An Efficient Strategy for the Synthesis of α,α'-*cis* and *trans*-Disubstituted Medium Ring Ethers

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Abstract: An asymmetric alkylation-ring-closing metathesis strategy was developed for the construction of α,α'-disubstituted medium ring ethers. The approach features an asymmetric alkylation of highly functionalized α-alkoxy acyl oxazolidinones followed by ring closure effected by Grubbs' ruthenium catalyst. The relationship between diene conformation and the rate of ring-closure was examined.

Key words: asymmetric-alkylation, ring-closing metathesis, marine natural products, gauche effect, cyclic ethers, ruthenium

Medium ring ethers are a common structural feature of many ladder ether marine toxins, as well as simpler metabolites from *Laurencia* species. This diverse collection of natural products often contains seven, eight, and nine membered ring ethers.[1] The challenge of efficient construction of medium ring ethers has led to the development of numerous strategies for their synthesis.[2–5] The vast majority of these approaches have focused on the α,α'-*cis*-disubstitution pattern rather than α,α'-*trans*-disubstituted medium ring ethers, despite their similar frequency of occurrence. *trans*-Isoprelaurefucin (**1**),[6] isolaurefucin methyl ether (**2**),[7] chlorofucin (**3**),[8] bromofucin (**4**),[9] isolaureatin (**5**),[10] and obtusenyne (**6**),[8] for example, all contain α,α'-*trans*-disubstituted medium ring ethers (Figure 1). Murai's synthesis of obtusenyne (**6**)[11] and our own recent syntheses of prelaureatin and laurallene[12] constitute the only known syntheses of medium ring ether natural products with the α,α'-*trans*-disubstitution arrangement. The investigation of a versatile, general strategy for the synthesis of both α,α'-*cis* and α,α'-*trans*-disubstituted medium ring ethers is described here.

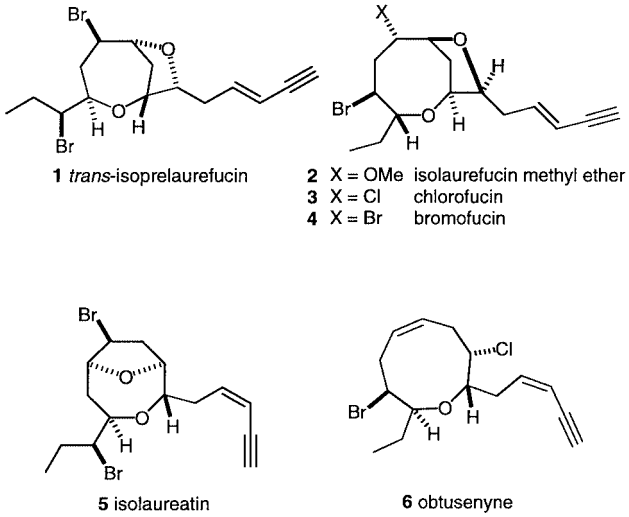
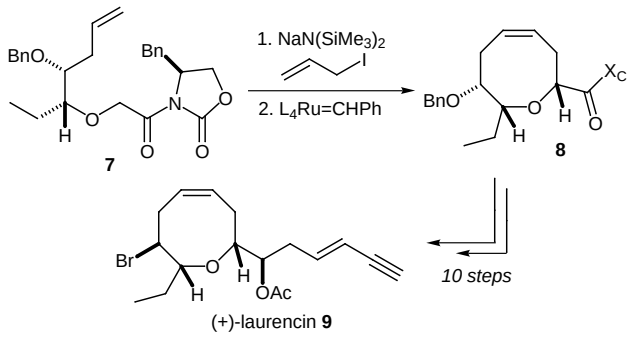


Figure 1 Some naturally occurring α,α'-*trans*-disubstituted medium ring ethers

We recently published a total synthesis of the marine natural product (+)-laurencin (**9**), in which the key steps were an asymmetric alkylation of the sodium enolate of substituted acyl oxazolidinone **7**, followed by ring-closing metathesis of the resultant diene to give cyclic ether **8** (Scheme 1).[2] Previous work in our laboratory has demonstrated that an asymmetric aldol-ring-closing metathesis strategy for the assembly of medium ring ethers was equally adaptable to both the α,α'-*cis* and α,α'-*trans*-disubstituted medium ring ethers.[3,12] The asymmetric alkylation-ring-closing metathesis approach to cyclic ethers also offered the potential for a similar adaptable strategy.



Scheme 1

We have found that by exploiting the known *gauche effect* of 1,2-dioxygen substitution, medium ring-closure can be accomplished without the use of cyclic conformational constraints. For example diene **10**, required for formation of the α,α'-*cis*-disubstituted eight-membered ring, has a low-energy conformation **10a** which orients the oxygen substituents *gauche*, positions the olefinic chains proximal, and allows the other two side chains to occupy pseudo-equatorial orientations (Figure 2). Significant rate increases in ring-closing metathesis result, in comparison to examples without vicinal oxygen substitution, thus allowing for ring-closure without dimerization. For instance, formation of oxocene **8** proceeds in 94% yield in three hours with only 5 mole percent of Grubbs' ruthenium catalyst ($[(C_6H_{11})_3P]_2Cl_2Ru{=}CHPh$).[2] Diene **11**, re-

quired for formation of the α,α'-*trans*-disubstituted eight-membered ring, also has a low-energy conformation **11a** with the oxygens gauche and the olefinic chains proximal; however, one of the other two side chains must occupy a pseudo-axial position for ring-closure to occur. The conformation **11b** that positions both the ethyl and allyl groups in pseudo-equatorial orientations should be more favorable and result in a slower rate of ring-closure than observed for **10**.

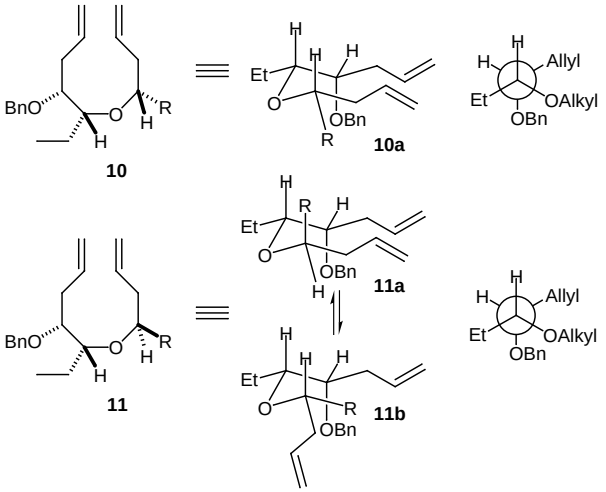


Figure 2 Low energy conformations of dienes **10** and **11** favoring ring closure

Diene **12**, required for formation of the α,α'-*trans*-disubstituted seven-membered ring, has a low-energy conformation **12a** with the olefinic chains oriented in opposite directions (Figure 3). For ring-closure to occur, one side chain must be oriented in a pseudo-axial fashion, as is illustrated in conformation **12b**. Diene **13**, required for formation of the α,α'-*cis*-disubstituted seven-membered ring, has two conformations of similar energy, **13a** and **13b** with psuedo-equatorial side-chains, one of which favors ring-closure. We set out to determine if the outlined conformational effects would influence the rate of the ring-closing metathesis reaction, particularly for the α,α'-*trans*-disubstituted ethers.[13]

Our first target was the α,α'-*trans*-disubstituted eight-membered ring **17** that comprises the oxocene core of isolaurefucin methyl ether (**2**), chlorofucin (**3**), and bromofucin (**4**). Synthesis of Δ-4-oxocene **17** began with acid **14**, which was previously prepared for our (+)-laurencin synthesis (Scheme 2).[2] By attaching the antipode of the auxiliary used in the laurencin synthesis, the α,α'-*trans* cyclic ether might be accessible. Treatment of the mixed pivalic anhydride with lithiated (*R*)-(−)-4-benzyl-2-oxazolidinone provided acyl oxazolidinone **15** in 78% yield. The sodium enolate of **15** was treated with excess allyl iodide at −45 ºC to give 71% yield of diene **16**. Upon exposure to standard ring-closing metathesis conditions (5 mol% of $[(C_6H_{11})_3P]_2Cl_2Ru$=CHPh, 0.005 M, CH_2Cl_2, 40 ºC, 8 h),

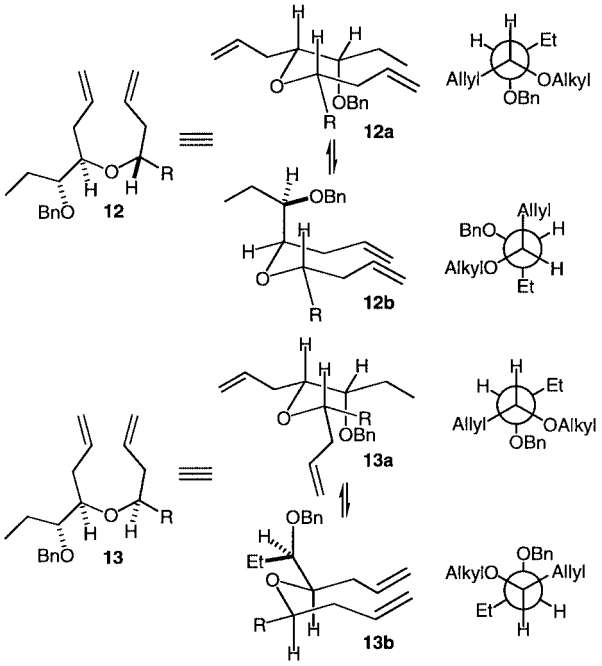
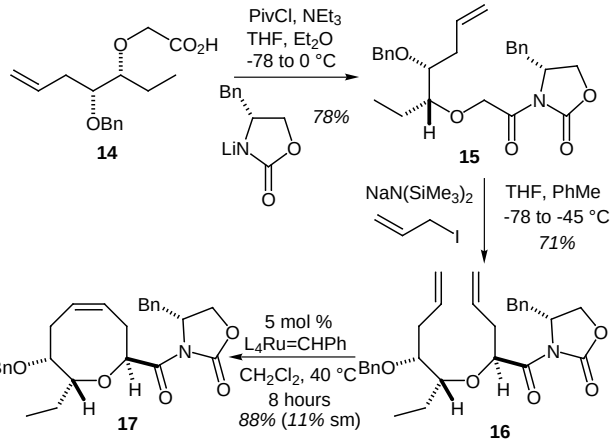


Figure 3 Low energy conformations of dienes **12** and **13** favoring ring closure

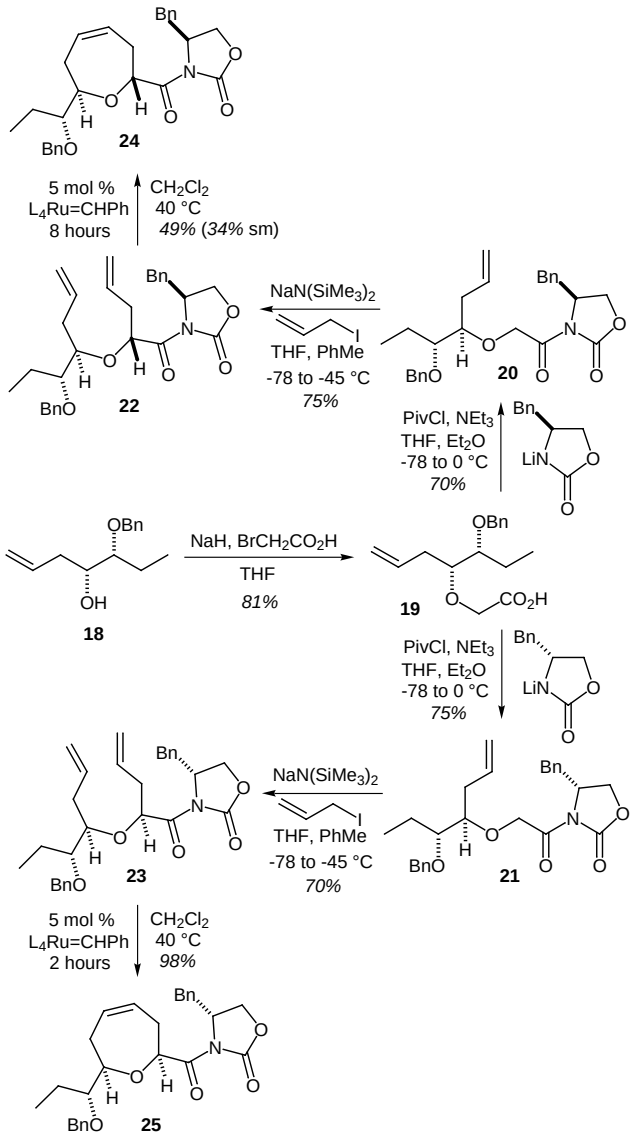
an 88% yield of cyclic ether **17** was isolated along with 11% of recovered diene **16**. The metathesis rate for diene **16** was considerably slower than the rate of the diene to produce the corresponding α,α'-*cis*-disubstituted eight-membered ring system. The conformation of diene **16** which positions the olefinic chains favorably for ring-closure is destabilized somewhat by the pseudo-axial side chain, slowing the metathesis. Nonetheless, it was demonstrated that the desired α,α'-*trans*-disubstituted eight-membered ring system could effectively be prepared utilizing an asymmetric alkylation-ring-closing metathesis approach.



Scheme 2

We next turned our attention to the α,α'-disubstituted seven-membered ring systems which represent the core of natural products such as *trans*-isoprelaurefucin (**1**). For this synthesis, we began with the known chiral alcohol **18** (Scheme 3).[14] The mixed pivalic anhydride of acid **19** was treated separately with both antipodes of lithiated 4-benzyl-2-oxazolidinone yielding acyl oxazolidinones **20** and **21**. The sodium enolate of each acyl oxazolidinone was treated with excess allyl iodide at −45 ºC to provide dienes **22** and **23**. In the case of diene **22**, exposure to the identical ring-closing metathesis conditions (5 mol% of $[(C_6H_{11})_3P]_2Cl_2Ru$=CHPh, 0.005 M, CH_2Cl_2, 40 ºC, 8 h) used for diene **16** gave a 49% yield of cyclic ether **24** along with 34% of recovered diene **22**. In diene **22** the apparent preference for the olefinic chains to orient in opposite directions due to the destabilization of the conformation with a pseudo-axial side chain has a profound effect on the rate of ring-closure. The rate of ring closure for this seven-membered ring is significantly slower than any other examples of seven, eight, or nine-membered ring formation in which there is a low-energy *gauche* conformation with the olefinic chains proximal.[2,3,12] Although the reaction was quite slow, the overall yield of the desired product could be increased to >70% after two recycles. In contrast, diene **23** underwent rapid ring-closure (5 mol% of $[(C_6H_{11})_3P]_2Cl_2Ru$=CHPh, 0.005 M, CH_2Cl_2, 40 ºC, 2 h) to form cyclic ether **25** in 98% yield in only two hours. This sequence clearly demonstrates the importance of diene conformation on the rate of the ring-closing metathesis reaction for cyclic ether formation.

In conclusion, we have demonstrated that an asymmetric alkylation-ring-closing metathesis strategy is effective for the construction of both α,α'-*cis* and α,α'-*trans*-disubstituted medium-ring ethers. We have also shown that the role of diene conformation with respect to the rate of ring-closure is significant. These studies bode well for the synthesis of marine natural products such as *trans*-isoprelaurefucin (**1**), isolaurefucin methyl ether (**2**), chlorofucin (**3**), and bromofucin (**4**), having already accessed the cyclic cores of these compounds. Current efforts are focused on the expansion of this strategy to the synthesis of these and other medium-ring ether containing natural products.



Scheme 3

IR spectra were obtained using a Perkin-Elmer 283 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker model DRX 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz). Optical rotations were measured using a Perkin-Elmer 241 polarimeter. TLC was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash chromatography was carried out using silica gel (32 to 63μm) purchased from Scientific Adsorbents, Inc. Et_2O, THF, and CH_2Cl_2 were dried by passing through a column of neutral alumina under N_2 immediately prior to use. Alkylamines were distilled from CaH_2 immediately prior to use. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of nitrogen and conducted under N_2.

(4*R*)-4-Benzyl-3-[2-((1*R*, 2*R*)-2-benzyloxy-1-ethylpent-4-enyloxy)acetyl]oxazolidin-2-one (15); Typical Procedure

To a solution of carboxylic acid **14** (3.98 g, 14.30 mmol) in Et_2O (60 mL) was added Et_3N (2.20 mL, 15.78 mmol) via a syringe, and the mixture was cooled to −78 ºC. Pivaloyl chloride (1.80 mL, 14.61 mmol) was added dropwise via a syringe. After 5 min, the mixture was warmed to 0 ºC, where it was stirred for 1 h and subsequently recooled to −78 ºC. In a separate flask, (*R*)-(+)-4-benzyl-2-oxazolidinone (2.54 g, 14.33 mmol) was dissolved in THF (25 mL) and cooled to −78 ºC. BuLi (1.6 M in hexanes, 9.40 mL, 15.04 mmol) was added dropwise via a syringe, and the mixture was stirred for 15 min. The lithiated oxazolidinone was added via a cannula to the mixed anhydride, and the mixture stirred for an additional 10 min before being warmed to 0 ºC, where stirring continued for 1 h. The reaction was quenched by the addition of H_2O and extracted twice with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration in vacuo and purification by flash chromatography gave 4.87 g (78%) of acyl oxazolidinone **15**; $[\alpha]_D^{25}$ −69.0 (*c* = 0.58, CH_2Cl_2).

IR (film): ν = 2925, 1780, 1720, 1390, 1260, 1130 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.13 (m, 10 H), 5.89 (ddt, 1 H, *J* = 17.2, 10.0, 7.0 Hz), 5.16−5.02 (m, 2 H), 4.81 (AB, 2 H, J_{AB} = 17.6 Hz, $\Delta\nu_{AB}$ = 31.6 Hz), 4.60 (AB, 2 H, J_{AB} = 11.8 Hz, $\Delta\nu_{AB}$ = 51.4 Hz), 4.40 (m, 1 H), 4.08 (dd, 1 H, *J* = 8.8, 2.8 Hz), 3.98 (dd, 1 H, *J* = 8.8, 8.8 Hz), 3.59 (m, 1 H), 3.39 (m, 1 H), 3.25 (dd, 1 H, *J* = 13.6, 3.2 Hz), 2.71 (dd, 1 H, *J* = 13.6, 9.6 Hz), 2.51 (m, 1 H), 2.27 (m, 1 H), 1.69 (m, 1 H), 1.55 (m, 1 H), 0.98 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2, 23.3, 34.5, 37.7, 54.6, 67.0, 71.4, 71.9, 80.9, 84.0, 117.1, 127.22, 127.24, 127.3, 128.2, 128.9, 129.4, 134.8, 135.1, 139.0, 153.3, 170.4.

(4*R*)-4-Benzyl-3-[(2*S*)-2-((1*R*, 2*R*)-2-benzyloxy-1-ethylpent-4-enyloxy)pent-4-enoyl]oxazolidin-2-one (16); Typical Procedure

Into a flask fitted with a low-temperature thermometer was added sodium bis(trimethylsilyl)amide (0.75 M in toluene/THF, 36.0 mL, 27.00 mmol). THF (20 mL) was added and the flask was cooled to −78 ºC. Acyl oxazolidinone **15** (5.85 g, 13.37 mmol) in THF (35 mL) was added via a cannula at a rate to maintain the reaction temperature below −60 ºC. After stirring for 30 min at −78 ºC, allyl iodide (6.10 mL, 66.71 mmol) was added via a syringe. After 10 min the reaction was warmed to −45 ºC and stirred at that temperature for 45 min. The reaction was quenched by the addition of aq sat. NH_4Cl and warmed to r.t. The solution was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography provided 4.50 g (71%) of diene **16**; $[\alpha]_D^{26}$ −102.4 (*c* = 0.84, CH_2Cl_2).

IR (film): ν = 2920, 1780, 1710, 1390, 1210, 1105 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.06 (m, 10 H), 5.97−5.80 (m, 2 H), 5.32 (dd, 1 H, *J* = 6.4, 4.8 Hz), 5.14−5.01 (m, 4 H), 4.49 (AB, 2 H, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 80.2 Hz), 4.04 (m, 1 H), 3.78 (dd, 1 H, *J* = 9.0, 3.4 Hz), 3.50 (dt, 1 H, *J* = 7.6, 4.4 Hz), 3.38 (m, 1 H), 3.15 (dd, 1 H, *J* = 8.6, 8.6 Hz), 3.12 (dd, 1 H, *J* = 13.6, 3.2 Hz), 2.56−2.39 (m, 4 H), 2.17 (m, 1 H), 1.64 (m, 1 H), 1.48 (m, 1 H), 1.01 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 23.9, 33.8, 38.0, 38.5, 54.6, 66.2, 69.9, 79.4, 81.7, 84.6, 117.2, 118.1, 125.9, 126.9, 127.2, 128.3, 128.8, 129.3, 133.4, 134.1, 135.3, 139.4, 153.0, 172.3.

(4*R*)-4-Benzyl-3-[(2*S*, 7*R*, 8*R*)-7-benzyloxy-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocine-2-carbonyl]oxazolidin-2-one (17); Typical Procedure

Into a flask equipped with a reflux condenser was added diene **16** (0.326 g, 0.683 mmol) in CH_2Cl_2 (137 mL). N_2 was bubbled through the stirring solution for 20 min. The solution was heated to reflux and $(Cy_3P)_2Cl_2Ru$=CHPh (0.028 g, 0.034 mmol) was added in one portion. The mixture was stirred at 40 ºC for 8 h and cooled to r.t. The mixture was then stirred open to air overnight and concentrated in vacuo. Purification by flash chromatography provided 0.037 g (11%) of recovered diene **16** and 0.270 g (88%) of oxocene **17**; $[\alpha]_D^{24}$ −166.4 (*c* = 0.55, CH_2Cl_2).

IR (film): ν = 2925, 1780, 1700, 1390, 1195, 1070 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.16 (m, 10 H), 5.97−5.86 (m, 2 H), 5.45 (dd, 1 H, *J* = 11.2, 3.2 Hz), 4.65 (m, 1 H), 4.60 (AB, 2 H, J_{AB} = 12.4 Hz, $\Delta\nu_{AB}$ = 107.6 Hz), 4.21 (dd, 1 H, *J* = 8.2, 8.2 Hz), 4.16 (dd, 1 H, *J* = 9.2, 2.8 Hz), 4.04 (dd, 1 H, *J* = 7.0, 7.0 Hz), 3.59 (d, 1 H, *J* = 6.4 Hz), 3.22 (dd, 1 H, *J* = 13.4, 3.4 Hz), 2.78 (dd, 1 H, *J* = 13.4, 9.4), 2.69−2.59 (m, 2 H), 2.40 (m, 1 H), 2.21 (dd, 1 H, *J* = 14.0, 5.6 Hz), 1.74−1.65 (m, 2 H), 0.67 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 26.0, 28.8, 29.2, 37.8, 55.0, 66.4, 70.9, 73.8, 77.9, 79.1, 127.4, 127.7, 128.2, 128.4, 128.9, 129.4, 130.0, 135.0, 138.3, 152.6, 173.0.

(4*S*)-4-Benzyl-3-{2-[(1*R*)-1-((1*R*)-1-benzyloxypropyl)but-3-enyloxy]acetyl}oxazolidin-2-one (20)

$[\alpha]_D^{26}$ +42.9 (*c* = 0.79, CH_2Cl_2).

IR (film): ν = 2940, 1780, 1720, 1395, 1260, 1220 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.13 (m, 10 H), 5.94 (ddt, 1 H, *J* = 17.2, 10.0, 3.2 Hz), 5.15−5.02 (m, 2 H), 4.82 (s, 2 H), 4.63 (m, 1 H), 4.62 (AB, 2 H, J_{AB} = 10.0 Hz, $\Delta\nu_{AB}$ = 19.6 Hz), 4.21 (dd, 1 H, *J* = 8.4, 8.4 Hz), 4.17 (dd, 1 H, *J* = 9.2, 3.2 Hz), 3.57 (m, 1 H), 3.49 (m, 1 H), 3.27 (dd, 1 H, *J* = 13.2, 3.2 Hz), 2.80 (dd, 1 H, *J* = 13.2, 9.6 Hz), 2.48 (m, 1 H), 2.33 (dt, 1 H, *J* = 14.4, 7.4 Hz), 1.72 (m, 1 H), 1.51 (m, 1 H), 0.97 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1, 22.8, 35.0, 37.7, 54.8, 67.1, 70.6, 72.7, 81.6, 82.0, 117.0, 127.4, 127.5, 127.8, 128.3, 129.0, 129.4, 135.0, 135.2, 138.8, 153.3, 170.4.

(4*R*)-4-Benzyl-3-{2-[(1*R*)-1-((1*R*)-1-benzyloxypropyl)but-3-enyloxy]acetyl}oxazolidin-2-one (21)

$[\alpha]_D^{26}$ −65.8 (*c* = 0.79, CH_2Cl_2).

IR (film): ν = 2940, 1780, 1720, 1395, 1265, 1220 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.13 (m, 10 H), 5.93 (ddt, 1 H, *J* = 17.2, 10.0, 7.2 Hz), 5.15−5.03 (m, 2 H), 4.81 (AB, 2 H, J_{AB} = 18.0 Hz, $\Delta\nu_{AB}$ = 21.2 Hz), 4.60 (AB, 2 H, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 14.4 Hz), 4.47 (m, 1 H), 4.11 (dd, 1 H, *J* = 9.2, 2.8 Hz), 4.04 (dd, 1 H, *J* = 8.6, 8.6 Hz), 3.57 (m, 1 H), 3.50 (m, 1 H), 3.26 (dd, 1 H, *J* = 13.6, 3.2 Hz), 2.73 (dd, 1 H, *J* = 13.6, 9.6 Hz), 2.46 (m, 1 H), 2.32 (dt, 1 H, *J* = 14.4, 7.6 Hz), 1.75 (m, 1 H), 1.51 (m, 1 H), 0.96 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 22.7, 35.1, 37.7, 54.7, 67.0, 71.1, 72.3, 81.9, 82.3, 116.9, 127.3, 127.4, 128.2, 128.9, 129.4, 135.0, 135.2, 139.0, 153.3, 170.3.

(4*S*)-4-Benzyl-3-{(2*R*)-2-[(1*R*)-1-((1*R*)-1-benzyloxypropyl)but-3-enyloxy]pent-4-enoyl}oxazolidin-2-one (22)

$[\alpha]_D^{26}$ +61.3 (*c* = 0.65, CH_2Cl_2).

IR (film): ν = 2925, 1780, 1715, 1390, 1215, 1105 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.16 (m, 10 H), 6.02−5.82 (m, 2 H), 5.28 (dd, 1 H, *J* = 7.2, 4.8 Hz), 5.17−4.98 (m, 4 H), 4.65 (m, 1 H), 4.54 (AB, 2 H, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 13.6 Hz), 4.18−4.08 (m, 2 H), 3.47 (dt, 1 H, *J* = 7.6, 4.4 Hz), 3.38 (dt, 1 H, *J* = 8.4, 4.0 Hz), 3.25 (dd, 1 H, *J* = 13.2, 3.2 Hz), 2.65 (dd, 1 H, *J* = 13.2, 10.0 Hz), 2.57−2.40 (m, 3 H), 2.25 (m, 1 H), 1.70 (m, 1 H), 1.47 (m, 1 H), 0.93 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4, 22.3, 34.9, 38.01, 38.03, 55.1, 66.7, 72.5, 76.6, 80.4, 81.4, 116.4, 118.3, 127.4, 127.5, 127.9, 128.3, 129.0, 129.4, 133.3, 135.1, 135.9, 138.8, 153.2, 172.7.

(4*R*)-4-Benzyl-3-{(2*S*)-2-[(1*R*)-1-((1*R*)-1-benzyloxypropyl)but-3-enyloxy]pent-4-enoyl}oxazolidin-2-one (23)

$[\alpha]_D^{26}$ −92.7 (*c* = 0.82, CH_2Cl_2).

IR (film): ν = 2930, 1780, 1715, 1390, 1215, 1110 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31−7.02 (m, 10 H), 5.89 (m, 2 H), 5.28 (dd, 1 H, *J* = 6.4, 4.8 Hz), 5.10−4.98 (m, 4 H), 4.45 (AB, 2 H, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 43.2 Hz), 4.08 (m, 1 H), 3.80 (dd, 1 H, *J* = 9.2, 3.2 Hz), 3.49 (m, 1 H), 3.42 (m, 1 H), 3.31 (dd, 1 H, *J* = 8.6, 8.6 Hz), 3.11 (dd, 1 H, *J* = 13.4, 3.2 Hz), 2.52−2.28 (m, 4 H), 2.21 (dt, 1 H, *J* = 14.4, 8.0 Hz), 1.72 (m, 1 H), 1.41 (m, 1 H), 0.88 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8, 21.8, 35.7, 38.0, 38.3, 54.7, 66.3, 70.4, 79.0, 82.3, 82.5, 116.9, 118.1, 126.3, 127.0, 127.2, 128.3, 128.8, 129.3, 133.4, 135.3, 135.5, 139.5, 153.0, 172.3.

(4*S*)-4-Benzyl-3-[(2*R*, 7*R*)-7-((1*R*)-1-benzyloxypropyl)-2,3,6,7-tetrahydrooxepine-2-carbonyl]oxazolidin-2-one (24)

$[\alpha]_D^{26}$ +55.1 (*c* = 0.69, CH_2Cl_2).

IR (film): ν = 2940, 1780, 1710, 1390, 1210, 1110 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.13 (m, 10 H), 5.77−5.63 (m, 3 H), 4.66−4.50 (m, 4 H), 4.11 (dd, 1 H, *J* = 9.2, 3.2 Hz), 4.06 (dd, 1 H, *J* = 8.4, 8.4 Hz), 3.43 (dt, 1 H, *J* = 8.4, 4.2 Hz), 3.22 (dd, 1 H, *J* = 13.4, 3.4 Hz), 2.78 (m, 1 H), 2.75 (dd, 1 H, *J* = 13.4, 9.4 Hz), 2.53 (m, 1 H), 2.45 (m, 1 H), 2.28 (m, 1 H), 1.67 (m, 1 H), 1.50 (m, 1 H), 0.96 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 22.4, 30.1, 30.8, 37.8, 55.0, 66.5, 72.5, 74.0, 74.5, 82.8, 125.2, 127.4, 127.7, 128.2, 128.9, 129.4, 129.6, 135.0, 139.0, 152.7, 172.5.

(4*R*)-4-Benzyl-3-[(2*S*, 7*R*)-7-((1*R*)-1-benzyloxypropyl)-2,3,6,7-tetrahydrooxepine-2-carbonyl]oxazolidin-2-one (25)

$[\alpha]_D^{26}$ −57.3 (*c* = 0.56, CH_2Cl_2).

IR (film): ν = 2940, 1790, 1715, 1390, 1205, 1110 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.13 (m, 10 H), 5.92−5.78 (m, 2 H), 4.97 (dd, 1 H, *J* = 10.4, 1.6 Hz), 4.62 (m, 1 H), 4.61 (AB, 2 H, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 55.6 Hz), 4.19−4.11 (m, 2 H), 3.73 (ddd, 1 H, *J* = 10.2, 4.6, 2.0 Hz), 3.33 (m, 1 H), 3.26 (dd, 1 H, *J* = 13.2, 3.2 Hz), 2.78 (dd, 1 H, *J* = 13.2, 9.6 Hz), 2.62 (m, 1 H), 2.51−2.25 (m, 3 H), 1.62 (m, 1 H), 1.43 (m, 1 H), 0.92 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6, 22.8, 31.5, 33.2, 37.8, 55.3, 66.5, 72.6, 77.7, 81.1, 82.8, 127.3, 127.4, 127.8, 128.0, 128.2, 129.0, 129.4, 130.6, 135.1, 139.1, 152.7, 170.6.

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References

(1) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.
Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113.
Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259.
Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75, and earlier reviews in the same series.
(2) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029.
(3) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.
(4) (a) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127.
(b) Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135.
(c) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.
(d) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983.
(e) Krüger, J.; Hoffman, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499.
(f) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728.
(g) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
(h) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345.
(i) Kotsuki, H. *Synlett* **1992**, 97.
(j) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
For examples of medium ring ether synthesis via RCM, see: Clark, J. S.; Hamelin O. *Angew. Chem. Int. Ed.* **2000**, *39*, 372, and references cited therein.
(6) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *42*, 4135.
(7) de Nys, R.; Coll, J. C.; Carroll, A. R.; Bowden, B. F. *Aust. J. Chem.* **1993**, *46*, 1073.
(8) Howard, B. M.; Schulte, G. R.; Fenical, W. *Tetrahedron*. **1980**, *36*, 1747.
(9) Coll, J. C.; Wright, A. D. *Aust. J. Chem.* **1989**, *42*, 1685.
(10) Ishihara, J.; Kanoh, N.; Fukuzawa, A.; Murai, A. *Chem. Lett.* **1994**, 1563.
(11) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616.
(12) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, in press.
For other isolated observations on diastereomer effects on rates of RCM, see:
Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919.
Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127.
(14) Mulzer, J.; Angermann, A.; Münch, W. *Liebigs. Ann. Chem.* **1986**, 825.

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