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Solution-Phase Ring Opening Cross-Metathesis of Bicyclic Alkenes with Styrene Derivatives and Its Application to "Resin Capture" Solid-Phase Synthesis

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Abstract: The solution-phase ring opening cross-metathesis (ROM) of bicyclic alkenes with styrene derivatives is described. The influence of bicyclic alkene substituents on the rate and product distribution of solution-phase ROM reactions with styrene derivatives is discussed. In addition, a method for the "resin capture" of solution-phase ROM products by resin-bound amines is also illustrated.

Olefin cross-metathesis has evolved over the past several years into a widely applicable methodology in organic synthesis. One cause of this heightened interest has been the recent development of highly active, structurally well-defined, and functional group-tolerant molybdenum and ruthenium catalysts, such as $(Cy_3P)_2Cl_2Ru{=}CHPh$, **1**.[1] The metathesis reaction has been utilized in a diverse array of synthetic strategies for constructing a variety of macrocyclic, carbocyclic and heterocyclic molecules.[2] Although ring closing metathesis (RCM) has proven to be a versatile strategy for assembling complex organic molecules in solution and on solid support, *inter*molecular ring opening cross-metathesis (ROM) has remained relatively unexplored due in part to a lack of regioselectivity.[3] However, methods of influencing the regioselectivity of ROM reactions, through steric and electronic factors are beginning to emerge.[4] In light of these reported methods, we now describe the solution-phase ROM of a variety of bicyclic alkenes with styrene derivatives, as well as the influence of bicyclic alkene substituents on the reaction rate and product distribution of solution-phase ROM reactions with an array of styrene derivatives. In addition, a method for the "resin capture" of solution-phase ROM products by resin-bound amines will be illustrated.

ROM of bicyclic olefins with terminal aryl alkenes provides an efficient means of constructing molecular platforms that display various motifs and organic functional groups in three-dimensional space.[5] Such molecular scaffolds are useful for "lead seeking" exercises in drug discovery. We previously reported the ROM of bicyclic alkene **2** with 4-vinylanisole, **3**, at room temperature for 24 h in the presence of **1** (5 mol%) yielding the tetrasubstituted cyclopentane **4** in 61% isolated yield (Scheme 1).[6] Unlike alkyl substituted alkenes,

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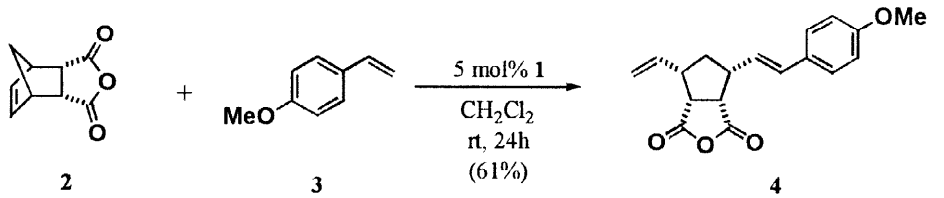
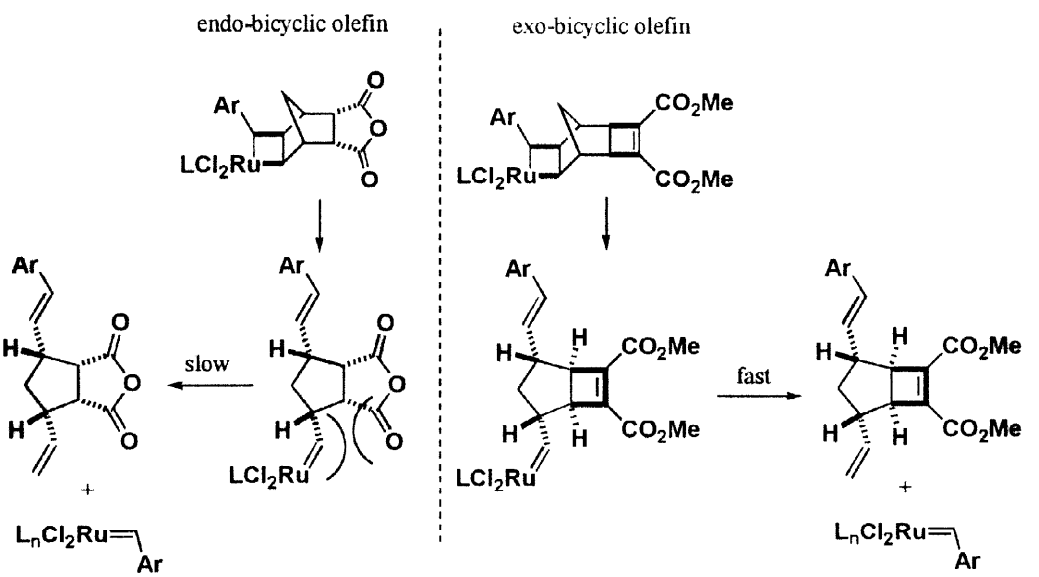
terminal aryl olefins lead to only the trans-substituted isomers.[3,4] Also, products arising from subsequent cross-metatheses of the initial product with another equivalent of 4-vinylanisole were not detected.



2 3 4

Scheme 1

The scope of the ROM of bicyclic olefins with styrene derivatives was further explored. The symmetrical bicyclic olefins **5** and **13**[7] were allowed to react with different terminal aryl olefins utilizing a standard protocol (1 equiv. bicyclic alkene, 0.07 M in dichloromethane, 2 equiv. styrene derivative, 2.5 mol% **1**). In most cases a single product was isolated in good yield (Table 1), and the structure of the products contained only one trans-substituted aryl alkene. However, when **5** was allowed to react with tert-butyl 4-vinylphenyl carbonate, **9**, three products were isolated: the trans-monoaryl alkene **10** (66%), the cis-monoaryl alkene **11** (7%), and the C-2 symmetric diaryl alkene **12** (6%).



Scheme 2

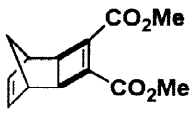
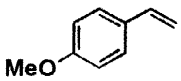
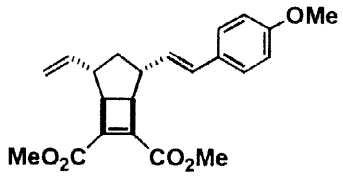
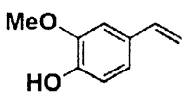
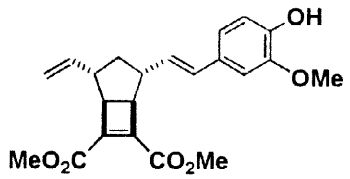
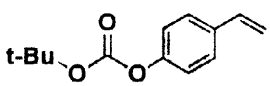
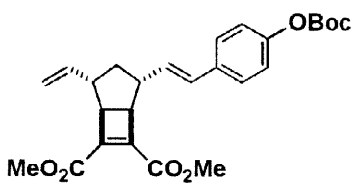
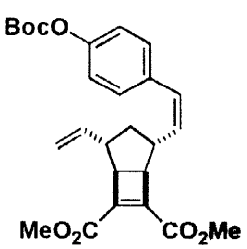
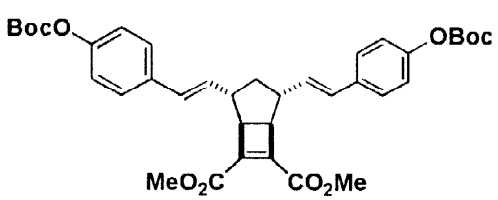
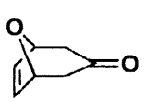
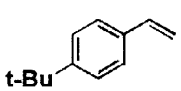
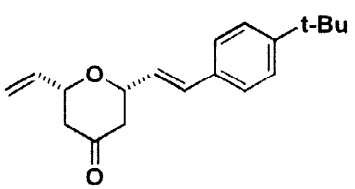
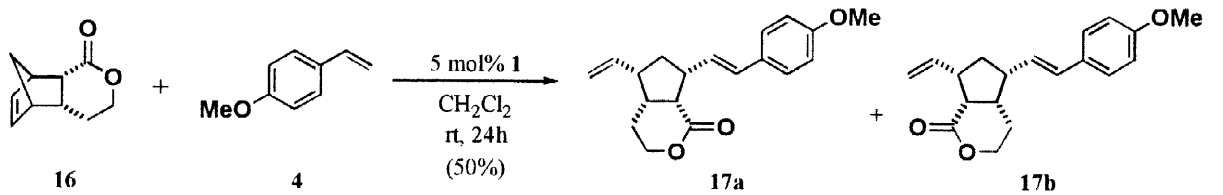
Bicyclic Olefin	Styrene	Reaction Time (h)	Isolated Products
 5	 4	2	 6 (68 %)
5	 7	2	 8 (82 %)
5	 9	2	 10 (66 %)  11 (7 %)  12 (6 %)
 13	 14	24	 15 (59 %; 83% based on recovered 13)

Table 1

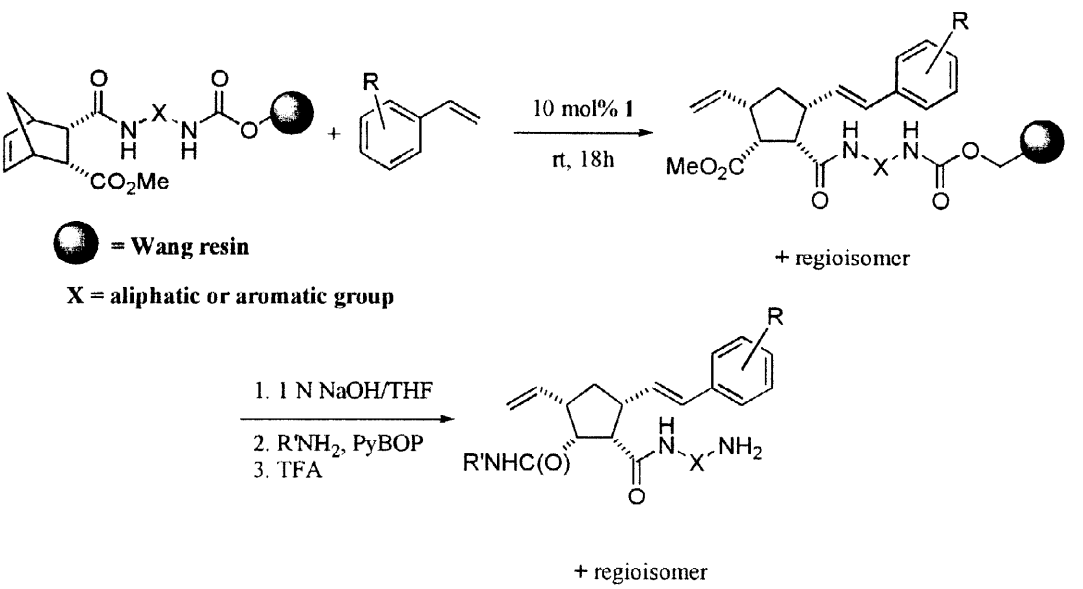
The rate of the ROM reaction was noticeably faster for the exo-substituted bicyclic olefins, such as **5** and **18**. For example, ROM with these substrates only required ~2 h, whereas the endo-substituted bicyclic olefins (**2**, **16**) and the [3.2.1]bicyclic olefin **13** required >18 h for complete consumption of starting materials. Assuming an exo-approach of the metal alkylidene to the bicyclic olefin, the exo- or endo-substituents should have little effect on the formation of the metallocyclobutane intermediate.[8] However, in the endo-substituted case the subsequent cross-metathesis step may be hampered by steric hindrance of the neighboring substituent (Scheme 2).[9]



16 **4** **17a** **17b**

Scheme 3

In the case of unsymmetrically substituted bicyclic alkenes, ROM with styrene derivatives yielded two regioisomer products, both containing trans-olefins. For example, the ROM of **16** utilizing the standard protocol (*vide supra*) gave a 50% yield of the 5,6-fused ring systems **17a** and **17b** in a 1:1 ratio (Scheme 3).

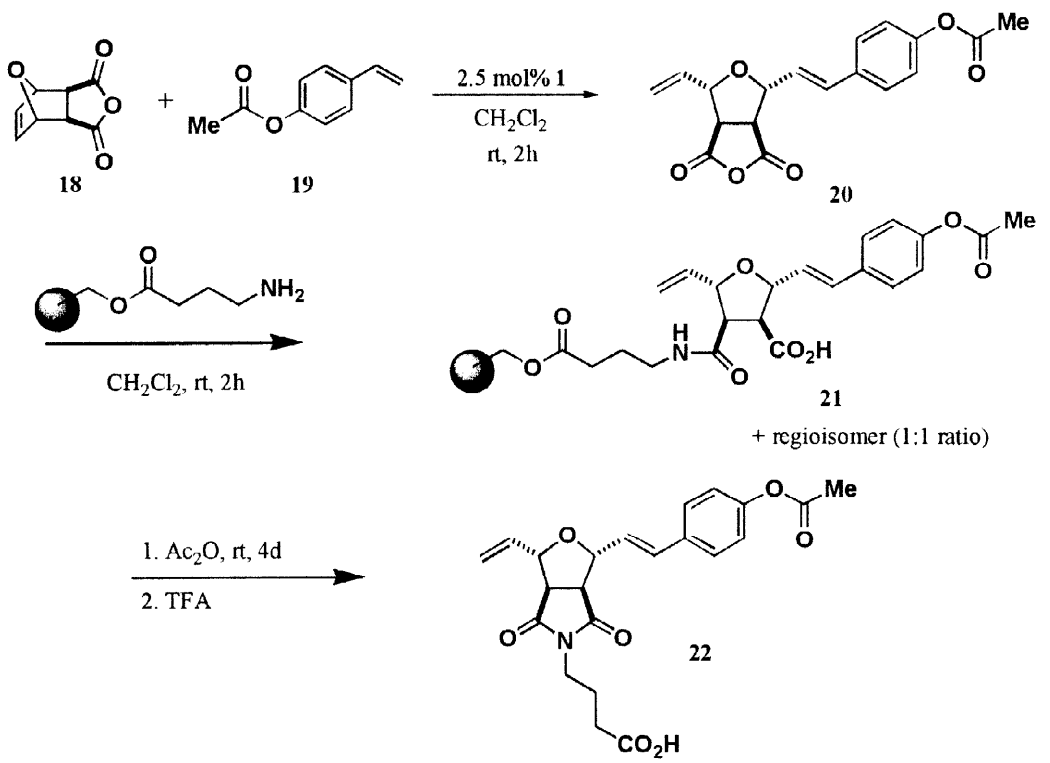


Scheme 4

We previously reported the solid-phase ROM of bicyclic alkenes with styrene derivatives and its applications to combinatorial library synthesis.[10] The general strategy utilized for ROM library production is outlined in Scheme 4. The bicyclic olefin was first attached to Wang resin via a diamine linker. The solid-phase ROM with a styrene derivative (10 equiv.) occurred in the presence of **1** (10 mol%) at room temperature for

18h. Ester hydrolysis of the ROM products allowed for the introduction of a third diversity element in the form of an amide. Finally, treatment of the resin with 50% trifluoroacetic acid (TFA) in CH_2Cl_2 yielded the products as a mixture of regioisomers.

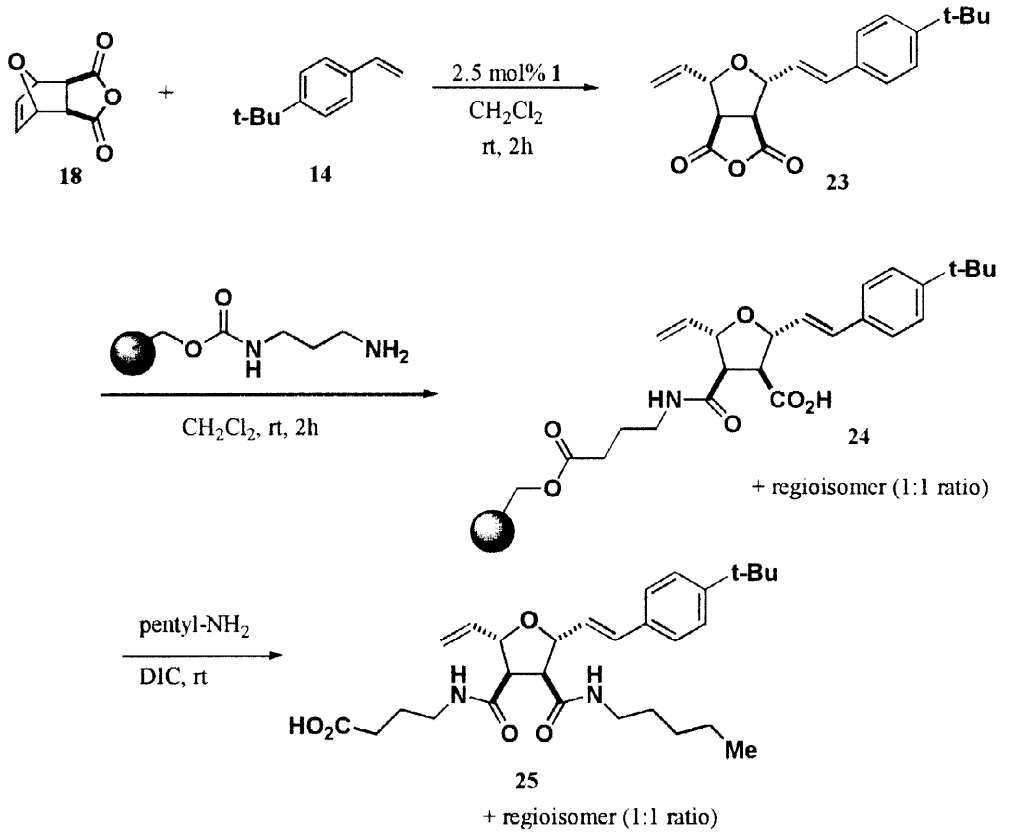
An alternative strategy to solid-phase ROM is the "resin capture" of solution-phase ROM products.[11] In the case of ROM, the "resin capture" strategy offers several advantages, such experimental simplicity and introduction of diversity elements during each reaction in the sequence. Resin capture is a method of initiating a combinatorial library synthesis in solution and transferring the solution-phase products to a solid support for subsequent transformations. For example, the solution-phase ROM of **18** with 4-acetoxystyrene, **19**, was performed utilizing the standard protocol (*vide supra*) to give **20** (Scheme 5). The crude reaction solution was concentrated to 0.45 M, then combined with resin(Wang)-bound γ-aminobutyric acid (GABA).[12] After 2h at room temperature, the resin was washed (CH_2Cl_2, DMF, MeOH, CH_2Cl_2). During this resin capture step the carboxylate is unmasked. Simple treatment with acetic anhydride (rt, 4d) followed by cleavage from the resin with TFA (50% in CH_2Cl_2 for 30 min) gave **22** (25% overall yield). The rather modest yield may be due to some premature cleavage from the resin and/or isolation difficulties of the final product, which was very hygroscopic. Alternatively, DIC mediated coupling of the carboxylate with a primary amine at room temperature resulted in the introduction of a third diversity element as outlined in Scheme 6, with improved mass recovery (>90 %).



Scheme 5

In summary, we have demonstrated the influence of bicyclic alkene substituents on the reaction rate and product distribution of solution-phase ROM reactions with styrene derivatives. Bicyclic substrates with exo-substituents react much faster than endo-substituted bicyclic alkenes and can also yield products resulting from

an additional cross-metathesis between the initial ROM product and styrene derivatives. Both of these results may stem from decreased steric hindrance in the exo-substituted bicyclic alkenes from neighboring substituents during the cross-metathesis step of the intermediate metalalkylidenes with styrene derivatives. In addition, a method for the "resin capture" of solution-phase ROM products by resin-bound amines was illustrated for the bicyclic anhydride **18**. Similar strategies can be envisioned for other bicyclic olefin substrates making this an attractive method for the combinatorial synthesis of molecular platforms that display various molecular motifs and organic functional groups in three-dimensional space.



Scheme 6

Experimental:

All metathesis reactions were conducted under an argon atmosphere in dichloromethane (Aldrich Chem. Co.) stored under nitrogen in Sure/Seal™ bottles. All reagents obtained from commercial sources were used without further purification, unless otherwise indicated. Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride, **1**, was purchased from Strem Chemicals, Inc. Wang Resin (1% divinylbenzene cross-linked; 0.85-1.01 mmol/g; 100-200 mesh) was purchased from Advanced ChemTech, Louisville, KY. The resin was saturated with reaction solvent prior to use. For metathesis reactions the resin was saturated with dichloromethane in an inert atmosphere prior to the addition of the other reagents. Elemental and mass spectral

analyses were performed by Atlantic Microlab, Inc., Norcross, GA and M-Scan, Inc., West Chester, PA, respectively.

General Solution-Phase ROM Procedure: A flask, under an atmosphere of argon, was charged with a bicyclic alkene (1.8 mmol), dichloromethane (25 mL), styrene derivative (3.6 mmol), and **1** (37 mg, 2.5 mol%). The reaction mixture was allowed to stir at room temperature for 2-24 h. The mixture was concentrated and the resulting residue purified by column chromatography on silica gel to give the products.

4: Purified residue by column chromatography on silica gel using hexane/ethyl acetate (75:25) as the eluant to give **4** (61% yield) as a white crystalline solid. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.54 (q, 1H, J=12.9 Hz); 2.10 (m, 1H); 3.00-3.20 (m, 2H); 3.50-3.59 (m, 2H); 3.79 (s, 3H); 5.18 (pent, 1H, J=1.2 Hz); 5.20-5.32 (m, 1H); 5.97 (sept, 1H, J_1=7.5 Hz, J_2= 3.0 Hz); 6.13 (dd, 1H, J_1= 15.8 Hz, J_2= 7.8 Hz); 6.47 (d, 1H, J=15.8 Hz); 6.86 (d, 2H, J=8.6 Hz); 7.32 (d, 2H, J=8.6 Hz) ; ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): δ 37.11, 46.69, 47.21, 50.06, 50.53, 55.78, 114.5, 117.29, 125.00, 128.01, 130.06, 131.80, 135.83, 159.91, 171.39, 171.46; Elemental Analysis: (cal.) C 72.47, H 6.08; (found) C 72.40, H 6.12.

6: Purified residue by column chromatography on silica gel using hexane/ethyl acetate (85:15) as the eluant to give **6** (68% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84-1.90 (m, 1H); 2.32-2.42 (m, 1H); 2.78-2.90 (m, 1H); 2.92-2.98 (m, 1H); 3.30-3.4 (m, 2H); 3.8 (s, 6H); 5.00-5.14 (m, 2H); 5.84-5.98 (m, 1H); 6.04-6.14 (m, 1H); 6.34 (d, 1H); 6.82 (d, 2H); 7.25 (d, 2H). HRMS (M+H): (cal.) 369.1702, (obs.) 369.1722.

8: Purified residue by column chromatography on silica gel using hexane/ethyl acetate (75:25) as the eluant to give **8** (82% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (dt, 1H, J_1=13.5 Hz, J_2=2.7 Hz); 2.37 (pent, 1H, J=7.2 Hz); 2.80-2.95 (m, 2H); 3.36-3.39 (m, 2H); 3.83 (s, 3H); 3.88 (s, 3H); 5.05 (tq, 2H, J_1=10.2 Hz, J_2=1.5 Hz); 5.92 (sept, 1H, J_1=8.7 Hz, J_2= 3.6 Hz); 6.07 (dd, 1H, J_1= 15.9 Hz, J_2= 7.5 Hz); 6.32 (dd, 1H, J_1=15.9 Hz, J_2=1.2); 6.80-6.87 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 39.20, 40.79, 41.13, 51.10, 51.81, 52.11, 55.97, 108.24, 113.96, 114.57, 119.59, 129.03, 130.25, 131.86, 142.23, 144.02, 144.10, 145.18, 146.71, 161.67, 161.69.

10, 11, and 12: Purified residue by spin plate chromatography on silica gel using hexane/ethyl acetate (85:15) as the eluant to give **11, 10,** and **12** (80% total yield) all as pale yellow oils. The ratio of **10**:**11**:**12** was 83:9:8 **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H); 1.85-1.92 (m, 1H); 2.38 (pent, 1H, J=7.2 Hz); 2.80-2.97 (m, 2H); 3.36-3.40 (m, 2H); 3.81 (s, 6H); 5.05 (tq, 2H, J_1=10.2 Hz, J_2=1.8 Hz); 5.89 (sept, 1H, J_1=8.4 Hz, J_2= 3.6 Hz); 6.17 (dd, 1H, J_1= 15.9 Hz, J_2= 7.8 Hz); 6.37 (d, 1H, J_1=15.9 Hz); 7.08-7.12 (m, 2H); 7.27-7.32 (m, 2H);

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 27.86, 39.00, 40.78, 40.98, 51.04, 51.64, 52.18, 83.74, 114.16, 121.48, 127.03, 128.31, 134.43, 135.38, 142.12, 143.88, 144.15, 150.16, 152.04, 161.66. **11**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H); 1.81-1.85 (m, 1H); 2.36 (pent, 1H, J=7.2 Hz); 2.83-2.88 (m, 1H); 3.27-3.32 (m, 2H); 3.43-3.45 (m, 1H); 3.76 (s, 3H); 3.80 (s, 3H); 5.06 (tq, 2H, J_1=11.7 Hz, J_2=1.5 Hz); 5.68 (dd, 1H, J_1= 11.4 Hz, J_2= 10.5 Hz); 5.94 (sept, 1H, J_1=8.1 Hz, J_2= 4.2 Hz); 6.30 (d, 1H, J_1=11.4 Hz); 7.12-7.16 (m, 2H); 7.32-7.36 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 27.87, 36.56, 39.12, 40.72, 51.01, 52.16, 52.68, 83.76, 114.26, 121.15, 127.20, 130.13, 134.79, 136.14, 142.27, 143.45, 144.23, 149.77, 152.03, 161.46, 161.66. **12**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 18H); 1.96-2.03 (m, 2H); 2.45 (pent, 2H, J=6.9 Hz); 2.98-3.02 (m, 4H); 3.44 (s, 4H); 3.83 (s, 6H); 5.68 (dd, 2H, J_1= 15.9 Hz, J_2= 7.2 Hz); 6.42 (d, 2H, J_1=15.9 Hz); 7.06 (d, 4H, J=8.7 Hz); 7.26 (d, 4H, J=8.7 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 27.86, 39.38, 40.48, 51.52, 52.21, 83.66, 121.50, 127.01, 128.53, 134.28, 135.20, 143.98, 150.22, 151.95, 161.63.

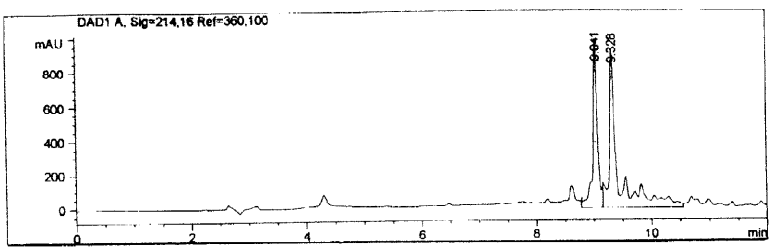
15: Purified residue by column chromatography on silica gel using hexane/diethyl ether (80:20) as the eluant to give **15** (59% yield; 83% based on recovered **13**) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H); 2.43-2.55 (m, 4H); 4.20-4.25 (m, 1H); 4.30-4.37 (m, 1H); 5.22-5.39 (m, 2H); 5.91-6.02 (m, 1H); 6.18-6.29 (m, 1H); 6.64 (octet, 1H, J_1=15.9 Hz, J_2= 7.5 Hz, J_3=1.2 Hz); 7.34-7.37 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): δ 31.43, 34.77, 47.48, 48.00, 116.68, 125.69, 126.51, 127.39, 131.53, 133.52, 137.15, 151.35, 206.13.

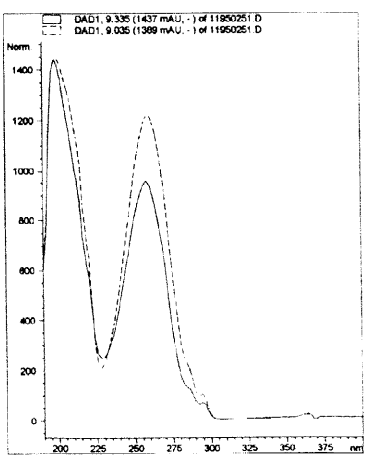
17a and 17b: Purified residue by column chromatography on silica gel using hexane/ethyl acetate (70:30) as the eluant to give a mixture of **17a** and **17b** (1:1 ratio; 50% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.62-1.78 (m, 3H); 2.10-2.20 (m, 1H); 2.45-2.60 (m, 1H); 2.65-2.97 (m, 1H); 3.18-3.40 (m, 2H); 3.78 and 3.81 (2s, 3H); 4.14-4.23 (m, 1H); 4.38-4.46 (m, 1H); 5.02-5.18 (m, 2H); 5.78-6.1 (m, 2H); 6.38-6.42 (m, 1H); 6.80-6.90 (m, 2H), 7.24-7.30 (m, 2H). HRMS (M+H): (cal.) 299.1647, (obs.) 299.1630.

Preparation of **22** *by ROM-Resin Capture Methodology*: A flask, under an atmosphere of argon, was charged with **18** (300 mg, 1.8 mmol), dichloromethane (25 mL), 4-acetoxystyrene, **19** (551 μL, 3.6 mmol), and **1** (37 mg, 2.5 mol%). The reaction mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and the resulting residue was dissolved in dichloromethane (4 mL). This solution was added to 400 mg of resin(Wang)-bound γ-aminobutyric acid (0.8 mmol/g). The mixture was shaken at room temperature for 4h and then washed with dichloromethane (3 x 5 mL). The resin was suspended in dichloroethane (3 mL) and acetic anhydride (1 mL) at room temperature for 4d. The mixture was allowed to cool to room temperature and then washed with dichloromethane (5 x 5 mL). The product was cleaved from the resin with 50% TFA in dichloromethane (4 mL). The filtrate was concentrated to give a yellow oil. The oil

was purified by reverse-phase prep-HPLC using acetonitrile/water (1:1) as the eluent to give **22** (25% yield) as a white crystalline solid upon lyophilization. Note: This product is quite hygroscopic. ^{1}H NMR (300 MHz, 50% $CDCl_3$ in d_8-THF): δ 1.82-1.92 (m, 2H); 2.24 (s, 3H); 2.27-2.31 (m, 2H); 3.28-3.40 (m, 2H); 3.50-3.57 (m, 2H); 4.43 (t, 1H, J=6.3 Hz); 4.57 (t, 1H J=6.0 Hz); 5.24 (dd, 1H, J_1=10.5 Hz, J_2=1.2 Hz); 5.41-5.47 (m, 1H); 6.03 (sept, 1H, J_1=8.0 Hz, J_2= 4.5 Hz); 6.33 (dd, 1H, J_1= 15.9 Hz, J_2= 6.3 Hz); 6.73 (d, 1H, J=15.9 Hz); 7.05 (d, 2H, J=8.7 Hz); 7.44 (d, 2H, J=8.7 Hz) ; ^{13}C{^{1}H} NMR (75 MHz, 50% $CDCl_3$ in d_8-THF): δ 20.46, 22.34, 30.88, 37.85, 51.89, 52.23, 81.20, 81.41, 117.16, 121.30 (2C), 126.99, 127.12, 131.10, 133.34, 135.77, 150.04, 168.60, 173.94, 175.38. HRMS (M+Na): (cal.) 436.1372, (obs.) 4361374.

Preparation of **25** *by ROM-Resin Capture Methodology*: A flask, under an atmosphere of argon, was charged with **18** (150 mg, 0.9 mmol), dichloromethane (12 mL), 4-t-butylstyrene, **14** (330 μL, 1.8 mmol), and **1** (18 mg, 2.5 mol%). The reaction mixture was allowed to stir at room temperature for 2 h. The mixture was concentrated and the resulting residue was dissolved in dichloromethane (2 mL). This solution was added to 200 mg of resin(Wang)-bound γ-aminobutyric acid (0.8 mmol/g). The mixture was shaken at room temperature for 2h and then washed with dichloromethane (3 x 5 mL). The resin was suspended in dichloromethane (3 mL) and then DIC (120 μL) and n-pentylamine (120 μL) was added. The mixture was shaken at room temperature overnight and then washed sequentially with DMF (2 x 5 mL), MeOH (2 x 5 mL) and CH_2Cl_2 (3 x 5 mL). The product was cleaved from the resin with 50% TFA in dichloromethane (2 mL) for 40 min. The filtrate was concentrated to give **25** (1:1 mixture of regioisomers) as a dark yellow oil (76 mg, 95% crude yield). HRMS (M+H): (cal.) 499.3172, (obs.) 499.3190. Crude HPLC and UV spectra of **25**:





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