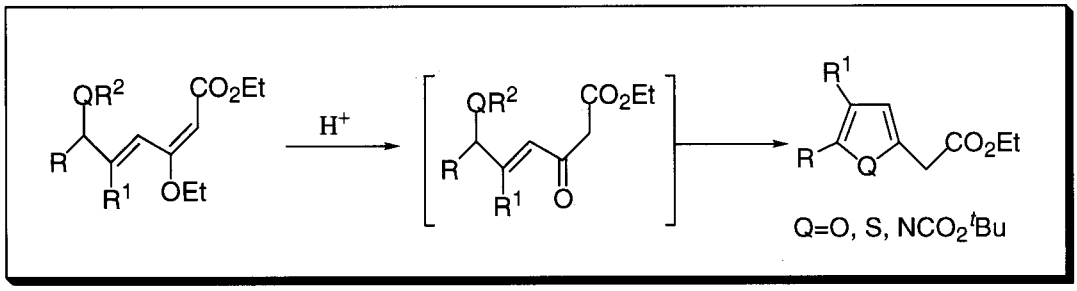
A FACILE SYNTHESIS OF 5-SUBSTITUTED 2-FURYL-, 2-THIENYL- AND 2-PYRROLYLACETATES BY CYCLODEHYDRATION OF γ-FUNCTIONALIZED α,β-UNSATURATED KETONES

Tomikazu Kawano, Toru Ogawa, Saiful Md. Islam, and Ikuo Ueda*

The Institute of Scientific and Industrial Research, Osaka University, 8-1, Mihogaoka, Ibaraki, Osaka 567-0047, Japan

Abstract – Synthesis of 5-substituted 2-furyl-, 2-thienyl- and 2-pyrrolyl-acetates is achieved by acid-catalyzed cyclodehydration of γ-hydroxy (γ-acetylthio and γ-amino)-α,β-unsaturated ketones generated from ethyl 6-substituted 3-ethoxy-6-hydroxy-(6-acetylthio and 6-amino)hexa-2,4-dienoates which are easily accessible from α-functionalized carbonyl compounds and Wittig reagents.

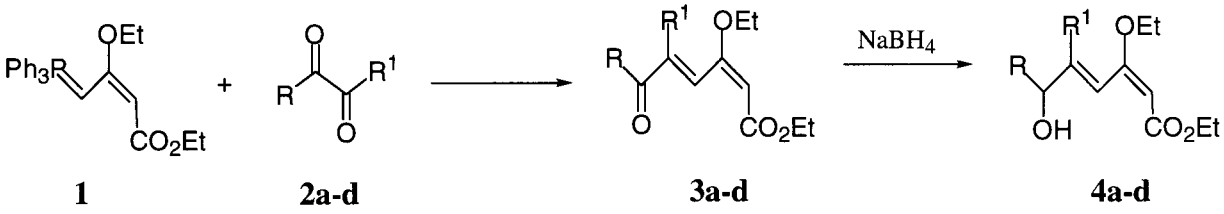
The furan, thiophene and pyrrole rings can be found in many natural products and industrially useful compounds: dyes, pesticides and medical preparations,[1] and these derivatives are of increasing interest in organic synthesis because of the facility of their transformation into a wide range of highly functionalized open-chain and cyclic structures.[2] Therefore, numerous furans, thiophenes and pyrroles have been synthesized by ring-forming processes or electrophilic substitution on the aromatic ring.[3] Also, many methods for the construction of these five-membered ring systems from acyclic precursors have been published.[4] Among them, the acid-catalyzed cyclization of γ-functionalized α,β-unsaturated ketone derivatives is the useful method; the limitation to this method, however, has been the scarce availability of suitably starting γ-functionalized α,β-unsaturated ketones.[5] Recently, we have reported that α-halocarbonyl compounds react regioselectively at the γ-position of (2*E*)-[2-ethox -(ethoxycarbonyl)-2-propenylidene]triphenylphosphorane (**1**) having two nucleophilic centers to give 1,3-cyclopentadienes.[6] On the other hand, the reaction of **1** with glyoxals has been shown to give normal Wittig products, which are easily converted to 3-ethoxy-6-hydroxyhexa-2,4-dienoates bearing a masked "γ-hydroxy-α,β-unsaturated ketone" moiety, indicating that the reaction occurs selectively at the α-position.[7] In a preliminary paper we have reported the synthesis of ethyl 6-substituted 3-ethoxy-6-hydroxyhexa-2,4-dienoates (**4**) and their conversion into 5-substituted 2-furylacetates (**12**).[8] In this paper, we disclose a full account of the synthesis of 2-furyl-, 2-thienyl- and 2-pyrrolylacetates *via* γ-hydroxy (γ-acetylthio and γ-amino)-α,β-unsaturated ketones generated from ethyl 6-substituted 3-ethoxy-6-hydroxy-(6-acetylthio and 6-amino)hexa-2,4-dienoates under acidic conditions.



Scheme 1 shows synthetic routes (A and B) for the preparation of ethyl 6-substituted 3-ethoxy-6-hydroxyhexa-2,4-dienoates (**4**).

Scheme 1.

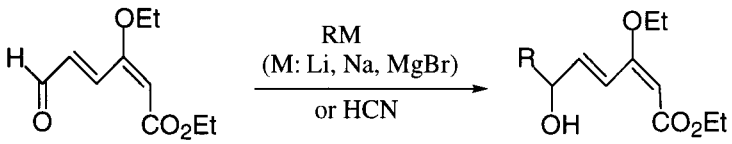
Route A



1 **2a-d** **3a-d** **4a-d**

a: R=R^1=H, **b**: R=Me, R^1=H, **c**: R=C$_6$H$_4$OMe-4 R^1=H, **d**: R=R^1=Me

Route B



3a **4e-i**

e: R=Et, **f**: R=CH$_2$NO$_2$ **g**: R= C≡CC$_6$H$_5$

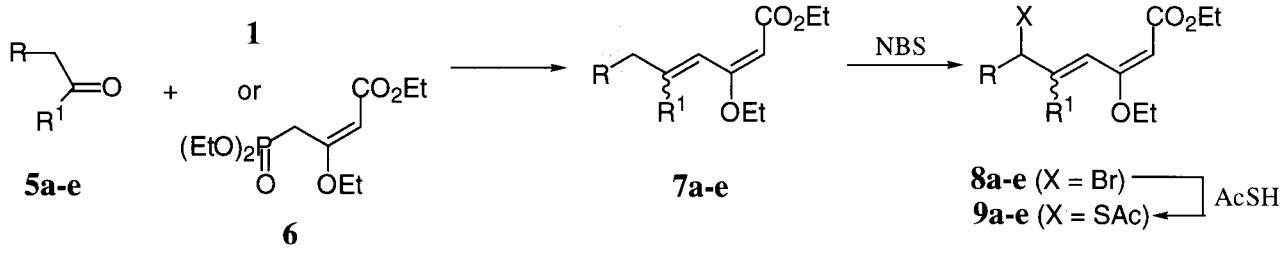
h: R=  , **i** : R=CN

Ethyl 6-substituted 3-ethoxy-6-oxohexa-2,4-dienoates (**3**), which are precursors for the preparation of **4**, were synthesized by the reaction of **1**[6] with glyoxals (**2a-c**) or α-diketone (**2d**) in considerably good yields. Compounds (**3**), which were synthesized by this method, were obtained as a mixture of ethyl (2*E*,4*E*)-3-ethoxy-6-oxohexa-2,4-dienoates and their (2*E*,4*Z*)-isomers in the ratio of about 10 to 1. Both isomers were separated easily by column chromatography on silica gel, and the conversion of the (2*E*,4*Z*)-isomer to the (2*E*,4*E*)-isomer was achieved in good yields by treating the mixture with saturated hydrochloric acid in ether. Thus, the diastereomixture with (2*E*,4*E*)- and (2*E*,4*Z*)-configurations was converted into the (2*E*,4*E*)-isomer on treatment with the acid, which was used for the following experiments. Compounds (**4**) were prepared by two methods; one involved sodium borohydride reduction of **3a-d**, and the other involved reaction of **3a** with nucleophiles. When **3a-d** were allowed to react with sodium borohydride in methanol at 0 ℃, **4a-d** were obtained in high yields. Reaction of **3a** with nucleophiles such as ethyl- and

phenylethynylmagnesium bromides, sodium salt of nitromethane, and 2-lithio-1,3-dithiane in THF gave the corresponding 2,4-hexadienoates (**4e-h**) in good yields. Reaction of **3a** with potassium cyanide in the presence of a catalytic amount of acetic acid gave **4i** in 75% yield.

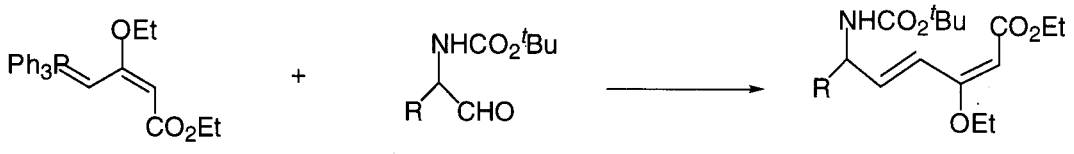
Ethyl 6-acetylthio-3-ethoxyhexa-2,4-dienoate derivatives (**9**) were prepared by the method shown in Scheme 2. Reaction of aldehydes (**5a-b**) with **1** gave normal Wittig products (**7a-b**) as only (2*E*,4*E*)-isomers in 83% and 71% yield, respectively. The Wittig reaction of **1** with ketones (**5c-e**) resulted in diminished yield due to the lower reactivity of the phosphorane for the ketones. This problem was solved by the use of phosphonate (**6**). Sodium salt of **6**, which was prepared *in situ* by reaction with sodium hydride in THF, was allowed to react with ketones (**5c-e**) to give **7c-e** as a (2:1) diastereomixture with (2*E*,4*E*)- and (2*E*,4*Z*)-configurations in 70 to 88% yields, respectively. As chromatographic separation of these isomers was unsuccessful, these diastereomixtures were used for the following experiments without separation of each isomer. Ethyl 2,4-hexadienoates (**7**) were allowed to react with *N*-bromosuccinimide (NBS) in carbon tetrachloride under reflux to give 6-bromo derivatives (**8**), which were used for the next step without purification because of the instability of these compounds. Treatment of **8** with thiolacetic acid in the presence of triethylamine in acetonitrile at 0 °C afforded the desired products (**9**) in moderate to good yields.

Scheme 2.



a: R=Me, R^1=H, **b**: R=Bu, R^1=H, **c**: R=H, R^1=C_6H_4I-4, **d**: R=H, R^1=C_6H_4OMe-4, **e**: R=H, R^1=$C_6H_4NO_2$-4

Scheme 3.

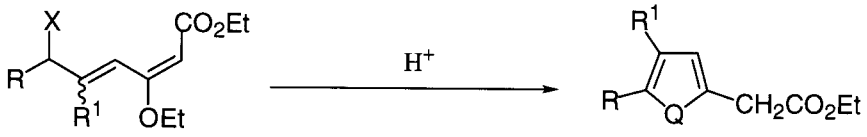


a: R=(*S*)-$C_6H_5CH_2$, **b**: R=(*S*)-^{i}Pr, **c**: R=C_6H_5

Ethyl (2*E*,4*E*)-(S)-6-amino-3-ethoxyhexa-2,4-dienoate derivatives (**11**) were synthesized by the Wittig reaction of α-aminoacetaldehydes (**10**), which were prepared by the Dess-Martin oxidation of the corresponding amino alcohols,[9] with **1** in THF at room temperature in good yields (Scheme 3).

Cyclodehydration of 3-ethoxyhexa-2,4-dienoates (**4**, **9** and **11**) to 2-furyl-, 2-thienyl- and 2-pyrrolylacetates (**12**, **13** and **14**) was carried out under various acidic conditions (Scheme 4). Tables 1a-c show results on studies of cyclodehydration of **4f**, **9a** and **11a** as typical examples. First, we examined cyclodehydration of **4f** to the furan ring (Table 1a). When **4f** was allowed to react with a (1:5; v/v) mixture of 3*N*-acetic acid in water and THF at room temperature, unchanged **4f** was recovered in a quantitative yield. Treatment with a (1:5; v/v) mixture of 3*N*-hydrochloric acid and THF at room temperature gave **12f** in 45% yield along with unchanged **4f**.

Scheme 4.



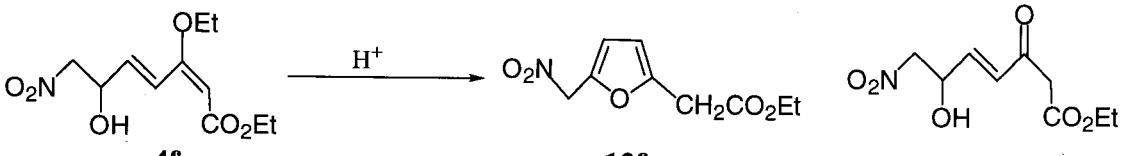
4: X=OH
9: X=SAc
11: X=NHCO$_2$^{t}Bu

12a-i: Q=O
a: R=R^1=H, **b**: R=Me, R^1=H, **c**: R=C$_6$H$_4$OMe-4, R^1=H,
d: R=R^1=Me, **e**: R=Et, R^1=H, **f**: R=CH$_2$NO$_2$, R^1=H,
g: R= C≡CC$_6$H$_5$, R^1=H, R^1=H,
h: R=  , R^1=H, **i** : R=CN, R^1=H

13a-e: Q=S
a: R=CH$_3$, R^1=H, **b**: R=C$_4$H$_7$, R^1=H, **c**: R=H, R^1=C$_6$H$_4$I-4,
d: R=H, R^1=C$_6$H$_4$OCH$_3$-4, **e**: R=H, R^1=C$_6$H$_4$NO$_2$-4

14a-c: Q=NCO$_2$^{t}Bu
a: R=C$_6$H$_5$CH$_2$, R^1=H, **b**: R=(*S*)-^{i}Pr, R^1=H, **c**: R=C$_6$H$_5$, R^1=H

Table 1a. Cyclodehydration of **4f** into **12f**



4f **12f** **15**

Entry	Conditions: Reagents, Solvent and Temperature	Time	Product (yield %)
1	3*N*-AcOH / THF (1:5; v/v), rt	48 h	**12f** (0)[a]
2	3*N*-HCl / THF (1:5; v/v), rt	24 h	**12f** (45)
3	47% HBr / THF (1:5; v/v), rt	10 min	**12f** (94)
4	15% H_2SO_4 in H_2O on SiO_2, CH_2Cl_2, rt	24 h	**15** (60)

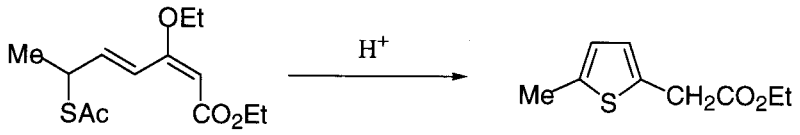
a) Unchanged **4f** was recovered in a quantitative yield.

When **4f** was allowed to react with a (1:5; v/v) mixture of 47% wt hydrobromic acid in water (47%

hydrobromic acid) and THF at room temperature, **12f** was obtained in 94% yield. Interestingly, reaction of **4f** with 15% aqueous sulfuric acid on silica gel[10] in dichloromethane at room temperature for 24 h gave **15** in 60% yield without giving **12f**. When **15** was treated with a (1:5; v/v) mixture of 47% hydrobromic acid and THF at room temperature, **12f** was obtained in a quantitative yield. This finding indicates that the reaction will be initiated with acid-hydrolysis of the enol ether bond at the 3- position, followed by cyclodehydration of the resulting γ-hydroxy-α,β-unsaturated ketone intermediate. Thus, cyclodehydration of **4** under the optimized conditions of a (1:5; v/v) mixture of 47% hydrobromic acid and THF at room temperature gave the corresponding 2-furylacetates (**12**) in 90% to quantitative yields.

Acid-catalyzed cyclodehydration of **9** into the thiophene ring was carried out under the conditions used for the construction of the furan ring (Table 1b). When **9a** was treated with a (1:5; v/v) mixture of 47% hydrobromic acid and THF at room temperature for 24 h, **13a** was obtained in 30% yield along with unchanged **9a** in 40% yield. We then surveyed a number of acids for the cyclodehydration of **9a**, and found that 97% concentrated sulfuric acid supported on silica gel (97% concd H_2SO_4 on silica gel) served as a catalyst.[10] When **9a** was treated with 97% concd H_2SO_4 (1.0 equiv.) on silica gel in dichloromethane at room temperature, **13a** was obtained 84% yield. Thus, **9** underwent smoothly the cyclodehydration under the optimized conditions to afford the desired 2-thienylacetates (**13**) in 82%-89% yields.

Table 1b. Cyclodehydration of **6a** into **13a**



9a **13a**

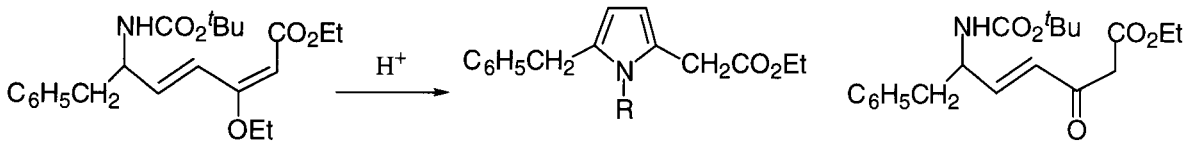
Entry	Conditions: Reagents, Solvent and Temperature	Conditions: Time	Product %Yield
1	47% HBr / THF (1:5; v/v), rt	24 h	30[a]
2	97% concd H_2SO_4 on SiO_2, CH_2Cl_2, rt	15 min	84

a) Unchanged **9a** was recovered in 40% yield.

Cyclodehydration of **11** into the pyrrole ring was attempted using the conditions for the construction of the furan and thiophene rings (Table 1c). When **11a** was reacted with 3*N*-hydrochloric acid in THF for 29 h at room temperature, pyrrole derivative (**14a**) was obtained in 22% yield along with an enol ether-hydrolysis product (**16a**) in 66% yield, indicating the beginning of the acid-hydrolysis of the enol ether group at the 3-position in the initial step. Reaction of **11a** with a stronger acid, 47% hydrobromic acid, in THF for 30 min

at room temperature gave **14a** in 52% yield. Under these conditions the formation of **16a** was not established. Compound (**11a**) was added to 97% concd H_2SO_4 (1.0 equiv.) on silica gel in dichloromethane at 0 °C and the resulting mixture was allowed to stand for 15 min at room temperature under vigorous stirring. After purification by silica gel chromatography with a (6:1) mixture of hexane and ethyl acetate as an eluent, **14a** was obtained in 91% yield. On the other hand, when a mixture of **11a** and 97% concd H_2SO_4 (1.0 equiv.) on silica gel was heated at 40 °C for 9.5 h, **17a** was obtained in a low yield of 36% without isolating **14a** and **16a**. Thus, the reaction of **11** with 97% concd H_2SO_4 (1.0 equiv.) on silica gel in dichloromethane afforded **14** in good yields. The removal of the *tert*-butoxycarbonyl moiety of **14** was achieved on treatment with trifluoroacetic acid (40 equiv.) in benzene at room temperature to give **17** in good yields.

Table 1c. Cyclodehydration of **11a** into **14a**

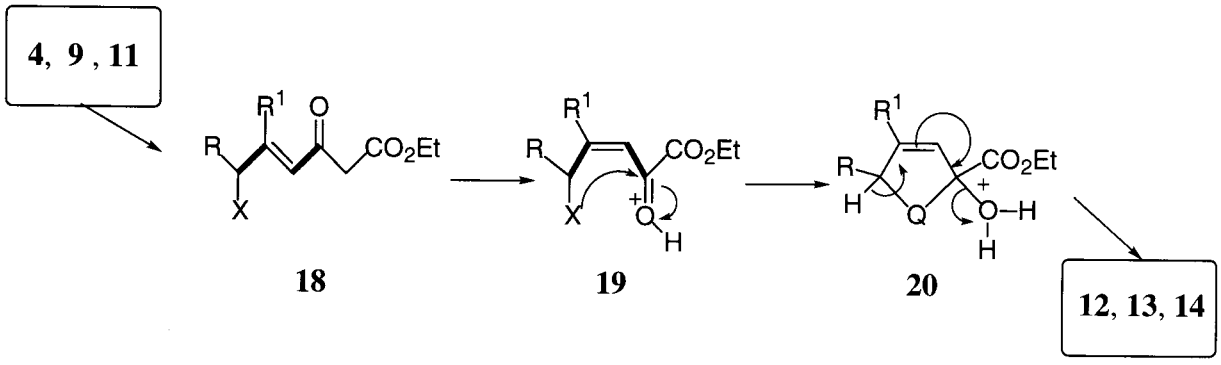


11a **14a**: R=$CO_2{}^t$Bu **17a**: R=H **16a**

Entry	Conditions: Reagents, Solvent and Temperature	Conditions: Time	Product (yield %)		
1	3*N* HClaq, THF, rt	29 h	**14a** (22)	**16a** (66)	
2	47% HBr, THF, rt	0.5 h	**14a** (52)	**16a** (n.d.)	
3	97% concd H_2SO_4 on SiO_2, CH_2Cl_2, 0°C to rt	15 min	**14a** (91)	**16a** (n.d.)	
4	97% concd H_2SO_4 on SiO_2, CH_2Cl_2, 40 °C,	9.5 h	**14a** (n.d.)	**16a** (n.d.)	**17a** (36)

n.d.: not detected

Scheme 5.



The construction of the furan, thiophene and pyrrole rings will proceed *via* the same mechanism (Scheme 5). At the initial step, the ethoxy group at the 3-position of **4**, **9** and **11** is hydrolyzed to give oxo derivative

(**18**) with *trans*-butene configuration. Under the acid conditions, the *trans*-butene (**18**) is transformed to *cis*-butene (**19**) which cyclizes to a dihydro derivative (**20**). Dehydration of **20** gives the final products (**12**, **13** and **14**).

In conclusion, it has been shown that 6-substituted 3-ethoxyhexa-2,4-dienoates bearing a masked "γ-functionalized α,β-unsaturated ketone" moiety undergo efficient cyclodehydration into 5-substituted 2-furyl-, 2-thienyl- and 2-pyrrolylacetates. The starting materials are easily accessible and the reaction takes place to give satisfying yields, representing a promising alternative to other cyclization methods.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on samples dissolved in $CDCl_3$ on JEOL JNM-LA400 (400 MHz), JEOL JNM-EX270 (270 MHz) and Hitachi R-90 (90 MHz) spectrometers, operating at 400 MHz, 270 MHz and 90 MHz for ^1H NMR and at 100 MHz and 67.5 MHz for ^{13}C NMR. Chemical shifts are reported in δ (ppm) relative to TMS (δ = 0) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. IR spectra were recorded on a Hitachi 260-30 infrared spectrophotometer. UV-visible spectra were recorded on a Hitachi U-3210 spectrophotometer. MS spectra were measured on a JEOL JMS-600. Optical rotation was measured on Perkin Elmer 241 polarimeter at 25 °C. All reactions were carried out under argon atmosphere, using dry and freshly distilled solvents under anhydrous conditions unless otherwise specified. Flash column chromatography was performed using Merck 60 silica gel, 230-400 mesh. Commercially available glyoxals (**2a-b**) and α-diketone (**2d**) were used without further purification. Glyoxal (**2c**)[11] and α-aminoacetaldehydes (**10**)[9] were synthesized according to the method described in the literature.

(*E*)-[2-Ethoxy-3-(ethoxycarbonyl)-2-propenylidene]triphenylphosphorane (1). This compound was prepared from (*E*)-[2-ethoxy-3-(ethoxycarbonyl)-2-propenylidene]triphenylphosphonium bromide according to the method described in a previous paper.[6]

Diethyl (2-ethoxy-3-ethoxycarbonyl-2-propenyl)phosphonate (6). A mixture of triethyl phosphite (4.21 g, 25.4 mmol) and ethyl 4-bromo-3-ethoxy-2-butenoate (5.01 g, 21.1 mmol) was heated for 10 min at 110 °C and for additional 3 h at 150 °C. The reaction mixture was evaporated *in vacuo* to give an oily residue. The residue was purified by distillation under reduced pressure to give pure **6**. Yield: 5.89 g (95%) (a colorless oil). bp 134.5-135 °C/0.4 mmHg. ^1H-NMR (270 MHz, $CDCl_3$) δ: 5.12 (d, 1H, J = 3.3 Hz), 4.13 (m, 6H), 3.89 (q, 2H, J = 6.9 Hz), 3.61 (d, 2H, J = 22 Hz), 1.39-1.24 (m, 12H). IR (neat) cm^{-1}: 3000, 1700, 1620. MS: *m/z* 294 (M^+). *Anal.* Calcd for $C_{12}H_{23}O_6P$: C, 48.98; H, 7.88; P, 10.53. Found: C, 48.71; H, 7.81; P, 10.31.

Compound (**3a**) was prepared from **2a** as follows: To a solution of **2a** (3.19 g, 22.0 mmol) in THF (10 mL) was added dropwise a solution of **1** (2.30 g, 5.49 mmol) in THF (40 mL) at rt. After stirring for 2 h at rt, the reaction mixture was evaporated *in vacuo* to give an oily residue, which was dissolved into Et_2O. The ethereal solution was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue, which involved a diastereomixture of **(2*E*,4*E*)-3a** and **(2*E*,4*Z*)-3a**, was purified by column chromatography using 10% AcOEt in hexane as an eluent to give the pure **(2*E*,4*E*)-3a** and **(2*E*,4*Z*)-3a**, respectively.

Ethyl (2*E*,4*E*)- and (2*E*,4*Z*)-3-ethoxy-5-formyl-2,4-pentadienoate (3a). **(2*E*,4*E*)-3a**: Yield: 544 mg (50%) (colorless needles). mp 37.0-39.0 °C (Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.75 (d, 1H, *J* = 7.9 Hz), 8.39 (d, 1H, *J* = 16 Hz), 6.70 (dd, 1H, *J* = 8.1, 16 Hz), 5.33 (s, 1H), 4.20 (q, 2H, *J* = 7.3 Hz), 3.94 (q, 2H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 1.30 (t, 3H, *J* = 7.0 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 190.0, 172.7, 165.3, 151.4, 133.8, 84.5, 60.6, 59.6, 15.2, 13.7. IR (KBr) cm^{-1}: 2830, 1700, 1680, 1580, 1390. MS: *m/z* 198 (M^+). *Anal.* Calcd for $C_{10}H_{14}O_4 \cdot 1/4\ H_2O$: C, 59.24; H, 7.21. Found: C, 59.29; H, 6.97. **(2*E*,4*Z*)-3a**: Yield: 54.3 mg (5%) (colorless needles). mp 93.5-94.5 °C (Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 10.4 (d, 1H, *J* = 7.9 Hz), 7.99 (d, 1H, *J* = 12 Hz), 6.08 (dd, 1H, *J* = 7.9, 12 Hz), 5.34 (s, 1H), 4.18 (q, 2H, *J* = 7.3 Hz), 4.00 (q, 2H, *J* = 7.3 Hz), 1.44 (t, 3H, *J* = 7.3 Hz), 1.30 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 190.0, 172.8, 165.0, 151.4, 133.6, 84.8, 60.9, 59.5, 15.2, 13.9. IR (KBr) cm^{-1}: 2850, 1700, 1680, 1580. MS: *m/z* 198 (M^+). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.80; H, 7.16.

Conversion of [(2*E*,4*Z*)-3a] to [(2*E*,4*E*)-3a]. To a solution of **(2*E*,4*Z*)-3a** (40 mg, 0.202 mmol) in Et_2O (30 mL) was added a solution of saturated HCl gas in Et_2O (5 drops) at rt. After stirring for 15 min at rt, the reaction mixture was evaporated *in vacuo* to give **(2*E*, 4*E*)-3a** (36.0 mg; 89% yield).

Diasteromixtures (**3b-d**), which were prepared from **1** and **2b-d** according to the method for the preparation of the diastereomixtures (**3a**), were converted into the corresponding (2*E*,4*E*)-isomers on treatment with the acid according to the method for the preparation of **(2*E*, 4*E*)-3a**.

Ethyl (2*E*,4*E*)-3-ethoxy-6-oxohepta-2,4-dienoate (3b). Yield: 885 mg (76%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.36 (d, 1H, *J* = 16 Hz), 6.68 (d, 1H, *J* = 16 Hz), 5.29 (s, 1H), 4.20 (q, 2H, *J* = 7.0 Hz), 3.92 (q, 2H, *J* = 7.0 Hz), 2.39 (s, 3H), 1.40 (t, 3H, *J* = 7.0 Hz), 1.31 (t, 3H, *J* = 7.0 Hz), 1.08 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.5, 172.7, 165.4, 141.6, 130.6, 84.5, 60.6, 59.5, 24.9, 15.2, 13.7. IR (neat) cm^{-1}: 3100, 2990, 1710, 1670, 1580. MS: *m/z* 212 (M^+). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.55; H, 7.16. Found: C, 62.22; H, 7.34.

Ethyl (2*E*,4*E*)-3-ethoxy-6-(4-methoxyphenyl)-6-oxohexa-2,4-dienoate (3c). Yield: 1.72 g (76%) (colorless needles). mp 140.0-141.5 °C (Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.39 (d, 1H, *J* = 15 Hz), 7.99-7.96 (m, 2H), 7.47 (d, 1H, *J* = 16 Hz), 6.98-6.95 (m, 2H), 5.31 (s, 1H), 4.19 (q, 2H, *J* = 7.0 Hz), 3.96 (q, 2H, *J* = 7.0 Hz), 3.88 (s, 3H), 1.45 (t, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 1.08 (t, 3H, *J* = 7.3 Hz). IR (KBr) cm^{-1}: 1710, 1620, 1600, 1580. FABMS: *m/z* 305 [(M+H)$^+$]. *Anal.* Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.91; H, 6.66.

Ethyl (2*E*,4*E*)-3-ethoxy-5-methyl-6-oxohepta-2,4-dienoate (3d). Yield: 769 mg (62%) (colorless crystals). mp 81.0-82.0 °C (Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 5.23 (s, 1H), 4.17 (q, 2H, *J* = 7.0 Hz), 3.94 (q, 2H, *J* = 7.0 Hz), 2.45 (s, 3H), 2.02 (d, 3H, *J* = 1.3 Hz), 1.42 (t, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.0 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.5, 172.7, 165.0, 140.0, 134.2, 84.9, 60.6, 59.8, 22.4, 15.2, 13.9, 10.8. IR (KBr) cm^{-1}: 1710, 1670, 1640, 1580. MS: *m/z* 226 (M^+). *Anal.* Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.99; H, 7.81.

Compounds (**4a-e**) were prepared from **3a-e** as follows: To a suspension of **3a** (500 mg, 2.52 mmol) in dry MeOH (5.0 mL) was added portionwise $NaBH_4$ (230 mg, 5.20 mmol) at 0 °C. After stirring for 30 min at rt, the resulting solution was quenched with ice-water, and adjusted to pH 6 with 1*N*-HCl. The resulting mixture was extracted with Et_2O. The extract was washed with brine, and dried over $MgSO_4$. After removal

of the solvent, the residue was purified by column chromatography using 10% AcOEt in hexane as an eluent to give pure **4a**.

Ethyl (2*E*,4*E*)-3-ethoxy-6-hydroxylhexa-2,4-dienoate (4a). Yield: 504 mg (100%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.56 (dt, 1H, *J* = 1.7, 16 Hz), 6.62 (dt, 1H, *J* = 5.3, 16 Hz), 5.06 (s, 1H), 4.32 (m, 2H), 4.15 (q, 2H, *J* = 7.0 Hz), 3.89 (q, 2H, *J* = 6.9 Hz), 1.62 (br, 1H), 1.38 (t, 3H, *J* = 6.9 Hz), 1.28 (t, 3H, *J* = 6.9 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.5, 172.7, 165.0, 140.0, 134.2, 84.9, 60.6, 59.8, 22.4, 15.2, 13.9, 10.8. IR (neat) cm^{-1}: 3550, 1680, 1580. HRMS: Found: *m/z* 200.1067 (Calcd for $C_{10}H_{16}O_4$: 200.1048).

Ethyl (2*E*,4*E*)-3-ethoxy-6-hydroxyhepta-2,4-dienoate (4b). Yield: 539 mg (100%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.53 (d, 1H, *J* = 16 Hz), 6.56 (dd, 1H, *J* = 5.0, 16 Hz), 5.07 (s, 1H), 4.42 (m, 1H), 4.14 (q, 2H, *J* = 7.3 Hz), 3.89 (q, 2H, *J* = 6.9 Hz), 1.59 (br, 1H), 1.43 (m, 9H). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.7, 165.3, 130.5, 128.7, 84.5, 71.8, 60.6, 59.9, 23.1, 15.3, 14.0. IR (neat) cm^{-1}: 3500, 1675, 1580. HRMS: Found: *m/z* 214.1196 (Calcd for $C_{11}H_{18}O_4$: 214.1204).

Ethyl (2*E*,4*E*)-6-(4-methoxyphenyl)-3-ethoxy-6-hydroxyhexa-2,4-dienoate (4c). Yield: 740 mg (96%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.64 (dd, 1H, *J* = 1.3, 16 Hz), 7.32 (d, 2H, *J* = 8.9 Hz), 6.89 (d, 2H, *J* = 8.9 Hz), 6.62 (dd, 1H, *J* = 6.3, 16 Hz), 5.33 (br d, 1H, *J* = 6.3 Hz), 5.07 (s, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.86 (q, 2H, *J* = 6.9 Hz), 3.80 (s, 3H), 2.42 (br, 1H), 1.35 (t, 3H, *J* = 6.9 Hz), 1.28 (t, 3H, *J* = 7.3 Hz). IR (neat) cm^{-1}: 3400, 2990, 1700, 1650, 1580. MS: *m/z* 306 (M^+). *Anal.* Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.61; H, 7.05.

Ethyl (2*E*,4*E*)-3-ethoxy-6-hydroxy-5-methylhepta-2,4-dienoate (4d). Yield: 557 mg (97%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.01 (s, 1H), 5.05 (s, 1H), 4.32 (q, 1H, *J* = 7.0 Hz), 4.12 (q, 2H, *J* = 7.0 Hz), 3.89 (q, 2H, *J* = 7.0 Hz), 2.00 (br, 1H), 1.35 (m, 12H). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.6, 165.1, 139.9, 121.3, 84.5, 76.4, 59.6, 20.6, 15.6, 13.5, 11.0. IR (neat) cm^{-1}: 3450, 2950, 1700, 1650, 1580. HRMS: Found: *m/z* 228.1359 (Calcd for $C_{12}H_{20}O_4$: 228.1360).

Ethyl (2*E*,4*E*)-3-ethoxy-6-hydroxyocta-2,4-dienoate (4e). To a stirred solution of **3a** (644 mg, 3.25 mmol) in THF (15 mL) was added dropwise a solution of ethylmagnesium iodide (3.26 mmol) in THF (10 mL) at rt. After stirring for 3 h at rt, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue obtained was purified by column chromatography using 8% AcOEt in hexane as an eluent to give pure **4e**. Yield: 615 mg (83%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.49 (dd, 1H, *J* = 1.0, 16 Hz), 6.49 (dd, 1H, *J* = 6.6, 16 Hz), 5.06 (s, 1H), 4.21 (m, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.89 (q, 2H, *J* = 6.9 Hz), 1.63 (q, 2H, *J* = 7.3 Hz), 1.39 (t, 3H, *J* = 7.0 Hz), 1.28 (t, 3H, *J* = 6.9 Hz), 0.95 (t, 3H, *J* = 6.9 Hz). IR (neat) cm^{-1}: 3400, 2980, 2230, 1700, 1600. MS: *m/z* 228 (M^+). *Anal.* Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.23; H, 8.98.

Ethyl (2*E*,4*E*)-3-ethoxy-6-hydroxy-7-nitrohepta-2,4-dienoate (4f). This compound was prepared from **3a** and sodium salt of nitromethane under the same conditions as the preparation of **4e** Yield: 699 mg (83%) (colorless crystals). mp 69.0-70.0 °C (*i*-PrOH). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.72 (d, 1H, *J* = 16 Hz), 6.40 (dd, 1H, *J* = 5.9, 16 Hz), 5.12 (s, 1H), 5.06 (m, 1H), 4.48 (m, 2H), 4.16 (q, 2H, *J* = 7.0 Hz), 3.89 (q, 2H, *J* = 6.9 Hz), 2.65 (d, 1H, *J* = 4.6 Hz), 1.38 (t, 3H, *J* = 7.0 Hz), 1.28 (t, 3H, *J* = 7.0 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.7, 165.0, 130.5, 128.7, 114.3, 84.5, 60.6, 59.9, 15.5,

13.7. IR (neat) cm^{-1}: 3480, 1680, 1580, 1550, 1430. MS: *m/z* 259 (M^+). *Anal.* Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.70; H, 6.43; N, 5.15.

Ethyl (2*E*,4*E*)-3-ethoxy-6-hydroxy-8-phenyl-7-ynylocta-2,4-dienoate (4g). This compound was prepared from **3a** and phenylethynylmagnesium bromide under the same conditions as the preparation of **4e**. Yield: 907 mg (93%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.65 (d, 1H, *J* = 16 Hz), 7.35 (s, 5H), 6.54 (dd, 1H, *J* = 6.6, 16 Hz), 5.40 (d, 1H, *J* = 6.6 Hz), 5.07 (s, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.86 (q, 2H, *J* = 6.9 Hz), 2.00 (br, 1H), 1.35 (t, 3H, *J* = 7.3 Hz), 1.28 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.6, 165.2, 132.1, 130.5, 128.7, 128.2, 128.1, 122.3, 89.4, 86.5, 84.5, 66.1, 60.6, 59.6, 15.2, 13.9. IR (neat) cm^{-1}: 3400, 2980, 2230, 1700, 1600. MS: *m/z* 300 (M^+). *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.73.

Ethyl (2*E*,4*E*)-6-(1,3-dithian-2-yl)-3-ethoxy-6-hydroxyhexa-2,4-dienoate (4h). This compound was prepared from **3a** and lithium salt of 1,3-dithiane under the same conditions as the preparation of **4e**. Yield: 641 mg (62%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.68 (d, 1H, *J* = 16 Hz), 6.59 (dd, 1H, *J* = 6.3, 16 Hz), 5.08 (s, 1H), 4.57 (m, 2H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.93 (d, 1H, *J* = 3.6 Hz), 3.89 (q, 2H, *J* = 6.9 Hz), 3.00-2.92 (m, 2H), 2.79-2.73 (m, 2H), 2.06 (m, 1H), 1.70 (br, 1H), 1.39 (t, 3H, *J* = 6.9 Hz), 1.28 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.9, 165.2, 130.5, 128.7, 84.5, 81.4, 60.9, 59.4, 55.8, 36.5 ,32.1, 15.5, 13.6. IR (neat) cm^{-1}: 3550, 1690, 1580, 1550. MS: *m/z* 318 (M^+). *Anal.* Calcd for $C_{14}H_{22}O_4S_2$: C, 52.80; H, 6.96; S, 20.14. Found: C, 52.75; H, 6.96; N, 20.15.

Ethyl (2*E*,4*E*)-7-cyano-3-ethoxy-6-hydroxyhepta-2,4-dienoate (4i). This compound was prepared from **3a** and potassium cyanide in the presence of a catalytic amount of AcOH under the same conditions as the preparation of **4e**. Yield: 775 mg (75%) (a yellow oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.76 (dd, 1H, *J* = 1.3, 16 Hz), 6.49 (dd, 1H, *J* = 5.6, 16 Hz), 5.16 (br, 2H), 4.16 (q, 2H, *J* = 7.3 Hz), 3.91 (q, 2H, *J* = 6.9 Hz), 2.05 (m, 1H), 1.40 (t, 3H, *J* = 6.9 Hz), 1.29 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.4, 165.2, 130.6, 128.9, 114.9, 84.5, 67.2, 60.4, 59.3, 15.5, 13.7. IR (neat) cm^{-1}: 3500, 2240, 1690, 1580. MS: *m/z* 318 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.51; H, 6.72; N, 6.35.

Compounds (**7a** and **7b**) were prepared from **1** and the corresponding carbonyl compounds as follows: To a stirred solution of propanal (400 mg, 6.88 mmol) in THF (5.0 mL) was added dropwise a solution of **1** (2.92 g, 6.98 mmol) in THF (50 mL) at rt. After stirring for 3 h at rt, the mixture was concentrated *in vacuo* to give an oily residue, which was purified by column chromatography using 5% AcOEt in hexane as an eluent to give pure **7a**.

Ethyl (2*E*,4*E*)-3-ethoxyhepta-2,4-dienoate (7a). Yield: 1.13 g (83%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.33 (d, 1H, *J* = 16 Hz), 6.59 (dt, 1H, *J* = 6.6, 16 Hz), 4.98 (s, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.88 (q, 2H, *J* = 6.9 Hz), 2.23 (m, 2H), 1.38 (t, 3H, *J* = 6.9 Hz), 1.28 (t, 3H, *J* = 6.9 Hz), 1.08 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.5, 165.3, 129.5, 125.7, 84.4, 60.3, 59.5, 26.5, 17.4, 15.2, 13.3. IR (neat) cm^{-1}: 3000, 1710, 1660, 1580. MS: *m/z* 198 (M^+). *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.54; H, 9.25.

Ethyl (2*E*,4*E*)-3-ethoxydeca-2,4-dienoate (7b). Yield: 1.17 g (71%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.33 (d, 1H, *J* = 16 Hz), 6.54 (dt, 1H, *J* = 6.9, 16 Hz), 4.98 (s, 1H), 4.14 (q, 2H,

J = 7.0 Hz), 3.87 (q, 2H, J = 7.0 Hz), 2.19 (dd, 2H, J = 1.3, 7.9 Hz), 1.28 (m, 12H), 0.88 (t, 3H, J = 6.9 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.5, 165.2, 133.5, 128.0, 84.2, 60.9, 59.4, 33.4, 32.3, 23.2, 15.2, 14.2, 13.3. IR (neat) cm^{-1}: 2950, 1710, 1650, 1580. MS: *m/z* 240 (M^+). *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.97; H, 10.07. Found: C, 70.04; H, 9.98.

Compounds (**7c-e**), which were obtained as a mixture of two stereoisomers in the ratio of about 2 to 1, were prepared from the corresponding carbonyl compounds and **6** as follows: To a suspension of the sodium salt of **6**, which was prepared from the phosphonate (**6**) (1.34 g, 4.54 mmol) and NaH [(60% dispersion in mineral oil) 181 mg, 4.53 mmol] in THF (10 mL), was dropwise 4-iodoacetophenone **5c** (0.740 g, 3.01 mmol) at rt. After stirring for 2 h at rt, the reaction mixture was poured into saturated aqueous NH_4Cl. The mixture was extracted with AcOEt and the extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography using 5% AcOEt in hexane as an eluent to give pure **7c** as a mixture of two stereoisomers.

Ethyl (2*E*, 4*E*)- and (2*E*, 4*Z*)-3-ethoxy-5-(4'-iodophenyl)hepta-2,4-dienoate (7c). Yield: 1.02 g (88%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) (**Major isomer**) δ: 7.60 (d, 2H, J = 8.3 Hz), 7.00 (s, 1H), 6.91 (d, 2H, J = 8.2 Hz), 4.95 (s, 1H), 4.15 (q, 2H, J = 7.3 Hz), 3.52 (q, 2H, J = 6.9 Hz), 2.17 (s, 3H), 1.28 (t, 3H, J = 7.3 Hz), 0.73 (t, 3H, J = 6.9 Hz). (**Minor isomer**) δ: 7.66 (d, 2H, J = 8.9 Hz), 7.33 (s, 1H), 7.26 (d, 2H, J = 8.6 Hz), 5.13 (s, 1H), 4.14 (q, 2H, J = 6.9 Hz), 3.95 (q, 2H, J = 6.9 Hz), 2.30 (s, 3H), 1.43 (t, 3H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.2, 164.8, 139.2, 137.2, 130.5, 129.5, 128.4, 94.5, 84.2, 60.3, 59.9, 38.3, 22.3, 15.2, 13.9. IR (neat) cm^{-1}: 3000, 1705, 1640, 1600, 1580. MS: *m/z* 386 (M^+). *Anal.* Calcd for $C_{16}H_{19}O_5I$: C, 49.76; H, 4.96; I, 32.86. Found: C, 49.51; H, 4.82; I, 32.79.

Ethyl (2*E*,4*E*)- and (2*E*,4*Z*)-3-ethoxy-5-(4-methoxyphenyl)hepta-2,4-dienoate (7d). Yield: 611 mg (70%) (a colorless oil).^{1}H-NMR (270 MHz, $CDCl_3$) (**Major isomer**) δ: 7.12 (d, 2H, J = 8.9 Hz), 6.90 (s, 1H), 6.81 (d, 2H, J = 8.9 Hz), 4.96 (s, 1H), 4.16 (q, 2H, J = 6.9 Hz), 3.80 (s, 3H), 3.55 (q, 2H, J = 6.9 Hz), 2.19 (s, 3H), 1.29 (t, 3H, J = 6.9 Hz), 0.76 (t, 3H, J = 6.9 Hz). (**Minor isomer**) δ: 7.49 (d, 2H, J = 8.9 Hz), 7.33 (s, 1H), 6.87 (d, 2H, J = 8.9 Hz), 5.10 (s, 1H), 4.15 (q, 2H, J = 7.0 Hz), 3.95 (q, 2H, J = 7.0 Hz), 3.81 (s, 3H), 2.33 (s, 3H), 1.44 (t, 3H, J = 6.9 Hz), 1.27 (t, 3H, J = 6.9 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.3, 165.2, 159.2, 132.3, 130.3, 128.7, 128.1, 114.0, 84.5, 60.6, 59.5, 56.2, 38.6, 22.3, 15.7, 14.0. IR (neat) cm^{-1}: 2950, 1710, 1640, 1580. MS: *m/z* 290 (M^+). *Anal.* Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 69.99; H, 7.51.

Ethyl (2*E*,4*E*)- and (2*E*,4*Z*)-3-ethoxy-5-(4-nitrophenyl)hepta-2,4-dienoate (7e). Yield: 771 mg (84%) (a colorless oil).^{1}H-NMR (270 MHz, $CDCl_3$) (**Major isomer**) δ: 8.15 (d, 2H, J = 8.9 Hz), 7.32 (d, 2H, J = 8.9 Hz), 7.17 (s, 1H), 5.19 (s, 1H), 4.17 (q, 2H, J = 7.0 Hz), 3.51 (q, 2H, J = 6.9 Hz), 2.20 (s, 3H), 1.29 (t, 3H, J = 7.3 Hz), 0.66 (t, 3H, J = 6.9 Hz). (**Minor isomer**) δ: 8.20 (d, 2H, J = 8.9 Hz), 7.66 (d, 2H, J = 8.9 Hz), 7.44 (s, 1H), 5.19 (s, 1H), 4.15 (q, 2H, J = 6.9 Hz), 3.97 (q, 2H, J = 6.9 Hz), 2.35 (s, 3H), 1.45 (t, 3H, J = 6.9 Hz), 1.28 (t, 3H, J = 6.9 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.3, 166.0, 146.0, 145.2, 130.3, 128.8, 128.4, 123.5, 84.2, 60.9, 60.0, 38.9, 22.6, 15.8, 14.0. IR (neat) cm^{-1}: 2970, 1700, 1640, 1600. MS: *m/z* 305 (M^+). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.87; H, 6.00; N, 4.51.

Ethyl 6-bromo-3-ethoxyhepta-2,4-dienoate (8a). To a stirred solution of **7a** (451 mg, 1.53 mmol) in CCl_4 (15 mL) was added NBS (275 mg, 1.55 mmol) and benzoyl peroxide (2 mg) at rt. After stirring for

3 h under reflux, the mixture was cooled at 0 °C and filtered. The filtrate was concentrated *in vacuo* to give **8a** which was used for the next step without purification because of the instability of **8a**.

Compounds (**9a-e**) were prepared from **8a-e**, which were prepared from **7a-e** and NBS, as follows: To a stirred solution of **8a** (0.43 mg, 3.09 mmol) in CH_3CN (30 mL) were added Et_3N (40 mg, 3.06 mmol) and thiolacetic acid (15 mg, 2.30 mmol) in CH_3CN (15 mL) at 0 °C. After being stirred for 3 h at 0 °C, the mixture was poured into ice-water and extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography using 10% AcOEt in hexane as an eluent to give **9a**. Compounds (**9c-e**) prepared by this method were obtained as a diastereomixture mixture with (2*E*,4*E*)- and (2*E*,4*Z*)-configurations in the ratio of about 2:1.

Ethyl (2*E*,4*E*)-6-acetylthio-3-ethoxyhepta-2,4-dienoate (9a). Yield: 526 mg (84%) (a yellow oil).^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.52 (d, 1H, *J* = 16 Hz), 6.47 (dd, 1H, *J* = 5.6, 16 Hz), 5.51 (m, 1H), 5.07 (s, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.88 (q, 2H, *J* = 6.9 Hz), 2.09 (s, 3H), 1.39 (t, 3H, *J* = 6.6 Hz), 1.38 (t, 3H, *J* = 6.9 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.5, 172.7, 165.0, 130.3, 128.7, 84.3, 60.8, 59.9, 40.5, 28.2, 19.9, 15.5, 13.6. IR (neat) cm^{-1}: 3000, 1740, 1700, 1660, 1590. MS: *m/z* 272 (M^+). *Anal.* Calcd for $C_{13}H_{20}O_4S$: C, 57.33; H, 7.40; S, 11.77. Found: C, 57.05; H, 7.41; S, 11.75.

Ethyl (2*E*,4*E*)-6-acetylthio-3-ethoxydeca-2,4-dienoate (9b). Yield: 614 mg (85%) (a colorless oil).^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.51 (d, 1H, *J* = 16 Hz), 6.42 (dd, 1H, *J* = 8.2, 16 Hz), 5.03 (s, 1H), 4.15 (q, 2H, *J* = 7.0 Hz), 3.87 (m, 3H), 2.32 (s, 3H), 1.70 (m, 3H), 1.27 (m, 10H), 0.89 (t, 3H, *J* = 6.9 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.5, 172.7, 165.0, 133.6, 128.2, 84.3, 60.6, 59.2, 43.5, 36.5, 28.3, 19.9, 15.2, 14.5, 13.6. IR (neat) cm^{-1}: 2950, 1740, 1700, 1650, 1580. MS: *m/z* 314 (M^+). *Anal.* Calcd for $C_{16}H_{26}O_4S$: C, 61.11; H, 8.33; S, 10.20. Found: C, 60.91; H, 8.00; S, 10.17.

Ethyl (2*E*,4*E*)- and (2*E*,4*Z*)-6-acetylthio-3-ethoxy-5-(4-iodophenyl)hepta-2,4-dienoate (9c). Yield: 624 mg (59%) (a colorless oil).^{1}H-NMR (270 MHz, $CDCl_3$) (**Major isomer**) δ: 8.20 (d, 2H, *J* = 8.9 Hz), 7.66 (d, 2H, *J* = 8.9 Hz), 7.57 (s, 1H), 5.24 (s, 1H), 4.38 (s, 2H), 4.15 (q, 2H, *J* = 7.0 Hz), 4.00 (q, 2H, *J* = 7.0 Hz), 2.28 (s, 3H), 1.47 (t, 3H, *J* = 7.0 Hz), 1.28 (t, 3H, *J* = 7.0 Hz). (**Minor isomer**) δ: 8.15 (d, 2H, *J* = 8.9 Hz), 7.44 (s, 1H), 7.35 (d, 2H, *J* = 8.9 Hz), 5.01 (s, 1H), 3.97 (m, 3H), 3.49 (q, 2H, *J* = 7.0 Hz), 2.29 (s, 3H), 1.29 (t, 3H, *J* = 7.0 Hz), 0.64 (t, 3H, *J* = 7.0 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.8, 172.6, 165.3, 138.2, 137.5, 127.5, 118.7, 96.3, 84.3, 61.0, 59.4, 41.3, 28.0, 15.4, 13.5. IR (neat) cm^{-1}: 3000, 1740, 1700, 1645, 1580. MS: *m/z* 460 (M^+). *Anal.* Calcd for $C_{18}H_{21}O_4IS$: C, 46.97; H, 4.60; I, 27.57; S, 6.97. Found: C, 46.99; H, 4.48; I, 27.33; S, 6.77.

Ethyl (2*E*,4*E*)- and (2*E*,4*Z*)-6-acetylthio-3-ethoxy-5-(4-methoxyphenyl)hepta-2,4-dienoate (9d). Yield: 553 mg (66%) (a colorless oil).^{1}H-NMR (270 MHz, $CDCl_3$) (**Major isomer**) δ: 7.12 (d, 2H, *J* = 8.9 Hz), 6.90 (s, 1H), 6.81 (d, 2H, *J* = 8.9 Hz), 4.96 (s, 1H), 4.16 (q, 2H, *J* = 7.3 Hz), 3.82 (s, 2H), 3.80 (s, 3H), 3.56 (q, 2H, *J* = 7.0 Hz), 2.19 (s, 3H), 1.29 (t, 3H, *J* = 7.0 Hz), 0.76 (t, 3H, *J* = 7.3 Hz). (**Minor isomer**) δ: 7.49 (d, 2H, *J* = 8.9 Hz), 7.33 (s, 1H), 6.87 (d, 2H, *J* = 8.9 Hz), 5.01 (s, 1H), 4.19 (s, 2H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.96 (q, 2H, *J* = 7.3 Hz), 3.80 (s, 3H), 2.33 (s, 3H), 1.43 (t, 3H, *J* = 7.0 Hz), 1.28 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.5, 172.5, 165.0, 161.2, 138.4, 127.4, 127.0, 118.7, 114.0, 84.6, 60.6, 59.5, 56.0, 41.4, 27.9, 15.2, 13.8. IR (neat) cm^{-1}: 3000, 1740, 1700, 1645, 1580. MS: *m/z* 364 (M^+). *Anal.* Calcd for $C_{19}H_{24}O_5S$: C, 62.62; H, 6.64; S, 8.80. Found: C, 62.53; H, 6.57; S, 8.81.

Ethyl (2*E*,4*E*)- and (2*E*,4*Z*)-6-acetylthio-3-ethoxy-5-(4-nitrophenyl)hepta-2,4-dienoate (9e). Yield: 549 mg (63%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) (**Major isomer**) δ: 7.66 (d, 2H, *J* = 8.9 Hz), 7.47 (s, 1H), 7.24 (d, 2H, *J* = 8.9 Hz), 5.18 (s, 1H), 4.34 (s, 2H), 4.14 (q, 2H, *J* = 6.9 Hz), 3.97 (q, 2H, *J* = 6.9 Hz), 2.27 (s, 3H), 1.45 (t, 3H, *J* = 6.9 Hz), 1.27 (t, 3H, *J* = 7.3 Hz). (**Minor isomer**) δ: 7.60 (d, 2H, *J* = 8.9 Hz), 7.23 (s, 1H), 6.93 (d, 2H, *J* = 8.9 Hz), 4.97 (s, 1H), 3.93 (m, 3H), 3.50 (q, 2H, *J* = 7.3 Hz), 2.29 (s, 3H), 1.26 (t, 3H, *J* = 7.0 Hz), 0.71 (t, 3H, *J* = 7.0 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 196.4, 172.7, 165.1, 147.5, 141.2, 138.1, 127.2, 123.8, 118.6, 84.6, 61.0, 59.7, 41.6, 27.9, 15.5, 13.6. IR (neat) cm^{-1}: 2950, 1740, 1700, 1650, 1580. MS: *m/z* 379 (M^+). *Anal.* Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69; S, 8.45. Found: C, 56.71; H, 5.44; N, 3.65; S, 8.32.

Compounds (**11a-c**) were prepared from **1** and α-aminoacetaldehydes (**10a-c**) as follows: To a stirred solution of **10a** (3.00 g, 12.0 mmol) in dry THF (150 mL) was added dropwise **1** (5.04 g, 12.0 mmol) in dry THF (150 mL) at rt. After being stirred for 24 h at ambient temperature, the mixture was evaporated *in vacuo* to give solids. The solids were purified by column chromatography using 15% AcOEt in hexane as an eluent to give **11a**.

Ethyl (*S*)-(-)-6-(*N*-*tert*-butoxycarbonyl)amino-3-ethoxy-7-phenylhepta-2,4-dienoate (11a). Yield: 4.62 g (99%) (colorless solids). mp 73.4-73.9 °C. (Hexane-Et_2O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44 (dd, 1H, *J* = 1.3, 15.8 Hz), 7.32-7.16 (m, 5H), 6.51 (br d, 1H), 5.03 (s, 1H), 4.75-4.26 (br s, 2H), 4.14 (q, 2H, *J* = 7.2 Hz), 3.86 (q, 2H, *J* = 7.0 Hz), 2.96 (dd, 1H, *J* = 6.0, 13.8 Hz), 2.90-2.74 (br, 1H), 1.44-1.33 (m, 12H), 1.27 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.8, 166.0, 156.5, 140.3, 128.5, 127.9, 127.3, 125.3, 85.2, 70.2, 60.0, 59.9, 55.1, 41.3, 29.0, 16.0, 14.0. IR ($CHCl_3$) cm^{-1}: 3360, 2990, 1700, 1655, 1585. FABMS (NBA): *m/z* 390 [(M+H)$^+$]. *Anal.* Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 68.10; H, 7.85; N, 3.33. $[\alpha]_D$: +2.5° (*c* 1.02, $CHCl_3$).

Ethyl (*S*)-(-)-6-(*N*-*tert*-butoxycarbonyl)amino-3-ethoxy-7-methylocta-2,4-dienoate (11b). Yield: 4.01 g (98%) (a colorless foam). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41 (dd, 1H, *J* = 1.6, 15.7 Hz), 6.50-6.30 (br d, 1H), 5.03 (s, 1H), 4.70-4.55 (br s, 1H), 4.25-4,10 (m, 3H), 3.87 (q, 2H, *J* = 7.0 Hz), 1.95-1.75 (br s, 1H), 1.45 (s, 9H), 1.37 (t, 3H, *J* = 6.9 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.3, 165.9, 156.2, 131.0, 128.5, 84.9, 70.5, 60.3, 59.9, 58.0, 32.1, 28.2, 15.7, 14.0. IR (neat) cm^{-1}: 3350, 2960, 1700, 1660, 1590. *Anal.* Calcd for $C_{18}H_{31}NO_5$ 1/4H_2O: C, 62.49; H, 9.03; N, 4.05. Found: C, 62.75; H, 9.09; N, 3.88. EIMS: *m/z* 341 (M^+). HRMS (EI): Found: *m/z* 341.2179 (Calcd for $C_{18}H_{31}NO_5$: 341.2203). $[\alpha]_D$: +4.6° (*c* 0.97, $CHCl_3$).

(±)-Ethyl 6-(*N*-*tert*-butoxycarbonyl)amino-3-ethoxy-6-phenylhexa-2,4-dienoate (11c). Yield: 3.79 g (84%) (colorless solid). mp 98.5-107.2 °C (Hexane- Et_2O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.54 (dd, 1H, *J* = 1.7, 15.6 Hz), 7.38-7.22 (m, 5H), 6.60 (br d, 1H), 5.60-5.25 (br s, 1H), 5.06 (s, 1H), 5.05-4.90 (br s, 1H), 4.14 (q, 2H, *J* = 7.2 Hz), 3.86 (q, 2H, *J* = 7.0 Hz), 1.44 (s, 9H), 1.35 (t, 3H, *J* = 7.0 Hz), 1.27 (t, 3H, *J* = 7.2 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.4, 165.2, 156.0, 157.4, 142.3, 128.5, 128.1, 127.3, 127.1, 126.5, 84.4, 70.9, 60.6, 59.1, 56.0, 28.9, 15.3, 13.2. IR (KBr) cm^{-1}: 3455, 3360, 3130, 2990, 1700, 1655, 1590. *Anal.* Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.02; H, 7.67; N, 3.56. FABMS (NBA): *m/z* 376 [(M+H)$^+$].

Compounds (**12a-j**) were prepared from **4a-i** as follows: To a stirred solution of **4a** (0.47 g, 2.34 mmol)

in THF (5 mL) was added dropwise 47% hydrobromic acid (1 mL) at rt. After being stirred for 10 min at rt, the reaction mixture was poured into saturated aqueous Na_2CO_3, and extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue obtained was purified by column chromatography using 10% AcOEt in hexane as an eluent to give pure **10a**.

Ethyl 2-furylacetate (12a). Yield: 361 mg (100%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.36 (s, 1H), 6.33 (d, 1H, J = 3.0 Hz), 6.23 (d, 1H, J = 2.7 Hz), 4.18 (q, 2H, J = 7.3 Hz), 3.68 (s, 2H), 1.27 (t, 3H, J = 7.3 Hz).

Ethyl 5-methyl-2-furylacetate (12b). Yield: 394 mg (100%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.08 (d, 1H, J = 3.1 Hz), 5.90 (d, 1H, J = 3.1 Hz), 4.18 (q, 2H, J = 7.0 Hz), 3.72 (s, 2H), 1.27 (t, 3H, J = 7.3 Hz).

Ethyl 5-(4-methoxyphenyl)-2-furylacetate (12c). Yield: 566 mg (93%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.56 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 6.44 (d, 1H, J = 3.3 Hz), 6.27 (d, 1H, J = 3.3 Hz), 4.20 (q, 2H, J = 7.3 Hz), 3.72 (s, 2H), 1.28 (t, 3H, J = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 170.3, 163.5, 152.2, 150.5, 128.0, 126.4, 113.8, 111.9, 100.4, 58.8, 57.0, 35.2, 14.5. IR (neat) cm^{-1}: 3000, 1740. MS: *m/z* 260 (M^+). *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.20; H, 6.35.

Ethyl 4,5-dimethyl-2-furylacetate (12d). Yield: 383 mg (90%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.97 (s, 1H), 4.18 (q, 2H, J = 7.3 Hz), 3.57 (s, 2H), 2.17 (s, 3H), 1.90 (s, 3H), 1.27 (t, 3H, J = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 171.0, 150.6, 146.2, 126.8, 108.3, 59.3, 36.7, 14.0, 8.5, 3.5. IR (neat) cm^{-1}: 3000, 1740, 1030. MS: *m/z* 182 (M^+). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.65; H, 7.56.

Ethyl 5-ethyl-2-furylacetate (12e). Yield: 426 mg (100%) (a pale yellow oil). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 6.08 (d, 1H, J = 3.1 Hz), 5.90 (d, 1H, J = 3.0 Hz), (4.18 (q, 2H, J = 7.0 Hz), 3.72 (s, 2H), 1.27 (t, 3H, J = 7.3 Hz), 1.37 (q, 2H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.0 Hz), 0.99 (t, 3H, J = 6.9 Hz). IR (neat) cm^{-1}: 3050, 1735, 1040. MS: *m/z* 182 (M^+). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.70; H, 7.86.

Ethyl 5-nitromethyl-2-furylacetate (12f). Yield: 469 mg (94%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.55 (d, 1H, J = 3.0 Hz), 6.31 (d, 1H, J = 3.3 Hz), 5.42 (s, 2H), 4.19 (q, 2H, J = 7.3 Hz), 3.70 (s, 2H), 1.27 (t, 3H, J = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 171.2, 150.9, 144.2, 106.4, 104.2, 73.3, 60.4, 35.2, 14.0. IR (neat) cm^{-1}: 2990,1740,1580. MS: *m/z* 213 (M^+). *Anal.* Calcd for $C_9H_{11}NO_5$: C, 50.60; H, 5.20; N, 6.57. Found: C, 50.36; H, 4.90; N, 6.31.

Ethyl 5-phenylethynyl-2-furylacetate (12g). Yield: 559 mg (94%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.43 (m, 5H), 6.60 (d, 1H, J = 3.0 Hz), 6.26 (d, 1H, J = 3.0 Hz), 4.19 (q, 2H, J = 7.3 Hz), 3.68 (s, 2H), 1.30 (t, 3H, J = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 174.2, 150.2, 150.1, 140.2, 133.9, 128.4, 127.9, 120.2, 110.8, 107.5, 88.4, 80.3, 59.0, 35.0, 14.1. IR (neat) cm^{-1}: 2970, 2230, 1740, 1030. MS: *m/z* 254 (M^+). *Anal.* Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.36; H, 5.28.

Ethyl 5-(1,3-dithian-2-yl)-2-furylacetate (12h). Yield: 586 mg (92%) (a colorless oil). ^{1}H-NMR

(270 MHz, $CDCl_3$) δ: 6.34 (d, 1H, *J* = 3.0 Hz), 6.19 (d, 1H, *J* = 3.3 Hz), 5.19 (s, 1H), 4.18 (q, 2H, *J* = 7.3 Hz), 3.67 (s, 2H), 2.94 (m, 4H), 2.10 (m, 2H), 1.26 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 171.5, 150.4, 149.2, 107.3, 106.5, 61.2, 56.7, 55.1, 35.0, 28.9, 14.1. IR (neat) cm^{-1}: 2950, 1740. MS: *m/z* 272 (M^+). *Anal.* Calcd for $C_{12}H_{16}O_3S_2$: C, 52.91; H, 5.92; S, 23.54. Found: C, 52.65; H, 5.75; S, 23.26.

Ethyl 5-cyano-2-furylacetate (12i). Yield: 586 mg (92%) (a colorless oil). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.05 (d, 1H, *J* = 3.5 Hz), 6.40 (d, 1H, *J* = 3.5 Hz), 4.21 (q, 2H, *J* = 7.3 Hz), 3.73 (s, 2H), 1.28 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 170.9, 158.0, 124.3, 122.9, 110.3, 109.6, 60.1, 33.9, 14.2. IR (neat) cm^{-1}: 3000, 2240, 1740. MS: *m/z* 272 (M^+). *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.30; H, 5.08; N, 7.71.

Compounds (**13a-e**) were prepared from **9a-e** as follows: A mixture of 97% concd H_2SO_4 (0.2 mL) and SiO_2 (100 mg) in CH_2Cl_2 (5.0 mL) was stirred for 5 min at 0 °C. To the resulting mixture was added **9a** (35 mg, 0.13 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C. After the reaction mixture was stirred for 20 min at 0 °C, the reaction was quenched with saturated aqueous Na_2CO_3 with care. The resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **13a** as an oil. Purification by flash column chromatography using 11% AcOEt in hexane as an eluent gave pure **13a**.

Ethyl 5-methyl-2-thienylacetate (13a). Yield: 20 mg (84%) (a yellow oil). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 6.70 (d, 1H, *J* = 3.5 Hz), 6.58 (d, 1H, *J* = 3.3 Hz), 4.17 (q, 2H, *J* = 7.0 Hz), 3.72 (s, 2H), 1.27 (t, 3H, J = 7.3 Hz).

Ethyl 5-*n*-butyl-2-thienylacetate (13b). Yield: 24 mg (82%) (a colorless oil). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 6.70 (d, 1H, *J* = 3.5 Hz), 6.56 (d, 1H, *J* = 3.5 Hz), 4.17 (q, 2H, *J* = 7.0 Hz), 3.70 (s, 2H), 2.76 (t, 2H, *J* = 6.9 Hz), 1.40 (m, 7H), 0.92 (m, 3H). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 170.9, 158.0, 124.3, 122.9, 110.3, 109.6, 60.1, 33.9, 14.2. IR (neat) cm^{-1}: 2970, 1740. MS: *m/z* 226 (M^+). *Anal.* Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.17. Found: C, 64.00; H, 8.11; S, 14.03.

Ethyl 4-(4'-iodophenyl)-2-thienylacetate (13c). Yield: 43 mg (89%) (colorless needles). mp 59.5-61.5 °C (C_6H_6-Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.25 (d, 2H, *J* = 8.9 Hz), 7.70 (d, 2H, *J* = 8.9 Hz), 7.52 (d, 1H, *J* = 1.3 Hz), 7.29 (d, 1H, *J* = 1.6 Hz), 4.23 (q, 2H, *J* = 7.0 Hz), 3.83 (s, 2H), 1.31 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 171.9, 140.2, 139.9, 136.4, 134.7, 128.4, 120.9, 99.3, 60.3, 38.6, 14.4. IR (KBr) cm^{-1}: 3100, 1730, 1600, 1510. MS: *m/z* 370 (M^+). *Anal.* Calcd for $C_{14}H_{11}O_2$ IS: C, 45.45; H, 2.99; I, 34.28; S, 8.66. Found: C, 45.31; H, 3.05; I, 34.51; S, 8.61.

Ethyl 4-(4'-methoxyphenyl)-2-thienylacetate (13d). Yield: 31 mg (87%) (colorless needles). mp 81.0-83.0 °C (C_6H_6-Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.49 (d, 2H, *J* = 8.9 Hz), 7.21 (d, 1H, *J* = 1.7 Hz), 7.18 (d, 1H, *J* = 1.8 Hz), 6.92 (d, 2H, *J* = 8.0 Hz), 4.21 (q, 2H, *J* = 7.3 Hz), 3.83 (s, 2H), 1.29 (t, 3H, *J* = 7.3 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 163.4, 140.2, 140., 129.4, 128.6, 122.9, 117.3, 113.8, 61.3, 53.0, 37.9, 14.3. IR (KBr) cm^{-1}: 2970, 1740. MS: *m/z* 274 (M^+). *Anal.* Calcd for $C_{15}H_{14}O_5S$: C, 65.67; H, 5.14; S, 11.69. Found: C, 65.69; H, 5.09; S, 11.78.

Ethyl 4-(4'-nitrophenyl)-2-thienylacetate (13e). Yield: 32 mg (85%) (colorless needles). mp 67.5-

70.0 °C (C_6H_6-Hexane). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.70 (d, 2H, J = 8.6 Hz), 7.32 (d, 1H, J = 1.7 Hz), 7.30 (d, 2H, J = 8.6 Hz), 7.19 (d, 1H, J = 1.7 Hz), 4.20 (q, 2H, J = 6.9 Hz), 3.84 (s, 2H), 1.29 (t, 3H, J = 7.0 Hz). IR (KBr) cm^{-1}: 2970, 1740. MS: *m/z* 289 (M^+).

Compounds (**14a-c**) were prepared from **11a-e** as follows: To a stirred suspension of 97% concd H_2SO_4 (0.1 mL) and SiO_2 (33 mg) in dry CH_2Cl_2 (0.7 mL) was added a solution of **11a** (51 mg, 0.13 mmol) in dry CH_2Cl_2 (0.7 mL) at 0 °C. After the reaction mixture was stirred for 20 min at 0° C, the reaction was quenched with saturated aqueous Na_2CO_3 with care. The resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give **14a** as an oil. Purification by flash column chromatography using 20% AcOEt in hexane as an eluent gave pure **14a**.

Ethyl 1-(*N-tert*-butoxycarbonyl)-5-benzyl-2-pyrrolylacetate (14a). Yield: 41 mg (91%) (a colorless oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27 (dd-like, 2H), 7.18 (dd-like, 1H), 7.11 (d-like, 2H), 5.97 (d, 1H, J = 3.2 Hz), 5.73 (d, 1H, J = 3.2 Hz), 4.18 (s, 2H), 4.15 (q, 2H, J = 7.2 Hz), 3.85 (s, 2H), 1.39 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 163.0, 137.9, 131.9, 129.9, 129.9, 128.4, 124.0, 109.2, 108.6, 73.0, 60.9, 28.2, 28.0, 25.0, 15.0. IR (neat) cm^{-1}: 2950, 1740. *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.94; H, 7.28; N, 3.98. FABMS (NBA): *m/z* 344 [$(M+H)^+$].

Ethyl 1-(*N-tert*-butoxycarbonyl)-5-(1-methylethyl)-2-pyrrolylacetate (14b). Yield: 31 mg (82%) (a colorless oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.94 (d, 1H, J = 3.4 Hz), 5.91 (dd, 1H, J = 0.7, 3.4 Hz), 4.14 (q, 2H, J = 7.1 Hz), 3.82 (s, 2H), 3.48 (sept, 1H, J = 6.7 Hz), 1.57 (s, 9H), 1.25 (t, 3H, J = 7.1 Hz), 1.21 (d, 6H, J = 6.6 Hz). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 172.0, 161.2, 130.8, 130. 2, 109.5, 108.5, 71.4, 59.0, 29.0 28.0, 26.3, 25.1, 14.0. IR (neat) cm^{-1}: 2960, 1740. *Anal.* Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.88; H, 8.33; N, 4.63. FABMS (NBA): *m/z* 296 [$(M+H)^+$].

Ethyl 1-(*N-tert*-butoxycarbonyl)-5-phenyl-2-pyrrolylacetate (14c). Yield: 38 mg (90%) (a colorless oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.26 (m, 5H), 6.11 (d, 1H, J = 2.9 Hz), 6.09 (d, 1H, J = 3.2 Hz), 4.17 (q, 2H, J = 7.2 Hz), 3.91 (s, 2H), 1.27 (t, 3H, J = 7.2 Hz), 1.20 (s, 9H). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 171.2, 160.3, 136.6, 131.2, 130.5, 129.2, 128.9, 127.2, 119.4, 108.7, 108.4, 71.1, 59.3, 28.7, 27.2, 13.9. IR (neat) cm^{-1}: 2990, 1740. *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.02; H, 7.18; N, 4.00. FABMS (NBA): *m/z* 330 [$(M+H)^+$].

Compounds (**17a-c**) were prepared from **14a-c** as follows: To a stirred solution of **14a** (195 mg, 0.57 mmol) in dry C_6H_6 (0.6 mL) was added TFA (1.75 mL, 22.7 mmol) at rt. After being stirred for 20 min at ambient temperature, the mixture was poured into saturated aqueous Na_2CO_3 with care at 0 °C. The pH of the mixture was adjusted to pH 7. The resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. The residue was purified by flash column chromatography using 9% AcOEt in hexane as an eluent to give pure **17a**.

Ethyl 5-benzyl-2-pyrrolylacetate (17a). Yield: 104 mg (75%) (a colorless oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.54-8.00 (br s, 1H), 7.33-7.16 (m, 5H), 5.90 (dd, 1H, J = 2.9, 2.9 Hz), 5.85 (dd, 1H, J = 2.9, 2.9 Hz), 4.12 (q, 2H, J = 7.2 Hz), 3.93 (s, 2H), 3.57 (s, 2H), 1.22 (t, 3H, J = 7.2 Hz). IR (neat) cm^{-1}: 3370, 2980, 1725, 1590. EIMS: *m/z* 243 (M^+). HRMS (EI): Found: *m/z* 243.1271 (Calcd for $C_{15}H_{17}NO_2$: 243.1260).

Ethyl 5-(1-methylethyl)-2-pyrrolylacetate (17b). Yield: 93 mg (84%) (a colorless oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.70-8.16 (br s, 1H), 5.89 (dd, 1H, *J* = 2.6, 2.6 Hz), 5.81 (dd, 1H, *J* = 2.9, 2.9 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 3.63 (s, 2H), 2.90 (sept, 1H, *J* = 7.0 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 1.25 (d, 6H, *J* = 6.8 Hz). IR (neat) cm^{-1}: 3390, 2960, 1730, 1595. EIMS: *m/z* 195 (M^+). HRMS (EI): Found: *m/z* 195.1234 (Calcd for $C_{11}H_{17}NO_2$: 195.1260).

Ethyl 5-phenyl-2-pyrrolylacetate (17c). Yield: 104 mg (80%) (colorless needles). mp 53.5-54.5 °C (Hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.20-8.76 (br s, 1H), 7.47 (dd, 2H, *J* = 1.0, 8.3 Hz), 7.35 (dd, 2H, *J* = 7.8, 7.8 Hz), 7.19 (dd, 1H, *J* = 7.3, 7.3 Hz), 6.42 (dd, 1H, *J* = 3.0, 3.0 Hz), 6.07 (dd, 1H, *J* = 2.9, 2.9 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 3.71 (s, 2H), 1.30 (t, 3H, *J* = 7.2 Hz). IR (KBr) cm^{-1}: 3355, 2980, 1720, 1610, 1590, 1510. *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.33; H, 6.53; N, 6.09. FABMS (NBA): *m/z* 230 [$(M+H)^+$].

ACKNOWLEDGMENTS

The authors are indebted to the Material Analysis Center of ISIR for the elemental analyses.

REFERENCE

1. (a) J. R. Carson, D. N. Mckinstry, and S. Wong, *J. Med. Chem.*, 1971, **14**, 646. (b) G. Tsuchihashi and K. Ogura, *Chem. Abstr.*, 1976, **85**, 159866p.
2. (a) A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, 'Comprehensive Heterocyclic Chemistry II,' Pergammon Press, Oxford, 1996. (b) A. R. Katritzky and C. W. Rees, 'Comprehensive Heterocyclic Chemistry,' Pergammon Press, Oxford, 1984.
3. (a) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795. (b) Y. Tamura, H. D. Choi, H. Shindo, and H. Ishibashi, *Chem. Pharm. Bull.*, 1982, **30**, 915.
4. (a) T. L. Gilchrist, *Contemp. Org. Synth.*, 1994, **1**, 205. (b) Y-C. Kuo, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, 1983, **31**, 883.
5. (a) M. L. Wolfrom, E. G. Wallace, and E. A. Metcalf, *J. Am. Chem. Soc.*, 1942, **64**, 265. (b) N. Clauson-Kaas, *Acta Chem. Scand.*, 1961, **15**, 1177. (c) M. S. F. Lie Ken Jie and C. H. Lam, *Chem. Phys. Lipids*, 1977, **20**, 1. (d) R. J. F. Linderman, E. A. Jamois, and S. D. Tennyson, *J. Org, Chem.*, 1994, **59**, 957.
6. M. Hatanaka, Y. Himeda, R. Imashiro, Y. Tanaka, and I. Ueda, *J. Org. Chem.*, 1994, **59**, 111.
7. Y. Tanaka, T. Kawano, S. Md. Islam, H. Nishioka, M. Hatanaka, and I. Ueda, *Chem. Pharm. Bull.*, 1996, **44**, 885.
8. T. Kawano, T. Ogawa, S. Md. Islam, and I. Ueda, *Tetrahedron Lett.*, 1995, **36**, 7685.
9. H. Hamada, M. Shibata, T. Sugiura, S. Kato, and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252.
10. E. Huet, A. Lechevallier, M. Pellet, and J. M. Conia, *Synthesis*, **1978**, 63.
11. M. B. Floyd, M. T. Du, P. F. Fabio, L. A. Jacob, and B. D. Johnson, *J. Org. Chem.*, 1985, **50**, 5022.

Received, 4th October, 1999