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Asymmetric multicomponent reactions: convenient access to acyclic stereocenters and functionalized cyclopentenoids

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Abstract—Asymmetric multicomponent reactions of optically active phenyl dihydrofuran, keto ester or *N*-tosyl imino ester, and allylsilane provided functionalized phenyl tetrahydrofurans with multiple stereogenic centers diastereoselectively. Cleavage of the resulting substituted tetrahydrofurans readily provided acyclic derivatives with three contiguous asymmetric centers via an acyloxycarbenium ion intermediate. Ring closing olefin metathesis, using Grubbs catalyst, afforded functionalized cyclopentene derivatives in optically active form. A one-pot tandem tetrahydrofuran ring cleavage followed by ring closing olefin metathesis also provided functionalized cyclopentenes in good yield.

1. Introduction

Recently, we reported the syntheses of a variety of substituted tetrahydrofurans and tetrahydropyrans with the creation of multiple stereogenic centers in a single operation by novel multicomponent coupling reactions.[1] The overall protocol is practical, efficient, and provided rapid access to functionalized heterocycles. Subsequently, we have shown that multicomponent reactions of optically active phenyl dihydrofuran, *N*-tosyl imino ester, and carbon nucleophiles can provide stereocontrolled synthesis of unnatural optically active heterocyclic amino acids with multiple stereocenters.[2] To broaden the scope and utility of this reaction further, we envisioned the cleavage of such functionalized phenyl tetrahydrofuran derivatives to provide access to acyclic derivatives with multiple stereocenters in optically active form. Also, for all previous investigation, we synthesized optically active 2-phenyl-2,3-dihydrofuran using the Hayashi–Heck[3] reaction of aryl triflate and dihydrofuran in 80–88% ee. While the methodology provided enantioenriched phenyldihydrofuran in a single step, operational complexity, low enantiomeric excess, and lack of generality led us to explore alternative synthesis of optically active dihydrofuran. Herein, we report an alternative synthesis of optically active phenyl dihydrofuran, its conversion to functionalized tetrahydrofurans in high diastereomeric purity, and a Lewis acid-catalyzed cleavage of the substituted tetrahydrofurans via an acyloxycarbenium ion intermediate to provide acyclic derivatives with three contiguous asymmetric centers. The acyclic precursors can be converted to functionalized cyclopentene derivatives in an optically active form by a ring closing metathesis using Grubbs catalyst. We have also demonstrated a one-pot tandem Lewis acid-catalyzed cleavage followed by ring closing olefin metathesis to afford functionalized cyclopentene derivatives in good yield. Such functionalized cyclopentenoids are often structural features of a variety of bioactive natural products.[4]

2. Results and discussion

The synthesis of optically active phenyldihydrofuran was carried out as outlined in Scheme 1. The known γ-lactone **1** was prepared in multigram quantity using an enantioselective CBS-reduction as the key step.[5,6] The reduction of **1** by DIBAL-H provided the corresponding lactol. Reaction of the resulting lactol with mesyl chloride and triethylamine at −50 °C provided the mesylate. Heating of the mesylate at 42 °C furnished phenyldihydrofuran **2** in 60% yield. The protocol is convenient and both enantiomers of phenyldihydrofuran **2** can be prepared in high enantiomeric purity (93–94% ee).[7]

An asymmetric multicomponent reaction was then carried out with this optically active phenyl dihydrofuran **2**.

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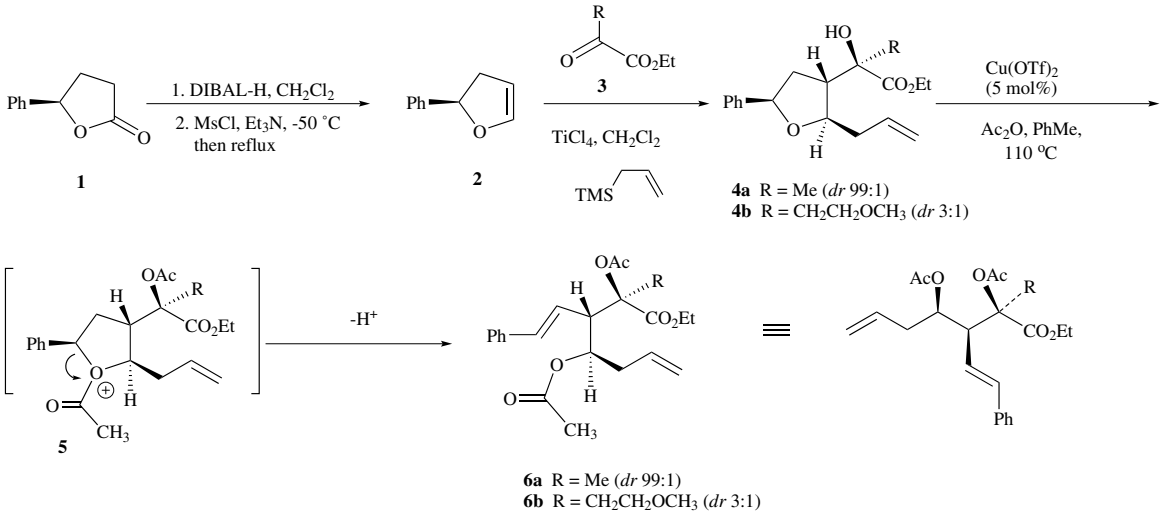


Scheme 1.

As described, the reaction of 2-phenyl-2,3-dihydrofuran **2** (1.2 equiv) and ethyl pyruvate **3a** (R = Me, 1 equiv) in the presence of $TiCl_4$ (1 M solution in CH_2Cl_2, 1.1 equiv) at −78 °C for 1 h, followed by the addition of trimethylsilane (3 equiv) at −78 °C and warming up the reaction to 23 °C for 1 h. The reaction was quenched with saturated $NaHCO_3$ solution, standard work up and flash chromatography over silica gel provided the single condensation product **4a** in 75% yield as a single diastereomer (by ^1H and ^{13}C NMR analysis). We have also carried out multicomponent reaction with ethyl 4-methoxy-2-oxobutanoate which was prepared according to published procedure.[8] Multicomponent reaction of **2** with ethyl 4-methoxy-2-oxobutanoate **3b** ($R = CH_2CH_2OCH_3$), as described above, furnished product **4b** as a 3:1 inseparable mixture of diastereomers in 67% yield. These multicomponent reactions afforded highly functionalized tetrahydrofuranyl derivatives **4a** and **4b** diastereoselectively with efficient construction of three contiguous asymmetric centers including a quaternary carbon center. Conceivably, the appropriate cleavage of the tetrahydrofuran ring would provide access to stereocontrolled acyclic derivatives in optically active form. As it turned out, the 2-phenyltetrahydrofuran is suitably positioned to be cleaved by an acyloxycarbenium ion mediated ring opening reaction. Unsubstituted phenyltetrahydrofuran was known to react with excess of metal halide in acetic anhydride to provide 4-acetoxy-1-phenylbut-1-ene.[9] Cleavage of a more substituted phenyltetrahydrofuran has been carried out by us recently using a catalytic amount of $ZnCl_2$ in acetic anhydride at 120 °C. We elected to utilize this protocol. Thus, 2-phenyl tetrahydrofuran derivative **4a** was exposed to the above reaction conditions for 4 h. This has afforded the styryl derivative **6a** in 25% yield. The reaction proceeded first by Lewis acid-catalyzed formation of the acetate (monitored by TLC and by ^1H NMR) followed by the formation of a possible acyloxycarbenium ion intermediate **5**, then stable benzylic carbonium ion and loss of a proton to provide **6a**.[10] To further improve the reaction yield, we have examined a number of Lewis acids under a variety of reaction conditions. The results are shown in Table 1. Entry 8 provided the optimum result.

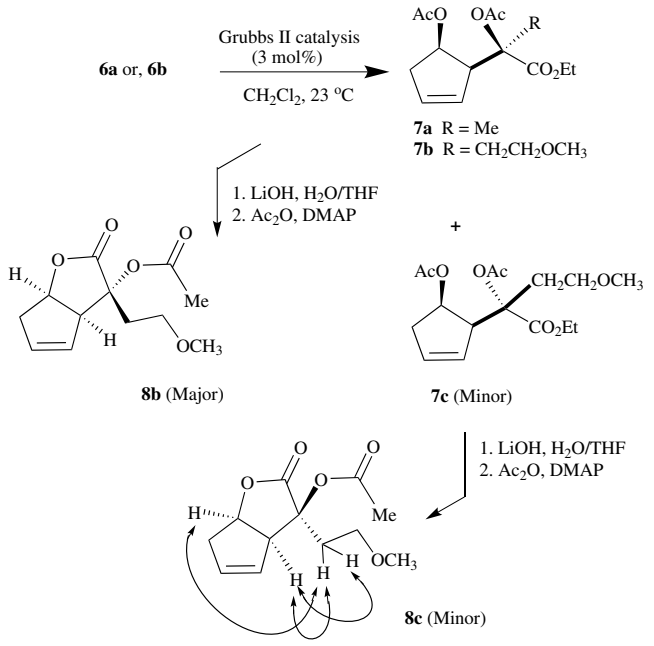
Table 1. Optimization of conditions of ring opening reaction

Entry	Lewis acid	Equivalents	Solvent[a]	Yield[b] (%)
1	$ZnCl_2$	0.06	Ac_2O	25
2	$ZnCl_2$	0.20	Ac_2O/toluene	—
3[b]	$Zn(OTf)_2$	1.00	Ac_2O/toluene	79
4	$Zn(OTf)_2$	0.20	Ac_2O/toluene	75
5	$Zn(OTf)_2$	0.10	Ac_2O/toluene	75
6	$Sc(OTf)_3$	0.20	Ac_2O/toluene	73
7	$Cu(OTf)_2$	0.20	Ac_2O/toluene	85
8	$Cu(OTf)_2$	0.05	Ac_2O/toluene	82

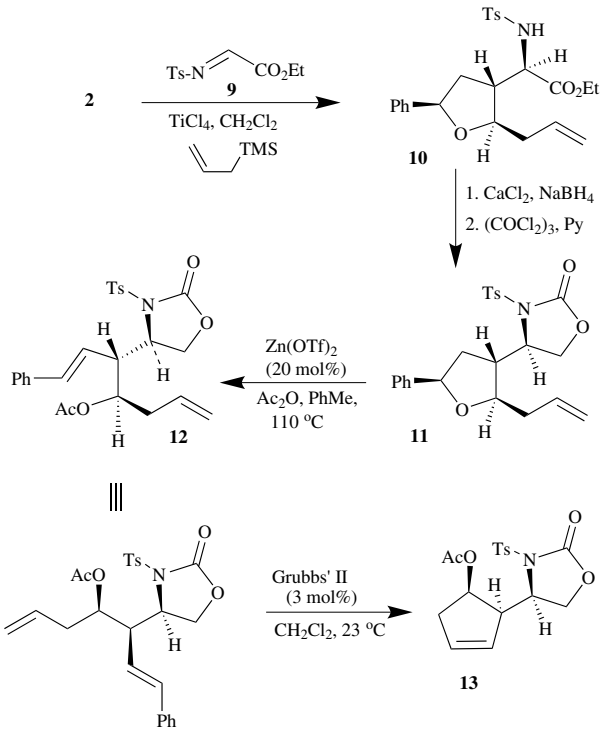
[a] Reaction temperature of 110 °C.
[b] Isolated yield after silica gel chromatography.

Thus, the reaction of **4a** with a catalytic amount of $Cu(OTf)_2$ in a mixture (10:1) of toluene and acetic anhydride at reflux provided acyclic derivative **6a** in 85% yield as a single diastereomer. Similarly, phenyltetrahydrofuran **4b** afforded acylic derivative **6b** in 83% yield as a 3:1 inseparable mixture of diastereomers. Thus, the asymmetric multicomponent reaction followed by acyloxycarbenium ion mediated ring opening afforded **6a** and **6b** (major product) containing multiple stereocenters in an optically active form. Both these derivatives are also suitable precursors for the synthesis of substituted cyclopentene derivatives by a ring closing olefin metathesis.[11] Thus, the exposure of **6a** to Grubbs II catalyst (3 mol %) in CH_2Cl_2 at 23 °C for 4 h afforded cyclopentene derivative **7a** in optically active form (Scheme 2).[12] We then attempted to carry out Lewis acid-catalyzed ring opening and ring closing metathesis in one operation. Indeed, treatment of **4a** with a catalytic amount (20 mol %) of $Zn(OTf)_2$ in the presence of acetic anhydride in toluene at 110 °C for 12 h followed by exposure of the resulting ring opening product to 3% Grubbs catalyst at 23 °C for 4 h afforded cyclopentene **7a** in 58% yield. Treatment of **4a** with 20 mol % $Zn(OTf)_2$ and 5 mol % Grubbs II catalyst at 110 °C for 12 h afforded only a trace amount of **7a** with starting material mostly unchanged.

Exposure of **6b** and its diastereomer to Grubbs II catalyst (3 mol %) in CH_2Cl_2 at 23 °C furnished cyclopentenes **7b**



Scheme 2.



Scheme 3.

and **7c**. The isomers were separated by flash column chromatography. The stereochemistry of the cyclopentenes was determined based on the NOESY studies on the corresponding bicyclic lactones **8b** and **8c**.

We had previously reported that the multicomponent reaction of *N*-tosyl imino ester[2a] with 2-phenyldihydrofuran **2** in the presence of $TiCl_4$ with allyltrimethylsilane as a nucleophile provided the single diastereomer **10** in 72% yield (Scheme 3). To determine the cyclic stereochemistry in an acyclic form, we attempted acycloxycarbenium ion mediated ring opening of tosylamine derivative **9** as described above for phenyltetrahydrofuran derivatives **4a** and **4b**. However, the above reaction conditions failed to provide any ring opening product, even in presence of 3 equiv of Lewis acid. The starting material remained mostly unchanged. The formation of the acyloxycarbenium ion was possibly retarded due to sequestering of the Lewis acid by the tosylamide functionality.[14] Therefore, ethyl ester **10** was reduced using $NaBH_4$ in the presence of $CaCl_2$ and resulting alcohol was treated with triphosgene in pyridine to provide oxazolidinone **11** in 61% yield (over two steps).[15] Oxazolidinone **11** was then treated with a catalytic amount (5 mol %) of $Cu(OTf)_2$ which gave the expected ring opening product **12** in 67% yield, and increasing the catalyst loading to 10 mol % resulted in the improvement of isolated yield to 73%. Exposure of oxazolidinone **11** to a catalytic amount (20 mol %) of $Zn(OTf)_2$ in presence of excess acetic anhydride in toluene however, provided the ring opening product **12** in 81% isolated yield. All three asymmetric centers in acyclic derivative **12** were constructed diastereoselectively during the multicomponent reaction. Diene **12** is set to form a functionalized cyclopentene derivative **13**. Thus, treatment of **12** with Grubbs catalyst (3 mol %) in CH_2Cl_2 at 23 °C for 4 h afforded cyclopentene in optically active form. The enantiomeric excess of compound **13** was determined by the reduction of this compound with Dibal-H in CH_2Cl_2 at −78 °C followed by the conversion of the alcohol to the Mosher ester. The ^{19}F NMR analysis of the Mosher ester established enantiomeric excess of **10** as 87% ee.[16]

3. Conclusions

In conclusion, the asymmetric multicomponent reaction diastereoselectively constructed functionalized tetrahydrofuran derivatives containing multiple stereocenters. Lewis acid-catalyzed cleavage of phenyltetrahydrofuran ring via acyloxycarbenium ion intermediate provided useful access to acyclic derivatives with three contiguous asymmetric centers. Acyclic derivatives were converted to functionalized cyclopentene derivatives in optically active form by ring closing olefin metathesis.

4. Experimental

4.1. General

All melting points were recorded on a melting point apparatus and are uncorrected. Anhydrous solvents were obtained as follows: THF and diethyl ether by distillation from sodium and benzophenone; pyridine and dichloromethane from CaH_2. All other solvents were reagent grade. All moisture-sensitive reactions were carried out in flame-dried flask under nitrogen atmosphere. Column chromatography was performed with 240–400 mesh silica gel under low pressure of 3–5 psi. TLC was carried out with Silica

Gel 60-F-254 plates. The title α-*N*-tosyl imino ester was made from ethyl glyoxylate and *N*-toluenesulfonylisocyanate by Weinreb's procedure.[13] Ethyl 4-methoxy-2-oxobutanoate **3b** was prepared according to the reported procedure.[8]

4.1.1. (*R*)-2-Phenyl-2,3-dihydrofuran 2. To a stirred solution of lactone **1** (0.5 g, 3 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added a solution of DIBAL-H (1 M in CH_2Cl_2, 3.7 mmol). After stirring at −78 °C for 1 h, the reaction was quenched with saturated aqueous potassium sodium tartrate. The mixture was diluted with CH_2Cl_2 and vigorously stirred at room temperature for 2 h. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to provide the crude lactol as a colorless oil, which was immediately used in the next reaction without further purification.

To a stirred solution of the above lactol in CH_2Cl_2 (25 mL) at −50 °C was added triethylamine (1.2 mL, 12.2 mmol) followed by methanesulfonyl chloride (0.3 mL, 3.9 mmol). The solution was stirred for 1 h at −50 °C and then the reaction mixture was warmed to 23 °C and heated at reflux for 12 h. The reaction mixture was then cooled to 23 °C, solvents were evaporated, and purified by column chromatography to afford phenyl dihydrofuran **2** (272 mg, 60% yield over 2 steps) as clear oil $R_f = 0.3$ (pentane: $CH_2Cl_2 = 3{:}1$), $[\alpha]_D^{23} = -66$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (qt, $J = 2$, 8 Hz, 1H), 3.06–3.13 (m, 1H), 4.98 (dd, $J = 2.5$, 6.4 Hz, 1H), 5.53 (dd, $J = 8.5$, 13.3 Hz, 1H), 6.47 (dd, $J = 2.4$, 4.7 Hz, 1H), 7.28–7.45 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$); 37.8, 82.3, 98.9, 125.5, 127.6, 128.5, 142.9, 145.2. IR (film, NaCl) 2928, 1619, 1135, 1051 cm^{-1}.

4.1.2. (*R*)-Ethyl2-((2*R*,3*R*,5*R*)-2-allyl-5-phenyltetrahydrofuran-3-yl)-2-hydroxypropanoate 4a. To a mixture of ethyl pyruvate (232 mg, 2 mmol) and (*R*)-2,3-dihydro-2-phenylfuran **1** (350 mg, 2.4 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was added a solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 2.2 mmol) and the resulting orange solution was stirred at −78 °C for 1 h. Allyltrimethylsilane (686 mg, 6 mmol) was added and the mixture was warmed from −78 °C to 23 °C over 1 h. Then the reaction mixture was quenched carefully with 15 mL saturated sodium bicarbonate solution and the aqueous layer was extracted with dichloromethane (3×). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified further by flash column chromatography on silica gel to afford the tertiary alcohol **4a** (454 mg, 75% yield) as a yellow oil, $R_f = 0.48$ (25% EtOAc in hexanes), $[\alpha]_D^{23} = +15.7$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, $J = 7$ Hz, 3H), 1.42 (s, 3H), 1.78–1.84 (m, 1H,), 2.03–2.07 (m, 1H), 2.42–2.48, (m, 2H), 2.61–2.66 (m, 1H), 3.51 (s, 1H), 4.20–4.28 (m, 3H), 4.89 (dd, $J = 10$, 6.5 Hz, 1H), 5.15–5.21 (m, 2H), 5.98–6.07 (m, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 24.8, 38.2, 40.9, 49.8, 62.3, 74.4, 75.3, 78.9, 80.6, 117.4, 125.8, 127.3, 128.2, 134.7, 142.2, 176.8; FT-IR (film, NaCl) 3462, 2979, 1784 cm^{-1}. *m*/*z* (CI) 305.05 $(M+H)^+$.

4.1.3. (*S*)-Ethyl2-((2*R*,3*S*,5*R*)-2-allyl-5-phenyltetrahydrofuran-3-yl)-2-hydroxy-4-methoxybutanoate 4b. The procedure described for **3a** was used for **3b**. Accordingly, ethyl-4-methoxy-2-oxobutanoate 1 (160 mg, 1 mmol), (*R*)-2,3-dihydro-2-phenylfuran 1 (175 mg, 1.2 mmol), $TiCl_4$ (1 M in CH_2Cl_2, 1.2 mmol) and allyltrimethylsilane (345 mg, 3 mmol) afforded furan **4b** (230 mg, 66% yield) as a 3:1 mixture of inseparable diastereomers, $R_f = 0.36$ (hex/EtOAc = 4:1), $[\alpha]_D^{23} = -15.3$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (t, $J = 7$ Hz, 3H, major), 1.34 (t, $J = 7.5$ Hz, minor), 1.76–1.97 (m, 2H), 1.98–2.11 (m, 2H), 2.17–2.23 (m, minor), 2.39–2.47 (m, 2H), 2.58–2.63 (m, 1H), 3.26 (s, minor), 3.27 (s, 3H, major), 3.41–3.46 (m, 1H), 3.49–3.56 (m, 1H), 3.75 (s, minor), 3.91 (s, 1H, major), 4.01–4.05 (m, minor), 4.16–4.30 (m, 3H), 4.87–4.92 (m, 1H), 5.09–5.20 (m, 2H), 5.92–6.04 (m, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (minor), 14.2 (major), 31.2 (minor), 37.0 (major), 37.2 (minor), 37.7 (minor), 37.9 (major), 39.5 (minor), 41.2 (major), 50.3 (major), 50.5 (minor), 58.9 (major), 61.2 (major), 68.4 (minor), 68.5 (major), 117.3 (minor), 117.4 (major), 126 (major), 126.1 (minor), 127.3 (major), 128.2 (major), 128.5 (minor), 134.7 (minor), 134.8 (major), 141.9 (major), 142.4 (minor), 175.6 (major), 175.9 (minor); FT-IR (film, NaCl) 3493, 2362, 1724 cm^{-1}. HRMS (CI) $[M+H]^+$ calcd for $C_{20}H_{28}O_5$ 349.2015, found 349.2018.

4.1.4. (2*R*,3*R*,5*R*)-1-Ethyoxy-2-methyl-1-oxo-3-styrylhept-6-ene-2,4-diyl diacetate 6a. A mixture of tertiary alcohol **4** (350 mg, 1.15 mmol), $Cu(OTf)_2$ (21 mg, 0.058 mmol), and acetic anhydride (5.5 mL, 57.5 mmol) was heated to 110 °C in toluene (50 mL) with stirring. After 2 h, the reaction mixture was cooled to room temperature and the reaction mixture was washed with saturated aqueous $NaHCO_3$ (2×). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified further by flash column chromatography on silica gel to afford styrene **6a** (355 mg, 80% yield) as a yellow oil, $R_f = 0.48$ (20% EtOAc in hexanes), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, $J = 7$ Hz, 3H), 1.67 (s, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.23–2.27 (m, 1H), 2.34–2.38 (m, 1H), 2.77 (d, $J = 10$ Hz, 1H), 4.07–4.20 (m, 2H), 5.07–5.11 (m, 2H), 5.38 (t, $J = 5$Hz, 1H), 5.76–5.88 (m, 1H), 6.24 (dd, $J = 16$, 10 Hz, 1H), 6.46 (d, $J = 16$ Hz, 1H), 7.26–7.30 (m, 1H), 7.35 (t, $J = 7$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.8, 21.2, 21.3, 37.9, 52.7, 61.4, 70.3, 81.8, 118.5, 122.7, 126.4, 127.7, 128.6, 133.1, 135.7, 136.6, 169.7, 169.9, 170.6; FT-IR (film, NaCl), 2981, 1742, 1642 cm^{-1}. HRMS (CI) $[M+H]^+$ calcd for $C_{22}H_{28}O_6$ 389.1964, found 389.1968.

4.1.5. (3*R*,4*S*,5*R*)-3-(Ethoxycarbonyl)-1-methoxy-4-styryloct-7-ene-3,5-diyl diacetate 6b. The procedure described for **5a** was used for **5b**. Accordingly furan **4b** (230 mg, 0.66 mmol), $Cu(OTf)_2$ (12 mg, 0.03 mmol), and acetic anhydride (3.1 mL, 33 mmol) were heated in toluene (30 mL) to give styrene **6b** (216 mg, 83% yield) as a 3:1 mixture of inseparable diastereomers, $R_f = 0.42$ (hex/EtOAc = 4:1), $[\alpha]_D^{23} = +44.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, $J = 7$ Hz, 3H, major), 1.99 (s, 3H, major), 2.01 (s, minor), 2.02 (s, minor), 2.08 (s, 3H, major), 2.23–2.32 (m, 1H), 2.33–2.41 (m, 3H), 2.52–

2.60 (m, 1H), 3.09 (d, $J = 10$ Hz, minor), 3.18 (d, $J = 10$ Hz, 1H), 3.26 (s, 3H), 3.27 (s, minor), 3.41–3.49 (m, 3H), 4.05–4.29 (m, 3H), 5.04–5.11 (m, 3H), 5.33 (t, $J = 7.5$ Hz, minor), 5.45 (t, $J = 7$ Hz, 1H), 5.65–5.79 (m, 1H), 6.17 (dd, $J = 16$, 10 Hz, 1H), 6.25 (dd, $J = 16$, 10 Hz, minor), 6.48 (d, $J = 16$ Hz, 1H), 7.13–7.19 (m, 2H), 7.34 (t, $J = 7.5$ Hz, 3H), 7.69 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (major), 21.0 (minor), 21.1 (major), 21.2 (major), 31.8 (minor), 32.1 (major), 37.9 (major), 38.0 (minor), 50.2 (major), 50.7 (minor), 58.4 (minor), 58.5 (major), 61.1 (minor), 61.3 (major), 67.7 (major), 67.9 (minor), 70.4 (major), 70.7 (minor), 82.3 (major), 82.6 (minor), 118.0 (major), 118.1 (minor), 126.3 (minor), 126.4 (major), 127.5 (minor), 127.7 (major), 128.5 (major), 133.2 (minor), 133.4 (major), 135.7 (minor), 136.0 (major), 136.8 (major), 137.1 (minor), 169.6 (major), 169.7 (minor), 169.8 (major), 169.9 (major), 170.0 (minor); FT-IR (film, NaCl) 2361, 1742 1370, 972 cm^{-1}. HRMS (CI) $[M+Na]^+$ calcd for $C_{24}H_{32}O_7Na$ 455.2046, found 455.2050.

4.1.6. (*R*)-Ethyl 2-acetoxy-2-((1*S*,5*R*)-5-acetoxycyclopent-2-enyl)propanoate 7a. To a stirring solution of **6a** (230 mg, 0.59 mmol) in CH_2Cl_2 (120 mL) was added a second generation Grubbs catalyst (15 mg, 0.018 mmol) under argon. The reaction was allowed to stir at 23 °C for 4 h. After this period the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel to afford cyclopentene **6a** (147 mg, 88% yield) as a colorless oil, $R_f = 0.4$ (20% EtOAc in hexanes), $[\alpha]_D^{23} = -3.5$ (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (t, $J = 7$ Hz, 3H), 1.69 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 2.23–2.37 (m, 1H), 2.69–2.74 (m, 1H), 3.40–3.42 (m, 1H), 4.14–4.22 (m, 2H), 5.51 (dt, $J = 6.5$, 3 Hz 1H), 5.38 (t, $J = 5$ Hz, 1H), 5.76–5.88 (m, 1H), 6.24 (dd, $J = 16$, 10 Hz, 1H), 6.46 (d, $J = 16$ Hz, 1H), 7.26–7.30 (m, 1H), 7.35 (t, $J = 7$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.8, 21.2, 21.3, 37.9, 52.7, 61.4, 70.3, 81.8, 118.5, 122.7, 126.4, 127.7, 128.6, 133.1, 135.7, 136.6, 169.7, 169.9, 170.6; FT-IR (film, NaCl), 2981, 1742, 1642 cm^{-1}. HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{20}O_6Na$ 307.1158, found 307.1155.

4.1.7. (*R*)-Ethyl-2-acetoxy-2-((1*S*,5*R*)-5-cetoxycyclopent-2-enyl)-4-methoxybutanoate 7b. The procedure described for **7a** was used for **7b**. Accordingly, styrene **6b** (210 mg, 0.16 mmol), second generation Grubbs catalyst (12 mg, 0.015 mmol) in CH_2Cl_2 (30 mL) afforded cyclopentenes **7b** (92 mg, 58%) and **7c** (25 mg, 16%).

Compound **7b**: $[\alpha]_D^{23} = -3.2$ (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, $J = 7$ Hz, 3H), 2.02 (s, 3H), 2.10 (s, 3H), 2.52 (dt, $J = 14.8$, 6.5 Hz, 1H), 2.60 (dt, $J = 14.8$, 6.5 Hz, 1H), 2.65–2.71 (m, 1H), 3.30 (s, 3H), 3.47–3.54 (m, 2H), 3.78–3.80 (m, 1H), 4.16–4.26 (m, 2H), 5.56 (dt, $J = 6.5$, 1.7 Hz, 1H), 5.82–5.85 (m, 1H), 5.87–5.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.0, 21.5, 34.2, 39.9, 54.5, 61.4, 68.1, 73.0, 82.7, 128.8, 129.5, 169.9, 170.1, 170.4; FT-IR (film, NaCl) 1739, 1370, 1236 cm^{-1}. HRMS (CI) $[M+H]^+$ calcd for $C_{16}H_{25}O_7$ 329.1600, found 329.1607.

Compound **7c**: $[\alpha]_D^{23} = -5.5$ (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, $J = 7$ Hz, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.31–2.37 (m, 2H), 2.43–2.47 (m, 1H), 2.65–2.71 (m, 1H), 3.32 (s, 3H), 3.49–3.54 (m, 2H), 3.80 (br s, 1H), 4.14–4.28 (m, 2H), 5.56 (t, $J = 7$ Hz, 1H), 5.81–5.87 (m, 1H), 5.99–6.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.1, 21.2, 33.2, 40.1, 53.7, 58.6, 61.4, 74.0, 81.8, 128.3, 130.4, 170.2, 170.4, 170.5; FT-IR (film, NaCl) 1738, 1371, 1233 cm^{-1}. HRMS (CI) $[M+H]^+$ calcd for $C_{16}H_{25}O_7$ 329.1600, found 329.1603.

4.1.8. (3*S*,3a*S*,6a*R*)-3-(2-Methoxyethyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-3-yl acetate 8b. To a stirred solution of **6b** (90 mg, 0.27 mmol) in a mixture (3:1:1) of THF/EtOH/H_2O (3 mL) at 0 °C was added solid LiOH (35 mg, 0.82 mmol) and the mixture was stirred for 6 h at 23 °C. After this period, the solvent was evaporated and aqueous layer was then acidified with 1 M HCl to pH 3 and extracted with EtOAc (3×). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and purified by flash column chromatography on silica gel to provide the lactone (34 mg, 64% yield) as colorless oil.

To the above lactone (34 mg, 0.17 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C were added DMAP (103 mg, 0.84 mmol) and acetic anhydride (160 μL, 1.7 mmol). The resulting solution was stirred at 23 °C for 12 h. After this time the reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl, water, and brine. The organic layer was concentrated under reduced pressure and the residue purified by column chromatography on silica gel to provide **8b** (37 mg, 92% yield) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07–2.11 (m, 2H), 2.13 (s, 3H), 2.66 (d, $J = 18$ Hz, 1H), 2.73–2.79 (m, 1H), 3.36 (s, 3H), 3.51–3.54 (m, 1H), 3.67–3.75 (m, 2H), 5.35 (t, $J = 6.7$ Hz, 1H), 5.76–5.79 (m, 1H), 5.84–5.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 34.3, 38.7, 56.5, 58.8, 67.3, 79.6, 81.4, 127.1, 131.8, 174.2.

4.1.9. (3*S*,3a*S*,6a*R*)-3-(2-Methoxyethyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-3-yl acetate 8c. The procedure described for **8b** was used for **8c**. Accordingly, cyclopentene **7c** (25 mg, 0.08 mmol), and LiOH (10 mg, 0.23 mmol) afforded lactone (13 mg, 85% yield) as colorless oil. The above lactone (12 mg, 0.06 mmol), DMAP (37 mg, 0.30 mmol), and acetic anhydride (57 μL, 0.6 mmol) in CH_2Cl_2 (2 mL) afforded **8c** (11 mg, 70% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.23–2.28 (m, 1H), 2.58–2.64 (m, 1H), 2.78–2.79 (m, 2H), 3.34 (s, 3H), 3.52–3.57 (m, 1H), 3.62–3.66 (m, 1H), 3.95–3.97 (m, 1H), 5.06–5.09 (m, 1H), 5.40–5.42 (m, 1H), 5.86–5.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 35.2, 40.0, 56.1, 58.7, 67.3, 80.3, 81.8, 126.7, 131.8, 169.8, 173.3.

4.1.10. (*R*)-Ethyl2-((2*R*,3*R*,5*R*)-2-allyl-tetrahydro-5-phenylfuran-3-yl)-2-(tosylamino)acetate (10). To a mixture of freshly distilled α-*N*-tosyl imino ester **9** (255 mg, 1 mmol) and (*R*)-2,3-dihydro-2-phenylfuran **1** (175 mg, 1.2 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added a solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 1.1 mmol) and the resulting

orange solution was stirred at −78 °C for 50 min. Dry acetonitrile (205 mg, 5 mmol) was added at −78 °C and the mixture was stirred at −78 °C for 10 min. Allyltrimethylsilane (342 mg, 3 mmol) was added and the mixture was stirred at −78 °C for 1 h. Then the mixture was warmed to −20 °C and stirred at −20 °C for 2 h. Then the mixture was cooled to −30 °C and the reaction was quenched carefully with 15 mL ice-cooled saturated sodium bicarbonate solution. After the mixture was warmed to room temperature, the aqueous layer was extracted with dichloromethane (3×). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford the α-*N*-tosylamino ester **10** (320 mg, 72% yield) as a yellow oil, $R_f = 0.38$ (hex/EtOAc 3:2), $[\alpha]_D^{23} = -11.8$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (t, $J = 7.1$ Hz, 3H), 1.7–1.80 (m, 1H), 2.21–2.29 (m, 1H), 2.31–2.33 (m, 1H), 2.38–2.22 (m, 5H), 3.87–3.91 (m, 3H), 4.04–4.06 (m, 1H), 4.89 (t, $J = 7.7$ Hz, 1H), 5.11–5.17 (m, 2H), 5.39 (d, $J = 9.9$ Hz, 1H), 5.87–5.93 (m, 1H), 7.33–7.23 (m, 7H), 7.73 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.5, 36.1, 38.6, 45.9, 55.9, 62.0, 79.5, 79.7, 117.7, 125.7, 127.4, 128.3, 129.7, 134.1, 136.3, 142.1, 144.0, 171.0; FT-IR (film, NaCl), 2980, 1746, 1349.2, 1163 cm^{-1}; *m/z* (ESI) 444.1 $(M+H)^+$, 466.3 $(M+Na)^+$.

4.1.11. (*S*)-4-((2*R*,3*R*,5*R*)-2-Allyl-5-phenyltetrahydrofuran-3-yl)-3-tosyloxazolidin-2-one (11). To a stirring mixture of furan **10** (220 mg, 0.5 mmol) in THF/ethanol (2 mL:3 mL) at 0 °C was added $CaCl_2$ (116 mg, 1.05 mmol) followed by the addition of $NaBH_4$ (80 mg, 2.1 mmol), and the resulting solution was allowed to warm to room temperature over 3 h. After this time the reaction mixture was cooled to 0 °C and quenched carefully with 5% citric acid solution. This mixture was then concentrated under vacuum and the aqueous layer was extracted with ethyl acetate (3×). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford the primary alcohol (153 mg, 76% yield) as a colorless solid, $R_f = 0.2$ (25% EtOAc in hexanes), $[\alpha]_D^{23} = +4.7$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78–1.82 (m, 1H), 2.08–2.18 (m, 2H), 2.31 (t, $J = 7$ Hz, 2H), 2.43 (s, 1H), 3.31–3.35 (m, 1H), 3.53 (d, $J = 4$ Hz, 2H), 3.76 (q, $J = 6$ Hz, 1H), 4.68 (dd, $J = 8.5$, 6.5 Hz, 2H), 5.07–5.11 (m, 2H) 5.24 (d, $J = 9.5$ Hz, 1H), 5.78–5.83 (m, 1H), 7.19–7.34 (m, 7H), 7.79 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 29.6, 36.5, 39.4, 44.7, 63.4, 79.6, 80.5, 117.6, 125.5, 127.1, 127.2, 128.2, 129.9, 134.4, 137.3, 142.2, 143.9; FT-IR (film, NaCl), 3546, 3263, 2844 cm^{-1}.

To a stirring mixture of above amino alcohol (133 mg, 0.33 mmol) in dry CH_2Cl_2 (3 mL) were added pyridine (158 mg, 2 mmol) and triphosgene (49 mg, 17 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature over 3 h. The reaction mixture was diluted with CH_2Cl_2 and was washed with water (3×) and saturated aqueous $CuSO_4$ (5×) followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford oxazolidinone **11** (115 mg, 81% yield) as a yellow oil, $R_f = 0.5$ (25% EtOAc in hexanes), $[\alpha]_D^{23} = -32.5$ (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03–2.08 (m, 1H), 2.24–2.29 (m, 1H), 2.37–2.44 (m, 2H), 2.45 (s, 3H), 2.58–2.62 (m, 1H) 4.06 (q, $J = 6.5$ Hz, 1H), 4.24 (dd, $J = 2$, 9 Hz, 1H), 4.38 (t, $J = 8.5$ Hz, 1H), 4.65–4.68 (m, 1H), 4.96 (t, $J = 7.5$ Hz, 1H), 5.13–5.19 (m, 2H), 5.85–5.97 (m, 1H), 7.27–7.38 (m, 7H), 7.96 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 36.5, 39.6, 47.4, 57.8, 67.3, 79.7, 79.8, 118.2, 125.6, 127.6, 128.5, 129.9, 134.0, 134.9, 142.3, 146.0, 152.6; FT-IR (film, NaCl), 2924, 1783 cm^{-1}.

4.1.12. (3*R*,4*R*)-3-(2-Oxo-3-tosyloxazolidin-4-yl)-1-phenylhepta-1,6-diene-4-yl acetate (12). A mixture of oxazolidinone **11** (80 mg, 0.19 mmol), $Zn(OTf)_2$ (14.0 mg, 0.04 mmol) and acetic anhydride (890 μL, 9.4 mmol) was heated to 110 °C in toluene (15 mL) with stirring. After 2 h the reaction mixture was cooled to room temperature and the reaction mixture was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash column chromatography on silica gel to afford acetate **12** (71 mg, 81% yield) as a yellow oil, $R_f = 0.4$ (25% EtOAc in hexanes), $[\alpha]_D^{23} = +41.4$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.1 (s, 3H), 2.22–2.25 (m, 1H), 2.32–2.38 (m, 1H), 2.40 (s, 3H), 2.92–2.95 (m, 1H) 4.31 (t, $J = 7$ Hz, 1H), 4.47 (dd, $J = 2$, 9 Hz, 1H), 4.60 (dt, $J = 2$, 8.5 Hz, 1H), 5.03–5.08 (m, 3H), 5.50–5.59 (m, 1H), 6.20 (dd, $J = 9.5$, 16 Hz, 1H), 6.57 (d, $J = 16$, 1H), 7.22–7.40 (m, 7H), 7.96 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 21.1, 21.7, 37.6, 48.5, 59.1, 66.3, 70.4, 118.8, 122.06, 126.6, 128.2, 128.5, 128.7, 129.7, 132.7, 135.1, 136.2, 137.4, 145.6, 152.4, 170.3; FT-IR (film, NaCl), 2921, 1786, 1596 cm^{-1}; HRMS (EI) $[M+H]^+$ calcd for $C_{25}H_{28}NO_6S$ 470.1637, found 470.1648.

4.1.13. (1*R*,2*R*)-2-((*R*)-2-Oxo-3-tosyloxazolidin-4-yl)cyclopent-3-enyl acetate 13. The procedure described for **7a** was used for **13**. Accordingly, styrene **12** (71 mg, 0.15 mmol), second generation Grubb's catalyst (6 mg, 0.008 mmol) in CH_2Cl_2 (45 mL) afforded cyclopentene **13** (48 mg, 86% yield) as a white solid, $R_f = 0.3$ (20% EtOAc in hexanes), $[\alpha]_D^{23} = -87.4$ (*c* 0.85, $CHCl_3$); ^{1}H NMR(500 MHz, $CDCl_3$): δ 1.60 (s, 3H), 2.04–2.09 (m, 1H), 2.26 (s, 3H), 2.66–2.74 (m, 1H), 3.58 (s, 1H), 4.00 (dd, $J = 4$, 9 Hz, 1H), 4.15 (t, $J = 9$ Hz, 1H), 4.57 (quintet, $J = 4$ Hz, 1H), 5.00 (dt, $J = 7.7$, 4 Hz, 1H), 5.34–5.36 (m, 1H), 5.73–5.77 (m, 1H), 7.17 (d, $J = 8$ Hz, 2H), 7.76 (d, $J = 8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 21.7, 40.9, 48.6, 56.1, 64.9, 73.6, 127.5, 128.1, 129.8, 132.6, 134.9, 146.7, 152.6, 169.9; FT-IR (film, NaCl) 1783, 1728, 1370, 1172 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{19}NO_6SNa$ 388.0831, found 388.0833.

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