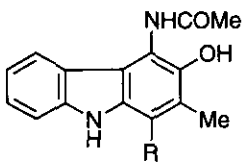
SYNTHESIS OF NEW TETRACYCLIC OXAZOLOCARBAZOLES AS FUNCTIONALIZED PRECURSORS TO ANTIOXIDATIVE AGENTS, ANTIOSTATINS AND CARBAZOQUINOCINS

Tominari Choshi, Hiroyuki Fujimoto, Eiichi Sugino, and Satoshi Hibino*

Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-02, Japan

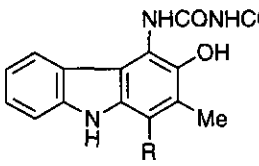
Abstract — New tetracyclic oxazolo[4,5-*c*]carbazole and oxazolo[5,4-*c*]-carbazole ring systems as functionalized precursors to antioxidative antiostatins ($A_{1\text{-}4}$ and $B_{2\text{-}5}$) and carbazoquinocins (A-F) were synthesized.

Antioxidative substances are now considered to be prospects as protective agents against a variety of diseases such as ischemia-reperfusion, autoimmune diseases, cardiovascular diseases, cancer-initiation and aging process.[1] Recently, antioxidative antiostatins (A_1 to A_4 and B_2 to B_5)[2] and carbazoquinocins (A to F)[3,4] have been isolated from *Streptomyces cyaneus* 2007-SV_1 and *Streptomyces violaceus* 2448-SVT2, respectively, and their structures have been elucidated by spectroscopic evidences and by comparison with spectral data[5] of the related carazostatin (Chart 1). Synthesis of these carbazole alkaloids is vital to the advancement of this field.



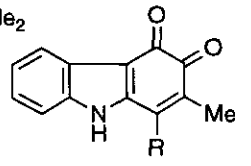
Antiostatins $A_{1\text{-}4}$

1a: R=$(CH_2)_4Me$ (A_1)
1b: R=$(CH_2)_2CH(CH_3)CH_2Me$ (A_2)
1c: R=$(CH_2)_4CH(Me)_2$ (A_3)
1d: R=$(CH_2)_6Me$ (A_4)



Antiostatins $B_{2\text{-}5}$

2a: R=$(CH_2)_5Me$ (B_2)
2b: R=$(CH_2)_4CH(Me)_2$ (B_3)
2c: R=$(CH_2)_6Me$ (B_4)
2d: R=$(CH_2)_5CH(Me)_2$ (B_5)



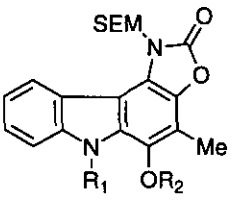
Carbazoquinocins A-F

3a: R=$(CH_2)_2CH(CH_3)CH_2Me$ (A)
3b: R=$(CH_2)_4CH(Me)_2$ (B)
3c: R=$(CH_2)_6Me$ (C)
3d: R=$(CH_2)_4CH(CH_3)CH_2Me$ (D)
3e: R=$(CH_2)_5CH(Me)_2$ (E)
3f: R=$(CH_2)_6CH(Me)_2$ (F)

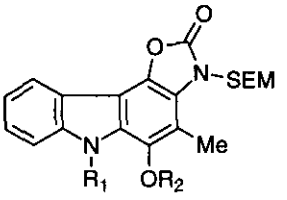
Chart 1

In seeking an efficient precursor for synthesizing these highly-substituted carbazole alkaloids, we assumed that a new type of tetracyclic oxazolo[5,4-*c*]carbazole (**4**) would be a functionalized key-intermediate.

Herein, we report the synthesis of novel tetracyclic oxazolocarbazoles (**4** and **5**) as functionalized precursors to antiostatins (**1** and **2**) and carbazoquinocins (**3**) (Chart 2).

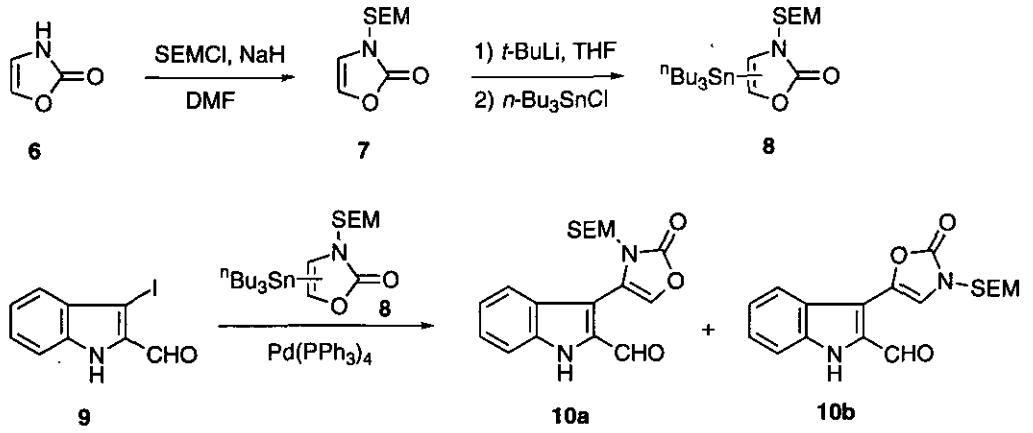


4a: R_1=SO_2Ph, R_2=MOM
4b: R_1=R_2=MOM
4c: R_1= R_2=H
4d: R_1=H, R_2=Tf



5a: R_1=SO_2Ph, R_2=MOM
5b: R_1=R_2=MOM
5c: R_1= R_2=H
5d: R_1=H, R_2=Tf

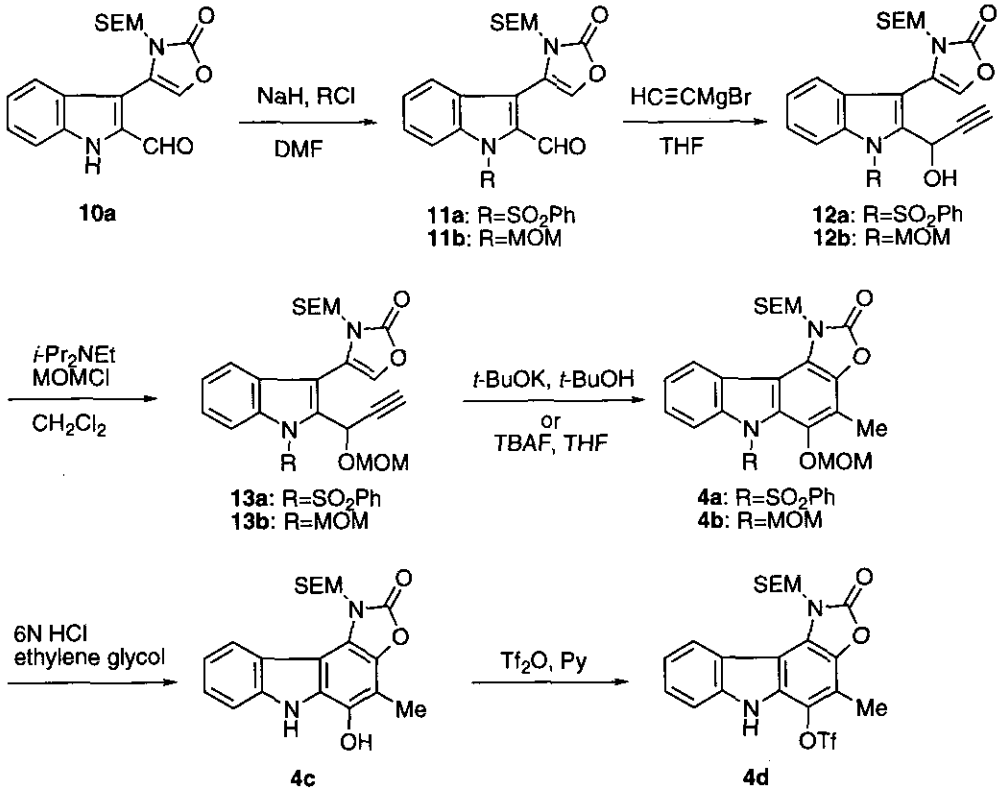
Chart 2



Scheme 1

Recently, we found that the carbazole nucleus can be synthesized in good yield by an allene-mediated electrocyclic reaction generated from the 3-alkenyl-2-propargylindole derivative in the presence of *t*-BuOK.[6] For the synthesis of this oxazolo[5,4-*c*]carbazole (**4**), we utilized this synthetic strategy in an extensive study. We initially attempted to use a cross-coupling reaction between 2-formyl-3-iodoindole (**9**)[7] and trimethylsilylethoxymethyl (SEM)-oxazolone (**7**: 99%) prepared from oxazolone (**6**)[8] (Scheme 1). Treatment of SEM-oxazolone (**7**) with *t*-BuLi at -78 °C followed by addition of tributyltin chloride gave the stannyloxazolone (**8**), which was subjected to the cross-coupling reaction with 3-iodoindole (**9**) [$Pd(PPh_3)_4$, 100 °C, 4 h, in DMF] to give about a 1:1 mixture of two isomeric 3-oxazolylindoles (**10a** and/or **10b**). The mixture could be separated by silica gel column chromatography [EtOAc/hexane (3:17)] to give the faster moving product and the slower moving product (33 and 29% yields from **9**), respectively. As a result, the directed metalation of the SEM-oxazolone (**7**) with *t*-BuLi did not work regioselectively.

Each structures of two separable 3-oxazolylindoles could not be elucidated by spectroscopy. Therefore, we tentatively speculated that the faster moving product is 3-(4-oxazolyl)indole (**10a**) and both products independently lead to tetracyclic carbazoles as shown in Schemes 2 and 3.



10a

11a: R=SO_2Ph
11b: R=MOM

12a: R=SO_2Ph
12b: R=MOM

13a: R=SO_2Ph
13b: R=MOM

4a: R=SO_2Ph
4b: R=MOM

4c

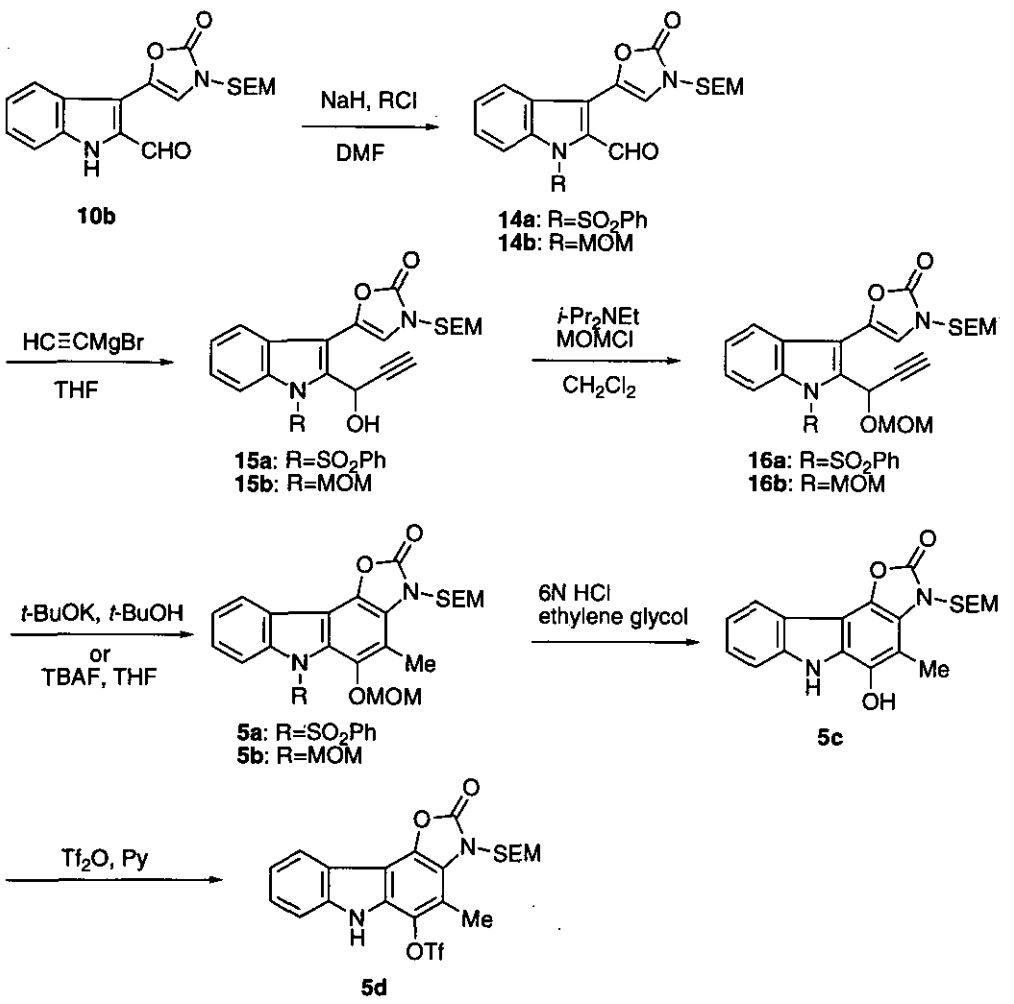
4d

Scheme 2

Treatment of indole (**10a**) with NaH followed by addition of benzenesulfonyl chloride or chloromethyl methyl ether (MOM-Cl) gave *N*-benzenesulfonyl-2-formylindole (**11a**: 67%) and *N*-MOM-2-formylindole (**11b**: 98%), respectively. Subsequent Grignard reaction of 2-formylindole (**11a** and **11b**) with ethynylmagnesium bromide in THF yielded the propargyl alcohols (**12a**: 86% and **12b**: 98%), which were protected with MOM-Cl and ethyl diisopropylamine to give MOM-ethers (**13a**: 95% and **13b**: 99%). Then *N*-benzenesulfonylindole (**13a**) was heated at 90 °C for 3 h in the presence of *t*-BuOK (2 eq.) in *t*-BuOH/THF (3:1) to give the tetracyclic carbazole (**4a**: 24%).[9] The *N*-MOM-indole (**13b**) was heated at 90 °C for 0.5 h in the presence of tetrabutylammomiun fluoride (TBAF; 5 eq.) in THF to produce the tetracyclic carbazole (**4b**: 80%). An exchange of base was not effective in either reaction.

On the other hand, the tentative product (**10b**) was converted to *N*-benzenesulfonylindole (**14a**: 46%) and *N*-MOM-indole (**14b**: 94%) by similar methods (Scheme 3). Grignard reaction of 2-formylindoles (**14a** and **14b**) with ethynylmagnesium bromide in THF yielded the propargyl alcohols (**15a**: 93% and **15b**: 86%), which were protected with MOM-Cl and ethyl diisopropylamine to give MOM-ethers (**16a**: 83% and

16b: 95%). *N*-Benzenesulfonylindole (**16a**) was heated at 90°C for 3 h in the presence of *t*-BuOK (2 eq.) in *t*-BuOH/THF (3:1) to yield the tetracyclic carbazole (**5a**: 11%).[9] In contrast, the *N*-MOM-indole (**16b**) was heated at 90 °C for 0.5 h in the presence of TBAF (5 eq.) in THF to give the tetracyclic carbazole (**5b**:



10b

14a: R=SO_2Ph
14b: R=MOM

15a: R=SO_2Ph
15b: R=MOM

16a: R=SO_2Ph
16b: R=MOM

5a: R=SO_2Ph
5b: R=MOM

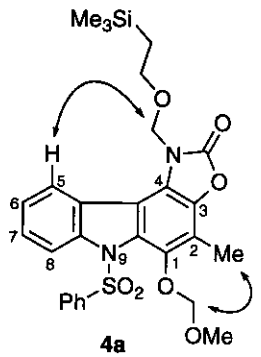
5c

5d

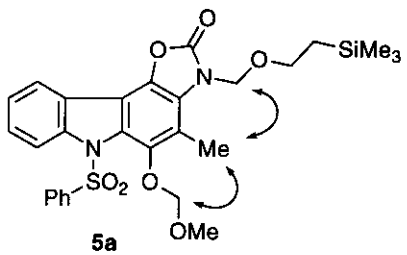
Scheme 3

82%). An exchange of base in an each reaction was also not effective in this case. The *N*-MOM-protecting group was better than the *N*-benzenesulfonyl-protecting group for the synthesis of tetracyclic oxazolocarbazole ring systems. For the deprotection of *N*- and *O*-MOM groups, compounds (**4b**) and (**5b**) were treated with 6N HCl in ethylene glycol[10] to give phenols (**4c**: 96% and **5c**: 85%), respectively. Subsequent treatment of **4c** and **5c** with trifluoromethanesulfonic anhydride and pyridine produced triflates (**4d**: 74% and **5d**: 94%) (Schemes 2 and 3).

The structures of two tetracyclic *N*-benzenesulfonylcarbazoles (**4a** and **5a**) were analyzed from the 2D-NOESY nmr spectra (Chart 3). In the ^{1}H-nmr spectrum of **4a**, the correlation was observed between

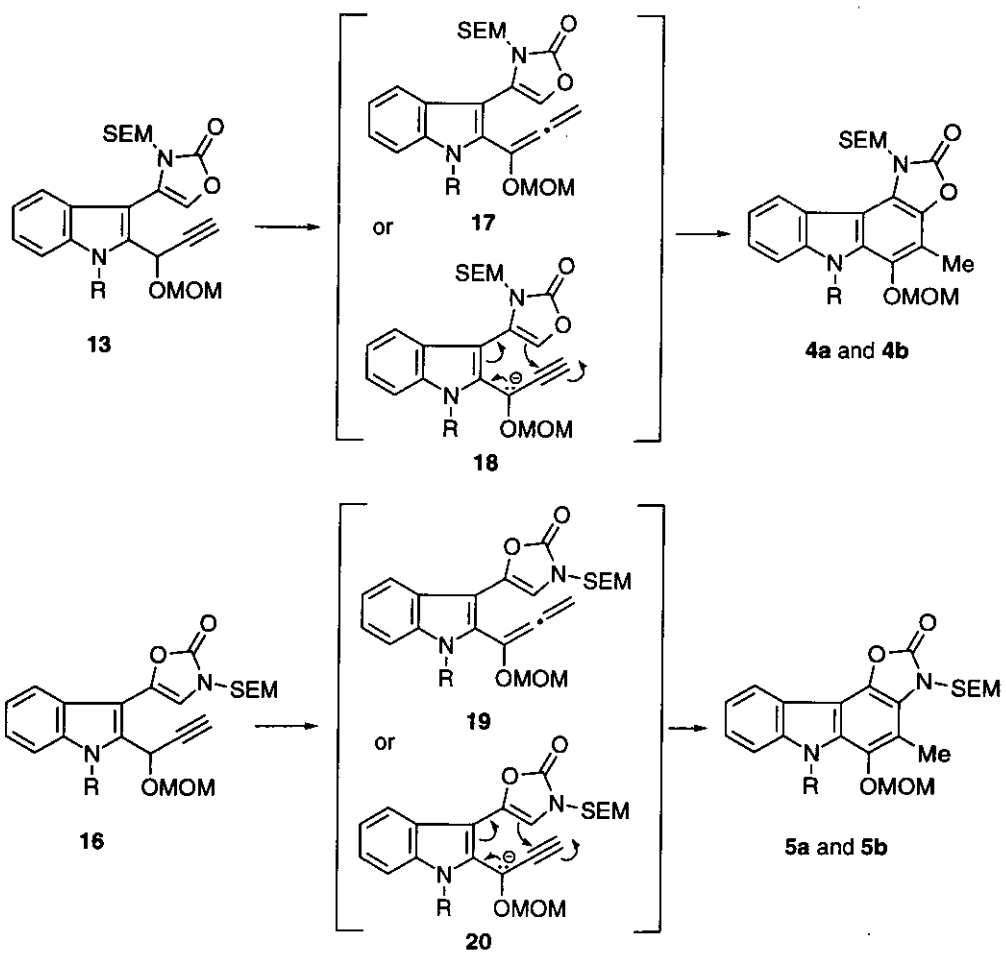


4a



5a

Chart 3



Scheme 4

methylene protons (δ 5.44) of the SEM group and the aromatic proton (δ 8.17) at C-5 position of carbazole ring. In the ^{1}H-nmr spectrum of **5a**, the correlation was observed between methylene protons (δ 5.61) of the SEM group and the methyl protons (δ 2.69) at the C-2 position of carbazole ring. Therefore, the structures of *N*-benzenesulfonylcarbazole (**4a**) derived from the faster moving product (**10a**) was the oxazolo[4,5-*c*]carbazole. The structure of another *N*-benzenesulfonylcarbazole (**5a**) derived from the slower moving product (**10b**) was the oxazolo[5,4-*c*]carbazole. Furthermore, the faster moving product was the 3-(4-oxazolyl)indole (**10a**) and the slower moving product was the 3-(5-oxazolyl)indole (**10b**) as tentatively speculated.

This benzo-annelation may proceed through either electrocyclic reaction of allene intermediates (**17** and **19**) derived from 3-oxazolyl-2-propargylindoles (**13** and **16**) or an ionic process such as **18** and **20** (Scheme 4). At present, this reaction may proceed by an allene-mediated electrocyclic reaction rather than the latter process.

In conclusion, although the cross-coupling reaction between **7** and **9** did not proceed regioselectively, two separable 3-oxazolylindole (**10a** and **10b**)[11] led to two types of isomeric oxazolocarbazoles (**4a-b** and **5a-b**). The structures of two oxazolocarbazoles (**4a** and **5a**)[12] could be determined from their 2D-NOESY nmr spectra, and the structures of **4b** and **5b**[13] could be also elucidated because the same materials (**10a** and **10b**) were used. Both oxazolo[4,5-*c*]carbazole (**4d**) and oxazolo[5,4-*c*]carbazole (**5d**)[14] might be efficient precursors for the syntheses of these highly-substituted carbazoles (**1**, **2** and **3**). Further studies are now in progress.

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7. 2-Formyl-3-iodoindole (**9**) was prepared by the following method. A solution of iodine (6.6 mmol) in DMF (30 ml) was added to a solution of 2-formylindole (6.6 mmol) and powder KOH (23.8 mmol) in DMF (30 ml). The mixture was stirred at r.t. for 4 h, which was poured into the aqueous solution (1500 ml) in the presence of 28% NH_4OH (100 ml) and $NaHSO_3$ (10 g) to give the crude 2-formyl-3-iodoindole (81%, mp 193-194 °C from EtOH); cf. T. Sakamoto, T. Nagano, T. Kondo, and Y. Yamanaka, *Chem. Pharm. Bull.*, **1988**, *36*, 2248.
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9. The nmr spectrum revealed the presence of a deprotecting (*N*-SO_2Ph) tetracyclic oxazolocarbazole produced together with an unknown compound, but it was difficult to separate these products.
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11. Compound (**10a**): mp 121-123 °C (Et_2O-pentane); ir (KBr) ν 3290, 1743, 1732 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.04 (9H, s), 0.97 (2H, t, *J*=8 Hz), 3.63 (2H, t, *J*=8 Hz), 5.05 (2H, s), 7.06 (1H, s), 7.10-7.81 (4H, m), 10.28 (1H, s); ms *m/z*: 358 (M^+). Compound (**10b**): mp 141-142 °C (Et_2O); ir (KBr) ν : 3294, 1759 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ : 0.06 (9H, s), 1.02 (2H, t, *J*=8 Hz), 3.60 (2H, t, *J*=8 Hz), 4.96 (2H, s), 6.99 (1H, s), 7.10-7.75 (4H, m), 9.76 (1H, s); ms *m/z*: 358 (M^+).
12. Compound (**4a**): ir (KBr) ν 1760, 1427, 1182 cm^{-1}; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 0.01 (9H, s), 0.92 (2H, t, *J*=8 Hz), 2.48 (3H, s), 3.55 (3H, s), 3.76 (2H, t, *J*=8 Hz), 5.32 (2H, s), 5.44 (2H, s), 7.15 (2H, t, *J*=8 Hz), 7.27 (2H, d, *J*=8 Hz), 7.29 (1H, t, *J*=7.5 Hz), 7.36 (1H, t, *J*=8 Hz), 7.46 (1H, t, *J*=7.5 Hz), 8.17 (1H, t, *J*=7.5 Hz), 8.23 (1H, t, *J*=7.5 Hz); ms *m/z*: 568 (M^+). Compound (**5a**): Ir (KBr) ν 1786, 1410, 1180 cm^{-1}; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 0.01 (9H, s), 0.99 (2H, t, *J*=8 Hz), 2.69 (3H, s), 3.60 (3H, s), 3.71 (2H, t, *J*=8 Hz), 5.59 (2H, s), 5.61 (2H, s), 7.18 (2H, t, *J*=8 Hz), 7.32 (2H, d, *J*=8 Hz), 7.34 (1H, t, *J*=7.5 Hz), 7.38 (1H, t, *J*=8.5 Hz), 7.49 (1H, t, *J*=8.5 Hz), 7.87 (1H, t, *J*=8.5 Hz), 8.25 (1H, t, *J*=8.5 Hz); ms *m/z*: 568 (M^+).
13. Compound (**4b**): mp 120-121.5 °C (Et_2O); ir (KBr) ν 1782 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.00 (9H, s), 1.00 (2H, t, *J*=8 Hz), 2.51 (3H, s), 3.27 (3H, s), 3.60 (3H, s), 3.85 (2H, t, *J*=8 Hz), 5.09 (2H, s), 5.62 (2H, s), 5.95 (2H, s), 7.20-7.59 (3H, m), 8.27-8.45 (1H, m); ms *m/z*: 472 (M^+). Compound (**5b**): mp 80-83 °C (pentane); ir (KBr) ν 1781 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.00 (9H, s), 0.98 (2H, t, *J*=8 Hz), 2.69 (3H, s), 3.22 (3H, s), 3.62 (3H, s), 3.74 (2H, t, *J*=8 Hz), 5.11 (2H, s), 5.36 (2H, s), 5.93 (2H, s), 7.07-7.60 (3H, m), 8.00-8.25 (1H, m); ms *m/z*: 472 (M^+).
14. Compound (**4d**): mp 164-166 °C (decomp) (Et_2O); ir (KBr) ν 1769, 1431, 1140 cm^{-1}; ^{1}H-nmr

($CDCl_3$) δ 0.00 (9H, s), 1.01 (2H, t, *J*=8 Hz), 2.56 (3H, s), 3.87 (2H, t, *J*=8 Hz), 5.69 (2H, s), 7.16-7.58 (3H, m), 8.27-8.52 (1H, m); ms *m/z*: 516 (M^+). Compound (**5d**): mp 158-159 °C (Et_2O); ir (KBr) ν 1765, 1402, 1190 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.00 (9H, s), 0.99 (2H, t, *J*=8 Hz), 2.70 (3H, s), 3.72 (2H, t, *J*=8 Hz), 5.40 (2H, s), 7.20-7.57 (3H, m), 8.07-8.40 (1H, m); ms *m/z*: 516 (M^+).

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