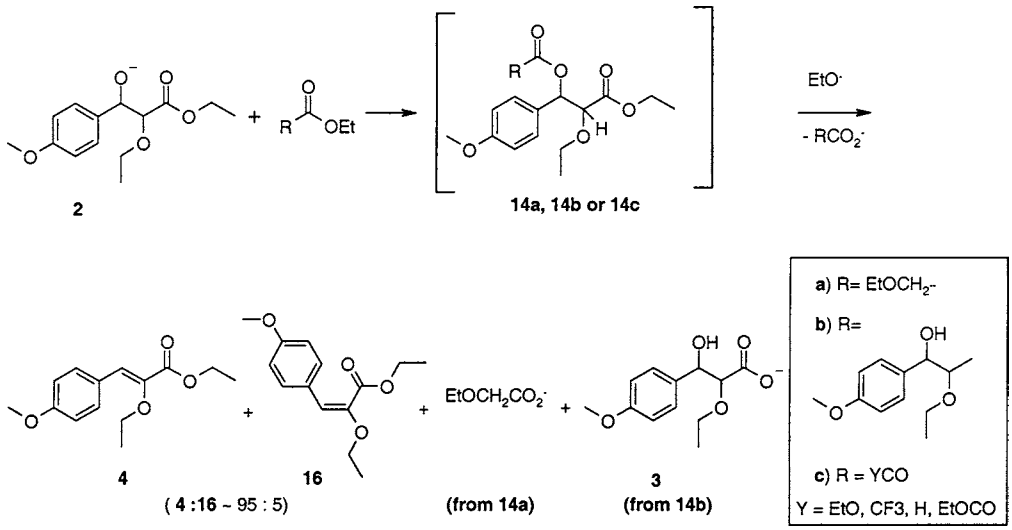
and subsequent hydrolysis to give the aldehyde (**10**) according to Scheme 2.

Hydrogenation of **5** gave racemic 2-ethoxy-3-(4-methoxyphenyl)propanoic acid (**6**) in 85% yield after crystallisation. Resolution using (*S*)-1-(1-naphthyl)ethylamine (*S*-NEA) in ^{i}PrOAc gave diastereomerically pure salt (**7a**) in 70−76% yield and 97−98.5% de. The absolute configuration of the acid **7b** was determined by X-ray crystallography of its naphthyl ethylamine salt **7a**.[21] The acid **7b** was released from the salt and extracted into EtOAc before the subsequent demethylation step. BBr_3 was initially tested for the demethylation of **7b**, but unexpectedly, it was found to cause cleavage of the ethyl ether, giving 2-hydroxy-3-(4-methoxyphenyl)propanoic acid (**13**) (Scheme 3). HI (57%, aq) gave a mixture containing 80% of (2*S*)-ethoxy-3-(4-hydroxyphenyl)propanoate **8**, 10% 2-hydroxy-3-(4-hydroxyphenyl)-propanoic acid (**12**), and 2% of **13**. Due to a poor recovery when crystallising the product, the isolated yield of **8** was, at best, 43%.

By contrast, sulphur nucleophiles[22] showed complete selectivity between the methyl and the ethyl group. Sodium

(21) Stensland, B.; Ertan, A. Unpublished results. X-ray crystallographic data for **7a**: The colourless compound crystallizes in the monoclinal space group $P2_1$. Unit cell dimensions: $a = 12.136$ (Å), $b = 7.047(1)$ Å, $c = 12.813(1)$ Å, $\alpha = 90°$, $\beta = 91.35(1)$, $\gamma = 90°$. $V = 1095.5(2)$ Å^3, Z (molecules/unit cell) = 2. $R = 0.0417$, $R_w = 0.0457$ observed with $F^2 > 3\sigma(F^2)$. Temperature: room temperature.

Scheme 4. **Proposed transesterification and elimination mechanism**



thiophenolate in DMF at 160−170 °C resulted in complete conversion in 7 h but gave approximately 4% racemization of **8**. With the use of sodium 1-octylthiolate in NMP or NaSEt in DMF at 120 °C about 95−99% conversion to the phenol was achieved within 24−40 h without any racemization. The acid **8** turned out to be difficult to crystallize, and it was consequently not obtained pure. Instead, esterification of crude acid, crystallisation through charging a solution of EEHP in EtOH into aqueous $NaHCO_3$, and recrystallisation from cyclohexane/EtOAc afforded EEHP in 66% isolated yield based on **7a** (99.7% purity and 99.8% de). The overall yield of EEHP from MBA was 11% on a 1000-L scale.

While the starting materials for this synthesis were inexpensive, the initial process suffered from several problems.

The steps from MBA to **6** gave a low overall yield and were very labour intensive and time consuming on a large scale.

The demethylation of **7b** was slow, frequently incomplete and involved a tedious workup.

However, the yield in the resolution step (70−74% of the *S*-enantiomer **7b** isolated as the diastereomeric *S*,*S*-salt **7a**) was relatively high, and the isolated yield of EEHP from **7a** (66%), after subsequent esterification and recrystallisation, was acceptable.

Method Development of the Condensation Step. Having successfully scaled up the initial synthetic route, our work then focused on improving the condensation reaction. NaOEt in EtOH was found to be a good substitute for ^{t}BuOK in THF, giving about 95% conversion of the aldehyde and the same product mixture. However, changing to the weaker base and a protic solvent resulted in an increase of the reaction time to about 20 h from 1 to 2 h. Combined with the alternative method[23] for the preparation of EEA from $ClCH_2$-CO_2Et and NaOEt in EtOH, the change of base made it possible to perform the first two synthetic steps as a one-pot procedure.

In the Claisen reaction between MBA and EEA using either NaOEt or ^{t}BuOK, in addition to the 3-hydroxy ester **2**, some of the unsaturated ester **4** (10−30%), the unsaturated acid **5** (2−9%) as well as the 3-hydroxy acid **3** were observed in the reaction mixture. An analysis of the results showed that the amount of the unsaturated components in the reaction mixture roughly reflected the excess of EEA used. Increasing the amount of EEA gave more of the elimination products and less formation of **3**. The intermediate **2** was fully converted in 20 h at 35 °C using 4.3 equiv of EEA and 2.5 equiv of NaOEt. Raising the temperature to increase the reaction rate resulted in disproportionation of the 4-methoxybenzaldehyde to ethyl 4-methoxybenzoate and 4-methoxybenzyl alcohol (Cannizzaro reaction) as a competing side-reaction.

A precedent case from the literature[5] shows a procedure for the condensation of ethyl methoxyacetate (3 equiv) and various aromatic aldehydes using NaOEt in toluene at room temperature to give α-methoxypropenoic esters without any acid-catalyzed dehydration. However, no mechanistic interpretation was presented in the article.

A detailed mechanistic study of the ester promoted elimination reaction has not yet been performed. Therefore, unambiguous evidence for our hypothesis (Scheme 4) cannot be presented. However, the available data strongly support the following rationale of our findings.

The positive effects of an excess EEA on the elimination could be rationalized by a reaction path starting with transesterification of EEA by the benzylic hydroxyl group in **2** to give the intermediate **14a**. This is then followed by elimination of ethoxy acetate. In other words, the reaction can be viewed as an in situ derivatisation of the benzylic alcohol **2**. The intermediate **14a** contains a carboxylate, being a better leaving group than hydroxide, and elimination across the C2−C3 bond occurs under basic conditions at 25−35 °C.

The results presented in Table 1 show that the ratio of the unsaturated compounds (**4** + **5**) to the saturated (**2** + **3**) increases with a larger excess of EEA.

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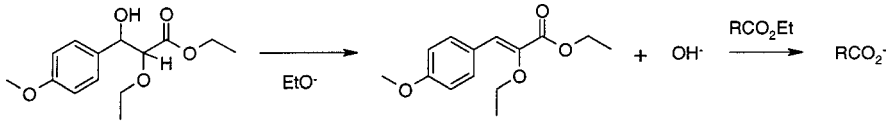
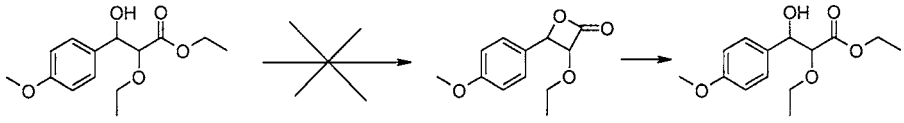
Scheme 5. **Alternative proposed mechanism for the elimination reaction**



2 **4**

Scheme 6. **Unlikely Mechanism for the Formation of 3 via a *β*-lactone**



2 **15** **3**

Table 1. **Condensation and dehydration reactions[a]**

entry	EEA (equiv)	NaOEt (equiv)	dehydration ester (equiv)	main components of crude product (area %, LC) MBA	2	3	4	5	MBnOH
1	1	1.5		25	4	16	29	6	11
2	2.3	2.5		6	4	16	62	9	1
3[b]	2.3	2.5		46	13	6	24	2	2
4	3	2.5		5	2	11	73	8	0
5	2.3	2.5	2 EEA[c]	6	0	8	75	4	1
6	2.3	2.5	4.2 HCl_2Et[d]	0	13	3	53	9	2
7	2.3	2.5	2 $(EtCO_2)_2$	80	1	0	10	0	1
8	2.3	2.5	2 CF_3CO_2Et	90	0	0	5	1	0
9	2.3	2.5	1.4 $(EtO)_2CO$	5	1	8	73	7	1
10	2.3	2.5	2.8 $(EtO)_2CO$	2	0	6	81	5	1

[a] The reactions were conducted at 35 °C for 19−22 h unless otherwise noted. Other minor components of the reaction mixtures such as ethyl 4-methoxybenzoate and the *E*-isomers of **4** and **5** and some unidentified compounds are not listed in the table. [b] Twice the amount of solvent as in entry 2. [c] Neat EEA added to keep volume down. [d] Reaction at room temperature.

It is known that transesterifications can occur under basic catalysis.[24] The fact that the intermediate **14a** has never been detected is a weak point in our hypothesis. An explanation could be that **14a** is very unstable under basic conditions and eliminates very fast to give **4**. The fact that a carboxylate is a better leaving group than a hydroxide ion could explain why the reaction gave more of **4** when increased amounts of esters were added.

An alternative explanation for the results has been suggested to us. According to that proposal hydroxide is the leaving group, and the excess of ester acts as a scavenger, thereby preventing hydrolysis of the ethyl ester group in **2** (Scheme 5). It is likely that elimination of hydroxide did occur when the stronger base, ^{t}BuOK, and a smaller excess of EEA was used. Quenching hydroxide ions by the excess of EEA is a good rational for the decreased amounts of the acids **3** and **5** found in the reaction mixtures. However, it cannot explain how the elimination step would be facilitated by an increased amount of ester since that reaction is virtually irreversible. A literature survey of the addition of H_2O or alcohols to cinnamic esters or ketones gave no hits.

The type of elimination (E1, E2, or E1cB) by which the reaction takes place has not been determined since such an investigation was beyond the scope of this work. A coming mechanistic study will hopefully clarify the details of this reaction.

Mechanisms for the Formation of the Carboxylic Acids in the Condensation Reaction. Despite the improvements, the byproduct **3** was still formed, although in decreased amounts (10−15%). Also 4−9% of the desired acid **5** was detected in the reaction mixture. The literature showed no precedents for the formation 3-hydroxy acids during similar condensation reactions under nonhydrolytic conditions, but a few cases with mixtures of α,*β*-unsaturated acids and esters have been reported.[25−28]

A mechanism for intramolecular cleavage of esters to α,*β*-unsaturated acids, involving the formation of a *β*-lactone,[25−28] was presented in the 1970s. Therein it was claimed that the initially formed benzyloxy anion attacks the ester function, giving a *β*-lactone as an intermediate, which then can undergo *β*-elimination to give the unsaturated acid. However, no evidence for the presence of a *β*-lactone was presented, and we have ruled out this path as a possible explanation for the formation of **3**.

If **2** would form the *β*-lactone **15** (Scheme 6), it is not likely that such a strained intermediate could survive in the presence of NaOEt but undergo ring opening. Comparing two condensations with the same excess of EEA and base, but at different concentration (entries 2 and 3, Table 1), gave less of the acids **3** and **5** in the more dilute reaction (corrected for a lower conversion of MBA). This would not have been the case for an intramolecular cleavage via the proposed *β*-lactone **15**.

The decreased formation of carboxylic acids from 20 to 30% with 1.2 equiv of EEA to 16−8% when using 2.5−4.3 equiv of the ester can instead be neatly explained by two alternative mechanisms. The first and likely main reaction path is a straightforward hydrolysis caused by hydroxide ions formed by the direct elimination as outlined in Scheme 5. A larger excess of EEA can both compete with the reaction path in Scheme 5 and act as a scavenger for hydroxide ions, thereby suppressing the formation of **3**.

In principle **3** could also be formed via a transesterification−elimination reaction analogous to the reaction between **2** and EEA shown above. Two molecules of **2** could form

(24) Smith, March *"Advanced Organic Chemistry"*, 5th ed.; Wiley: New York, 2001; pp 486.

(25) Patwardhan, B. H.; Bagavant, G. *Indian J. Chem.* **1972**, *10*, 59−61.
(26) Patwardhan, B. H. *Indian J. Chem.* **1974**, *12*, 891−892.
(27) Paranjpe, P. P.; Bagavant, G. *Indian J. Chem. Sect. B* **1976**, *14*, 547−548.
(28) Gurjar, M. K.; Bagavant, G. *Indian J. Chem. Sect. B* **1976**, *14*, 548−549.

the benzylic ester **14b** (Scheme 4). The carboxylate of **3** would then be eliminated from **14b**. A larger excess of EEA competes with the formation of **14b** by giving more of **14a** and thereby reducing the amount of **3**.

Forming the intermediate **14b** from two molecules of **2** would be more difficult than transesterifying EEA with the benzylic alcohol group, due to a greater steric hindrance around the ester function of **2**. Therefore, elimination of a hydroxide ion, followed by an attack of that hydroxide on the ester in **2** or **4** to give the corresponding acids, is clearly the most probable of the two explanations for the appearance of the acids. The ester hydrolysis might, however, occur via both the two proposed mechanisms of which the former is the dominating. Most likely, small amounts of NaOH in the NaOEt and traces of H_2O in the solvent also contributed to the hydrolysis of **2** and **4**.

Another potential route to the 3-hydroxy acid **3** is condensation of MBA and ethoxy acetic acid (formed by hydrolysis of the ethyl ester by NaOH, an impurity in NaOEt). However, a model experiment with the ethoxy acid, two equivalents of the base and MBA did not produce any of the 3-hydroxy acid **3** due to insufficient base strength of NaOEt to generate the dianion of the acid.

Attempts To Suppress the Formation of the Hydroxy Acid 3 and To Facilitate the Elimination Reaction. We investigated two approaches to the problem with the formation of **3**. The first was to try to convert the byproduct **3** to **6** by hydrogenolysis of the hydroxyl group. The reaction turned out to be difficult and required harsh conditions (30 mol % H_2SO_4 in EtOH, 4 bar H_2 pressure, 50 °C during 16 h). Under those conditions the main component **4** was not stable.

The second approach was to suppress the acid formation by competitive transesterification. Increasing the excess of EEA had given reduced content of **3** in the reaction mixture together with high conversion of **2** to **4**. To use a larger excess of the crude EEA solution in EtOH would lead to a loss of volume efficiency. As an alternative approach, the addition of other esters which could form the intermediate **14c** (Scheme 4) and thereby promote the transesterfication−elimination reaction of **2** to **4** and consequently suppress the formation of **3** were investigated. To avoid condensations of enolates competing with EEA, esters without α-hydrogens were chosen, and the results are shown in Table 1.

Of the five esters tested ethyl formate gave the lowest content of **3**. However, due to decomposition under basic conditions that ester was unsuitable for safety reasons,[29] and in addition it gave a poor conversion to **4**. Diethyl oxalate and ethyl trifluoroacetate both gave poor conversion of MBA. The carbonyl groups of these two esters are more electrophilic than the aldehyde and therefore reacted faster with EEA, giving diethyl 2-ethoxy-3-oxosuccinate ($M^+ = 232$) and ethyl 2-ethoxy-4,4,4-trifluoro-3-oxobutanoate ($M^+ = 228$) respectively, detected by GC−MS.

The best result (defined as the largest sum of **4** + **5** and the least amount of **3**) was obtained using 2.8 equiv of diethyl carbonate as the dehydration ester (entry 10). The ability of $(EtO)_2CO$ to suppress the formation of **3** appears to be of the same order of magnitude as that of EEA (entries 5 and 9) but, unlike EEA, this reagent is commercially available in large quantities and is inexpensive. On laboratory scale the advantage of using $(EtO)_2CO$, compared to that with using a larger excess of EEA, did not appear to be great. The disadvantages of using it appeared in the acidic workup procedure where its decomposition led to foaming and evolution of CO_2 and EtCl (detected by GC−MS). However, on a large scale the use of the carbonate ester has turned out to be the preferred procedure. Consequently, the acid-catalyzed dehydration step and preceding solvent swap could be eliminated from the reaction sequence, considerably simplifying the process.

Hydrolysis, Hydrogenation, and Resolution. The reaction mixture was hydrolyzed using aqueous NaOH at room temperature. EtOH was evaporated off followed by acidification using HCl (aq). At this stage there were two options: either to carry the crude material further or to isolate the pure acid **5**. In most of the lab experiments we chose to extract the crude acid into ^{i}PrOAc for hydrogenation. The crystallisation of **6** was shown to be unnecessary and was hence excluded. Instead, the acid was precipitated as the salt **7a** from the ^{i}PrOAc solution by the addition of *S*-NEA. The purifying effect of the crude crystallisation was very good, completely removing the main impurity **3**. The amount of the byproduct ethoxyacetic acid (EAA) strongly affected the outcome of crystallisation, while the amount of **3** was less critical for the yield but lowered the ee somewhat. Reducing the level of EAA by effective washing of the ^{i}PrOAc solution with water was found to be important. Resolution afforded the diastereomeric amine salt **7a** in 19% yield on a 5-L scale based on MBA.

The second alternative, crystallisation of **5** prior to the hydrogenation, was used for the first pilot plant batches. Extraction with ^{i}PrOAc, washing with H_2O, solvent swap to toluene, and concentration to ∼2 mL/g crude material gave **5** in 66% yield and 100% purity by LC (78% recovery). Although this procedure involved isolation of an intermediate after three instead of five steps, it resulted in a more robust crystallisation of the salt **7a** during the later resolution. Another advantage was that the amount of the costly *S*-NEA could be reduced. On a 600-L scale, the yield of **7a** from MBA was 24% (after recrystallisation).

Further development of the process resulted in a simplified isolation procedure of the acid **5** with a higher yield (81%) and 97% purity by LC. After the alkaline hydrolysis and acidification the intermediate **5** was collected by filtration, washed with H_2O, and dried. Applying all the improvements to the process gave the amine salt **7a** in a total yield of 30% from MBA (Scheme 7) on a 2000-L scale.

Scale-Up Effects. Since the condensation is carried out as a slurry reaction, a more efficient agitation on a larger scale probably accounts for a higher conversion of MBA to **5** compared to the results from the 5-L scale. An efficient stirring is also important for the demethylation reaction, in which a thick slurry is formed.

(29) *Brethrick's Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth & Heinemann: 1995; Part 1, pp 320.

Scheme 7. **Improved process for the synthesis of the naphthylethylamine salt 7a**

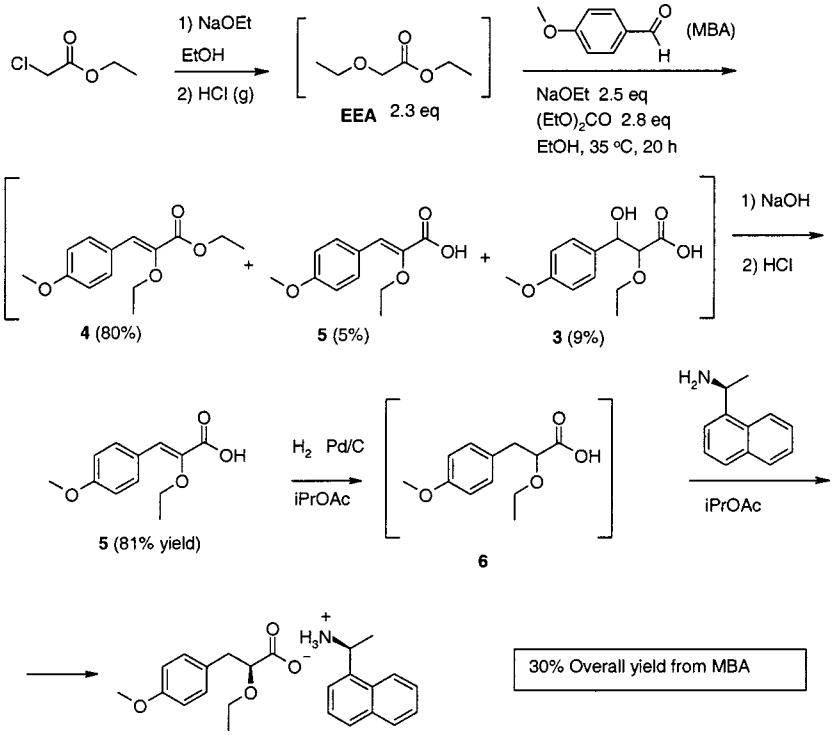


Table 2. **Comparison between the new and the old process**

	old method	new method	Δ (%)
batch cycle time (h)	243	100	−60
yield of **7a** (%)	17	30	+76
yield of EEHP (%)	11	19	+73
capacity (kg/1000 L)	17	31	+82

Conclusions

The improvements achieved in the condensation reaction had a great impact on the process. The use of EEA prepared in situ from ethyl chloroacetate, instead of from chloroacetic acid, simplified the process considerably. The change of base from ^{t}BuOK in THF to NaOEt in EtOH and the removal of the acid-catalyzed dehydration step, including a solvent swap, improved the process further. Although it is possible to conduct the first five of seven steps telescoped, we chose to isolate the intermediate **5** after the third step to get a robust crystallisation in the resolution. By performing the hydrogenation and the resolution without isolating the racemic acid **6**, the batch cycle time was reduced by 60%. Key figures are shown in Table 2.

Experimental Section

General. Ethyl chloroacetate (99%), 4-methoxybenzaldehyde (99%), and NaOEt (21% solution in EtOH) and NaOEt (96%) were purchased from Lancaster. Diethyl carbonate (99%) was purchased from Janssen, (*S*)-1-(1-naphthyl)ethylamine (99.5%) from Arran Chemicals Ltd., and 1-octhanethiol (98%) from Aldrich. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with Me_4Si as internal standard. Mass spectra were obtained using a Varian Micromass ZQ or a Hewlett-Packard 6890 GC with a 5973 mass selective detector. Melting points were measured on a Buchi B-540 apparatus. The HPLC analyses were performed using a Waters 2690/2487 system with a Waters Symmetry C_8, 3.9 mm × 150 mm, 5 μm column. For analysis of enantiomeric purity a Chiral-AGP 5 μm, 100 mm × 4.0 mm column was used. Flash column chromatography was performed using Merck silica gel 60 (0.040−0.063 mm). Preparative HPLC was performed using a YMC ODS-A 250 mm × 20 mm, 5 μm column. X-ray diffraction intensities were collected at room temperature with graphite monochromatized Mo Kα radiation on a KappaCCD single-crystal diffractometer equipped with a κ-axis goniometer and an image CCD area detector. Elemental analyses were carried out by Micro Kemi AB, S 752 28 Uppsala, Sweden.

(*Z*)-2-Ethoxy-3-(4-methoxyphenyl)propenoic Acid (5). Ethyl chloroacetate (89 mL, 842 mmol) and EtOH (60 mL) were charged to a 1-L reactor and cooled to 12 °C. A solution of NaOEt in EtOH (21% w/w, 330 mL, 842 mmol) was added during 40 min at 12−16 °C. After completed addition the reaction mixture was warmed to 25 °C, where it was stirred for 1 h and then cooled to 10 °C. Solid NaOEt (66.5 g, 977 mmol) was added portionwise to the slurry over 1 h at 10−14 °C. Additional EtOH (20 mL) was added followed by diethyl carbonate (62 mL, 512 mmol). The slurry was cooled to 5 °C and 4-methoxybenzaldehyde (44.6 mL, 359 mmol) was charged over 2 h at 5−6 °C using a Dosimat pump. After completed addition the temperature was raised to 35 °C, and the reaction mixture was stirred for 15 h. The slurry was cooled to 15 °C, and H_2O (75 mL) was added. A NaOH solution (10 M, 110 mL, 1.10 mol) was added at 15−19 °C, and the slurry (pH 14) was thereafter stirred at 20 °C for 2.5 h. The mixture was diluted with H_2O (120 mL), and about 540 mL of EtOH/H_2O was distilled off under reduced

pressure, at a jacket temperature of 45 °C. The thick slurry was again diluted with H_2O (210 mL) and cooled to 10−13 °C. HCl (10 M, 215 mL, 2.15 mol) was charged to the thick gel, over 50 min at 12−14 °C, initially causing foaming. The slurry was stirred for 2 h prior to filtration. The filter cake was washed with H_2O (4 × 340 mL), dried in vacuo at 55 °C to give 65.9 g of the title compound (80% yield, corrected for 96.8% purity by LC) as small, brownish granules.

An analytical sample of the solution was evaporated to dryness and crystallised from toluene (2 volumes) giving the pure acid **5** (99.5%, LC). Light-yellow crystals: mp 113−115 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.9 Hz, 2 H), 7.14 (s, 1 H), 6.92 (d, J = 8.9 Hz, 2 H), 4.02 (q, J = 7.1 Hz, 2 H), 3.85 (s, 3 H), 1.39 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 160.5, 141.8, 132.1, 126.6, 126.0, 114.0, 67.7, 55.3, 15.5; MS (ESI$^-$ 30 V) m/z 221 (M − 1)$^-$. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4. Found: C, 64.5; H, 6.2.

2-Ethoxy-3-(4-methoxyphenyl)propanoic Acid (6). Isopropyl acetate (540 mL, 10 vol) and **5** (54.2 g, 244 mmol) were mixed in a 1-L flask and stirred until a clear solution was obtained (some heating was required). A 1-L Buchi steel autoclave was flushed with N_2 and Pd/C (13.6 g, 5% w/w to C, containing 60% H_2O, Johnson-Matthey Type 87 L) was added followed by the solution of **5**. The acid was hydrogenated at 22−25 °C, 4 bar and 1000 rpm for 3 h. Analysis by HPLC showed complete conversion of **5** to **6**. The catalyst was filtered off (Supra 1000) and the solution was concentrated under vacuum. To ensure taking dry material into the next step additional ^{i}PrOAc (300 mL) was added, and the solution was azeo-dried, adjusting the total volume to 590 mL (10 vol ^{i}PrOAc to **6**). The solution of **6** was used directly in the next step. An analytical sample of the solution was evaporated to dryness and recrystallised from toluene/isooctane (2 + 8 volumes) giving white crystals: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 4.05 (dd, J = 4.3 and 7.7 Hz, 1 H), 3.79 (s, 3 H), 3.62 and 3.59 (2 q, J = 7.0 Hz, 1 H), 3.46 and 3.44 (2 q, J = 7.0, 1 H), 3.08 (dd, J = 4.2 and 14.2 Hz, 1 H), 2.96 (dd, J = 7.7 and 14.2 Hz, 1 H), 1.18 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.0, 158.5, 130.5, 128.5, 113.8, 79.8, 66.9, 55.2, 37.7, 15.1; MS (ESI$^-$ 30 V)$^-$ m/z 223 (M-1)$^-$. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.4; H, 7.2.

(2*S*)-Ethoxy-3-(4-methoxyphenyl)propanoic Acid (*S*)-1-(1-Naphthyl)ethylamine Salt (7a). A solution of **5** (54 g, 240 mmol) in ^{i}PrOAc (540 mL, 10 vol) was heated to 45 °C and (*S*)-1-(1-naphthyl)ethylamine (23 mL, 142 mmol) was added at 45−47 °C over 10 min. The solution was seeded with **7a** (0.3 g) and cool-ramped (20 °C/h) to −15 °C. The crystallisation started within 2 min after seeding. The slurry was stirred at −15 °C for 13 h and filtered on a glass filter (P3). The filter cake was rinsed with chilled ^{i}PrOAc (60 mL). Drying under vacuum (40 °C) gave 41.0 g of crystalline material. Isopropyl acetate (820 mL, 20 vol) and the salt (41.0 g) were charged to a 1-L reactor and heated to 84 °C. The solution was cool-ramped (20 °C/h) to −1 °C. Seeding with **7a** at 80 °C resulted in crystallisation within 5 min. The slurry was stirred at −1 °C for 2 h before filtration on glass filter (P3). The filter cake was rinsed with chilled ^{i}PrOAc (60 mL). Drying under vacuum (40 °C) afforded 35.2 g of **7a** (38% yield from **5**, 76% of the *S*-enatiomer **7b** by chiral HPLC) as white needles: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1 H), 7.87 (d, J = 8.8 Hz, 1 H), 7.81−7.77 (m, 2 H), 7.58−7.45 (m, 3 H), 6.89 (d, J = 8.6 Hz, 2 H), 6.64 (d, J = 8.6 Hz, 2 H), 5.80 (br, 3 H), 5.16 (q, J = 6.6 Hz, 1 H), 3.68 (s, 3 H), 3.65 (dd, J = 3.6 and 8.9 Hz, 1 H), 3.40 and 3.38 (2 q, J = 7.0 Hz, 1 H), 3.05 and 3.03 (2 q, J = 7.0, 1 H), 2.77 (dd, J = 3.6 and 14.1 Hz, 1 H), 2.57 (dd, J = 8.9 and 14.1 Hz, 1 H), 1.69 (d, J = 6.7 Hz, 3 H), 0.97 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.9, 157.8, 137.2, 133.8, 130.9, 130.2, 130.1, 129.1, 128.5, 126.7, 125.9, 125.7, 122.5, 122.2, 113.2, 82.1, 65.6, 55.1, 46.6, 38.5, 22.4, 15.1; Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.9; H, 7.4; N, 3.5. Found: C, 72.3; H, 7.4; N, 3.6. Chiral HPLC showed 97% ee of the *S*-enantiomer **7b**.

(2*S*)-Ethoxy-3-(4-hydroxyphenyl)propanoic Acid (8). The salt **7a** (35.0 g, 88 mmol) was suspended in toluene (98 mL), and the mixture was then treated with NaOH (3.89 g, 97 mmol) in H_2O (98 mL). The upper layer containing the chiral amine was separated off. The aqueous layer was washed with toluene (2 × 98 mL) and was acidified to pH 1 with HCl (10.5 mL, 32%, 106 mmol). The acid **7b** was extracted with EtOAc (2 × 98 mL). The combined EtOAc layer was washed with H_2O (98 mL). The solvent was evaporated, and NMP (35 mL) was added to the residue. Remaining EtOAc was coevaporated with NMP (35 mL) at 90 °C. After distilling off ∼22 mL of the solvent, additional NMP (200 mL) was added to the crude acid. NaOH (16 g, 400 mmol) and 1-octanethiol (54 mL, 310 mmol) were charged, and the reaction mixture was heated to 125 °C for 19 h with vigorous stirring. Analysis by HPLC showed 95% conversion of **7b** to **8**. The reaction mixture was cooled to 50 °C and H_2O (130 mL) was added to the slurry. By the addition of HCl (51 mL, 32%, 515 mmol) pH was adjusted to ∼2 and the temperature rose to 60 °C. Two layers were formed, the upper layer containing mainly 1-octanethiol and the corresponding methyl ether. The layers were separated, and the aqueous NMP layer was concentrated to 3−4 volumes under vacuum at 90 °C. The residue was partitioned between H_2O (140 mL) and EtOAc (105 mL). The aqueous layer was extracted with EtOAc (105 mL), and the combined organic layer was washed with a NaCl solution (3 × 90 mL, 15%, containing 44 mM HCl). Lacking an assay for **8** the EtOAc solution was concentrated under vacuum at 90 °C to give 19.0 g of brownish oil. HPLC analysis showed 95% of **8**, 4% of the starting material **7b**, and 1% of NMP while ^{1}H NMR showed 88% w/w of **8** and 9% w/w of NMP. *On a large scale the EtOAc solution was used in the following step without evaporating to dryness.*

An analytical sample of the oil was crystallised from toluene to yield white crystals: mp 107−108 °C; ^{1}H NMR (DMSO-d_6) δ 12.57 (s, 1 H), 9.17 (s, 1 H), 6.99 (d, J = 8.5 Hz, 2 H), 6.63 (d, J = 8.4 Hz, 2 H), 3.88 (2 q, J = 5.3 and 7.7 Hz, 1 H), 3.50 and 3.47 (2 q, J = 7.0 Hz, 1 H), 3.29 and

3.26 (2 q, $J = 7.0$ Hz, 1 H), 2.94 (dd, $J = 5.3$ and 7.7 Hz, 1 H), 2.80 (dd, $J = 5.2$ and 14.0 Hz, 1 H), 2.73 (dd, $J = 7.7$ and 14.0 Hz, 1 H), 1.03 (t, $J = 7.0$, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.3, 155.8, 130.1, 127.5, 114.8, 79.4, 64.8, 15.1; MS (ESI$^-$ 30 V) m/z 209 $(M - 1)^-$. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.9; H, 6.7. Found: C, 63.1; H, 6.8.

Ethyl (2*S*)-Ethoxy-3-(4-hydroxyphenyl)propanoate (EEHP). The crude acid **8** (19.0 g, 4.16 mol) was dissolved in EtOAc (28 mL) and EtOH (65 mL, 99.5%). Hydrochloric acid (1 mL, 10 M, 0.48 mol) was added, and the solution was heated to 79−80 °C distilling off a mixture of EtOAc/EtOH/H_2O (48 mL). Over a period of 5 h additional EtOH (3 × 44 mL) was charged and distilled off to remove H_2O formed in the reaction. A sample was analysed by HPLC showing 99% conversion of the acid to EEHP. The brown solution was concentrated to a volume of 44 mL and cooled to 20 °C.

The EEHP solution was slowly charged (2 h) to a solution of $NaHCO_3$ (76 mL, 7% w/w), containing 0.2 g of finely ground EEHP, under vigorous stirring at 0−1 °C. Crystallisation started after a few minutes. After completed addition, the slurry was stirred at 0 °C for 15 min before filtering off the precipitate. The filter cake was washed with H_2O (2 × 38 mL, ∼1 °C) and dried under vacuum at 40 °C giving 17.4 g of crude EEHP.

The crude product was mixed with cyclohexane (105 mL, 6 vol) and EtOAc (4.5 mL, 0.25 vol) and heated to 60 °C. The unclear solution was cool-ramped (10 °C/h) to 5 °C. At 35 °C the solution was seeded and the crystallisation started within 5 min. The slurry was stirred for 1 h at 5 °C before filtering off the product. Washing with cyclohexane (2 × 13 mL, 10 °C) and drying under vacuum, at 35 °C, afforded 13.8 g of EEHP (73% yield, with 99.3% purity by HPLC) as light-brown granules: mp 56−57 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, $J = 8.5$ Hz, 2 H), 6.74 (d, $J = 8.5$ Hz, 2 H), 4.99 (s, 1 H), 4.17 (q, $J = 7.1$ Hz, 2 H), 3.98 (t, $J = 6.7$ Hz, 1 H), 3.62 and 3.59 (2 q, $J = 7.0$ Hz, 1 H), 3.37 and 3.35 (2 q, $J = 7.0$ Hz, 1 H), 2.95 (d, $J = 6.6$ Hz, 2 H), 1.23 (t, $J = 7.2$ Hz, 3 H), 1.17 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 154.4, 130.6, 129.1, 115.1, 80.4, 66.2, 60.9, 38.5, 15.1, 14.2; MS (ESI$^-$ 30 V)$^-$ m/z 237 $(M - 1)^-$. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.5; H, 7.6. Found: C, 65.6; H, 7.7. Chiral HPLC showed 99.8% ee.

Spectral Data for the Intermediates 2 and 4 and the Byproduct 3 Isolated from the Condensation Reaction prior to the Hydrolysis. *Ethyl 2-ethoxy-3-hydroxy-3-(4-methoxyphenyl)propanoate (**2**).* The compound was purified by flash column chromatography on silica using toluene/EtOAc (10:1) as the eluent. Colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.31 and 7.29 (2 d, $J = 8.7$ Hz, 2 H), 6.87 (d, $J = 8.7$ Hz, 2 H), 4.93 and 4.82 (2 m, 1 H), 4.12 and 4.06 (2 q, $J = 7.1$ Hz, 2 H), 4.00 and 3.91 (2 d, $J = 6.0$ and 6.2 Hz, 1 H), 3.80 (s, 3 H), 3.70−3.62 (m, 1 H), 3.50−3.37 (2 m, 1 H), 3.00 and 2.90 (2 d, $J = 4.0$ and 5.0 Hz, 1 H), 1.23, 1.17 and 1.10 (3 t, $J = 7.0$ Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.6, 159.5, 159.3, 131.8, 131.0, 129.0, 128.6, 128.5, 128.1, 127.9, 113.7; 113.6, 113.5, 85.3, 83.9, 82.7, 81.8, 79.2, 74.5, 74.4, 73.7, 66.9, 66.8, 66.5, 60.0, 55.3, 55.2, 27.8, 15.1, 15.0, 14.1, 14.0; MS (APCI) m/z 286 $(M + NH_4)^+$, 250 $(M - 18)$.

*2-Ethoxy-3-hydroxy-3-(4-methoxyphenyl)propanoic Acid (**3**).* The compound was purified by preparative LC using a YMC ODS-A column and CH_3CN/Na-phosphate pH 3.2, 10 mM (45:55) as the eluent and extracted with CH_2Cl_2. Colourless oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, $J = 8.6$ Hz, 2 H), 6.89 (d, $J = 8.8$ Hz, 2 H), 5.00 and 4.95 (2 d, $J = 4.2$ and 5.8 Hz, 1 H), 4.05 and 4.00 (2 d, $J = 5.9$ and 4.3 Hz, 1 H), 3.81 (s, 3 H), 3.69−3.60 (m, 1 H), 3.48−3.37 (m, 1 H), 1.18 and 1.17 (2 t, $J = 7.0$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.5, 173.1, 159.6, 159.5, 131.3, 130.9, 128.1, 127.7, 113.8, 113.7, 82.9, 82.3, 68.0, 67.8, 15.0; MS (ESI$^-$ 30 V) m/z 239 $(M - 1)^-$.

*Ethyl 2-Ethoxy-3-(4-methoxyphenyl)-2-propenoate (**4**).* The compound was purified by flash column chromatography twice on silica using toluene/EtOAc (10:1 and 20:1) as the eluents. Yellowish oil; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, $J = 8.9$ Hz, 2 H), 6.97 (s, 1 H), 6.90 (d, $J = 8.8$ Hz, 2H), 4.29 (q, $J = 7.2$ Hz, 2 H), 3.98 (q, $J = 7.1$ Hz, 2 H), 3.83 (s, 3 H), 1.37 (t, $J = 7.1$ Hz, 3 H), 1.36 (t, $J = 7.1$, Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.0, 160.0, 143.0, 131.7, 126.4, 113.9, 67.5, 61.0, 55.3, 15.6, 14.3; MS (EI, 70 eV) m/z 250 (M^+) 193, 148, 137, 121, 120.

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