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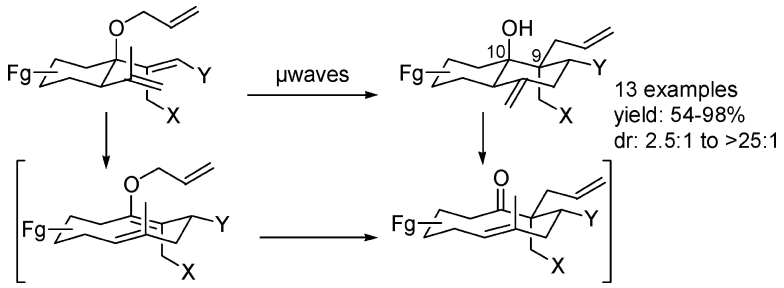

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Highly Efficient Transfer of Chirality from Macrocyclic Conformation in the Tandem Oxy-Cope/Claisen/Ene Reaction

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Abstract: We report three highly stereoselective pericyclic reactions occurring in cascade leading to the synthesis of Decalins skeletons possessing two contiguous quaternary centers. The tandem reaction is triggered by an oxy-Cope rearrangement to create in situ a 10-membered ring enol ether macrocyle **6**, which immediately rearranges via a Claisen [3,3] shift to the corresponding *E*-cyclodec-6-en-1-one **7**. The latter spontaneously cyclizes via a transannular ene reaction to produce Decalin **5**. Analysis of the mechanism with respect to the origin of the high diastereoselectivity of the tandem oxy-Cope/Claisen/ene reaction is presented.

Introduction

The development of efficient synthetic methods that create architecturally complex polycyclic molecules in very few steps constitutes a formidable challenge for synthetic chemists. Among them, reactions occurring in cascade are emerging as powerful tools for the diastereoselective formation of multiple carbon−carbon bonds.[1] One of the problems encountered in the synthesis of polycyclic compounds is the stereoselective formation of quaternary carbon centers.[2] As an example, bioactive natural diterpenes such as teucrolivin A (**1**)[3] and LL-S491β (**2**)[4] and myrocin C (**3**)[5] possess a quaternary center at C9 and a tertiary alcohol C10 (Figure 1). The retrosynthetic analysis of these particular molecules reveals that the main framework can be generated from a common Decalin intermediate **5** which bears the requisite quaternary carbon center at C9 adjacent to a tertiary alcohol C10. We have envisaged the formation of **5** via a thermal cyclization of the allylic ether **4**. Heating of the allyl ether **4** produces the enol intermediate **6** via an oxy-Cope reaction. The latter is transformed into ketone **7** through a Claisen rearrangement. The resulting macrocyclic ketone can undergo a transannular ene reaction to give **5**.

A closer examination of the process reveals that the relative stereochemistry at the newly formed carbon centers is entirely controlled by the macrocyclic conformations of **6** and **7**. This means that a predominant macrocyclic transition state conformation for the Claisen rearrangement and the ene reaction will ensure a high transfer of chirality, thereby controlling the stereoselective formation of the contiguous stereogenic centers at C5, C8, C9, and C10 in Decalin **5**. The pioneering work of Still demonstrated that the conformation of medium and large macrocycles affords an effective vehicle in which the asymmetric synthesis of stereogenic centers can be achieved.[6] This idea was further explored by other groups.[7,8] In our case, the effectiveness of the chirality transfer in the tandem process relies upon conformational preference of the macrocyclic transition

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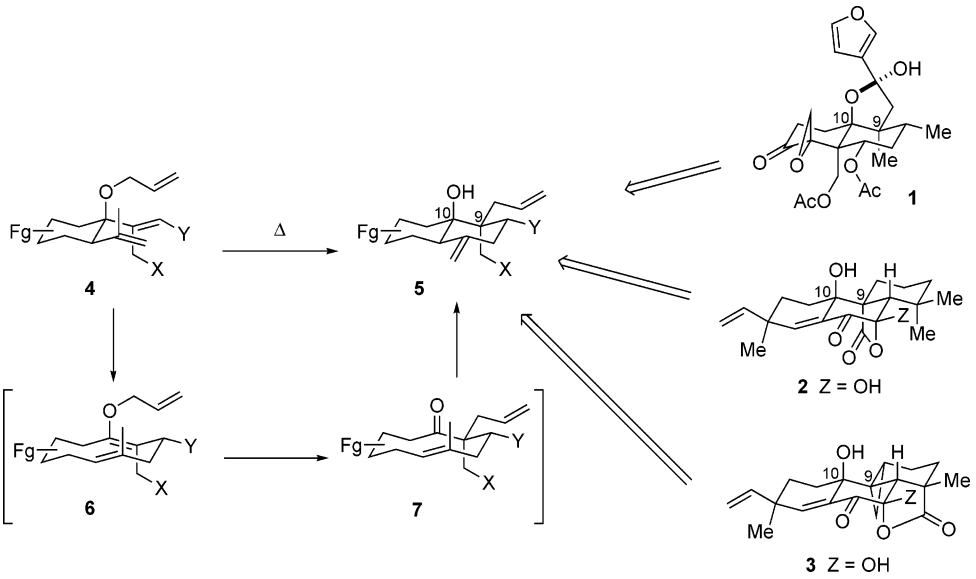
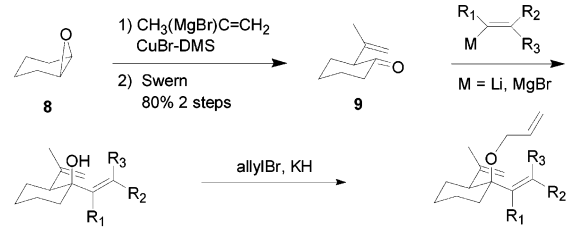


Figure 1. Tandem oxy-Cope/Claisen/ene reaction.

Scheme 1. Synthesis of Precursors **17**−**23**



10 R_1 = Me, R_2 = H, R_3 = H (60%)
11 R_1 = Me, R_2 = Me, R_3 = H (60%)
12 R_1 = Me, R_2 = H, R_3 = Me (30%)
13 R_1 = Me, R_2 = CH_2OTBS, R_3 = H (60%)
14 R_1 = OEt, R_2 = H, R_3 = H (46%)
15 R_1 = SEt, R_2 = H, R_3 = H (89%)
16 R_1 = OMOP, R_2 = OMOP, R_3 = H (77%)

17 R_1 = Me, R_2 = H, R_3 = H (65%)
18 R_1 = Me, R_2 = Me, R_3 = H (40%)
19 R_1 = Me, R_2 = H, R_3 = Me (24%)
20 R_1 = Me, R_2 = CH_2OTBS, R_3 = H (42%)
21 R_1 = OEt, R_2 = H, R_3 = H (67%)
22 R_1 = SEt, R_2 = H, R_3 = H (91%)
23 R_1 = OMOP, R_2 = OMOP, R_3 = H (92%)

state for the Claisen and ene reactions. In this Article, we report the scope and limitation of the tandem oxy-Cope/Claisen/ene reaction and a detailed mechanistic analysis to explain the origin of the diastereoselectivity of the tandem process.

Results and Discussion

Precursors for the tandem oxy-Cope/Claisen/ene reaction were synthesized via one of three general routes. Substrates **17**−**23** (Scheme 1) were made starting from commercially available cyclohexene oxide **8**. Treatment of **8** with isopropenylmagnesium bromide in the presence of catalytic CuBr−DMS,[9] followed by a Swern oxidation[10] of the crude product, gave known compound **9**[11] in 80% yield overall. Alkylation by a variety of organometallic reagents gave intermediates **10**−**16** with yields ranging from 30% to 89%.[12] These tertiary alcohols were then exposed to allyl bromide, potassium hydride, and catalytic sodium iodide in DME to give the desired precursors **17**−**23** in 24−92% yield.

Also of interest for this study were those substrates bearing an equatorial methyl group β to the hydroxyl group. The synthesis of these precursors began from isopulegone **24**,[13] which was alkylated by several different vinyllithium species to give compounds **25**−**27** in 50−92% yield (Scheme 2). Subsequent allylation using the conditions described above gave precursors **28**−**30** with yields ranging from 24% to 91%. Finally, preparation of **33** was accomplished by treatment of commercially available **31** with isopropenylmagnesium bromide, generating **32** in 40% yield (as well as 21% of its diastereomer resulting from axial attack). Allylation of **32** with allyl bromide, potassium hydride, and sodium iodide in DME afforded **33** in 54% yield.

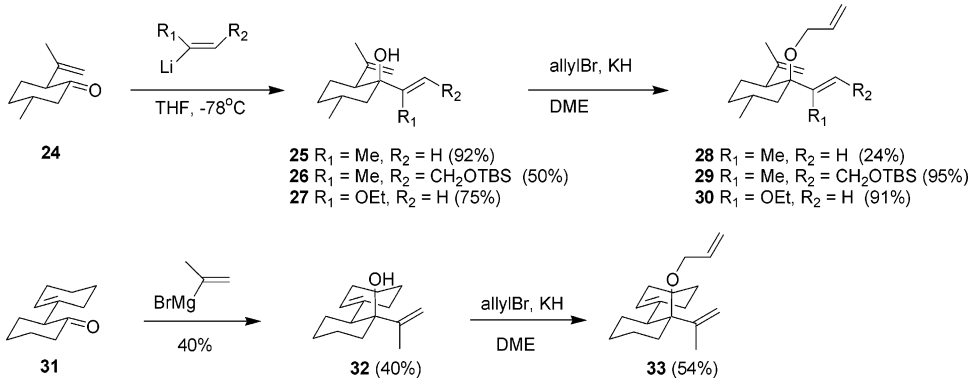
Substrates 17−**23**, **28**−**30**, and **33** were dissolved in toluene, degassed with argon, and subjected to microwave radiation[14] at temperatures ranging from 180 to 220 °C for 1−2 h.[15] The products of the resulting oxy-Cope/Claisen/ene reaction are summarized in Table 1. Yields for this tandem sequence ranged from 54% (entry 11) to 98% (entry 8) with diastereomeric ratios varying between 2.5:1 and greater than 25:1.

The observed selectivity for this reaction sequence can be rationalized through careful examination of the reaction mechanism. The results of entries 1−6 will be examined first and can be represented by the mechanism shown in Figure 2.

Microwave irradiation of substrate **17** (entry 1, R_1 = Me, R_4 = H) afforded a 2.5:1 mixture of isomers **34a** and **34b** in 87% yield. These diastereomers correspond to isomers **H**(**I**) and **G**(**J**), respectively, in the above mechanism (note that since $R_4 \simeq$ H, **H** and **I** are enantiomers of each other, as are **G** and **J**). Following the oxy-Cope rearrangement of **17**, one generates the 10-membered macrocycle **A**. Ring inversion of **A** gives its

(9) Linstrumelle, G.; Derguini-Boumechal, F.; Huynh, C. *Tetrahedron Lett.* **1979**, *20*, 1503.
(10) Swern, D.; Mancuso, A. J. *Synthesis* **1981**, 165.
(11) Barriault, L.; Warrington, J. M.; Yap, G. P. A. *Org. Lett.* **2000**, *2*, 663.
(12) Preferential equatorial attack of the nucleophile occurs as expected to avoid interaction with the 3,5-axial hydrogens. See: (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (b) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107. (c) Brown, H. C.; Dickason, W. C. *J. Am. Chem. Soc.* **1970**, *92*, 709.
(13) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380.
(14) For a review on microwaves in organic synthesis, see: (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (b) Majetich, G.; Hichs, R. J. *J. Microwave Power and Electromagnetic Energy* **1995**, *30*, 27. (c) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199. (d) Lidström, P.; Tierny, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(15) Nonpolar solvents such as toluene do not absorb microwaves; therefore, a glass-coated ferrite disk was placed inside the reaction cell. Ferrite readily absorbs microwaves energy and transmits heat to the reaction mixture through conduction. This microwave oven is equipped with fiber optic probes placed inside the reaction cell to monitor the temperature and pressure of the reaction.

Scheme 2. Synthesis of Precursors **28**−**30** and **33**



enantiomer **B**.[16] Because we were using racemic **17** in this study, we can therefore ignore the right-hand side of the reaction mechanism for this substrate. The product of the oxy-Cope rearrangement, **A**, is now perfectly set up to undergo a Claisen rearrangement, generating ketone **D**. This intermediate can now undergo either a ring inversion process to give its diastereomer **C** followed by a transannular ene reaction to give the minor product **34b** (**G**) or give directly the product of the ene reaction **34a** (**H**).

The selectivity at this point in the mechanism can be rationalized as follows. If one assumes that the ring inversion process is fast and that a rapid equilibrium between **D** and **C** exists,[17] the product ratio (**H**:**G**) should be determined solely by the relative values of the absolute transition state energies for the two ene reactions.[18] For the ene reaction leading to the minor product **34b** (**G**), the corresponding transition state of macrocycle **C** has its allyl group axial, while the methyl group (R_1) is equatorial. By contrast, the transition state for the ene reaction of macrocycle **D** has the allyl group in an equatorial position, while the methyl group is axial. The observed ratio of 2.5:1 corresponds to a difference of 0.86 kcal/mol (at 200 °C) between the two transition states leading to Decalins **34a** and **34b**, respectively. On the basis that an allyl group is slightly larger than a methyl group, one can assume that the absolute value of the transition state leading to **34b** (**G**) should be slightly higher in energy than that leading to the major product **34a** (**H**), thus explaining the observed diastereoselectivity of the reaction.

Allyl ether **21** (R_1 = OEt, R_4 = H) was irradiated with microwaves to produce **35** in 91% yield as a single diastereomer corresponding to isomer **H**/**I** (entry 2). In comparison to substrate **9** (entry 1, R_1 = Me), the diastereoselectivity has been increased from 3:1 to greater than 25:1 upon changing R_1 from a methyl to an ethoxy group. Looking to the mechanism in Figure 1, the Claisen rearrangement of **A** gives macrocyclic ketone **D**, which rearranges directly to yield the solely observed product **35** (**H**). In an effort to rationalize the exclusive formation of **35** (**H**), one might begin by proposing the existence of a rapid equilibrium between **D** and **C**. Of relevance then become the absolute transition state energies for the two ene reactions which should differ according to the relative positions of the ethoxy and allyl groups. It seems unlikely, however, that a greater than 25:1 diastereoselectivity could have been induced solely by the steric effects of the axial or equatorial positioning of these two substituents.[19] A more viable explanation assumes that the ring inversion process is relatively slow and competes with the ene reaction of **D** to **H**. With R_1 = OEt, the ene reaction of **D** should be accelerated relative to the rate of ring inversion, giving rise to the exclusive formation of **35** (**H**). This assumption fits nicely when one considers that ene reactions are known to be accelerated by the presence of electron-withdrawing groups α to the enophile.[20]

When R_1 is changed from an ethoxy to an ethyl sulfide, as for substrate **22** (entry 3), a mixture of products **36a** (**H**/**I**) and **36b** (**G**/**J**) is obtained in 91% yield with a diastereomeric ratio of 3:1. It is important to point out that this ratio of products is nearly identical to that obtained when R_1 was a methyl group (entry 1). Given that sulfur has an electronegativity close to that of carbon,[21] this result further supports the influence of R_1's electronegativity on the selectivity of this reaction mechanism.

Entry 4 shows that when R_4 is changed from a proton to a methyl group, as with substrate **28**, the diastereoselectivity of the tandem reaction increases from 3:1 (entry 1) to greater than 25:1 for a single diastereomeric product **37** (**H**) in 84% yield. This dramatic increase in selectivity can once again be rationalized by looking at the mechanism in Figure 1. Following an oxy-Cope rearrangement of **28**, one generates macrocycle **A** which can undergo a Claisen rearrangement directly to give intermediate **D** or invert itself to form, in this case, its diastereomer **B**. Looking ahead to the final product, **37** (**H**), we know that intermediate **A** is the reactive conformer because

(16) Although no stereocenters exist on intermediates A and B, by virtue of planar chirality, they are enantiomers. For further information on planar chirality, see refs 7 and 7o.

(17) Horibe et al. observed that 10-membered ring macrocycles undergo a rapid ring inversion at temperatures above 105 °C at the NMR time scale. (a) Takeda, K.; Tori, K.; Horibe, I. *Tetrahedron Lett.* **1973**, *10*, 735. (b) Takeda, K.; Tori, K.; Horibe, I.; Ohtsuru, M.; Minato, H. *J. Chem. Soc. C* **1970**, 2697.

(18) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. (c) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962. (d) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1970; Chapter 5. (e) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (f) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42.

(19) One might also consider that the observed diastereoselectivity results from the minimization of the carbonyl and ethoxy dipoles at the transition state of the ene reaction. Repeating the experiment in a more polar solvent, such as DMF, however, gave no change in the product ratio (entry 2), thereby suggesting the dipoles have only a minor role, if any, in governing the outcome of this tandem reaction.

(20) (a) Snider B. B. In *Comprehensive Organic Synthesis, Combining C*−*C π Bond*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 1.1. (b) Snider B. B. In *Comprehensive Organic Synthesis, Addition to C*−*X π Bond*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 2.1.

(21) From the Pauling electronegativity scale, carbon's electronegativity is 2.55, while sulfur's is 2.58.

Table 1. Tandem Oxy-Cope/Claisen/Ene Results

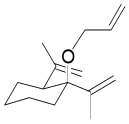
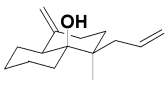
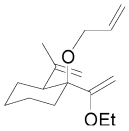
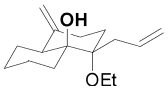
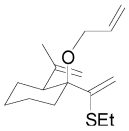
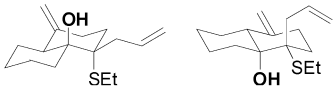
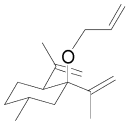
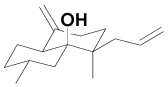
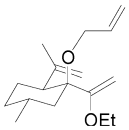
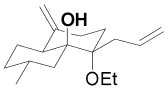
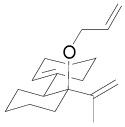
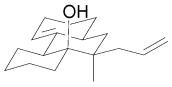
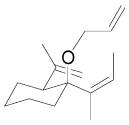
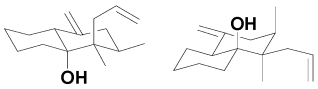
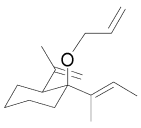
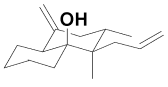
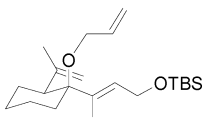
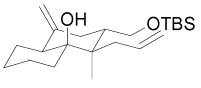
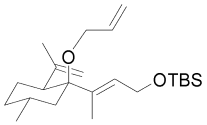
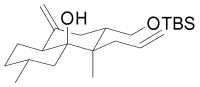
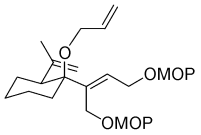
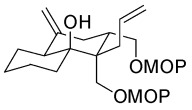
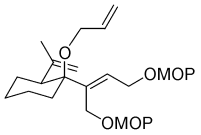
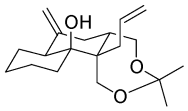
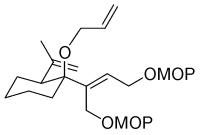
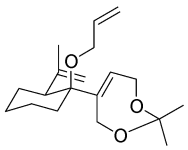
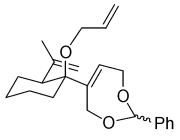
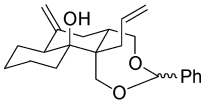
Entry	Substrate	Temp. (°C)[a]	Product[b]	Yield (%)[c]	dr[d]
1	 **17**	200	 **34a** **34b**	87	2.5:1
2	 **21**	200	 **35**	91 86[e]	>25:1
3	 **22**	200	 **36a** **36b**	91	3:1
4	 **28**	200	 **37**	84	>25:1
5	 **30**	200	 **38**	83	>25:1
6	 **33**	220	 **39**	93	>25:1
7	 **19**	200	 **40a** **40b**	73	4:1
8	 **18**	210	 **41**	98	>25:1
9	 **20**	180	 **42**	90	17:1

Table 1 (Continued)

Entry	Substrate	Temp. (°C)[a]	Product[b]	Yield (%)[c]	dr[d]
10	 **29**	220	 **43**	90	>25:1
11	 **23**	180[f]	 **44**	62	>25:1
12	 **23**	180	 **45**	54[g] 60[h] 55[i]	>25:1
13	 **23**	140	 **46**	87	---
14	 **47**	200	 **48**	74	>25:1

[a] Irradiation at 600 W for 1.5 h. [b] The relative stereochemistry was established by 2-D ^{1}H NMR experiments and chemical transformations; see Supporting Information. [c] Isolated yields. [d] Ratios were determined by ^{1}H NMR or GC-MS of the crude mixture. [e] Reaction carried out in DMF. [f] Six equivalents of triethylamine was added. [g] A catalytic amount of silica gel was added. [h] A catalytic amount of BHT was added. [i] No additive.

neither of the isomers corresponding to **I** or **J** are formed. Assuming the tandem reaction is governed by the Curtin−Hammett principle, the two macrocycles **A** and **B** are in rapid equilibrium, and the product ratio for the Claisen rearrangement should correspond to the relative values of the absolute energies for the two transition states. Transformation of **B** to **E**, where R_4 = Me is axial, should have the higher transition state energy and thus be the less favored process as compared to the Claisen rearrangement of **A** to **D**. From **D**, one can either undergo a ring inversion to **C** followed by an ene reaction to give **G** (not observed) or give directly the solely observed product **37** (**H**). Recall that in entry 1 (R_1 = Me, R_4 = H) the reaction followed both of these pathways and gave a mixture of products. In this case, however, the ene reaction for the formation of **G** should have a higher transition state energy than that for the formation of **H** because of not only the axial allyl group, but now also the axial methyl group (R_4). This clearly demonstrates that the diastereoselectivity of the oxy-Cope/Claisen/ene can be directed by a remote stereogenic center.

Heating of allyl ether **30** gave the Decalin **38** in 83% yield as the only detectable isomer (entry 5). Subjection of **33** to standard conditions also led to the formation of a single isomer, **39**, in 93% yield (entry 6). In this case, the selectivity can be readily explained due to conformational restrictions imposed by the cyclohexene ring, which would prevent the ring inversions of **A** to **B** and **C** to **D** from taking place. Consequently, only one pathway remains available, and a single isomer, **39**, is formed as expected.

At this point in the study, our attention was turned to those substrates bearing substituents at R_2 and R_3. These results are represented by entries 7−10 in Table 1 and will be examined with reference to the mechanism shown in Figure 3.

Entry 7 shows that when **19** (R_2 = H, R_3 = Me, R_4 = H) was treated under standard conditions, a mixture of **40a** (**Q**)

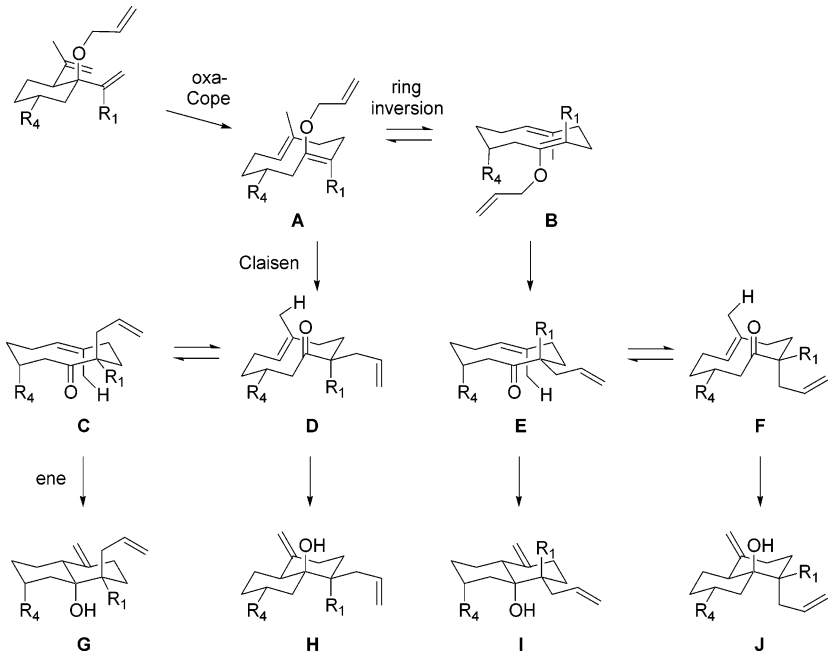


Figure 2. Mechanism of the oxy-Cope/Claisen/ene reaction for entries 1−6.

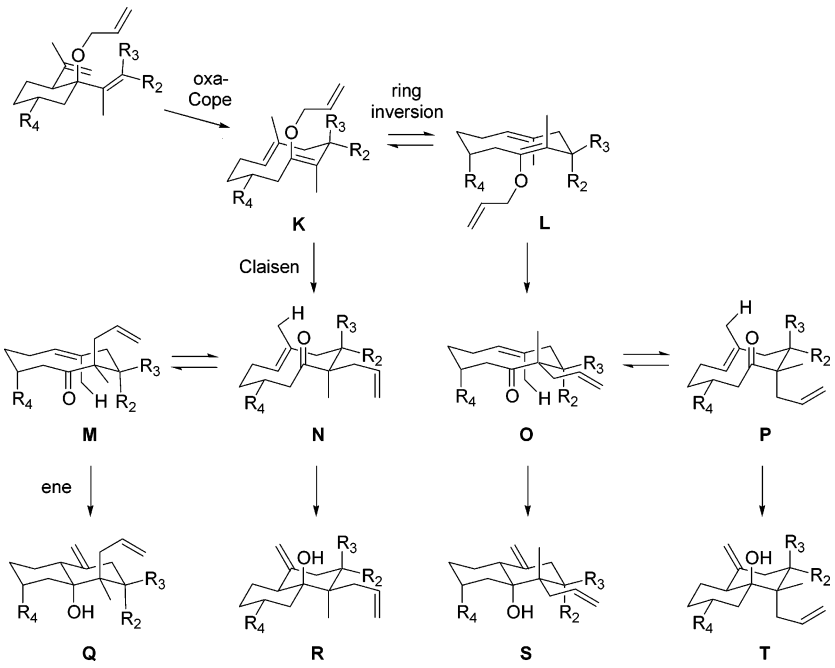


Figure 3. Oxy-Cope/Claisen/ene mechanism for entries 7−10.

and **40b** (**R**) was obtained in 73% yield with a diastereomeric ratio of 4:1. This result proves interesting upon closer analysis as it provides some key insight into the mechanism. Following the oxy-Cope rearrangement of **19**, intermediate **K** (R_2 = H, R_3 = Me, R_4 = H) has the option of undergoing a ring inversion to form its diastereomer **L**. Because no products corresponding to either **S** or **T** were observed, one can assume that **K** is the reactive conformer. However, if one examines the relative energies of **K** and **L**, one finds that **K** where R_3 = Me is axial should be higher in energy than **L**. Similarly, the absolute transition state energies for the corresponding Claisen rearrangements should reflect this energy difference. Thus, the existence of a rapid equilibrium between **K** and **L** can be ruled out because its existence would predict the formation of isomers **S** and/or **T** via the lower energy Claisen rearrangement of **L** to **O**. In light of this result, we can now assume that the rate of ring inversion between intermediates **K** and **L** is significantly slower than the Claisen rearrangement of **K** to **N**. Furthermore, if one extends this assumption to other substrates, the formation of isomers corresponding to **S** and **T** is no longer expected for this tandem sequence. Examining the remainder of the mechanism for substrate **19**, one finds no further surprises. Assuming the transannular ene reaction follows the Curtain−Hammett principle, one predicts the preferred formation of isomer **Q** because of the more favorable diequatorial methyl groups versus diaxial methyl groups at the transition state.

Allyl ether **18** was irradiated (entry 8, R_2 = Me, R_3 and R_4 = H) to provide Decalin **41** (**R**) in 98% yield as a single

diastereomeric product. Keeping in mind the mechanistic insight gained from previous examples, this remarkable selectivity is now readily explained. Oxy-Cope rearrangement of **18** gives intermediate **K**, which immediately undergoes a Claisen reaction to **N** before any ring inversion to **L** has a chance to occur. Intermediate **N** then undergoes an ene reaction to give the solely observed product **41** (**R**). As entry 8 clearly illustrates, the tandem oxy-Cope/Claisen/ene reaction sequence allows for the precise control of two contiguous quaternary centers and their adjacent stereocenters with excellent yield and excellent diastereoselectivity. To apply this methodology to synthesis, however, it would be necessary for the tandem sequence to be tolerant of additional functional groups (entries 9−12). To this end, substrate **20** was prepared and subjected to our standard microwave conditions (entry 9, $R_2 = CH_2OTBS$, R_3, $R_4 = H$). Decalin **42** (**R**) was isolated in 90% yield, corresponding to a diastereomeric ratio of 17:1. It should be noted, however, that the diastereomeric ratio for this reaction was found to be temperature dependent. On going from 220 to 180 °C, the ratio improved from 10:1 to 17:1. Temperatures lower than 180 °C, however, proved detrimental to the reaction rate and resulted in primarily the recovery of starting material. In an effort to see if we could further improve on the 17:1 diastereoselectivity found for **20**, we prepared substrate **29** ($R_2 = CH_2OTBS$, $R_3 = H$, $R_4 = Me$) and subjected it to our standard conditions (entry 10). As expected, a single diastereomeric product, **43** (**R**), was obtained in 90% yield.

Acetal **23** (where $OMOP = OC(CH_3)_2OCH_3$) was heated at 220 °C in the presence of a proton scavenger (6 equiv of triethylamine) to give Decalin **44** in 62% yield (entry 11). The same acetal **23** was irradiated both with and without additives such as BHT and silica gel to give Decalin **45** in 54−60% yield (entry 12). It is noteworthy that the formation of a seven-membered ring acetonide through an acid-catalyzed trans-acetalization of the MOP groups occurs prior to the thermal pericyclic rearrangement as indicated by the isolation of allyl ether **46** in 87% yield after heating **23** at 140 °C for 30 min (entry 13).

Finally, as expected, benzylidene acetal **47**,[22] readily prepared from **23**, was transformed into the corresponding Decalin **48** in 74% yield (entry 14).

Conclusion

A careful analysis of the reaction mechanism indicates that the stereochemical outcome of the tandem process is controlled by the conformational preferences of macrocycles at the transition state for the Claisen and ene reactions. Initially, the diastereoselectivity of the tandem reaction was rationalized by assuming that the ring inversions are fast, thereby taking into account only the transition state energies for the Claisen and ene reactions. However, the above fails to explain the results obtained in entries 2 and 7. Deviation of entry 2 may be rationalized by an electronic acceleration of the ene reaction. The result of entry 7, along with the fact that isomers corresponding to **S** and **T** were never observed, suggests that ring inversion is generally slow as compared to the Claisen rearrangement. In summary, the tandem oxy-Cope/Claisen/ene reaction proves to be a powerful and simple method to produce Decalin frameworks of neo-clerodane and pimarane diterpenes possessing an anti−anti stereochemistry at C8, C9, and C10 and adjacent quaternary centers at C9 and C10. This method is currently being used in the total synthesis of teucrolivin A (**1**) and LL-491β (**2**) (Figure 1).

Acknowledgment. L.B. dedicates this article to Professor Pierre Deslongchamps for his mentorship and scientific achievements. We thank the Natural Science and Engineering Research Council of Canada (NSERC), Merck-Frosst, Boehringer Ingelheim, Bristol Myers Squibb, AstraZeneca Canada, Canada Foundation for Innovation, Ontario Innovation Trust, and the University of Ottawa for generous funding. E.L.O.S. thanks the NSERC for a PGS-A Julie-Payette postgraduate scholarship.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H, ^{13}C, and relevant 2D NMR for compounds **10**−**48** (PDF and zip files). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Hydrolysis of MOP acetals in **23** with PTSA in MeOH gave the corresponding diol which was then treated with benzaldehyde (4 equiv) and PTSA (5 mol %) in CH_2Cl_2 to afford **47** in 82% overall yield.