Synthesis of all-*E*- and 9*Z*-Heteroaryl-retinoic Acid Applying Palladium Catalyzed Coupling Reaction of (Arylvinyl)tributyl Stannane with Vinyl Triflate

Akimori Wada,* Govindarajuru Babu, Sayaka Shimomoto, Masayoshi Ito*

Kobe Pharmaceutical University, 4-19-1, Motoyamakita-machi, Higashinada, Kobe 658-8558, Japan
E-mail: a-wada@kobepharma-u.ac.jp

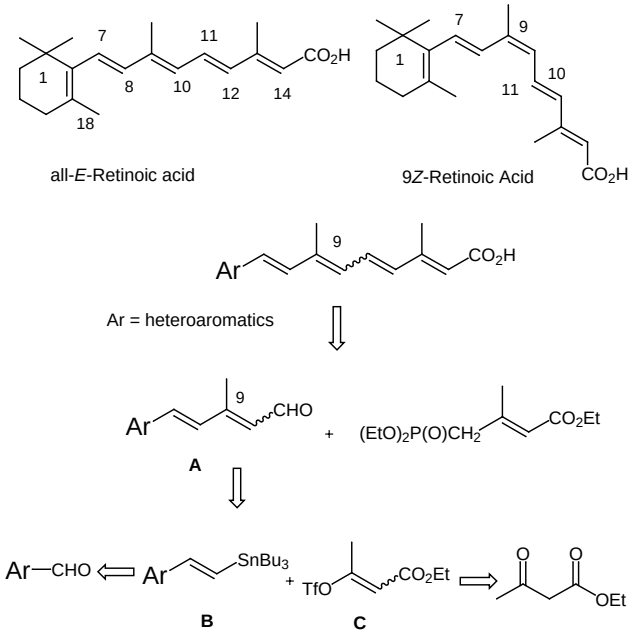
Received 28 August 2001

Abstract: Palladium catalyzed cross coupling reactions of (arylvinyl)tributyl stannanes with vinyl triflates resulted in the production of stereochemically pure trisubstituted *E*- and *Z*-olefins in very good yields. These olefins were transformed to the corresponding all-*E*- and 9*Z*- heteroaryl-retinoic acid analogs via Horner–Emmons reaction and subsequent basic hydrolysis in excellent yields.

Key words: retinoid X receptors, heteroaryl-retinoic acid, coupling reaction, vinyl triflate, (arylvinyl)tributyl stannane

It is well known that all-*E*-retinoic acid and 9*Z*-retinoic acid (Scheme 1) are the ligand molecules for retinoic acid receptors (RARα, β, γ) and retinoid X receptors (RXRα, β, γ), respectively.[1] They are members of the nuclear receptor superfamily and exhibit significant biological functions which include cell differentiation, cell proliferation, embryonic development etc. through gene transcription.[2] In biological system, RXRs form functional heterodimers with other proteins of the nuclear receptors such as the RARs, the thyroid hormone receptor (TR), the vitamin D receptor (VDR) and the peroxisome proliferator-activated receptors (PPAR). These heterodimers bind to co-activator or co-repressor proteins with changing their conformation depending on the nature of the ligand molecule, and then activate or repress a wide variety of gene transcription. Currently great efforts have been found for the preparation of receptor-selective retinoids in order not only to define the functions of each receptor but also to develop the therapeutic agents.[3] In connection with our study on the stereoselective synthesis of retinoids,[4,5] we wish to report a convenient synthesis of all-*E*- and 9*Z*-heteroaryl-retinoic acid analogs **12** and **14** (Scheme 3), which replace the 2,6,6-trimethylcyclohexene ring of retinoic acid by the heterocyclic rings in order not only to decrease a hydrophobic character of analogs but also to investigate the interaction between the ligand and the receptor protein, by the application of a stereoselective, palladium catalyzed cross coupling reaction of (arylvinyl)-tributyl stannanes with *E*- and *Z*-vinyltriflates.[6,7]

As the conversion of β-ionylideneacetaldehyde analog **A** to the corresponding retinoic acid has been already established using Horner–Emmons or Wittig reaction,[3,4] key step in our synthetic strategy is based on the coupling reaction of two segments **B** and **C.** Segment **C** was obtained from ethyl acetoacetate by the reported method[8] and the separation of two stereoisomers was easily performed by column chromatography (Scheme 1).



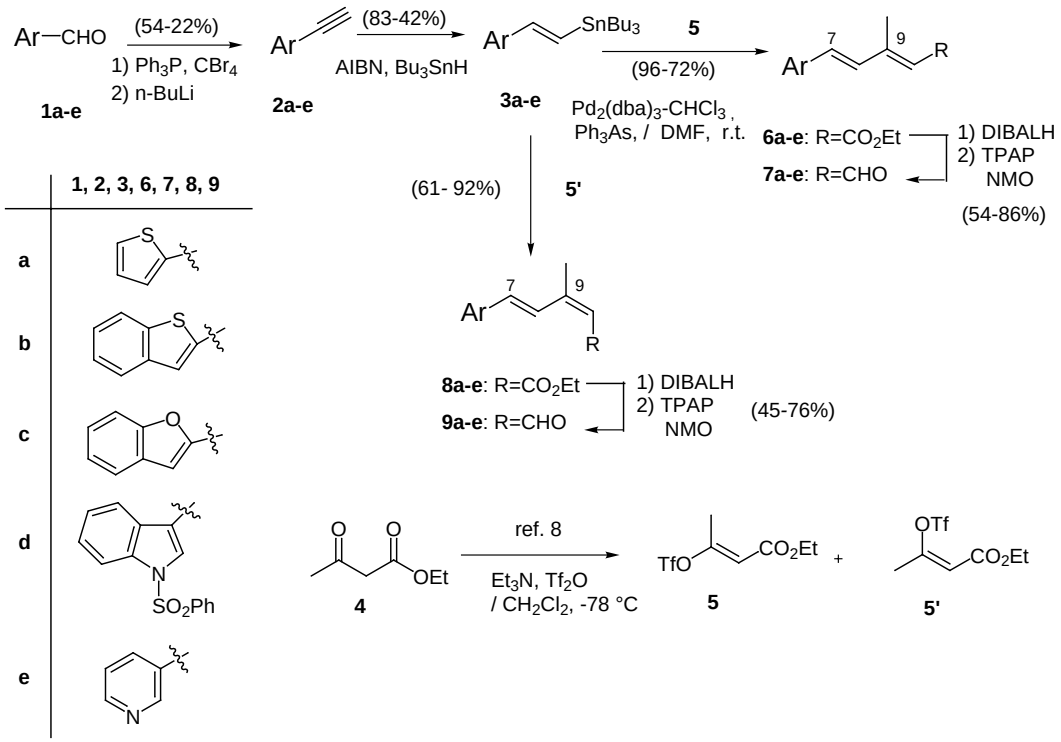
Scheme 1

Our synthetic approach toward heteroaryl-retinoic acids starts from the synthesis of (arylvinyl)tributyl stannanes **3** (Scheme 2). The arylaldehydes **1** were transformed to the acetylenes **2** by the standard procedure using carbon tetrabromide and triphenylphosphine and subsequent treatment with *n*-butyllithium.[9] Hydrostannylation[10] of **2** with *n*-Bu_3SnH in the presence of a catalytic amount of AIBN at 50 °C for 12–16 hours afforded the corresponding (arylvinyl)tributyl stannanes **3**[11] in moderate to good yields.

Stille coupling reaction of **3a** with *(E)*-vinyl triflate **5**[8] in the presence of a catalytic amount of tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct ($Pd_2(dba)_3$-$CHCl_3$) with triphenylarsine ($AsPh_3$)[12] provided the 9*E*-ester **6a** in 72% yield.[13] Under the same conditions, the coupling reaction of **3a** with *(Z)*-triflate **5'**[8] also proceeded smoothly to afford the 9*Z*-ester **8a**[13] in 78% yield

Synlett 2001, No. 11, 26 10 2001. Article Identifier:
1437-2096,E;2001,0,11,1759,1762,ftx,en;Y16601ST.pdf.

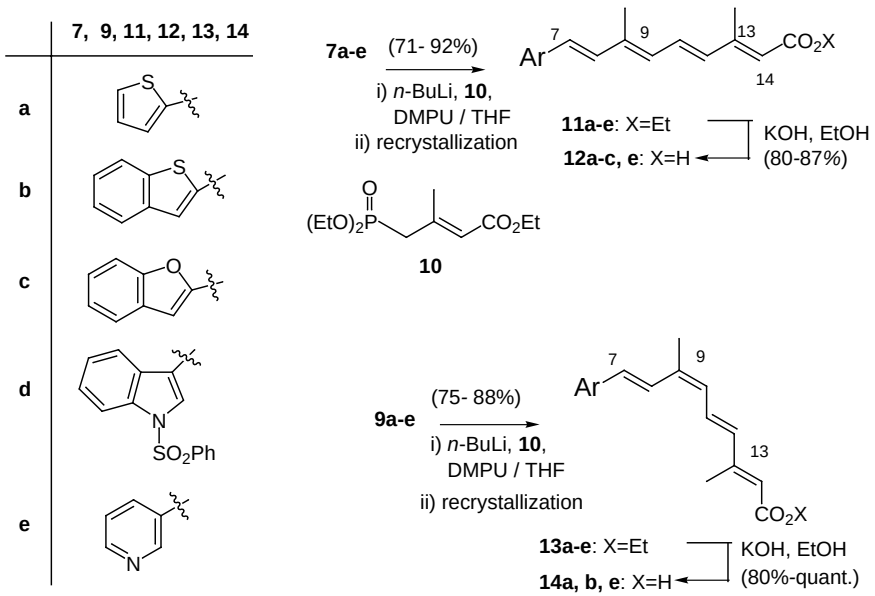
ISSN 0936-5214



Scheme 2

(Scheme 2). The esters **6a** and **8a** were converted to the aldehydes **7a** and **9a** without isomerization of double bond by DIBALH reduction and subsequent oxidation using tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-Oxide (NMO)[14] in 58% and 68% yields, respectively.[15] The structures of **7a** and **9a** were determined on the basis of their spectral data by the comparison of those of the corresponding β-ionylideneacetaldehydes,[16] and it was found that this coupling reaction proceeded stereospecifically with retention of the configuration of the double bonds.

As we could develop a stereocontrolled synthesis of β-ionylideneacetaldehyde analogs, our attention was focused on the synthesis of heteroaryl-retinoic acid analogs. The Horner–Emmons reaction of aldehyde **7a** with C-5 phos-



Scheme 3

phonate **10** using *n*-BuLi as a base in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[17] first at –78 °C and then at 0 °C gave the ester **11** as a mixture of the double bond isomers in good yield. Pure all-*E*-isomer was obtained by recrystallization of the crude product from ether-*n*-hexane, and this compound was transformed to the corresponding all-*E*-heteroaryl-retinoic acid **12a** by basic-hydrolysis in excellent yield. In a similar fashion, the 9*Z*-aldehyde **9a** was converted to the corresponding 9*Z*-retinoic acid analog **14a** in good yield[18] (Scheme 3).

By adopting the same methodology used for the thiophenecarbaldehyde **1a**, other heteroaromatic aldehydes **1b**–**e** were also transformed to the corresponding ethyl all-*E* and 9*Z*-retinoate analogs (**11b**–**e** and **13b**–**e**) in good to excellent yields except for **13c**.[19] The esters **11b,c,e** and **13b,e** were converted to the corresponding acids and these results are summarized in Tables 1 and 2.

Table 1 Yields of Reactions for the Synthesis of all-*E*-Heteroaryl-retinoic Acids

Run	Substituent Ar	Yield of **6** (%)[a]	Yield of **7** (%)[b]	Yield of **11** (%, 13*E*/13*Z*)	Yield of **12** (%)
1	2-thienyl	72	58	79/13	80
2	2-benzo[*b*]thienyl	91	86	81[c]	87
3	2-benzo[*b*]furyl	88	63	61/10	87
4	*N*-SO_2Ph-3-indolyl	96	54	63/27	–[d]
5	3-pyridyl	75	57	85/7	83

[a] $Pd_2(dba)_3$-$CHCl_3$, $AsPh_3$ and **5** in DMF at r.t.
[b] Yield in 2 steps.
[c] 13*Z*-isomer was not detected at all.
[d] Not obtained.

In the case of indolylesters **11d** and **13d**, our first attempts to isolate *N*-unsubstituted acids by basic-hydrolysis[20] were unsuccessful. Therefore, the ester **11d** was converted to the *N*-methylated acid **16** by the sequence of desulfonylation, methylation and subsequent basic-hydrolysis (Scheme 4).

In conclusion, we have stereoselectively synthesized the trisubstituted *E*- or *Z*- olefin using a modified Stille coupling reaction of (arylvinyl)tributyl stannane with *E*- or *Z*-vinyl triflate and have achieved the synthesis of previously unreported heteroaryl-retinoic acid analogs. The biological evaluation of these new analogs is currently in progress.

Table 2 Yields of Reactions for the Synthesis of 9*Z*-Heteroaryl-retinoic Acids

Run	Substituent Ar	Yield of **8** (%)[a]	Yield of **9** (%)[b]	Yield of **13** (%, 13*E*/13*Z*)	Yield of **14** (%)
1	2-thienyl	78	68	62/13	96
2	2-benzo[*b*]thienyl	91	76	77/9	quant.
3	2-benzo*[b]*furyl	61	50[c]	-[d]	–[d]
4	*N*-SO_2Ph-3-indolyl	92	60	74/10	–[e]
5	3-pyridyl	92	45	77/8	80

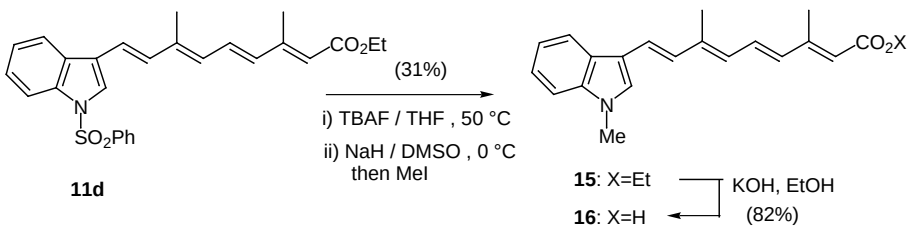
[a] $Pd_2(dba)_3$-$CHCl_3$, $AsPh_3$ and **5** in DMF at r.t.
[b] Yield in 2 steps.
[c] As a mixture of *Z*- and *E* -isomer (*Z*:*E* = 2:1).
[d] Not performed.
[e] Not obtained.

Acknowledgement

This work was supported in part by the Kobe Pharmaceutical University Collaboration Fund and The Science Research Promotion Fund from the Japan Private School Promotion Foundation. We thank the Kobe Pharmaceutical University for a postdoctoral fellowship (to G. B.).

References and Notes

(1) Mangelsdorf, D. J.; Umesono, K.; Evans, R. M. *In The Retinoids*; Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds.; Raven: New York, **1994**, 2nd ed., 319.
(2) (a) Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichele, G.; Evans, R. M.; Thaller, C. *Cell* **1992**, *68*, 397. (b) Hong, W. K.; Sporn, M. B. *Science* **1997**, *278*, 1073.
(3) (a) Beard, R. L.; Klein, E. S.; Standeven, A. M.; Escobar, M.; Chandraratna, R. A. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 765. (b) Njar, V. C. O.; Nnane, I. P.; Broddie, A. M. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1905. (c) Kikuchi, K.; Hibi, S.; Yoshimura, H.; Tai, K.; Hida, T.; Tokuhara, N.; Yamauchi, T.; Nagai, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 619. (d) Viligonda, V.; Garst, M. E.; Chandraratna, R. A. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 589. (e) Wong, M. F.; Repa, J. J.; Clagett-Dame, M.; Curley, R. W. J. r. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2313. (f) Yu, K.-L.; Chen, S.; Ostrowski, J.; Tramposch, K. M.; Reczek, P. R.; Mansuri,



Scheme 4

M. M.; Starrett, J. E. Jr *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2859. (g) Trost, B. M.; Harms, A. E. *Tetrahedron Lett.* **1996**, *37*, 3971. (h) Boehm, M. F.; Zhang, L.; Zhi, L.; McClurg, M. R.; Berger, E.; Wagoner, M.; Mais, D. E.; Suto, C. M.; Davies, P. J. A.; Heyman, R. A.; Nadzan, A. M. *J. Med. Chem.* **1995**, *38*, 3146. (i) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. *J. Med. Chem.* **1994**, *37*, 2930. (j) Vaezi, M. F.; Alam, M.; Sani, B. P.; Rogers, T. S.; Simpson-Herren, L.; Wille, J. J.; Hill, D. L.; Doran, T. I.; Brouillette, W. J.; Muccio, D. D. *J. Med. Chem.* **1994**, *37*, 4499.

(4) (a) Wada, A.; Hiraishi, S.; Ito, M. *Chem. Pharm. Bull.* **1994**, *42*, 757. (b) Wada, A.; Tanaka, Y.; Fujioka, N.; Ito, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2049. (c) Wada, A.; Hiraishi, S.; Takamura, N.; Date, T.; Aoe, K.; Ito, M. *J. Org. Chem.* **1997**, *62*, 4343. (d) Wada, A.; Fujioka, N.; Tanaka, Y.; Ito, M. *J. Org. Chem.* **2000**, *65*, 2438.

(5) (a) Wada, A.; Nomoto, Y.; Tano, K.; Yamashita, E.; Ito, M. *Chem. Pharm. Bull.* **2000**, *48*, 1391. (b) Wada, A.; Fukunaga, K.; Ito, M. *Synlett* **2001**, 800.

(6) Several similar cross coupling reactions for the stereoselective synthesis of retinoids have already been reported; for all-*E*-retinoids see: (a) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435. (b) Torrado, A.; López, S.; Alvarez, R.; de Lera, A. R. *Synthesis* **1995**, 285. (c) Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **1999**, 141. (d) Dominguez, B.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **1998**, *63*, 4135.

(7) (a) For 9*Z*-retinoic acid see: Pazos, Y.; de Lera, A. R. *Tetrahedron Lett.* **1999**, *40*, 8287. (b) For 11*Z*-retinal see:Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Wada, A.; Ito, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 320.

(8) (a) Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320. (b) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.

(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(10) (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.

(11) Stannylcupration of **2** with lithium butyltributylstannylcyanocuprate at –78 °C in THF also afforded the(arylvinyl)tributyl stannane **3** in good yield. ^{1}H NMR data of **3a** are as follows; (300 MHz, $CDCl_3$)δ 0.8–1.6 (27 H, m), 6.59 (1 H, d, *J* = 19 Hz), 6.8–7.0 (2 H, m), 6.95 (1 H, d, *J* = 19 Hz), 7.13 (1 H, d, *J* = 5 Hz).

(12) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(13) **Typical coupling procedure**: To a stirred solution of(arylvinyl)tributyl stannane (**3**, 1 mmol), vinyl triflate (**5** or **5'**, 1.5 mmol) and $AsPh_3$ (20 mol%, 60 mg) in DMF (2 mL) was added $Pd_2(dba)_3$-$CHCl_3$ adduct (2.5 mol%, 26 mg) all at once at r.t. under nitrogen. After stirring for an additional 2 h, the reaction was quenched with saturated aq KF solution (3 mL) and extracted with Et_2O (10 mL × 3). The extracts were washed with aq sat. NaCl solution (10 mL) and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the coupled ester.
6a: IR ($CHCl_3$)cm^{-1}: 2960, 1702, 1608; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (3 H, t, *J* = 7 Hz), 2.37 (3 H, s), 4.18 (2 H, q, *J* = 7 Hz), 5.86 (1 H, s), 6.63 (1 H,d, *J* = 16 Hz), 7.01 (1 H, dd, *J* = 3.5, 5 Hz), 7.05 (1 H, d, *J* = 16 Hz), 7.09 (1 H, d, *J* = 3.5 Hz), 7.24 (1 H, d, *J* = 5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5, 14.3, 59.7, 119.5, 125.9, 126.9, 127.7, 127.8, 131.4, 141.9, 151.6, 167.0; HRMS (EI) $C_{12}H_{14}O_2S$: requires 220.0715, found 220.0721.
8a: IR ($CHCl_3$) cm^{-1}: 2984, 1697, 1612; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (3 H, t, *J* = 7 Hz), 2.08 (3 H, s), 4.19 (2 H, q, *J* = 7 Hz), 5.71 (1 H, s), 7.00 (1 H, dd, *J* = 3.5, 5.5 Hz), 7.03 (1 H, d, *J* = 15 Hz), 7.13 (1 H, d, *J* = 3.5 Hz), 7.25 (1 H, d *J* = 5.5 Hz), 8.20 (1 H, d *J* = 15 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 14.3, 20.7, 59.8, 117.6, 125.6, 126.3, 127.7, 127.8, 128.1, 142.5, 150.0, 166.3; HRMS (EI) $C_{12}H_{14}O_2S$: requires 220.0715, found 220.0722.

(14) Griffith, W. P.; Ley, S. V.; Whitecombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(15) Spectral data are as follows; **7a**: IR ($CHCl_3$)cm^{-1}: 3012, 1658, 1600; ^{1}H NMR (300 MHz) δ: 2.34 (3 H, s), 6.05 (1 H, d, *J* = 8 Hz), 6.72 (1 H, d, *J* = 16 Hz), 7.04 (1 H, dd, *J* = 3.5, 5 Hz), 7.16 (1 H, d *J* = 3.5 Hz), 7.22 (1 H, d, *J* = 16 Hz), 7.32 (1 H, d *J* = 5 Hz), 10.14 (1 H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.9, 126.9, 128.0, 128.5, 128.7, 129.6, 130.6, 141.5, 153.8, 191.0; HRMS (EI) $C_{10}H_{10}O_2S$: requires 178.0452, found 178.0457. **9a**: IR ($CHCl_3$) cm^{-1}: 3012, 1658, 1605; ^{1}H NMR (300 MHz) δ: 2.16 (3 H, s), 5.92 (1 H, d, *J* = 8 Hz), 7.05 (1 H, dd, *J* = 3.5, 5 Hz), 7.12 (1 H, d, *J* = 16 Hz), 7.17 (1 H, d *J* = 3.5 Hz), 7.32 (1 H, d, *J* = 5 Hz), 7.64 (1 H, d, *J* = 16 Hz), 10.26 (1 H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0, 122.7, 127.0, 128.0, 128.3, 128.9, 129.5, 141.5, 153.6, 189.7; HRMS (EI) $C_{10}H_{10}O_2S$: requires 178.0452, found 178.0450.

(16) (a) Dugger, R. W.; Heathcock, C. H. *Synth. Commun.* **1980**, *10*, 509. (b) Robeson, C. D.; Cawley, J. D.; Weisler, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 4111.

(17) Bennani, Y. L. *J. Org. Chem.* **1996**, *61*, 3542.

(18) Spectral data are as follows; **12a**: IR ($CHCl_3$) cm^{-1}: 3300–2600, 1683, 1590; ^{1}H NMR (300 MHz) δ: 2.04 (3 H, s), 2.37 (3 H, s), 5.83 (1 H, s), 6.32 (1 H, d, *J* = 11 Hz), 6.38 (1 H, d, *J* = 15 Hz), 6.72 (1 H, d, *J* = 16 Hz), 6.85 (1 H, d, *J* = 16 Hz), 6.99 (1 H, dd, *J* = 3.5, 5 Hz), 7.03 (1 H, d, *J* = 3.5 Hz), 7.08 (1 H, dd, *J* = 11, 15 Hz), 7.19 (1 H, d, *J* = 5 Hz), COOH signal was not present; ^{13}C NMR (75 MHz, $CDCl_3$)δ: 12.9, 14.0, 118.0, 122.6, 124.7, 126.3, 127.7, 131.3, 131.5, 132.7, 135.8, 139.2, 143.1, 155.0, CO signal was not present; HRMS (EI) $C_{15}H_{16}O_2S$: requires 260.0870, found 260.0860. **14a**: IR ($CHCl_3$) cm^{-1}: 3300–2600, 1681, 1590; ^{1}H NMR (500 MHz)δ: 2.03 (3 H, s), 2.38 (3 H, s), 5.81 (1 H, s), 6.13 (1 H, d, *J* = 11 Hz), 6.29 (1 H, d, *J* = 15 Hz), 6.82 (1 H, d, *J* = 15 Hz), 6.99 (1 H, dd, *J* = 3.5, 5 Hz), 7.05 (1 H, d, *J* = 3.5 Hz), 7.16 (1 H, d, *J* = 5 Hz), 7.20 (1 H, d, *J* = 15 Hz), 7.21 (1 H, dd, *J* = 11, 15 Hz), COOH signal was not present; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 20.8, 117.3, 122.7, 123.9, 124.6, 125.0, 126.7, 127.8, 129.7, 130.1, 135.1, 142.9, 154.0, CO signal was not present; HRMS (EI) $C_{15}H_{16}O_2S$: requires 260.0870, found 260.0872.

(19) It was difficult to obtain the 9*Z*-aldehyde **9c** in pure form due to its easy isomerization.

(20) Nagarathnam, D. *J. Heterocyclic Chem.* **1992**, *29*, 953.