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Exploration of the Enantioselective Birch−Cope Sequence for the Synthesis of Carbocyclic Quaternary Stereocenters

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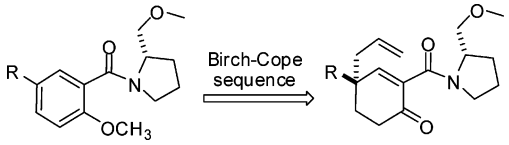
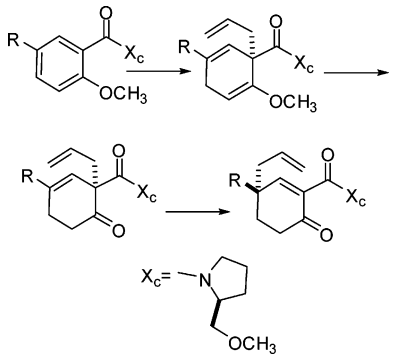


Quaternary stereocenters on a 2-cyclohexen-1-one ring are synthesized with good to excellent levels of enantioselectivity. The quaternary stereocenter is created through a new synthetic sequence involving three reactions: the enantioselective Birch reduction-allylation, enol ether hydrolysis, and the Cope rearrangement. To illustrate the ability of the sequence to enantioselectively generate complex structures, a variety of substrates are described. Notably, the sequence works for the enantioselective generation of vicinal quaternary-tertiary stereocenters, the generation of congested arylic quaternary stereocenters, and hydroxyalkyl substituted quaternary stereocenters.

Introduction

The enantioselective construction of quaternary stereocenters is a significant challenge in contemporary synthetic organic chemistry.[1] New synthetic tools capable of generating quaternary carbons with stereocontrol are necessary due in part to the abundance of bioactive natural products containing quaternary stereocenters. In a preliminary report,[2] we related a new method, the Birch−Cope sequence, which can enantioselectively generate quaternary stereocenters on a carbocyclic ring. The Birch−Cope sequence combines three reactions: an enantioselective Birch reduction-allylation,[3] an enol ether hydrolysis reaction, and a Cope rearrangement[4] (Scheme 1). The product of the sequence is a 4,4-disubstituted-2-carboxamide-2-cyclohexen-1-one, which is a versatile intermediate in natural product synthesis[5] as previously illustrated in a succinct synthesis of (+)-mesembrine.[2] Our earlier report contained only two substrate examples. For the Birch−Cope sequence to have broad applicability in the synthesis of carbocyclic quaternary stereo-

SCHEME 1. Birch−Cope Sequence



(1) (a) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738−7739. (b) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581−1587. (c) Lee, K-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182−7184. (d) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774−2775. For reviews see: (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (f) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Federal Republic of Germany, 2005. (g) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (h) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (i) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (j) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (k) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(2) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007−4010.

(3) (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828−7841. For reviews of the asymmetric Birch reduction-alkylation, see: (b) Schultz, A. G. *Chem. Commun.* **1999**, 1263−1271. (c) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207−213.

(4) For reviews of the Cope rearrangement see: (a) Nubbemeyer, U. *Synthesis* **2003**, 961−1008. (b) Hill, R. K. Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, Chapter 7.1, pp 785−826. For recent examples of the Cope rearrangement see: (c) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485−2490. (b) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *124*, 8569−8575.

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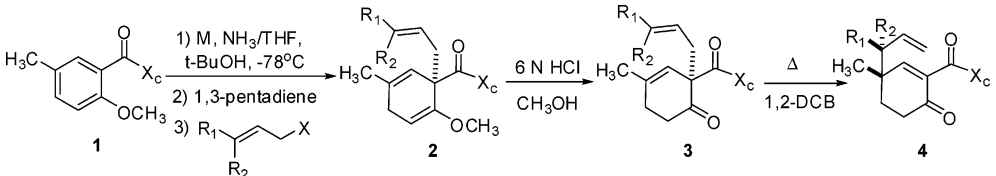
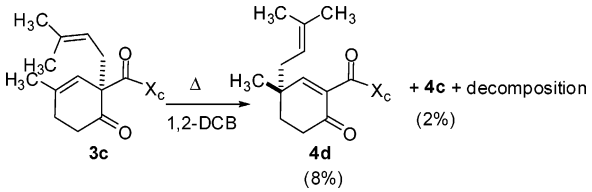
SCHEME 2. Allyl Derivatives in Birch−Cope Sequence



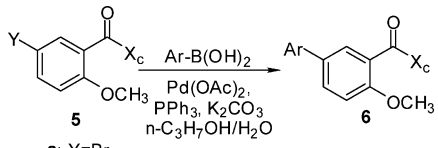
entry	allylating reagent	M	X	dr	yield (%)	yield (%)	yield (%)
1	**a**: R_1=R_2=H	K	Br	110:1	72	97	88
2	**b**: R_1=CH_3, R_2=H	K	Br	8:1	62	--	--
3	**b**	Li	Br	11:1	60	99	70
4	**b**	K	Cl	>99:<1	73	--	--
5	**c**: R_1=R_2=CH_3	Li	Br	11:1	88	86	0

X_c=(S)-2-(methoxymethyl)pyrrolidine

SCHEME 3. Cope Rearrangement Results for 3c



SCHEME 4. Suzuki Reactions with C-5-Halo-*o*-anisic Acid Derivatives



a: Y=Br
b: Y=I

Ar	yield (%)
a: Ph	Y=Br, 100; Y=I, 79
b: 4-(CH_3O)-Ph	Y=I, 96
c: 3,4-(CH_3O)$_2$-Ph	Y=Br, 93; Y=I, 96
d: 2,3-(CH_3O)$_2$-Ph	Y=I, 96

X_c=(S)-2-(methoxymethyl)pyrrolidine

centers, the sequence will have to permit variations of the *o*-anisic acid structure and the allylation agent. In this report, a more thorough exploration of the Birch−Cope sequence is undertaken, with particular attention to variability in the allyl group[6] and the R group[7] (Scheme 1).

Results and Discussion

Allyl Derivatives in the Birch−Cope Sequence. As previously communicated,[2] Birch reduction-allylation of the 5-methyl-*o*-anisic acid derivative, **1**, afforded exceptionally high levels of enantioselectivity (dr = 110:1) in the new quaternary center of **2a** (entry 1, Scheme 2).[8] The absolute sense of the new quaternary center in **2a** and of all subsequent Birch products is based on the preferences reported by Schultz et al.[3] and was confirmed in the previous report[2] with the enantioselective synthesis of (+)-mesembrine. The enantioselectivities seen in the reactions reported herein are similar to those previously reported for related C-5 substituted L-prolinol benzamide substrates.[7]

Hydrolysis of the enol ether provided 3-cyclohexen-1-one **3a**. Heating **3a** at reflux for 10 h in 1,2-dichlorobenzene (1,2-DCB) resulted in complete conversion to the more thermodynamically stable 2-cyclohexen-1-one **4a**.[9] Microwave reactor heating of **3a** provided a comparable yield (96%) of **4a** but in a much shorter time (1 h). This represents the first example of acceleration of a standard Cope rearrangement through microwave heating.[10] The three-step Birch−Cope sequence with the 5-methyl derivative **1** was performed on gram scale in 61% overall yield.

Under identical conditions, substitution of *trans*-crotyl bromide for allyl bromide in the Birch reduction-alkylation provided a 62% yield of **2b** (entry 2, Scheme 2) and much lower enantioselectivity (dr = 8:1). Performing the Birch reduction with lithium instead of potassium afforded the less reactive lithium enolate (entry 3), which upon reaction with *trans*-crotyl bromide improved the enantioselectivity slightly (dr = 11:1). Use of a less reactive alkylating agent, *trans*-crotyl chloride (entry 4), restored the excellent stereoselectivity to the process with either lithium or potassium. Presumably, the more reactive enolates or alkylating agents contributed to a less selective outcome.

Reaction of the lithium enolate generated in the Birch reduction of **1** with dimethylallyl bromide afforded an 88% yield

(5) For previous examples of asymmetric syntheses of 4,4-dialkyl-cyclohexenones, see: (a) Trost, B. M.; Bream, R. N. Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109−3112. (b) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712−1713. (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562−9573. (d) Meyers, A. I.; Berney, D. *Org. Synth.* **1990**, *69*, 55−65. For previous examples of asymmetric syntheses of 4-alkyl-4-aryl-cyclohexenones, see: (e) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711−7714. (f) Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymmetry* **1993**, *4*, 21−24. (g) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936−1938. (h) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2125−2129.

(6) For previous examples of Birch reduction-allylation with L-prolinol benzamides see: (a) Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931−4936. (b) Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 2456−2464. (c) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493−6502. (d) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591−4594.

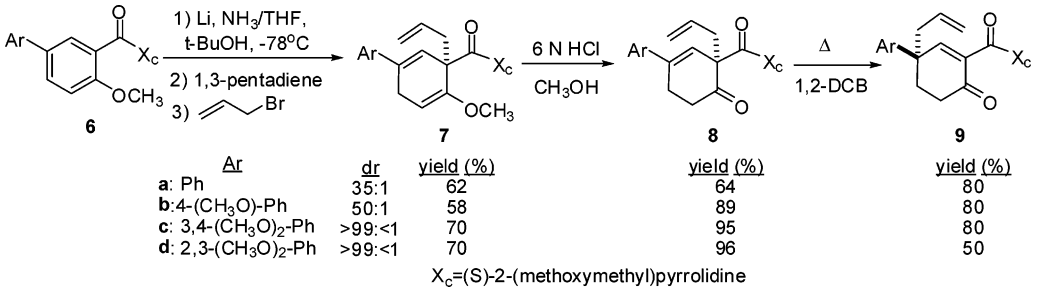
(7) For previous examples of Birch reduction-alkylation with C-5 substituted L-prolinol benzamides see: (a) Guo, Z.; Schultz, A. G. *Tetrahedron Lett.* **2004**, *45*, 919−921. (b) Khim, S.-K.; Dai, M.; Zhang, X.; Chen, L.; Pettus, L.; Thakkar, K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7728−7733. (c) Schultz, A. G.; Malachowski, W. P.; Pan, Y. *J. Org. Chem.* **1997**, *62*, 1223−1229. (d) Reference 3a.

(8) Diastereomeric ratios for all compounds were determined on purified material by comparison with an independently synthesized diastereomeric mixture. The most convenient manner to generate the mixture was to remove ammonia after the Birch reduction and prior to alkylation.

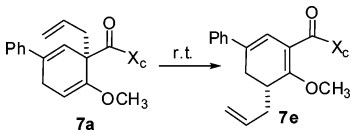
(9) Attempted Cope rearrangement of **2a** leads to a mixture of products resulting from competing rearrangements between the two different 1,5-diene systems.

(10) For examples of oxy-Cope rearrangements accelerated by microwave see: (a) Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382−1388. (b) Farand, J. A.; Denissova, I.; Barriault, L. *Heterocycles* **2004**, *62*, 735−748. For examples of silyloxy-Cope rearrangements accelerated by microwave see: (c) Schneider, C.; Khaliel, S. *Synlett* **2006**, 1413−1415. (d) Davies, H. M. L.; Beckwith, R. E. J. *J. Org. Chem.* **2004**, *69*, 9241−9247. For examples of aza-Cope rearrangements accelerated by microwave see: (e) Kvaerno, L;, Norrby, P-O; Tanner, D. *Org. Biomol. Chem.* **2003**, *1*, 1041−1048. (f) Yadav, J. S.; Subba Reddy, B. V.; Abdul Rasheed, M.; Sampath Kumar, H. M. *Synlett* **2000**, 487−488.

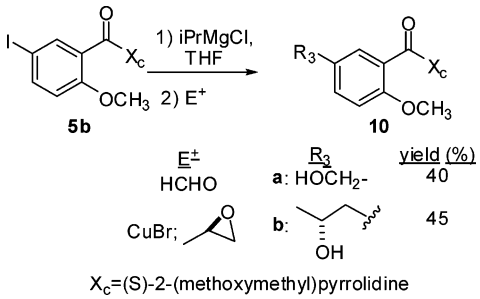
SCHEME 5. C-5 Aryl Derivatives in Birch−Cope Sequence



SCHEME 6. Spontaneous Cope Rearrangement of 7a



SCHEME 7. Synthesis of C-5 Hydroxyalkyl *o*-Anisic Acid Derivatives



of **2c** (entry 5, Scheme 2) with modest enantioselectivity (dr = 11:1). In all probability, the factors that compromised the enantioselectivity in the alkylation with crotyl bromide were also present with dimethylallyl bromide. Nevertheless, with our focus on the amenability of **3c** to generate adjacent quaternary centers in the Cope rearrangement (vide infra), we did not attempt to further optimize the enantioselectivity of the Birch reduction-alkylation to **2c**. In all the Birch reduction-allylation reactions described, the most common side product results from gamma-allylation of the enolate at the C-3 carbon (*o*-anisic acid numbering).

Hydrolysis of both **2b** and **2c** occurred efficiently to afford **3b** and **3c** in 99 and 86% yield, respectively. As anticipated, the equilibrium in the Cope rearrangement of **3b** to **4b** was less favorable than for **3a/4a** due to the concomitant creation of a tertiary carbon center adjacent to the quaternary center. Nevertheless, a 70% yield of the rearranged product **4b** was isolated, along with the recovery of 24% of the starting material, **3b**. Despite the high temperatures of the Cope rearrangement, little decomposition occurs. Consequently, the recovered starting material can be recycled making the process efficient.

Besides forming the highly congested contiguous tertiary-quaternary carbon centers, the Cope rearrangement of **3b** to **4b** occurred with complete stereocontrol. Chromatography of **4b** showed only one diastereomer, and NOESY studies identified the product to be the result of a boat transition state (see Supporting Information).[11] In addition to the transfer of chiral information generated in the Birch reduction-allylation to the C-4 quaternary center, the alkene stereochemistry is translated into the new tertiary chiral center through the stereospecific Cope rearrangement.

Under Cope rearrangement conditions, **3c** afforded a very small amount (∼2%) of the expected product, **4c** (Scheme 3). The more common transformation of **3c** involved 1,3-migration of the dimethylallyl group to form **4d** (∼8% yield), along with a considerable amount of decomposition. The creation of two adjacent quaternary centers is not favored under the equilibrium conditions of the Cope rearrangement of **3c**.

C-5 Aryl *o*-Anisic Acid Derivatives. A variety of biaryl *o*-anisic acid derivatives were prepared that would lead to arylated quaternary carbocyclic stereocenters. Their synthesis was easily accomplished using a divergent strategy involving Suzuki coupling reactions of the 5-bromo (**5a**) or the 5-iodo *o*-anisic acid derivative (**5b**).[2] Besides the previously reported 3,4-dimethoxyphenylboronic acid which lead to the synthesis of (+)-mesembrine,[2] phenyl-, 4-methoxyphenyl-, and 2,3-dimethoxyphenylboronic acid, all provided excellent yields of the biaryl products (Scheme 4).

Birch reduction-allylation of **6a−d** afforded good yields and high enantioselectivities for all cases (Scheme 5). In our experience, lithium worked better than potassium for the reduction of the biaryl compounds.[12] The isolated phenyl derivative **7a** was unstable and spontaneously underwent a Cope rearrangement to form **7e** (Scheme 6) while being stored at room temperature. All other aryl derivatives were stable and did not show any propensity to undergo rearrangements or degrade.

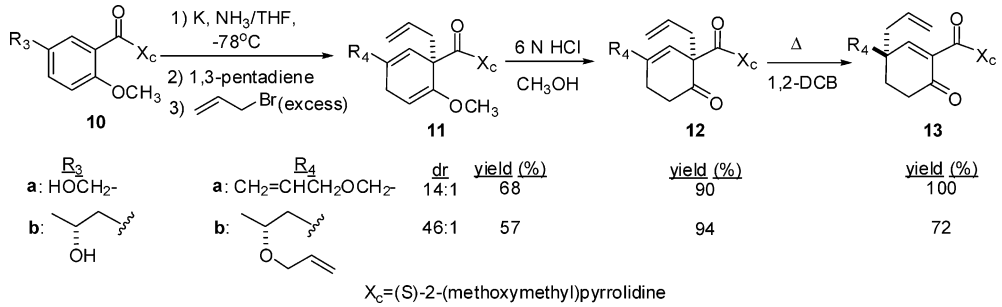
Hydrolysis of the enol ether occurred uneventfully in high yield for **7b−d** to form **8b−d** (Scheme 5). The lower hydrolysis yield for **7a** was partially due to its inherent instability. Cope rearrangement of **8a−d** occurred in high yield for most cases, but a less favorable equilibrium than for **3a** was seen because of the loss of styrene conjugation in **8a−d** and due to the formation of more congested quaternary centers (**9d**). Nevertheless, the starting material is recovered and can be resubjected to the Cope equilibrium making for an efficient transformation. Surprisingly, the styrene conjugation in **8a−d** is not a prohibitive barrier to formation of the 2-cyclohexen-1-one systems of **9a−d**. This represents the first case of a Cope equilibrium that balances the stabilization of phenyl group conjugation versus conjugation with a ketone. Amide conjugation is expected to be weak because the steric bulk of the amide forces it orthogonal to the enone system (vide infra).[2]

C-5 Hydroxyalkyl *o*-Anisic Acid Derivatives. Functionalized alkyl groups were appended at the C-5 position of the

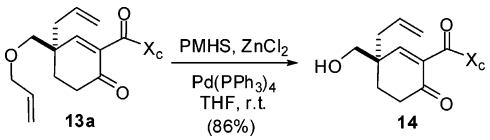
(11) For examples of Cope rearrangements occurring by a boat transition state in sterically constrained 1,5-dienes see: (a) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354−356. (b) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 6576−6577.

(12) For other examples of chemoselective biaryl Birch reduction-alkylations, see: (a) Lebeuf, R.; Frederic, R.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557−4560. (b) Guo, Z.; Schultz, A. G.; Antoulinakis, E. *Org. Lett.* **2001**, *3*, 1177−1180. (c) See also refs 6a, 7a, and 7b.

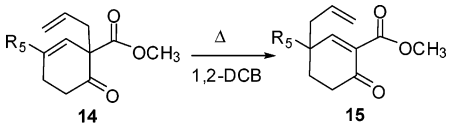
SCHEME 8. C-5 Hydroxyalkyl Derivatives in Birch−Cope Sequence



SCHEME 9. Deprotection of Allyl Ether in 13a



SCHEME 10. Cope Equilibrium with Methyl Ester Derivative



1 ratio=**14**/**15** as determined by GC
2 13% of decarbomethoxylated **15** also seen

o-anisic acid derivatives through Grignard reactions. Although conventional Grignard formation did not work, the transmetallation conditions of Knochel et al.[13] were successful when applied to **5b**. Quenching the Grignard reagent with formaldehyde provided **10a**, while adding CuBr and reacting with (*R*)-propylene oxide provided **10b** (Scheme 7).

Both **10a** and **10b** were successfully subjected to Birch reduction-allylation (Scheme 8). *tert*-Butyl alcohol was not needed in the Birch reduction due to the presence of an alcohol in **10a/b**, which provides a proton source to quench the radical anion intermediate. Allylation of the alkoxide could not be avoided during the alkylation step. To avoid inseparable mixtures, we used an excess of allyl bromide to alkylate both the enolate and the alkoxide.

The diastereoselectivity in Birch reduction-allylation of **10a** and **10b** was somewhat compromised by the presence of the alkoxide, a strong chelating group. Through the formation of aggregates, the alkoxide might disrupt the enolate structure that results in the higher levels of enantioselectivity normally seen.[14] The detrimental effect of chelation on the reaction stereoselectivity was more pronounced with **10a**. Nevertheless, this represents a rare example of an asymmetric Birch reduction-alkylation with a substrate containing a kinetically acidic proton.[15] The amenability of these complex substrates to Birch reduction-alkylation further illustrates the versatility of this underutilized synthetic tool.

The hydrolysis reaction of **11a/b** and the Cope rearrangement of **12a/b** occurred in high yield (Scheme 8). The larger hydroxypropyl substituent of **12b** made the Cope equilibrium slightly less favorable than **12a**, with approximately 27% of the starting material recovered. The allyl ether of **13a** has been selectively cleaved without isomerization of the other terminal alkene (Scheme 9).[16] In this manner, two uniquely functionalized alkyl groups can be created in the C-4 position of the 2-cyclohexen-1-one.

Controlling Elements in the Cope Equilibrium. As previously described,[2] the Cope rearrangement equilibrium is controlled primarily by the formation of the stable conjugated enone system. Computational studies[2] and previous reports[17] with related systems show the amide is orthogonal to the enone system, therefore, offering no stabilization through conjugation.

Nevertheless, besides inducing stereocontrol in the enolate alkylation step, the amide also plays an essential role in controlling the Cope equilibrium. Studies with the analogous methyl esters **14a/b** (Scheme 10) showed the equilibrium of the Cope rearrangement was much less favorable under identical thermal conditions. Furthermore, computational studies[18] that determined the lowest energy conformation of **15a** showed the methyl ester substituent to be coplanar with the enone (see Supporting Information). Despite the more extensive conjugation

(13) (a) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, (4), 565−569. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320.

(14) With the *o*-anisic acid derivatives, enantioselectivity in the Birch reduction-alkylation arises from the rigid structure created from the coordination of the metal between the enolate oxygen and the 2-methoxy group. The alkoxide ion generated in the Birch reduction of **10a/b** might compete intermolecularly with the 2-methoxy group for metal coordination, thereby compromising the structure of the normal enolate intermediate.

(15) For previous examples of asymmetric Birch reduction-alkylations with kinetically acidic N−H groups see: (a) Casimiro-Garcia, A.; Schultz, A. G. *Tetrahedron Lett.* **2006**, *47*, 2739−2742. (b) Schultz, A. G.; McClosky, P. J.; Sundararaman, P. *Tetrahedron Lett.* **1985**, *26*, 1619−1622. (c) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493−6502.

(16) Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Tetrahedron* **2001**, *57*, 3435−3438.

(17) Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926−4931.

(18) Energy minimization calculations were accomplished with semiempirical calculations (AM1) using Gaussian 03 suite of programs. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.05; Gaussian, Inc.: Wallingford, CT, 2004.

with the methyl ester analogue **15a**, the Cope equilibrium is more favorable for the formation of **4a**. The absence of coplanarity for the amide in **4a** is due to its steric bulk; however, the steric bulk of the amide creates considerable congestion at the quaternary center of **3a**, which is relieved in the Cope rearrangement to form **4a**. Therefore, the Cope equilibria in the Birch−Cope sequence benefit from both the conjugation of the enone system in the products and the reduction of steric strain in the starting materials.

Conclusion

The Birch−Cope sequence has demonstrated the ability to efficiently and enantioselectively generate quaternary stereocenters on a carbocyclic ring. Importantly, a variety of substituents have been incorporated at the quaternary center of the 2-cyclohexen-1-one product in good yield and with good to excellent levels of enantioselectivity. Use of a defined allylic alkylating agent allows the generation of two adjacent chiral centers. Quaternary stereocenters with ortho-substituted aryl substituents and hydroxyalkyl substituents were both efficiently generated with stereocontrol. In the process of this study, an understanding of the unique features of the Cope equilibria in the Birch−Cope sequence has been developed. As previously illustrated,[2] the prolinol chiral auxiliary can be easily removed with hydroxylamine reagents, and subsequent transformations of the 2-cyclohexen-1-one structures into complex natural product targets have been accomplished. Future applications of the Birch−Cope sequence to challenges in natural product synthesis are underway and will be reported in due course.

Experimental Section

General Procedure for the Suzuki Reaction. The 5-halo-*o*-anisic acid derivative (1.0 equiv) was dissolved in 1-propanol (5.5 mL/mmol halo derivative) with the arylboronic acid derivative (1.1 equiv) and was treated with $Pd(OAc)_2$ (0.05 equiv), Ph_3P (0.15 equiv), and the 10% K_2CO_3 solution (1.25 equiv K_2CO_3). The dark green reaction was heated at reflux overnight turning progressively darker with time. The crude reaction was partially concentrated and filtered through a plug of cotton. The product was extracted with EtOAc and the organic layer was washed with 5% $NaHCO_3$ and brine, was dried with $MgSO_4$, and was concentrated. Purification by column chromatography afforded pure product.

(*S*)-(4-Methoxybiphenyl-3-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (6a). Use of the general procedure with **5a** and phenylboronic acid afforded a 100% yield of a white crystalline product. Column eluted with 7:3 EtOAc/hexanes. TLC $R_f = 0.40$ (7:3 EtOAc/hexanes), mp = 80−81 °C. ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.60−7.45 (m, 4H), 7.44−7.36 (m, 2H), 7.31−7.26 (m, 1H), 6.98−6.94 (m, 1H), 4.50−4.38 (m, 1H), 3.85 (s, 3H), 3.75 (dd, 1H, $J = 9.4$, 3.3 Hz), 3.57 (dd, 1H, $J = 9.4$, 6.8 Hz), 3.41, 3.05 (two s, 3H), 3.30−3.20 (m, 2H), 3.10−3.05 (m, 1H), 2.10−1.86 (m, 3H), 1.78−1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 128.8, 128.7, 127.0, 126.7, 126.4, 111.6, 59.1, 58.8, 57.4, 56.4, 55.8; δ_d 167.9, 167.8, 154.8, 140.1, 134.0, 133.9, 128.0, 127.6, 73.6, 72.4, 48.5, 45.8, 28.5, 27.8, 24.2, 22.2. IR ($CDCl_3$) 1617 cm^{-1}. GC $t_R = 27.54$ min. EI-MS *m*/*z* (%): 325 (M^+, 1), 293 (9), 280 (32), 211 (100).

(*S*)-(4,4′-Dimethoxybiphenyl-3-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (6b). Use of the general procedure with **5b** and 4-methoxyphenylboronic acid afforded a 96% yield. Column eluted with 1:1 EtOAc/hexanes. TLC $R_f = 0.50$ (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.52−7.43 (m, 4H), 6.96−6.92 (m, 3H), 4.45−4.40, 3.92−3.80 (two m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (dd, 1H, $J = 9.5$, 3.5 Hz), 3.56 (dd, 1H, $J = 6.9$, 9.4 Hz), 3.42, 3.06 (two s, 3H), 3.32−3.23, 3.10−3.06 (two m, 1H), 2.10−1.70 (m, 4H). ^{13}C NMR ($CDCl_3$, a mixture of rotational isomers) δ_u 128.3, 128.0, 126.0, 114.2, 111.6, 59.1, 58.8, 57.3, 56.3, 55.8, 55.7, 55.3; δ_d 167.9, 158.9, 154.3, 133.7, 133.6, 132.8, 127.7, 127.5, 73.5, 72.4, 48.5, 45.8, 29.7, 28.5, 27.8, 24.2, 22.2. IR ($CDCl_3$) 1610 cm^{-1}. GC $t_R = 22.73$ min. EI-MS *m*/*z* (%): 356 (2, $M^+ + 1$), 355 (M^+, 1), 310 (8), 242 (17), 241 (100).

(*S*)-(2-(Methoxymethyl)pyrrolidin-1-yl)(2′,3′,4-trimethoxybiphenyl-3-yl)methanone (6d). Use of the general procedure with **5d** and 2,3-dimethoxyphenylboronic acid afforded a 96% yield. Column eluted with 1:1 EtOAc/hexanes. TLC $R_f = 0.40$ (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.57 (dd, 1H, $J = 8.6$, 2.2 Hz), 7.45 (d, 1H, $J = 2.2$ Hz), 7.09 (t, 1H, $J = 8.0$ Hz), 6.99−6.88 (m, 3H), 4.50−4.40, 3.87−3.78 (two m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.75 (dd, 1H, $J = 9.4$, 3.3 Hz), 3.67−3.50 (m, 1H), 3.57 (s, 3H), 3.41, 3.09 (two s, 3H), 3.35−3.25 (m, 1H), 3.15−3.08 (m, 1H), 2.08−1.72 (m, 4H). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 132.0, 130.9, 128.5, 124.0, 122.2, 111.2, 110.8, 60.3, 59.0, 58.6, 57.2, 56.1, 55.8, 55.6, 55.5; δ_d 167.7, 154.4, 153.0, 146.3, 134.7, 130.5, 127.1, 126.6, 73.3, 72.2, 48.6, 45.7, 28.3, 27.7, 24.1, 22.1. IR ($CDCl_3$) 1623 cm^{-1}. GC $t_R = 21.9$ min. EI-MS *m*/*z* (%): 385 (M^+, 3), 353 (11), 340 (16), 272 (28), 271 (100).

(*S*)-(5-(Hydroxymethyl)-2-methoxyphenyl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (10a). Isopropyl magnesium chloride (0.73 mL, 2.0 M soln in THF) was added dropwise to **5b** (500 mg, 1.33 mmol) in THF (7 mL) at 0 °C. The reaction was warmed to rt, was stirred for 1 h, and then was recooled to 0 °C. Formaldehyde gas (generated by heating paraformaldehyde) was passed through the reaction solution for several minutes, after which the reaction was stirred at 0 °C for 1 h. The reaction was quenched with cold water, was warmed to rt, was treated with saturated NH_4Cl, and the product was extracted with EtOAc. The combined organic layers were washed with brine, were dried with Na_2SO_4, and were concentrated. Column chromatography (4:1, EtOAc/hexanes) of the crude product provided pure **10a**, 150 mg (40% yield). TLC $R_f = 0.20$ (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.34 (dd, 1H, $J = 8.5$, 1.9 Hz), 7.26 (s, 1H), 6.90 (d, 1H, $J = 8.5$ Hz), 4.62 (s, 2H), 4.43−4.38, 3.80−3.76 (two m, 1H), 3.84 (s, 3H), 3.73 (dd, 1H, $J = 9.4$, 3.3 Hz), 3.57 (dd, 1H, $J = 9.4$, 6.7 Hz), 3.42, 3.09 (two s, 3H), 3.30−3.15 (m, 2H), 3.08−3.03 (m, 1H), 2.10−1.70 (m, 4H). ^{13}C NMR ($CDCl_3$, a mixture of rotational isomers) δ_u 129.0, 126.5, 111.1, 59.0, 58.7, 57.3, 56.3, 55.7; δ_d 168.1, 154.4, 133.8, 127.3, 126.8, 73.3, 72.2, 64.0, 48.4, 45.7, 28.3, 27.7, 24.1, 22.1. IR ($CDCl_3$) 1611 cm^{-1}. GC $t_R = 15.76$ min. EI-MS *m*/*z* (%): 279 (M^+, 1), 247 (10), 234 (18), 164 (11), 165 (100).

(5-((*R*)-2-Hydroxypropyl)-2-methoxyphenyl)((*S*)-2-(methoxymethyl)pyrrolidin-1-yl)methanone (10b). Isopropyl magnesium chloride (1.50 mL, 2.0 M soln. in THF) was added dropwise to **5b** (1.00 g, 2.67 mmol) in THF (14 mL) at 0 °C. The reaction was warmed to rt, was stirred for 1 h, and then was recooled to −15 °C. CuBr (211 mg, 1.47 mmol) was added and the reaction was stirred for several minutes at −15 °C. A solution of (*R*)-propylene oxide (0.41 mL, 5.85 mmol) in THF (0.5 mL) was added dropwise and the reaction was stirred overnight at 0 °C. The reaction was quenched with cold water, was warmed to rt, was treated with saturated NH_4Cl, and the product was extracted with EtOAc. The combined organic layers were washed with brine, were dried with Na_2SO_4, and were concentrated. The crude product was purified with column chromatography (4:1, EtOAc/hexanes) to afford pure **10b** (370 mg, 45% yield). TLC $R_f = 0.20$ (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.17 (dd, 1H, $J = 8.4$, 2.2 Hz), 7.09 (d, 1H, $J = 2.2$ Hz), 6.85 (d, 1H, $J = 8.4$ Hz), 4.42−4.37, 3.85−3.75 (two m, 1H), 4.00−3.90 (m, 1H), 3.81 (s, 3H), 3.73 (dd, 1H, $J = 9.4$, 3.4 Hz), 3.55 (dd, 1H, $J = 9.4$, 6.8 Hz), 3.41, 3.09 (two s, 1H), 3.27−3.12 (m, 1H), 3.27−3.12, 3.10−3.03 (two m, 1H), 2.75−2.59 (m, 2H), 2.06−1.70 (m, 4H), 1.21 (d, 3H, $J = 6.2$ Hz). ^{13}C NMR ($CDCl_3$, a mixture of rotational isomers) δ_u

131.0, 128.4, 111.2, 68.6, 59.0, 58.6, 57.3, 56.2, 55.6, 22.5; δ_d 167.9, 153.8, 130.9, 127.4, 126.9, 73.4, 72.2, 48.3, 45.6, 44.6, 28.4, 27.7, 24.1, 22.1. IR ($CDCl_3$) 3413, 1617 cm^{-1}. GC t_R = 21.57 min. EI-MS *m*/*z* (%): 307 (M^+, 1), 275 (11), 262 (18), 193 (100).

General Procedure for the Birch Reduction-Allylation. To a solution of benzamide (1.0 equiv) and *tert*-butyl alcohol (1.0 equiv) in THF (10 mL/mmol amide) and NH_3 (130 mL/mmol amide) at −78 °C was added alkali metal in small pieces until a blue coloration was maintained for 20 min. Piperylene was added dropwise to consume the excess metal, and then allyl bromide (2.5 equiv) was added. The solution was stirred at −78 °C and was allowed to slowly warm to rt to allow the NH_3 to evaporate. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, was dried (Na_2SO_4), and was concentrated in vacuo to give 2,5-cyclohexadiene product. Pure product was obtained by column chromatography (3:7 or 1:3 EtOAc/hexanes). Diastereomeric ratios were determined by GC or LC on purified material in comparison with independently synthesized diastereomeric mixtures.

((*R*)-1-((*E*)-but-2-enyl)-2-methoxy-5-methylcyclohexa-2,5-dienyl)((*S*)-2-(methoxymethyl)-pyrrolidin-1-yl)methanone (2b). Use of the general procedure with **1** and potassium followed by the addition of crotyl chloride instead of allyl bromide afforded a 73% yield. TLC R_f = 0.80 (EtOAc). ^1H NMR ($CDCl_3$, mixture of rotational isomers) δ 5.40−5.28 (m, 1H), 5.27−5.14 (m, 1H), 5.04 (s, 1H), 4.69 (t, 1H, *J* = 3.6 Hz), 4.40−4.28 (m, 1H), 3.58 (dd, 1H, *J* = 9.4, 3.4 Hz), 3.48 (s, 3H), 3.44−3.21, 3.15−2.98 (two m, 3H), 3.35 (s, 3H), 2.79−2.55 (m, 3H), 2.34 (dd, 1H, *J* = 14.0, 6.6 Hz), 2.00−1.55 (m, 4H), 1.74 (s, 3H), 1.59 (d, 3H, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ_u 127.0, 121.9, 92.6, 58.8, 57.7, 54.2, 22.3, 18.1; δ_d 171.2, 152.8, 133.0, 72.0, 52.9, 46.1, 40.0, 31.5, 26.5, 24.7. IR ($CDCl_3$) 1618 cm^{-1}. GC t_R = 16.88 (major), 16.92 (minor) min. dr = >99:<1. EI-MS *m*/*z* (%): 319 (M+, 7), 304 (3), 288 (3), 264 (15), 176 (39), 149 (100).

((*R*)-1-Allyl-2-methoxy-5-phenylcyclohexa-2,5-dienyl)((*S*)-2-(methoxymethyl)pyrrolidin-1-yl)methanone (7a). Use of the general procedure with **6a** and lithium afforded a 62% yield. TLC R_f = 0.50 (1:1 EtOAc/hexanes). ^1H NMR ($CDCl_3$) δ 7.44−7.28 (m, 5 H), 5.82 (t, 2 H, *J* = 1.5 Hz), 5.80−5.65 (m, 1H), 5.05−4.87 (m, 3 H), 4.40−4.32 (m, 1 H), 3.64 (dd, 1 H, *J* = 9.5, 3.2 Hz), 3.58−3.52 (m, 1 H), 3.56 (s, 3H), 3.38−3.32 (m, 2 H), 3.36 (s, 3H), 3.30−3.15 (m, 2 H), 2.91−2.84 (m, 1 H), 2.68 (dd, 1 H, *J* = 14.1, 6.7 Hz), 1.92−1.65 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 169.9, 152.8, 139.9, 135.7, 134.8, 128.5, 127.6, 125.2, 123.5, 117.1, 92.7, 72.0, 58.9, 58.2, 54.4, 53.1, 46.1, 41.4, 28.8, 26.4, 24.9. IR (film) 1620 cm^{-1}. GC t_R = 26.99 (minor), 27.68 (major) min. dr = 35:1. EI-MS *m*/*z* (%): 367 (M^+, 5), 326 (9), 225 (72), 224 (100), 211 (95), 184 (87), 142 (98).

((*R*)-1-Allyl-2-methoxy-5-(4-methoxyphenyl)cyclohexa-2,5-dienyl)((*S*)-2-(methoxymethyl)-pyrrolidin-1-yl)methanone (7b). Use of the general procedure with **6b** and lithium afforded a 58% yield. TLC R_f = 0.60 (EtOAc). ^1H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.37 (d, 2H, *J* = 8.9 Hz), 6.89 (d, 2H, *J* = 8.9 Hz), 5.73 (s, 1H), 5.72−5.62 (m, 1H), 5.03−4.86 (m, 3H), 4.38−4.28 (m, 1H), 3.81 (s, 3H), 3.64 (dd, 1H, *J* = 9.5, 3.2 Hz), 3.57−3.50 (m, 1H), 3.55 (s, 3H), 3.40−3.28 (m, 2H), 3.36 (s, 3H), 3.22−3.10 (m, 2H), 2.90−2.83 (m, 1H), 2.66 (dd, 1H, *J* = 14.0, 6.7 Hz), 1.90−1.67 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_u 134.7, 126.1, 121.6, 113.7, 92.6, 58.8, 58.0, 55.2, 54.2; δ_d 170.0, 159.1, 152.6, 134.9, 132.2, 116.9, 71.8, 52.8, 46.0, 41.3, 28.7, 26.2, 24.8. IR ($CDCl_3$) 1617 cm^{-1}. HPLC t_R = 15.32 (major), 16.24 (minor) min. dr = 50:1.

((*R*)-1-Allyl-5-(2,3-dimethoxyphenyl)-2-methoxycyclohexa-2,5-dienyl)((*S*)-2-(methoxymethyl)-pyrrolidin-1-yl)methanone (7d). Use of the general procedure with **6d** and lithium afforded a 70% yield. TLC R_f = 0.70 (EtOAc). ^1H NMR ($CDCl_3$) δ 7.00 (t, 1H, *J* = 7.9 Hz), 6.85 (dd, 1H, *J* = 8.2, 1.3 Hz), 6.71 (dd, 1H, *J* = 7.6, 1.2 Hz), 5.85−5.65 (m, 1H), 5.43 (s, 1H), 5.06−4.98 (m, 2H), 4.83 (t, 1H, *J* = 3.6 Hz), 4.38−4.28 (m, 1H), 3.90−3.76 (m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.66−3.62 (m, 1H), 3.54 (s, 3H), 3.43−3.30 (m, 2H), 3.35 (s, 3H), 3.17 (dq, 2H, *J* = 22, 2.8 Hz), 2.87 (dd, 1H, *J* = 14.2, 7.7 Hz), 2.63 (dd, 1H, *J* = 14.2, 7.0 Hz), 2.00−1.68 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 170.0, 152.8, 152.3, 146.4, 136.4, 136.3, 135.0, 125.5, 124.0, 121.3, 116.9, 111.5, 93.2, 72.0, 60.9, 58.8, 58.1, 55.7, 54.2, 52.8, 46.1, 41.3, 30.5, 26.4, 25.0. IR ($CDCl_3$) 1616 cm^{-1}. HPLC t_R = 8.752 (minor), 9.121 (major) min. dr = >99:<1.

((*R*)-1-Allyl-5-(allyloxymethyl)-2-methoxycyclohexa-2,5-dienyl)-((*S*)-2-(methoxymethyl)-pyrrolidin-1-yl)methanone (11a). Use of the general procedure with **10a** and potassium afforded a 68% yield. TLC R_f = 0.67 (7:3 EtOAc/hexanes). ^1H NMR ($CDCl_3$) δ 5.94−5.85 (m, 1H), 5.66−5.57 (m, 1H), 5.38−5.16 (m, 3H), 5.00−4.93 (m, 2H), 4.78 (t, 1H, *J* = 3.6 Hz), 4.35−4.25 (m, 1H), 3.94−3.91 (m, 4H), 3.62 (dd, 1H, *J* = 9.5, 3.2 Hz), 3.55−3.48 (m, 1H), 3.51 (s, 3H), 3.36−3.25 (m, 2H), 3.34 (s, 3H), 2.90−2.68 (m, 3H), 2.55 (dd, 1H, *J* = 14.1, 7.0 Hz), 1.95−1.69 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_u 134.8, 124.4, 123.7, 92.5, 58.8, 58.1, 54.2; δ_d 169.8, 152.8, 134.3, 116.9, 116.8, 72.9, 71.9, 70.5, 52.5, 46.0, 41.1, 27.4, 26.3, 24.8. IR ($CDCl_3$) 1623 cm^{-1}. GC t_R = 20.73 (minor), 21.06 (major) min. dr = 16:1. EI-MS *m*/*z* (%): 361 (M^+, 1), 346 (1), 320 (2), 290 (5), 258 (7), 218 (8), 205 (10), 200 (10), 176 (9), 161 (37), 142 (100). HPLC t_R = 11.07 (major), 11.91 (minor) min. dr = 14:1.

((*R*)-1-Allyl-5-((*R*)-2-(allyloxy)propyl)-2-methoxycyclohexa-2,5-dienyl)((*S*)-2-(methoxymethyl)-pyrrolidin-1-yl)methanone (11b). Use of the general procedure with **10b** and potassium afforded a 57% yield. TLC R_f = 0.70 (3:1 EtOAc/hexanes). ^1H NMR ($CDCl_3$, mixture of rotational isomers) δ 5.95−5.82 (m, 1H), 5.71−5.57 (m, 1H), 5.28, 5.23 (two d, 1H, *J* = 1.6 Hz), 5.16, 5.13 (two s, 2H), 4.99, 4.94, 4.91 (three s, 2H), 4.72 (t, 1H, *J* = 3.5 Hz), 4.35−4.25 (m, 1H), 4.04 (dd, 1H, *J* = 12.6, 5.5 Hz), 3.89 (dd, 1H, *J* = 12.5, 5.5 Hz), 3.65−3.54 (m, 3H), 3.49 (s, 3H), 3.35 (s, 3H), 3.32−3.21 (m, 2H), 2.90−2.66 (m, 3H), 2.53 (dd, 1H, *J* = 14.1, 6.5 Hz), 2.31 (dd, 1H, *J* = 14.2, 6.8 Hz), 2.12 (dd, 1H, *J* = 14.2, 5.8 Hz), 1.90−1.65 (m, 4H), 1.14 (d, 3H, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ_u 135.1, 122.9, 92.7, 73.7, 58.9, 58.0, 57.8, 54.2, 19.5; δ_d 170.3, 152.8, 134.7, 116.5, 116.4, 72.0, 69.3, 52.7, 46.0, 43.2, 41.2, 30.7, 26.3, 24.9, 24.7. IR ($CDCl_3$) 1617 cm^{-1}. GC t_R = 23.09 min. EI-MS *m*/*z* (%): 389 (M^+, 1), 348 (20), 233 (26), 189 (100). HPLC t_R = 4.72 (minor), 4.951 (major) min. dr = 47:1.

General Procedure for the Hydrolysis Reaction. Enol ether (1.0 equiv) was dissolved in MeOH (6 mL/mmol enol ether) and was treated with 6 N HCl (2.5 mL/mmol enol ether). After stirring at rt for 15 h, the reaction solution was diluted with H_2O and was extracted with CH_2Cl_2. The organic layers were combined and washed with saturated $NaHCO_3$ and brine and then were dried with $MgSO_4$. Concentration afforded an oil which was purified by column chromatography (1:3 or 3:7 EtOAc/hexanes).

(*R*)-2-((*E*)-But-2-enyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)-4-methylcyclohex-3-enone (3b). Use of the general procedure with **2b** afforded a 99% yield. TLC R_f = 0.60 (EtOAc). ^1H NMR ($CDCl_3$, mixture of rotational isomers) δ 5.47−5.40 (m, 2H), 5.33 (s, 1H), 4.38−4.27 (m, 1H), 3.53 (dd, 1H, *J* = 9.3, 3.1 Hz), 3.40−3.29 (m, 1H), 3.33 (s, 3H), 3.28−3.18 (m, 1H), 3.13−3.01 (m, 1H), 2.67−2.38 (m, 6H), 1.96−1.70 (m, 4H), 1.64, 1.59 (two d, 3H, *J* = 3.6 Hz). ^{13}C NMR ($CDCl_3$) δ_u 128.6, 126.5, 123.6, 58.9, 57.7, 23.1, 17.9; δ_d 208.7, 169.4, 135.4, 72.0, 61.3, 46.6, 40.5, 36.9, 30.5, 26.7, 24.5. IR ($CDCl_3$) 1709, 1628 cm^{-1}. GC t_R = 17.58 min. EI-MS *m*/*z* (%): 306 (M^+ + 1, 3), 305 (M+, 17), 260 (39), 249 (46), 206 (25), 163 (43), 142 (100).

(*R*)-2-Allyl-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)-4-phenylcyclo hex-3-enone (8a). Use of the general procedure with **7a** provided a 64% yield. TLC R_f = 0.30 (7:3 EtOAc/hexanes). ^1H NMR ($CDCl_3$) δ 7.43−7.29 (m, 5H), 5.99 (s, 1H), 5.95−5.80 (m, 1H), 5.11 (s, 1H), 5.07 (d, 1H, *J* = 3.9 Hz), 4.35−4.20 (m, 1H), 3.68−3.60 (m, 1H), 3.43−3.28 (m, 2H), 3.36 (s, 3H), 3.20−3.08 (m, 1H), 3.05−2.84 (m, 2H), 2.80−2.57 (m, 4H), 1.98−1.65 (m, 4H).^{13}C NMR ($CDCl_3$) δ_u 134.3, 128.5, 127.9, 125.2, 125.0, 58.8,

57.9; δ_d 207.0, 168.0, 139.8, 138.4, 118.3, 71.7, 61.3, 46.7, 41.3, 36.7, 27.7, 26.5, 24.5. IR 1710, 1635 cm^{-1}. GC t_R = 28.52 min. EI-MS *m*/*z* (%): 353 (M^+, 6), 308 (11), 297 (19), 211 (24), 142-(100).

(*R*)-2-Allyl-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)-4-(4-methoxyphenyl)cyclohex-3-enone (8b). Use of the general procedure with **7b** provided an 89% yield. TLC R_f = 0.50 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.35 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.9 Hz), 5.90 (s, 1H), 5.95−5.80 (m, 1H), 5.10 (s, 1H), 5.05 (d, 1H, J = 4.1 Hz), 4.35−4.25 (m, 1H), 3.82 (s, 3H), 3.64 (dd, 1H, J = 9.3, 2.9 Hz), 3.40−3.30 (m, 2H), 3.36 (s, 3H), 3.15−3.07 (m, 1H), 3.02−2.83 (m, 2H), 2.80−2.55 (m, 4H), 1.98−1.65 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_u 134.2, 126.4, 123.2, 113.9, 58.9, 57.9, 55.3; δ_d 207.4, 168.3, 159.5, 137.7, 132.2, 118.3, 71.7, 61.3, 46.5, 41.6, 36.9, 27.7 26.6, 24.5. IR ($CDCl_3$) 1712, 1610 cm^{-1}. HPLC t_R = 20.32 min.

(*R*)-2-Allyl-4-(2,3-dimethoxyphenyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)cyclohex-3-enone (8d). Use of the general procedure with **7d** provided a 96% yield. TLC R_f = 0.50 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 7.03 (t, 1H, J = 7.9 Hz), 6.89 (dd, 1H, J = 8.2, 1.4 Hz), 6.76 (dd, 1H, J = 7.6, 1.4 Hz), 5.96−5.82 (m, 1H), 5.73 (s, 1H), 5.11 (d, 1H, J = 1.4 Hz), 5.06 (d, 1H, J = 2.4 Hz), 4.35−4.25 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.72−3.60 (m, 1H), 3.58−3.48 (m, 1H), 3.45−3.30 (m, 1H), 3.36 (s, 3H), 3.27−3.17 (m, 1H), 2.95−2.83 (m, 2H), 2.77 (d, 2H, J = 7.4), 2.72−2.52 (m, 2H), 2.03−1.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 207.4, 168.2, 152.8, 146.3, 139.1, 136.0, 134.2, 127.1, 124.1, 120.9, 118.3, 112.0, 71.8, 61.5, 60.8, 59.0, 57.9, 55.8, 46.5, 41.2, 37.1, 29.3, 26.7, 24.6. IR ($CDCl_3$) 1710, 1628 cm^{-1}. HPLC t_R = 15.04 min.

(*R*)-2-Allyl-4-(allyloxymethyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)cyclohex-3-enone (12a). Use of the general procedure with **11a** provided a 90% yield. TLC R_f = 0.60 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 5.96−5.72 (m, 2H), 5.65 (s, 1H), 5.30−5.17 (m, 2H), 5.06 (s, 1H), 5.01 (d, 1H, J = 6.6 Hz), 4.35−4.15 (br s, 1H), 3.97 (s, 4H), 3.61 (dd, 1H, J = 9.3, 2.7 Hz), 3.40−3.25 (m, 2H), 3.34 (s, 3H), 3.10−3.03 (m, 1H), 2.69−2.42 (m, 6H), 2.00−1.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ_u134.4, 134.0, 125.0, 58.9, 57.9; δ_d 207.6, 168.1, 136.7, 118.2, 117.1, 72.7, 71.8, 71.1, 70.0, 46.5, 41.2, 36.6, 26.6, 26.1, 24.5. IR ($CDCl_3$) 1712, 1629 cm^{-1}. GC t_R = 16.25 min. EI-MS *m*/*z* (%): 347 (M^+, 8), 302 (45), 291 (19), 244 (14), 205 (21), 142 (100).

(*R*)-2-Allyl-4-((*R*)-2-(allyloxy)propyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)cyclohex-3-enone (12b). Use of the general procedure with **11b** provided a 94% yield. TLC R_f = 0.60 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 5.93−5.76 (m, 2H), 5.42 (s, 1H), 5.28, 5.23 (two d, 1H, J = 1.5 Hz), 5.17, 5.14 (two s, 1H), 5.06 (s, 1H), 5.02 (d, 1H, J = 5.8 Hz), 4.35−4.25 (m, 1H), 4.06 (dd, 1H, J = 12.6, 5.4 Hz), 3.88 (dd, 1H, J = 12.6, 5.6 Hz), 3.63 (dd, 2H, J = 9.2, 3.1 Hz), 3.36 (s, 3H), 3.35−3.25 (m, 2H), 3.12−3.05 (m, 1H), 2.67 (d, 2H, J = 7.3 Hz), 2.60−2.44 (m, 4H), 2.36 (dd, 1H, J = 14.2, 7.1 Hz), 2.23 (dd, 1H, J = 14.2, 5.2 Hz), 1.97−1.67 (m, 4H), 1.18 (d, 3H, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ_u 134.9, 134.3, 124.7, 73.5, 58.9, 57.8, 19.5; δ_d 207.9, 168.5, 137.4, 118.0, 116.7, 71.8, 61.2, 46.4, 44.1, 41.4, 36.9, 29.2, 26.6, 24.6. IR ($CDCl_3$) 1709, 1627 cm^{-1}. GC t_R = 17.34 min. EI-MS *m*/*z* (%): 375 (M^+, 4), 330 (37), 319 (35), 246 (22), 142 (100).

General Procedure for the Cope Rearrangement. The 1,5-diene was dissolved in 1,2-dichlorobenzene (2 mL/mmol diene) and was heated at reflux temperature for 10 h. The solvent was removed in vacuo and the crude product was purified by chromatography (1:1 or 3:7 EtOAc/hexanes).

Microwave Procedure for the Cope Rearrangement of 3a. The 1,5-diene **3a** (70 mg, 0.24 mmol) was transferred as a neat oil to a reactor tube, was capped, and was placed in the microwave reactor. The reaction was conducted neat with the following parameters: temperature, 250 °C; max pressure, 250 psi; max power, 300 W; ramp time, 2 min; reaction time, 30 min. The heating period was repeated a second time. After a total of 1-h heating, GC analysis showed the reaction was 96% product **4a** and 4% starting material **3a**. The product obtained was identical to that previously reported[2] for conventional heating over a 10-h period.

(*R*)-4-((*S*)-but-3-en-2-yl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)-4-methylcyclohex-2-enone (4b). Use of the general procedure with **3b** afforded a 70% yield of **4b**, along with 24% of recovered starting material. TLC R_f = 0.40 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 6.84 (t, 1H, J = 6.0 Hz), 5.88−5.65 (m, 1H), 5.15−5.02 (m, 2H), 4.35−4.25, 3.81−3.72 (two m, 1H), 3.67 (dd, 1H, J = 9.5, 3.4 Hz), 3.43 (dd, 1H, J = 9.4, 7.2 Hz), 3.38, 3.26 (two s, 3H), 3.30−3.10 (m, 2H), 2.58−2.48 (m, 2H), 2.40−2.20 (m, 1H), 2.10−1.68 (m, 6H), 1.18, 1.17 (two s, 3H), 1.06 (d, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 156.7, 156.5, 139.4, 139.0, 59.1, 58.9, 57.6, 56.3, 47.0, 46.1, 21.4, 21.2, 15.4, 14.4, 14.3; δ_d 195.6, 195.2, 165.9, 137.2, 116.7, 116.2, 116.1, 74.0, 72.1, 48.4, 48.3, 45.5, 38.2, 38.1, 33.9, 30.9, 30.6, 30.0, 28.3, 27.6, 24.1, 21.8. IR ($CDCl_3$) 1684, 1617 cm^{-1}. GC t_R = 15.83 min. EI-MS *m*/*z* (%): 306 (M^+ + 1, 1), 305 (M+, 3), 260 (89), 250 (39), 206 (100), 191 (31), 163 (33), 137 (56).

(*S*)-4-Allyl-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)-4-phenylcyclo hex-2-enone (9a). Use of the general procedure with **8a** afforded an 80% yield of **9a** along with 18% recovered starting material. TLC R_f = 0.42 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.38−7.23 (m, 5H), 7.19, 7.15 (two s, 1H), 5.61−5.47 (m, 1H), 5.13−5.06 (m, 2H), 4.39−4.29, 3.87−3.80 (two m, 1H), 3.68 (dd, 1H, J = 9.5, 3.4 Hz), 3.49 (dd, 1H, J = 9.5, 6.9 Hz), 3.38, 3.21 (two s, 3H), 3.33−3.18 (m, 2H), 2.77−2.68 (m, 1H), 2.65−2.52 (m, 1H), 2.45−2.26 (m, 4H), 2.05−1.78 (m, 4H). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ 195.8, 195.3, 166.0, 165.9, 153.4, 152.6, 142.6, 139.2, 138.6, 133.0, 132.9, 128.8, 128.7, 127.0, 126.7, 119.4, 119.3, 74.0, 72.2, 59.1, 58.9, 58.0, 56.5, 48.5, 46.2, 46.0, 45.4, 43.8, 43.7, 35.2, 35.1, 34.6, 34.5, 28.4, 27.7, 24.3, 22.0. IR ($CDCl_3$) 1684, 1617 cm^{-1}. GC t_R = 10.983 min. EI-MS *m*/*z* (%): 353(M^+, 6), 312 (30), 308 (93), 239 (100), 198 (71), 141 (52).

(*S*)-4-Allyl-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)-4-(4-methoxyphenyl)cyclohex-2-enone (9b). Use of the general procedure with **8b** afforded an 80% yield of **9b** along with 15% recovered starting material. TLC R_f = 0.30 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.23 (d, 2H, J = 8.8 Hz), 7.17, 7.12 (two s, 1H), 6.89 (d, 2H, J = 8.8 Hz), 5.62−5.48 (m, 1 H), 5.12−5.06 (m, 2H), 4.38−4.30, 3.88−3.75 (two m, 1H), 3.80 (s, 3H), 3.69 (dd, 1H, J = 9.5, 3.3 Hz), 3.49 (dd, 1H, J = 9.4, 7.1 Hz), 3.39, 3.24 (two s, 3H), 3.30−3.18 (m, 2H), 2.75−2.65 (m, 1H), 2.60−2.49 (m, 1H), 2.45−2.20 (m, 4H), 2.08−1.79 (m, 4H). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 153.6, 152.7, 133.0, 127.8, 114.1, 59.1, 58.9, 58.0, 56.5, 55.2; δ_d 195.9, 195.4, 165.9, 158.4, 139.0, 138.3, 134.3, 119.3, 74.0, 72.2, 48.5, 46.2, 46.0, 45.4, 43.0, 35.3, 34.5, 28.3, 27.7 24.3, 21.9. IR ($CDCl_3$) 1685, 1617 cm^{-1}. GC t_R = 22.67 min. EI-MS *m*/*z* (%): 384 (M^+ + 1, 2), 383 (M^+, 9), 342 (23), 338 (53), 269 (100), 241 (22), 228 (50).

(*S*)-4-Allyl-4-(2,3-dimethoxyphenyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)cyclohex-2-enone (9d). Use of the general procedure with **8d** afforded a 50% yield of **9d** along with 40% recovered starting material. TLC R_f = 0.40 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.40 (d, 1H, J = 1.6 Hz), 7.34 (d, 1H, J = 1.5 Hz), 6.99 (q, 1H, J = 8.0 Hz), 6.89 (d, 1H, J = 8.2 Hz), 6.79, 6.78 (two dd, 1H, J = 7.8, 1.5 Hz), 5.63−5.47 (m, 1H), 5.12−5.04 (m, 1H), 4.39−4.30, 3.97−3.78 (two m, 1H), 3.88 (s, 6H), 3.68 (dd, 1H, J = 9.5, 3.3 Hz), 3.49 (dd, 1H, J = 9.4, 7.0 Hz), 3.39, 3.22 (two s, 3H), 3.29 (t, 1H, J = 6.6 Hz), 3.20−3.15 (m, 1H), 2.85 (dd, 1H, J = 6.2 Hz), 2.70−2.58 (m, 2H), 2.50−2.30 (m, 2H), 2.23−2.08 (m, 1H), 2.08−1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 155.6, 153.9, 133.5, 133.3, 123.3, 123.1, 120.5, 120.3, 111.8, 60.3, 58.9, 58.6, 57.8, 56.2, 55.5; δ_d 196.0, 195.6, 166.0, 153.3, 147.8, 136.7, 136.4, 134.6, 134.4, 118.6, 118.5, 73.7, 72.0, 48.2, 45.3, 44.3, 44.2, 43.6, 43.5, 34.8, 33.1, 32.8, 28.2, 27.5, 24.1, 21.8. IR ($CDCl_3$) 1680, 1622 cm^{-1}.

GC t_R = 23.78 min. EI-MS *m*/*z* (%): 414 (M^+ + 1, 2), 413 (M^+, 9), 372 (15), 368 (56), 350 (15), 300 (20), 299 (100), 271 (28), 258 (51).

(*S*)-4-Allyl-4-(allyloxymethyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)cyclohex-2-enone (13a). Use of the general procedure with **12a** afforded a 100% yield of **13a**. TLC R_f = 0.55 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 6.85, 6.83 (two s, 2H), 5.92−5.70 (m, 2H), 5.28−5.10 (m, 4H), 4.32−4.26, 3.83−3.70 (two m, 1H), 3.97−3.95 (m, 2H), 3.66 (dd, 1H, J = 9.5, 3.4 Hz), 3.48−3.30 (m, 3H), 3.37, 3.25 (two s, 3H), 3.23−3.16 (m, 2H), 2.63−2.45 (m, 2H), 2.38−2.25 (m, 2H), 2.05−1.70 (m, 6H). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 152.6, 152.4, 134.3, 132.8, 59.1, 58.9, 57.6, 56.3; δ_d 195.7, 195.3, 166.1, 165.9, 138.9, 119.2, 117.2, 117.1, 74.4, 74.1, 72.3, 72.2, 48.4, 45.6, 40.1, 39.8, 39.6, 34.0, 33.9, 28.5, 28.4, 27.6, 24.1, 22.0. IR ($CDCl_3$) 1681, 1619 cm^{-1}. GC t_R = 17.33 min. EI-MS *m*/*z* (%): 347 (M^+, 2), 332 (1), 315 (2), 306 (9), 303 (20), 302 (100), 246 (52).

(*R*)-4-Allyl-4-((*R*)-2-(allyloxy)propyl)-2-((*S*)-2-(methoxymethyl)pyrrolidine-1-carbonyl)cyclohex-2-enone (13b). Use of the general procedure with **12b** afforded a 72% yield of **13b** along with 27% recovered starting material. TLC R_f = 0.43 (EtOAc). ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 7.00, 6.96 (two s, 1H), 5.98−5.70 (m, 2H), 5.32−5.08 (m, 4H), 4.35−4.25, 3.70−3.60 (two m, 1H), 4.15−4.05 (m, 1H), 3.90−3.78 (m, 1H), 3.78−3.65 (m, 2H), 3.53−3.40 (m, 1H), 3.38, 3.27 (two s, 3H), 3.32−3.08 (m, 2H), 2.51 (t, 2H, J = 7 Hz), 2.36 (t, 2H, J = 7 Hz), 2.05−1.70 (m, 7H), 1.55 (dd, 1H, J = 14.7, 2.1 Hz), 1.17 (d, 3H, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ_u 156.6, 156.1, 134.9, 134.8, 133.2, 133.1, 71.8, 59.1, 58.9, 57.7, 56.3, 20.3; δ_d 195.8, 195.3, 166.1, 136.9, 136.5, 119.1, 116.9, 116.8, 73.7, 72.1, 69.2, 48.2, 45.5, 45.3, 45.2, 42.3, 41.5, 38.2, 38.1, 34.0, 32.1, 32.0, 28.3, 27.6, 24.1, 21.9. IR ($CDCl_3$) 1679, 1616 cm^{-1}. GC t_R = 18.18 min. EI-MS *m*/*z* (%): 375 (M^+, 1), 360 (1), 343 (2), 334 (24), 331 (24), 330 (100), 274 (27), 203 (45).

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Supporting Information Available: General experimental details; experimental procedures for the synthesis of **2c**, **3c**, **5a**, and **14**; copies of ^{1}H and ^{13}C NMR spectra and chromatographs for compounds described in the Experimental Section and in the Supporting Information; NOESY for **4b**; COSY for **13b**; and minimized structures of **4a** and **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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