Pergamon

Tetrahedron 56 (2000) 2183–2194

TETRAHEDRON

Electronic Tuning of Fischer Carbene Complexes in the Preparation of Bicyclo[3.1.1]heptanones as Taxane A-ring Synthons

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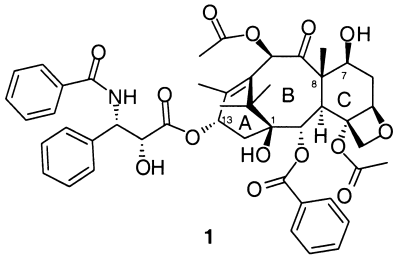
Accepted 7 December 1999

Abstract—A synthetic route to taxol and other *Taxus* diterpenes is described which employs as a key step the reaction between a Fischer carbene complex and a 1,6 enyne to construct 1-substituted-7,7-dimethyl-2-methylenebicyclo[3.1.1]heptan-6-ones. It was found that the reaction between complex **2** and 7-methyl-3-methylene-6-octen-1-yne (dienyne **30**) yielded a mixture of bicyclo[3.1.1]heptanone **35** and cyclobutenone **36**, the latter possibly arising from the migration of the chromium fragment from an electron-rich alkene to a less electron-rich alkene in the vinyl carbene complex intermediate (i.e. **40**–**42**). On this basis, it was expected that bicycloheptanone yields would increase with increasing electron deficiency in the intermediate **40** since this should lead to more competitive CO insertion. This was observed with a series of electronically modified carbene complexes (**45** and **48a**–**d**). The more electron deficient complexes gave good yields of bicycloheptanones, thus providing an efficient means for preparing taxane A-ring synthons.

Introduction

In the past 20 years few natural products have created a greater impact in the areas of clinical oncology and biomedical research than paclitaxel (Taxol®) **1**. Its FDA-approved use in the treatment of metastatic breast[1] and ovarian cancers[2] constitutes one of the major breakthroughs in chemotherapy today; it is currently the number-one selling anticancer drug in the world.[3] Taxol, the primary representative of a new class of compounds called taxoids, was first isolated from the bark of the Pacific yew tree, *Taxus brevifolia*, in 1969;[4] its complex structure was elucidated two years later by Wani and collaborators.[5] The discovery in 1979 by Horwitz and coworkers[6] describing the unique mechanism by which taxol inhibits cell replication has since served as an impetus for intense pharmacological studies aimed at its therapeutic development. They demonstrated that the cellular target of taxol is tubulin; however, in contrast to colchicine and the vinca alkaloids which are known to prevent the assembly of tubulin into microtubules,[7] taxol acts as a promoter of tubulin assembly as well as an inhibitor of the disassembly process. This novel overstabilization renders the microtubules dysfunctional in their role in the formation of mitotic spindles during interphase,[8] leading to cell death. The highly oxygenated complex structure shared by the *Taxus* diterpenes thus has been heavily scrutinized and of the numerous reported efforts[9] towards entry into the ABC tricyclic core, six have culminated successfully into total syntheses of **1**.[10]



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The strategy for the synthesis of taxol upon which we have recently focused relies on the chromium-mediated intramolecular [2+2] cycloaddition of a vinyl ketene and alkene, an intermediate that is generated from the reaction between a Fischer carbene complex[11] and a 1,6 enyne.[12] The preparation of cyclobutanones, which have proven to be versatile synthetic intermediates,[13] through similar intramolecular cycloadditions involving metal-free ketenes with tethered olefins are well documented.[14] In our earlier study on the stereoselectivity of these metal-mediated cycloadditions, we reported that the reaction between carbene complex **2** and enyne **3** afforded bicyclo[3.1.1]heptanone **4** in good yield[15] (Scheme 1). The mechanistic pathway is believed to involve the generation of intermediate **6** via alkyne insertion. This is followed by the migration of a CO ligand into the carbene ligand to form vinyl ketene complex **7**, which then undergoes a formal [2+2] cycloaddition with the tethered alkene to afford **8** and upon hydrolysis, the diketone

Keywords: taxoids; Fischer carbene complexes; cycloadditions; ketenes.

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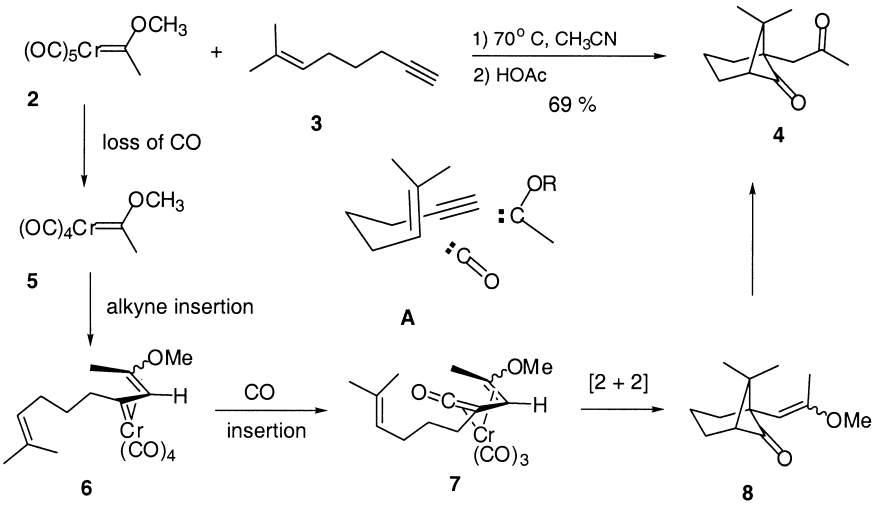
PII: S0040-4020(99)01101-1

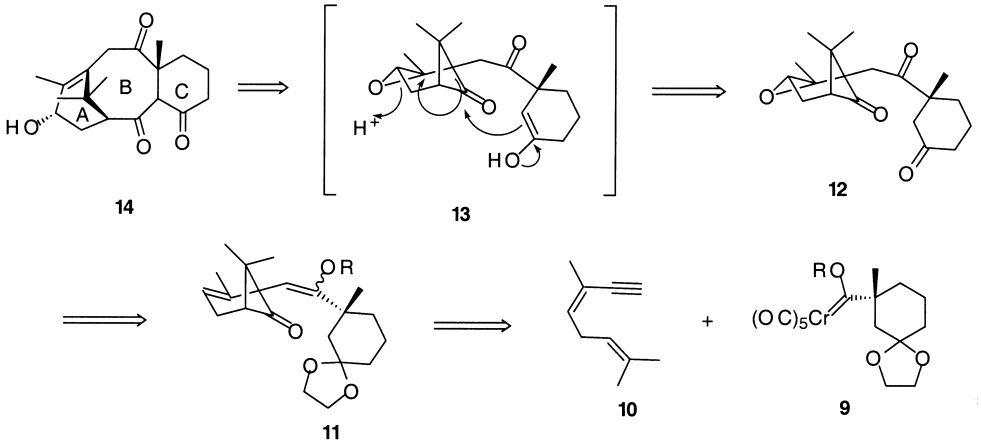


Scheme 1.

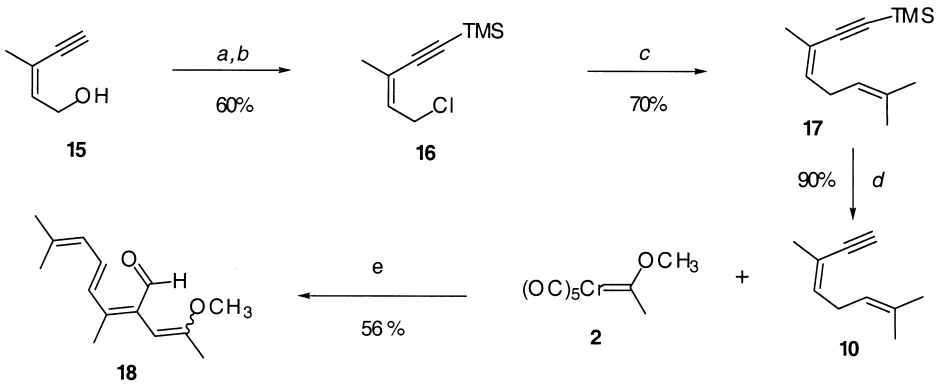
4. The regiochemistry for the [2+2] cycloaddition is that expected given the substitution pattern about the double bond.[16] We therefore envision rapid entry into the carbocyclic core of the taxane family of compounds by utilizing an appropriately functionalized enyne such as **10** and carbene complex **9** to construct bicyclo[3.1.1]heptanone **11**, a suitable A–C system that can be further manipulated for subsequent condensation and fragmentation into the ABC skeleton **14**, for example, via acid- (or base-) induced epoxide-ring cleavage as shown in Scheme 2. In this paper, we report our initial studies on the evaluation of this overall strategy which finds that the outcome of the reaction of carbene complexes with 1,6-enynes containing an additional double-bond is a consequence of the nature of the enyne.

Results and Discussion

The most obvious choice for an alkyne that would conveniently set up the necessary epoxidation in bicycloheptanone **11** is dienyne **10**. This compound was synthesized from the Stille coupling[17] between allyl chloride **16** and 1-trimethylstannyl-2-methyl-1-propene to afford **17** in 70% yield. This was followed by deprotection of the terminal alkyne using $AgNO_3$/NaI[18] as shown in Scheme 3. However, we were disappointed that the reaction between complex **2** and dienyne **10** did not yield any bicycloheptanone. Instead an aldehyde tentatively assigned as compound **18** was obtained as a mixture of isomers in 56% yield. Aldehyde products of this type have been reported for both metal-free[14f,19b] and coordinated vinyl ketenes.[19a] According to the mechanism that they proposed, the formation of aldehyde **18** could be accounted for by insertion of the alkyne into the carbene complex to give the η^1,η^3-vinyl carbene complexed intermediate **19** followed by CO insertion to produce the ketene complex **22** and finally, a 1,5-H migration to give the aldehyde **18** (Scheme 4). An alternative possible mechanism for the formation of aldehyde **18** is also shown in Scheme 4. It has been demonstrated by Herndon and Hayford that an η^1,η^3-vinyl carbene complex of the type **19** derived from a conjugated enyne will undergo rearrangement to an isomeric η^1,η^3-vinyl carbene complex (**21**) faster than the CO insertion that gives rise to a vinyl ketene complex.[20] Based on a number of observations in the literature,[21] they have proposed that CO insertion occurs faster from the η^1,η^3-vinyl carbene complexed intermediate in which the chromium is coordinated to the more electron poor



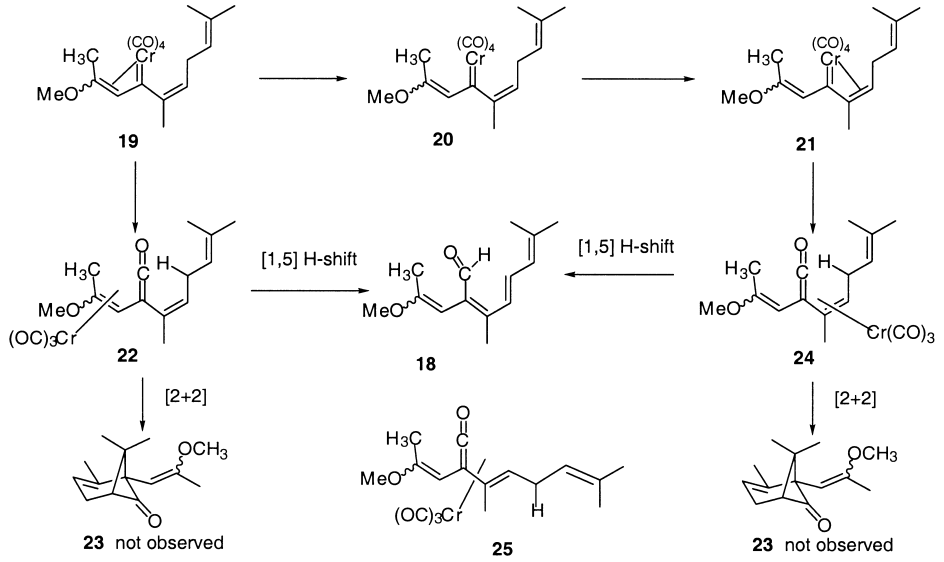
Scheme 2.



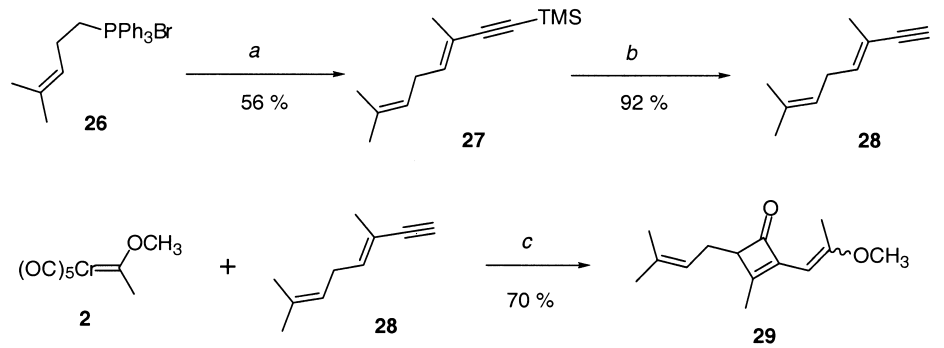
Scheme 3. (a) 2.2 eq. *n*-BuLi, −78–0°C; 2.2 eq. TMSCl; 1.1 eq. citric acid, MeOH, 0°C. (b) PPh_3, CCl_4, THF, reflux, 3 h. (c) 3 mol% $Pd(PPh_3)_2Cl_2$, 1-trimethylstannyl-2-methyl-1-propene, THF, 70°C, 14 h. (d) $AgNO_3$, $EtOH/H_2O$, rt, 30 min; NaI. (e) CH_3CN, 70°C, 3.5 h.

double-bond. In the present case, this would lead to the expectation that CO-insertion occurs faster in **21** than **19** to generate ketene complex **24**, upon which a [1,5] sigmatropic hydrogen shift would give aldehyde **18**. At this point, it cannot be determined whether the aldehyde is formed from one of the vinyl ketene complexes or the other, or from both, but Harvey has suggested that the [1,5]-migration should occur faster on a vinyl ketene that was coordinated to a transition metal.[19a]

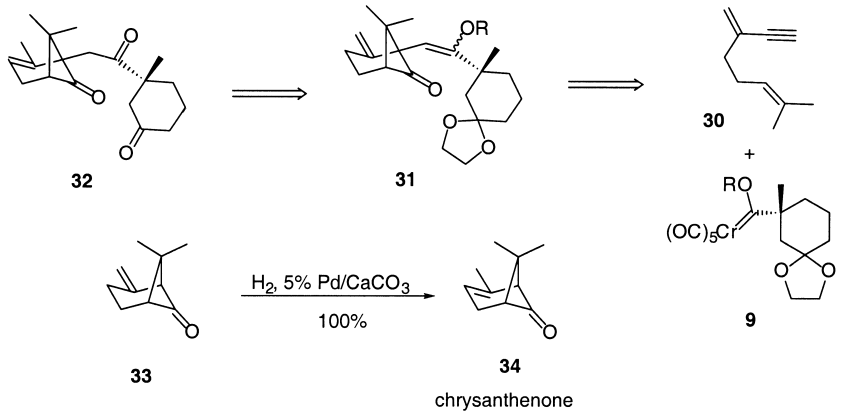
Given the proposed mechanism for the formation of aldehyde **18**, we thought that it would be interesting to probe the reaction between complex **2** and dienyne **28**, since the formation of both bicyclo[3.1.1]heptanone through [2+2]



Scheme 4.



Scheme 5. (a) NaHMDS, THF, 25°C, 30 min; 4-trimethylsilylbut-3-yn-2-one, HMPA, −78°C to 25°C, 1 h. (b) $AgNO_3$, $EtOH/H_2O$, 25°C, 30 min; NaI. (c) CH_3CN, 70°C, 3.5 h.



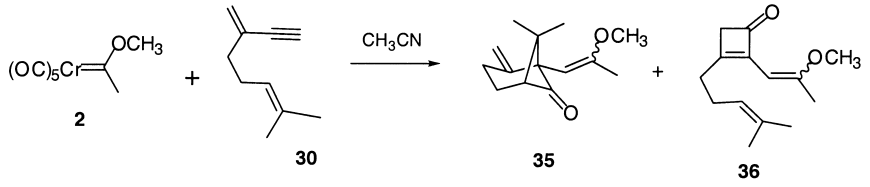
Scheme 6.

cycloaddition and an aldehyde via [1,5] hydrogen shift would be geometrically prevented by the *E*-configuration of the alkene. An intramolecular [2+2] cycloaddition in the resulting vinyl ketene complex **25** would produce a *trans*-double-bond in a six-membered ring and a [1,5]-sigmatropic H-shift could not be concerted.

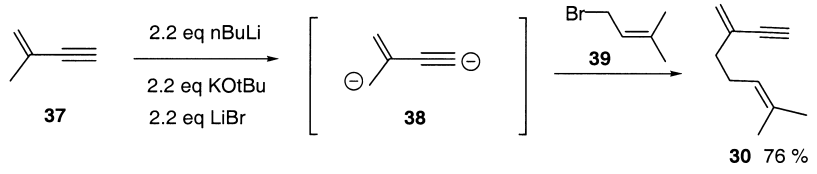
Compound **28** was synthesized according to Scheme 5. The phosphonium salt **26** was treated with NaHMDS and the resulting ylide was allowed to react with 4-trimethylsilyl-but-3-yn-2-one in the presence of HMPA to give **27** (60:1 *E*/*Z* ratio) in fair yield. Removal of the TMS group with $AgNO_3$/NaI[18] provided **28** in 92% yield. When dienyne **28** was reacted with carbene complex **2**, we observed a new product, cyclobutenone **29**, in 70% yield (2:1 *E*/*Z* ratio). Cyclobutenone products have been observed previously from the reactions of chromium carbene complexes with alkynes via electrocyclic ring closure of vinyl ketene complexes,[22] and cyclobutenone **29** may have resulted from ring-closure in the vinyl ketene complex **25**.

The failure of enyne **10** to form bicyclo[3.1.1]heptanone products upon reaction with Fischer carbene complex **2** suggests that the strategy for the synthesis of taxol outlined in Scheme 2 is not viable. A slight modification of the strategy was suggested by the known isomerization of the bicyclo[3.1.1]heptanone **33** to chrysanthenone.[23] If the same isomerization could be affected on intermediate **31** then the strategy would be saved since epoxidation of **32** would intersect with intermediate **12** in Scheme 2 and the new retrosynthesis would descend to enyne **30** and carbene complex **9** (Scheme 6).

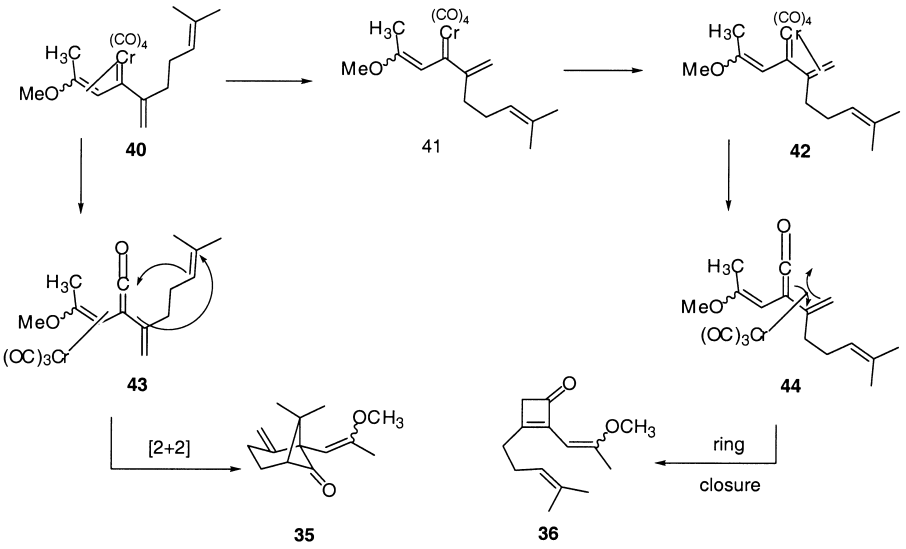
Dienyne **30** can be conveniently synthesized in 76% yield in one pot by utilizing Brandsma's method[24] for generating the lithiated dianion of isopropenyl acetylene and following that by the addition of prenyl bromide (Scheme 7). We were pleased to find that the reaction between **30** and complex **2** (0.01 M in CH_3CN) did result in the formation of the bicyclo[3.1.1]heptanone **35**; however, a substantial amount of cyclobutenone **36** was formed as a side-product. Attempts to thermally isomerize **36** into **35** by refluxing in toluene were unsuccessful. The *E*/*Z* assignment of the enol ethers were based on Strobel's empirical rule.[25] The product distribution is a function of temperature with the ratio reversing from a predominance of cyclobutenone



Temp (°C)	Time (h)	% Yield **35**	**35E / 35Z**	% Yield **36**	**36E / 36Z**	**35 : 36**
100	2	19	100 : 0	68	100 : 0	22 : 78
70	4	36	100 : 0	61	58 : 42	37 : 63
45	48	63	100 : 0	31	67 : 33	67 : 33



Scheme 7.

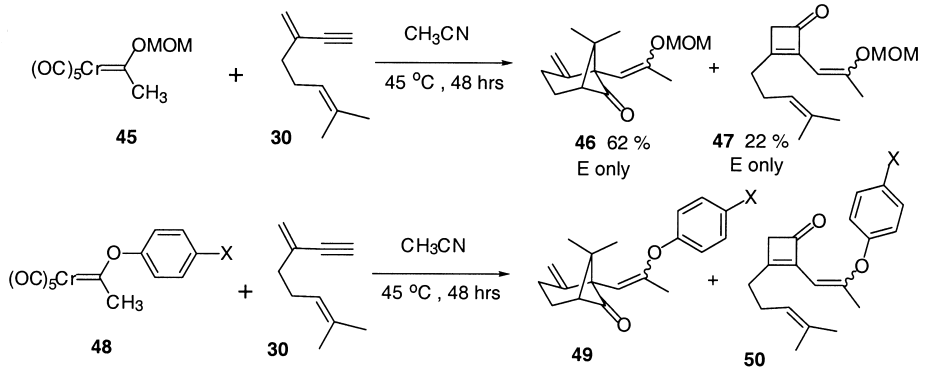


Scheme 8.

36 at 100°C to a distribution in favor of the bicyclo[3.1.1]-heptanone **35** at 45°C. The source of the temperature dependence is not known but it may be related to solvent displacement of the metal from the vinyl ketene complexes **43** and **44** at higher temperature where the metal-free vinyl ketene gives a different distribution of products.

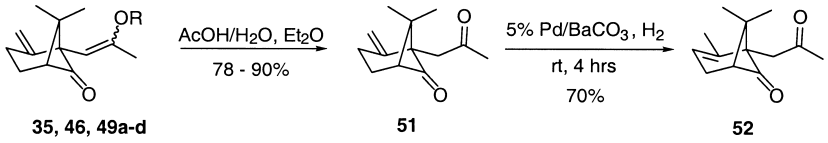
The mechanistic issues discussed above (Scheme 4) suggest that the ratio of the bicyclo[3.1.1]heptanone **35** to the cyclobutenone **36** could be enhanced by electronic tuning of the carbene complex. If the electron density in the coordinated olefin of intermediate **40** could be decreased, then the rate of CO-insertion would be enhanced and thus greater proportions of the desired bicycloheptanone product **35** may be expected, if as indicated in Scheme 8, **35** is derived from η^1,η^3-vinyl ketene complex **43** and the cyclobutenone **36** is derived from the isomeric η^1,η^3-vinyl ketene complex **44**.

The methyloxymethoxy group is more electron withdrawing than a methoxyl group and thus if the above analysis is correct, MOM complex **45** (Scheme 9) would be expected to give a greater proportion of the bicyclo[3.1.1]heptanone product than the methoxyl complex **2**. As can be seen by the data in Schemes 7 and 9, this expectation was realized as the ratio of bicycloheptanone to cyclobutenone products was 2.0 for the methoxyl complex **2** and 2.8 for the MOM complex **45**. To further probe this effect, a series of para-substituted phenoxy complexes of type **48** were prepared according to the procedure developed by Fischer[26] as described in the Experimental section. The data for the reaction of the four complexes **48a–d** with enyne **30** are summarized in Scheme 9. This series of experiments



48	X	% Yield 49	49E : 49Z	% Yield 50	50E : 50Z	49 : 50	% Yield 49 + 50
a	OCH_3	48	67 : 33	34	33 : 67	1.4	82
b	H	71	67 : 33	16	33 : 67	4.3	87
c	Br	69	67 : 33	9	33 : 67	7.3	78
d	CF_3	66.5	67 : 33	9.5	33 : 67	7.0	76

Scheme 9.



Scheme 10.

provides an even better correlation of electron density of the alkoxy group of the carbene complex with the product distribution with the highest selectivities for the bicycloheptanone product observed for the electron withdrawing *para*-bromo and *para*-trifluoromethyl complexes.

The data in Scheme 9 are consistent with the mechanistic picture presented in Scheme 8 but certainly do not demand it. Regardless of the mechanism of the reaction, the success of the phenoxy complexes **48** increases the flexibility of the general strategy to taxol outlined in Scheme 2 since it not only allows a method of suppressing the formation of cyclobutenone side-products, but the phenoxy group is also a true auxiliary and can easily be removed by hydrolysis of the enol ether function in the intermediate **11**. The trifluoromethylphenyl complex **48d** is relatively sensitive and while it can be purified by rapid chromatography on silica gel, losses are incurred during purification. The *para*-bromo complex is more stable and would be the complex of choice in a synthetic application. Attempts to isomerize the cyclobutenone **50** to bicycloheptanone **49** by refluxing in toluene were unsuccessful; decomposition of **50** was the only observation.

The success of the reaction of enyne **30** with carbene complex **2** and **45** in producing bicycloheptanones and the success of electronic modification of the aryl complex **48** to enhance the yield of bicycloheptanones were necessary but not sufficient for proof of concept of the modified strategy for the synthesis of taxol outlined in Scheme 6. What yet remains is the demonstration that an *exo* to *endo* isomerization can be achieved in molecules of type **31**. Any of the product enol ethers **35**, **46** and **49a–d** can be hydrolyzed efficiently with aqueous acetic acid to give diketone **51** in 78–90% yield. Subjection of **51** to hydrogen in the presence of 5% Pd on $BaCO_3$ in ethanol gave the desired *endo*-isomer **52** in 70% yield (Scheme 10). Thus, this alternate route which incorporates enyne **30** for providing the *endo*-cyclic double bond required for epoxidation and subsequent Grob fragmentation offers a viable approach to the synthesis of taxol and other taxane derivatives. The utilization of this methodology for entry into the ABC ring system of taxol will be reported in due course.

Conclusion

We have presented a methodology for the efficient preparation of 1-substituted-7,7-dimethyl-2-methylenebicyclo[3.1.1]-heptan-6-ones as potential synthons for taxane derivatives. It was shown that dienyne **10** does not give bicyclo[3.1.1]-heptanone products but that the isomeric exo-methylene dienyne **30** gives a mixture of bicyclo[3.1.1]heptanone and cyclobutenone products. Furthermore, it was shown that the ratio of these products could be controlled by variation of the electronic nature of the carbene complexes to the point where good yields of the bicyclo[3.1.1]heptanone products can be obtained. Finally, the double-bond isomerization in the bicyclo[3.1.1]heptanone products could be affected to give endo-methylene derivatives which are required for the retrosynthetic plan for the synthesis of members of the taxane family.

Experimental

General information

The atmosphere under which synthetic reagents were combined was argon. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Prior to use, tetrahydrofuran and diethyl ether were distilled from Na/benzophenone ketyl. Methylene chloride and carbon tetrachloride were distilled from CaH_2. All of the above compounds were stored under N_2 after distillation. Hexamethylphosphoramide was distilled under reduced pressure onto activated 4 Å molecular sieves and stored under Ar. All other reagents obtained from commercial suppliers were used as received. Flash chromatography was carried out using 230–240 mesh silica gel. Routine ^1H NMR spectra were recorded on a Bruker DMX-500 and DRX-400 500 MHz and 400 MHz, respectively, spectrometer with tetramethylsilane (δ 0.0) as an internal reference. Routine ^{13}C NMR spectra were recorded on the above Bruker instruments at 100 or 125 MHz with the central peak of the $CDCl_3$ triplet (δ 77.0) as an internal reference. Infrared spectra were recorded on a Nicolet 20SXB FTIR spectrometer. Mass spectral data were obtained at the Michigan State University Mass Spectrometry Facility which is supported, in part, by a grant (DRR-00480) from the Biotechnology Research Technology Program, National Center for Research Resources, National Institutes of Health. Elemental analyses were performed by Gailbraith Laboratories Inc., Knoxville, Tennessee.

Allylic chloride 16. *cis*-3-Methyl-2-penten-4-yn-1-ol (1.00 g, 10.4 mmol) was dissolved in 15 mL THF and to this solution was added 11.4 mL 2.0 M *n*BuLi/pentane (22.9 mmol) at −78°C. The solution was brought to 0°C and stirred for 20 min, after which time TMSCl (2.48 g, 22.9 mmol) was added slowly. After stirring at room temperature for 1 h, the temperature was brought down to 0°C and the reaction was quenched with sat. aq. NH_4Cl. Ether (40 mL) was added and after separation of layers, the organic phase was dried over $MgSO_4$. Evaporation of volatiles yielded crude alcohol as a yellow oil, which was immediately dissolved in 5 mL THF and 10 mL CCl_4. Upon the addition of 5 g PPh_3, the mixture was heated to reflux

for 3 h. After cooling, 25 mL pentane was added and the white solids were filtered off. The filtrate was concentrated and the resulting yellow oil was subjected to silica gel chromatography (100% hexanes) to yield 1.165 g (60% yield) of **16** as a clear oil. Spectral data for **16**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.21 (s, 9 H), 1.90 (s, 3 H), 4.26 (d, J=8.0 Hz, 2 H), 5.84 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −0.1, 22.8, 42.4, 101.1, 102.1, 123.2, 132.7; IR (neat, cm^{-1}): 2960s, 2144m, 1251s, 937s, 840s; HRMS (EI) calcd for $C_9H_{15}{}^{35}ClSi$ m/z 186.0632, found 186.0638. Anal. Calcd for $C_9H_{15}ClSi$: C, 57.88; H, 8.10. Found: C, 58.16; H, 8.24.

***cis*-Dienyne 17.** A 50 mL flask with a threaded Teflon high-vacuum stopcock was charged with 600 mg (3.2 mmol) **16**, 840 mg (3.8 mmol) 1-trimethylstannyl-2-methyl-1-propene, 67 mg (0.096 mmol) $Pd(PPh_3)_2Cl_2$, and 25 mL THF. The resulting yellow solution was heated to 80°C and stirred for 14 h. The black solution then was diluted with ether and the organic phase was washed with 10% KF (aq.) followed by brine. After drying the ethereal layer with $MgSO_4$ and filtration, the solvent was stripped to yield a yellow oil that was subjected to chromatography on silica gel (100% hexanes), giving 460 mg (70% yield) of **17** as a clear oil. Spectral data for **17**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.20 (s, 9 H), 1.67 (s, 3 H), 1.70 (s, 3 H), 1.83 (d, J=1.0 Hz, 3 H), 2.96 (d, J=7.5 Hz, 2 H), 5.13 (t, J=7.5 Hz, 1 H), 5.64 (tm, J=7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 0.1, 17.8, 22.7, 25.7, 30.1, 97.4, 104.7, 117.5, 121.4, 132.6, 137.8; IR (neat, cm^{-1}): 2960s, 2141s, 1249s, 885s, 842s, 760s; MS (EI) m/z (relative intensity) 205 (M^+−1, 14), 189 (50), 179 (34), 173 (30), 165 (60), 159 (29), 149 (72), 141 (29), 135 (89), 125 (100), 119 (34), 105 (43); HRMS (EI) calcd for $C_{13}H_{22}Si$ m/z 206.1491, found 206.1488. Anal. Calcd for $C_{13}H_{22}Si$: C, 75.65; H, 10.74. Found: C, 75.81; H, 10.90.

***cis*-Dienyne 10.** To 400 mg (1.9 mmol) of *cis*-dienyne **17** in 8 mL EtOH was added a solution of 807 mg (4.75 mmol) $AgNO_3$ in 4 mL H_2O. Another 8 mL of EtOH was then added and the mixture was stirred vigorously at room temperature for 30 min. At this time 750 mg (5.0 mmol) NaI was added slowly followed by the addition of 5 mL ether. After stirring for 30 min at room temperature the mixture was diluted with pentane and the organic layer was washed with brine and then dried over $MgSO_4$. Filtration followed by concentration of the organic phase left an oily residue that was subjected to silica gel chromatography (100% hexanes) to afford 230 mg (90% yield) of **10** as a clear oil. Spectral data for **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67 (s, 3 H), 1.72 (s, 3 H), 1.87 (s, 3 H), 2.96 (t, J=7.3 Hz, 2 H), 3.11 (s, 1 H), 5.11 (t, J=7.3 Hz, 1H), 5.67 (t, J=7.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8, 22.8, 25.6, 29.9, 80.5, 103.2, 116.6, 121.3, 132.8, 138.2; IR (NaCl plate, thin film, cm^{-1}): 3296s, 2925s, 2100m,; MS (EI) m/z (relative intensity) 134 (M^+, 3), 119 (22), 115 (4), 91 (20), 79 (8), 73 (100), 57 (90); HRMS (EI) calcd for $C_{10}H_{14}$ m/z 134.1095, found 134.1078.

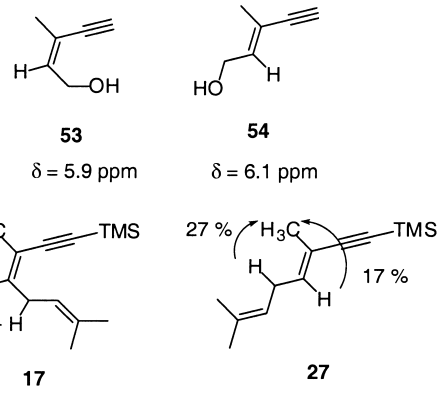
Aldehyde 18. A 200 mL flask with a threaded Teflon high-vaccuum stopcock was charged with 100 mg (0.4 mmol) carbene complex **2**,[27] 59 mg (0.44 mmol) dienyne **10**, and 80 mL CH_3CN. The solution was deoxygenated by the freeze–thaw method (−196/25°C, 3 cycles), back-filled with argon at room temperature, sealed, and then heated at 70°C for 3.5 h. After evaporation of solvent, aldehyde **18** was isolated by NEt_3-treated silica gel chromatography (10% EtOAc/hexane) and was obtained as a 1.5:1 mixture of isomers (49 mg, 56% yield). A small amount of the minor isomer could be obtained pure. The spectral data on the major isomer was extracted from that of the mixture with the aid of the data of the minor isomer. The two observed diastereomers were tentatively assigned as isomeric about the enol ether. The chemical shift differences of carbons of the enol ethers of each isomer were too similar to allow for assignment by Strobel's rule.[25] Spectral data for **18** (*major*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (s, 3 H), 1.88 (s, 3 H), 1.90 (s, 3 H), 2.36 (s,3 H), 3.68 (s, 3 H), 5.03 (s, 1 H),6.02 (d, J=11.0 Hz, 1 H), 6.54 (d, J=15.3 Hz, 1 H), 6.96 (dd, J=15.2, 11.3 Hz, 1 H), 10.16 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 18.2, 18.9, 26.6, 55.0, 92.5, 126.4, 131.5, 132.0, 141.7, 150.1, 158.3, 191.5, 1 C not located: IR (NaCl plate, thin film, cm^{-1}): 2920m, 1753m, 1653s, 1582m, 1436m, 1352m, 1226m, 1170m, 1077m; MS (EI) m/z (relative intensity): 220 (M^+, 12), 205 (8), 188 (56), 173 (32), 159 (7), 145 (100), 130 (24), 117 (16), 105 (26), 99 (4), 91 (19), 86 (15), 83 (2), 77 (14), 71 (8), 65 (6), 59 (7), 53 (8); HRMS (EI) calcd for $C_{14}H_{20}O_2$ m/z 220.1463, found 220.1463; R_f=0.35 (10% EtOAc/hexanes). Spectral data for **18** (*minor*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63 (s, 3 H), 1.88 (s, 3 H), 1.89 (s, 3 H), 2.09 (s,3 H), 3.66 (s, 3 H), 5.05 (s, 1 H), 6.02 (d, J=10.9 Hz, 1 H), 6.80 (dd, J=14.6, 11.5 Hz, 1 H), 7.13 (d, J=14.9 Hz, 1 H), 10.19 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 18.2, 18.4, 26.6, 55.0, 93.7, 126.1, 132.3, 132.5, 141.3, 151.5, 158.1, 190.5, 1 C not located; R_f=0.41 (10% EtOAc/hexanes).

***trans*-Dienyne 27.** To a suspension of 5.0 g (11.8 mmol) phosphonium bromide **26** (prepared from PPh_3 and 5-bromo-2-methyl-2-pentene in benzene) in 30 mL THF was added 11.8 mL 1.0 M NaHMDS in THF slowly at room temperature and the resulting yellow mixture was stirred for 30 min. At −60°C, 4.22 g (23.6 mmol) HMPA was added and after cooling to −78°C, a solution of 1.65 g (11.8 mmol) 4-trimethylsilyl-but-3-yn-2-one in 2 mL THF was added dropwise. After 1 h at room temperature, the solvent was removed under reduced pressure and the residue was taken up in 100 mL ice water and 100 mL hexane. Following separation of phases, the aqueous layer was washed with hexane (3×30 mL) and the combined organic portions were washed sequentially with 10% HCl (2×100 mL), sat. aq. $NaHCO_3$, brine, and finally dried over $MgSO_4$. Filtration and concentration left a brown oil and white solid (phosphine oxide) which was removed by filtration over a plug of Celite with hexanes. After removal of solvent, the product was purified by distillation (89–99°C/2 mmHg) to give **27** as a colorless liquid (1.35 g, 56% yield). The selectivity for **27** over **17** was determined to be ≥60:1 by ^{1}H NMR. Spectral data for **27**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.17 (s, 9 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.79 (d, J=1.0 Hz, 3 H), 2.75 (d, J=9.2 Hz, 2 H), 5.07 (t, J=9.0 Hz, 1 H), 5.88 (tm, J=9.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.1, 17.0, 17.7, 25.6, 27.5, 89.9, 108.5, 117.4, 121.0, 132.7, 138.0; IR (NaCl, thin film, cm^{-1}): 2962m, 2142m, 1249m, 842s, 760m; MS (EI) m/z (relative intensity) 206 (M^+,14), 189 (24), 179 (9), 173 (8), 163 (14),149 (28), 132 (15), 125

(14), 109 (9), 97 (32), 91 (13), 83 (28), 73 (100), 59 (70), 53 (9): HRMS (EI) calcd for $C_{13}H_{22}Si$ *m/z* 206.1491, found 206.1493. Anal. Calcd for $C_{13}H_{22}Si$: C, 75.65; H, 10.74. Found: C, 76.04; H, 10.81.

Assignment of the stereochemistry of dienynes 17 and 27

The stereochemistry expected from the Wittig reaction of a non-stabilized ylide is that with the larger carbonyl substituent *cis* to the ylide derived group.[28] Thus, the product from the Wittig reaction would be expected to have an *E*-configuration as in **27**. This is supported by the ^{1}H NMR shifts of the conjugated enyne vinyl hydrogens in **17** and **27** (δ=5.64 and 5.88 ppm, respectively) which were found to correlate with those shifts in the commercially available compounds **53** and **54**. Additionally, this assignment is consistent with the NOE experiments on **17** and **27** which are summarized below.



***trans*-Dienyne 28.** The same deprotection procedure for the preparation of **10** was used to furnish **28** as a clear oil from **27** in 92% yield. Spectral data for **28**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64 (s, 3 H), 1.71 (s, 3 H), 1.83 (s, 3 H), 2.75 (m, 3 H), 5.07 (t, *J*=5.0 Hz, 1 H), 5.89 (t, *J*=5.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3,18.0, 26.0, 28.0, 74.2, 87.2, 117.3, 121.5, 133.2, 138.6; IR (NaCl plate, thin film, cm^{-1}): 3311s, 3294s, 2972s, 2916s, 1448m, 1377m; MS (EI) *m/z* (relative intensity) 134 (M^+,14), 133 (M^+-1, 45), 119 (80), 91 (100), 79 (58), 69 (50); HRMS (EI) calcd for $C_{10}H_{14}$ *m/z* 134.1095, found 134.1087.

Cyclobutenone 29. A 100 mL flask with a threaded Teflon high-vacuum stopcock was charged with 108.2 mg (0.433 mmol) carbene complex **2**, 87 mg (0.649 mmol) dienyne **28**, and 100 mL CH_3CN (0.00433 M in **16**). The solution was deoxygenated by the freeze–thaw method (−196/25°C, 3 cycles), back-filled with argon at room temperature, sealed, and then heated at 70°C for 3.5 h. After evaporation of solvent, the cyclobutenones **29** were isolated by column chromatography on NEt_3-treated silica gel (10% EtOAc/hexane). The *E*-isomer was isolated (R_f=0.22) as a pale yellow oil in 56% yield (53.1 mg) and the *Z*-isomer (R_f=0.19) as a pale yellow oil in 26% yield (25.0 mg). The assignment of the stereochemistry was made by the difference in chemical shift of the enol ether carbons by the method of Strobel.[25] A reaction at 0.01 M gave a 70% yield (*E*/*Z*=2.0:1) and a reaction at 0.1 M gave 65% yield (*E*/*Z*=2.7:1). Spectral data for **29*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.62 (s, 3 H), 1.70 (s, 3 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 2.28-2.34 (m, 2 H), 3.37 (t, *J*=7.1 Hz, 1 H), 3.57 (s, 3 H), 4.82 (s, 1 H), 5.12 (t, *J*=7.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.9, 19.2, 25.9, 28.1, 55.3, 62.8, 87.8 (enol ether), 122.3, 133.6, 143.7, 161.3, 169.0 (enol ether), 191.0; IR (NaCl plate, thin film, cm^{-1}): 2928w, 1749s, 1656m, 1239s, 1135s; MS (EI) *m/z* (relative intensity) 220 (M^+, 20), 204 (18), 177 (35), 161 (75), 123 (49), 91 (56), 69 (100); HRMS (EI) calcd for $C_{14}H_{20}O_2$ *m/z* 220.1463, found 220.1471. Spectral data for **29*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (s, 3 H), 1.66 (s, 3 H), 1.93 (s, 3 H), 2.18 (s, 3 H), 2.29-2.35 (m, 2 H), 3.33 (t, *J*=6.3 Hz, 1 H), 3.67 (s, 3 H), 4.78 (s, 1 H), 5.12 (t, *J*=5.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 18.2, 18.4, 26.4, 28.2, 55.9, 63.3, 93.7 (enol ether), 121.4, 133.7, 141.7, 157.1, 170.0 (enol ether), 193.0; IR (NaCl plate, thin film, cm^{-1}): 2967m, 2915m, 1753s, 1653s, 1437m, 1352m, 1088s; MS (EI) *m/z* (relative intensity) 220 (M^+,15), 204 (42), 179 (75), 161 (55), 137 (100), 125 (42), 109 (49), 89 (28), 80 (20), 69 (38); HRMS (EI) calcd for $C_{14}H_{20}O_2$ *m/z* 220.1463, found 220.1515.

Dienyne 30. To 4.32 mL (45 mmol) of isopropenyl acetylene in 60 mL THF was added at −78°C 51 mL (100 mmol) 1.96 M *n*BuLi/hexanes followed by freshly prepared KO*t*Bu [from 4.38 g (109 mmol) KH and 7.41 g (100 mmol) *t*BuOH] in 80 mL THF. The yellow mixture was stirred for 30 min before warming to 0°C for 15 min. The reaction was then brought down to −30°C and a solution of 8.69 g (100 mmol) LiBr in 40 mL THF was added slowly. After 20 min the yellow-orange solution was cooled to −78°C and 5.23 mL (45 mmol) of prenyl bromide was added dropwise over 10 min. The mixture was allowed to warm to room temperature and after 1 h, 75 mL sat. aq. NH_4Cl and 150 mL pentane was added. The organic phase was separated and washed sequentially with water and brine. Drying with $MgSO_4$, filtration, and concentration left the crude dienyne which was further purified by distillation (95–98°C, 80 mmHg) to yield 6.04 g **30** as a clear oil in 76% yield. Spectral data for **30**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.62 (s, 3 H), 1.69 (s, 3 H), 2.20 (m, 4 H), 2.89 (s, 1 H), 5.10 (m, 1 H), 5.29 (s, 1 H), 5.41 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 25.6, 26.6, 37.1, 76.8, 84.1, 122.8, 123.1, 130.5, 132.3; IR (NaCl plate, thin film, cm^{-1}): 3297s, 2968s, 2916s, 1611m, 1449m, 1376m; MS (EI) *m/z* (relative intensity) 133 (M^+-1, 14), 109 (17), 95 (22), 87 (40), 73 (100), 67 (16), 57 (61), 43 (49); HRMS (EI) calcd for $C_{10}H_{14}$ *m/z* 134.1096, found 134.1100.

Reaction between carbene complex 2 and dienyne 30

A 100 mL flask with a threaded Teflon high-vacuum stopcock was charged with 125 mg (0.5 mmol) carbene complex **2**, 74 mg (0.55 mmol) dienyne **30**, and 50 mL CH_3CN. The solution was deoxygenated by the freeze–thaw method (−196/25°C, 3 cycles), back-filled with argon at room temperature, sealed, and then heated at 70°C for 3.5 h. After evaporation of solvent, products were isolated as colorless oils by silica gel chromatography (5% EtOAc/hexane) in the following amounts: 40 mg (36%) bicycloheptanone **35*E***, 67 mg (61%) cyclobutenones **36*E*** and **36*Z*** in a 1.4:1 ratio, respectively. When the reaction was performed at 45°C for 48 h, the product distribution was

69 mg (63%) **35*E***, 34 mg (31%) **36*E*** and **36*Z*** in a 2:1 ratio, respectively. When the reaction was performed at 100°C for 2 h, the product distribution was 19% yield **35*E*** and a 68% yield of **36*E***. Careful chromatography can provide a pure sample of **36*Z***. The spectral data for **35*E*** and **36*Z*** were obtained on pure compounds and the spectral data for **36*E*** was extracted from that of a mixture of **36*E*** and **36*Z***. The assignment of the stereochemistry of the isomers of **36** was made by the difference in chemical shift of the enol ether carbons by the method of Strobel.[25] Since **35** was only obtained as the one isomer it could not be assigned by Strobel's rule. Compound **35** was assumed to have the same stereochemistry as the products **49a–d**. Spectral data for **35*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (s, 3 H), 1.09 (s, 3 H), 1.73 (s, 3 H), 2.05–2.20 (m, 2 H), 2.28–2.37 (m, 1 H), 2.46 (dd, J=16.5, 8.0 Hz, 1 H), 2.68 (dd, J=4.8, 1.5 Hz, 1 H), 3.55 (s, 3 H), 4.23 (s, 1 H), 4.80 (m, 1 H), 4.87 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 19.2, 24.6, 25.1, 27.4, 29.7, 54.5, 63.0, 76.1, 89.7, 109.3, 150.4, 156.6, 210.2; IR (NaCl plate, thin film, cm^{-1}): 2953s, 1777s, 1657s, 1228s; MS (EI) *m/z* (relative intensity) 220 (M^+, 45), 205 (20), 192 (95), 177 (100), 161 (34), 145 (75), 135 (45), 110 (30), 105 (45), 91 (40), 77 (25), 69 (25), 59 (20), 55 (2); R_f=0.31 (10% EtOAc/hexanes). Spectral data for **36*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63 (s, 3 H), 1.70 (s, 3 H), 2.15 (s, 3 H), 2.90 (q, J=7.5 Hz, 2 H), 2.58 (t, J=7.5 Hz, 2 H), 3.11 (s, 2 H), 3.56 (s, 3 H), 4.85 (s, 1 H), 5.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 19.0, 24.8, 25.7, 29.7, 49.2, 54.9, 87.4 (enol ether), 122.8, 133.1, 143.4, 160.9 (enol ether), 167.2, 187.4; R_f=0.26 (10% EtOAc/hexanes). Spectral data for **36*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64 (s, 3 H), 1.70 (s, 3 H), 1.96 (s, 3 H), 2.27 (q, J=7.5 Hz, 2 H), 2.68 (t, J=7.5 Hz, 2 H), 3.10 (s, 2 H), 3.68 (s, 3 H), 4.80 (s, 1 H), 5.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 17.5, 25.1, 25.6, 31.1, 49.6, 55.2, 93.2 (enol ether), 123.2, 132.6, 141.6, 156.3 (enol ether), 168.2, 188.5; IR (NaCl plate, thin film, cm^{-1}): 2965m, 2916m, 1757s, 1653m, 1658m, 1378w, 1358w, 1224m, 1085m; MS (EI) *m/z* (relative intensity) 220 (M^+, 55), 205 (20), 189 (20), 179 (30), 163 (15), 145 (22), 135 (22), 123 (20), 117 (10), 109 (30), 89 (65), 84 (63), 69 (100), 77 (15), 65 (10), 59 (24), 55 (27), 49 (15); R_f=0.12 (10% EtOAc/hexanes).

Carbene complex 45. To a solution of 1.0 g (3.2 mmol) of tetramethylammonium [(methyl)oxidomethylene]pentacarbonyl chromium[27] in 15 mL CH_2Cl_2 was added 0.44 g (3.5 mmol) of MOMBr at rt. The resulting orange solution was stirred for 30 min after which time 5 mL sat. aq. $NaHCO_3$ was added. The organic phase was separated, dried with $MgSO_4$, filtered, and concentrated to leave an oil that was subjected to silica gel chromatography (100% hexane) to yield 760 mg (85% yield) of **45** as a dark orange oil. Spectral data for **45**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (s, 3 H), 3.68 (s, 3 H), 5.89 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.7, 58.4, 103.5, 216.1, 223.4, 359.1; IR (NaCl, thin film, cm^{-1}): 2065s, 1951brs, 651s; MS (EI) *m/z* (relative intensity) 280 (M^+, 100), 252 (75), 224 (44), 196 (34), 168 (30), 151 (14), 140 (61), 123 (16), 110 (12), 95 (16), 80 (18), 63 (8), 52 (35), 45 (24); HRMS (EI) calcd for $C_9H_8O_7Cr$ *m/z* 279.9675, found 279.9678.

Phenoxy carbene complexes 48a–d. To a solution of 2.00 g (6.5 mmol) of tetramethylammonium [(methyl)oxidomethylene]pentacarbonyl chromium[27] in 20 mL CH_2Cl_2 was slowly added 0.80 g (6.5 mmol) freshly distilled acetyl bromide at −78°C. After the deep red solution was stirred for 2 h, a 20 mL THF solution of the corresponding sodium phenoxide (prepared by reacting 6.5 mmol NaH with 6.5 mmol of *para*-substituted phenol) was added over 15 min and the mixture was slowly warmed to −10°C over 1 h. After 2 h at this temperature, the solvent was removed under reduced pressure and 50 mL nitrogen-purged pentane was added. The solids were filtered through Celite and after concentration of the filtrate, the orange–red oil was flashed through a short pad of NEt_3-treated silica gel using 1:1 hexane/CH_2Cl_2 as eluent. Removal of solvent left complexes **48a–d** as an orange–red oil which solidified upon cooling. Yields ranged from 20 to 60% and depended on the quickness of purification. They were often taken on to the next reaction immediately. Spectral data for **48a**: red solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (s, 3 H), 3.84 (s, 3 H), 6.98 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.3, 55.7, 115.1, 121.9, 152.4, 158.7, 215.7, 224.0, 363.9; IR (NaCl, thin film, cm^{-1}): 2064s, 1938brs, 1502s, 1251m, 1210s, 1099m; HRMS (EI) calcd for $C_{14}H_{10}O_7Cr$ 341.9832, found 341.9833: Anal. Calcd for $C_{14}H_{10}O_7Cr$: C, 49.13; H, 2.94. Found: C, 49.05; H, 3.07. Spectral data for **48b**: orange solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.11 (s, 3 H), 7.08 (d, J=7.8 Hz, 2 H), 7.39 (t, J=7.4 Hz, 1 H), 7.49 (t, J=7.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.3 121.2, 127.5, 130.2, 158.4, 215.6, 223.9, 363.3; IR (NaCl, thin film, cm^{-1}): 2065s, 1944brs, 1485m, 1211s, 1106m; HRMS (EI) calcd for $C_{13}H_8O_6Cr$ 311.9726, found 311.9724: Anal. Calcd for $C_{13}H_8O_6Cr$: C, 50.01; H, 2.58. Found: C, 49.84; H, 2.66. Spectral data for **48c**: orange–red oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (s, 3 H), 6.98 (d, J=8.0 Hz, 2 H), 7.60 (t, J=8.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.4, 118.8, 123.0, 133.2, 157.2, 215.4, 223.5, 363.9; IR (NaCl, thin film, cm^{-1}): 2066s, 1948brs, 1484s, 1200s, 1012m. Spectral data for **48d**:: orange–red oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (s, 3 H), 7.25 (d, J=8.5 Hz, 2 H), 7.78 (d, J=8.5 Hz, 2 H); IR (NaCl, thin film, cm^{-1}): 2058s, 1950brs, 1317s, 1185s, 1124m, 1059s.

Reaction between complexes 45 and 48a–d and dienyne 30

A 100 mL flask with a threaded Teflon high-vacuum stopcock was charged with 125 mg (0.5 mmol) carbene complex, 74 mg (0.55 mmol) dienyne **30**, and 50 mL CH_3CN. The solution was deoxygenated by the freeze–thaw method (−196/25°C, 3 cycles), back-filled with argon at room temperature, sealed, and then heated at 45°C for 48 h. After evaporation of solvent, the bicyclo[3.1.1]heptanone and cyclobutenone products were isolated by silica gel chromatography (5–10% EtOAc/hexane) in the yields shown below. While the products **49** and **50** could be separated, the *E* and *Z* isomers could not be easily separated. Pure samples of the *E*-isomers of **49a–d** and [Z-isomers] **50a–d** could be obtained by careful chromatography. The spectral data of their corresponding isomers were obtained by extraction from the spectral data obtained from a mixture of *E* and *Z* isomers with the aid of the authentic spectral data of one pure isomer. Compounds **46** and **47** were each formed as only one isomer and could be separated. The stereochemistry was assigned by the

difference in chemical shift of the enol ether carbons according to Strobel's rule.[25] The bicycloheptanones and the cyclobutenone **47** were formed as predominately the *E* isomer while the cyclobutenones **50a** and **50c** were formed as predominately the *Z* isomer. Cyclobutenones **50b** and **50d** could not be assigned by Strobel's rule and the major isomer was assumed to be *Z* in each case.

Bicycloheptanone 46. 62% yield, *E*-isomer only, pale yellow oil, R_f=0.46 (10% EtOAc/hexanes). Spectral data for **46*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 3 H), 1.08 (s, 3 H), 1.75 (s, 3 H), 2.01–2.19 (m, 2 H), 2.27–2.37 (*J*=16.5, 10.0, 2.5, 2.5 Hz, 1 H), 2.44–2.49 (dd, *J*=16.3, 8.0 Hz, 1 H), 2.66–2.68 (dd, 1 H), 3.42 (s, 3 H), 4.54 (s, 1 H), 4.80 (m, 1 H), 4.87 (m, 1 H), 4.95 (dd, *J*=29.3, 6.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 18.8, 24.5, 25.0, 27.4, 29.7, 55.8, 62.9, 76.1, 93.4, 95.0, 109.2, 150.3, 155.3, 209.9; IR (NaCl, thin film, cm^{-1}): 2952s, 1776s, 1650m, 1222w, 1178w, 1150m, 1048s; MS (EI) *m/z* (relative intensity) 250 (M^+, 2), 218 (5), 205 (8), 188 (7), 177 (38), 159 (6), 147 (10), 133 (8), 119 (8), 105 (12), 91 (14), 79 (8), 69 (16), 61 (18), 55 (8), 45 (100); HRMS (EI) calcd for $C_{15}H_{22}O_3$ *m/z* 250.1596, found 250.1588: Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.98; H, 8.86.

Cyclobutenone 47. 22% yield, *E*-isomer only, R_f=0.26 (10% EtOAc/hexanes). Spectral data for **47*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65 (s, 3 H), 1.71 (s, 3 H), 2.01 (s, 3 H), 2.30 (m, 2 H), 2.70 (m, 2 H), 3.12 (s, 2 H), 3.45 (s, 3 H), 4.91 (s, 1 H), 4.99 (s, 2 H), 5.10 (brs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 18.7, 24.7, 25.6, 29.6, 49.1, 58.4, 91.6, 108.2, 122.7, 133.0, 143.1, 157.8, 168.2, 187.0; IR (NaCl, thin film, cm^{-1}): 2925m, 1759s, 1152m, 1041m; MS (EI) *m/z* (relative intensity) 250 (M^+, 4), 218 (5), 205 (8), 191 (4), 177 (32), 163 (15), 147 (16), 135 (32), 121 (20), 105 (30), 93 (44), 79 (20), 69 (34), 55 (23), 45 (100); HRMS (EI) calcd for $C_{15}H_{22}O_3$ *m/z* 250.1596, found 250.1590.

Bicycloheptanone 49a*E*. 32% yield, spectral data for **49a*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (s, 6 H), 1.87 (s, 3 H), 2.03–2.20 (m, 2 H), 2.27–2.39 (m, 1 H), 2.46 (dd, *J*=14.5, 7.8 Hz, 1 H), 2.66 (dd, *J*=5.0, 2.5 Hz, 1 H), 3.79 (s, 3 H), 4.51 (s, 1 H), 4.84 (m, 1 H), 4.90 (m, 1 H), 6.84, (d, *J*=9.0 Hz, 2 H), 6.94 (d, *J*=9.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(17.6, 18.2, 24.5, 25.0, 27.4, 34.9, 55.6, 62.9, 75.9, 100.3 (enol ether), 109.3, 114.6, 120.7, 149.3, 150.0, 155.5, 157.0 (enol ether), 209.4; IR (NaCl, thin film, cm^{-1}): 2947w, 1766s, 1504s, 1214s; MS (EI) *m/z* (relative intensity) 312 (M^+, 7), 284 (4), 269 (11), 241 (15), 227 (5), 199 (5), 188 (51), 173 (15), 161 (96), 145 (32), 124 (27), 105 (19), 91 (16), 84 (100), 77 (9), 65 (5), 49 (92); HRMS (EI) calcd for $C_{20}H_{24}O_3$ *m/z* 312.1725, found 312.1725: Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.70; H, 8.11.

Bicycloheptanone 49a*Z*. 16% yield, spectral data for **49a*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (s, 3 H), 1.16 (s, 3 H), 1.82 (s, 3 H), 2.03–2.20 (m, 2 H), 2.27–2.39 (m, 1 H), 2.44 (dd, *J*=15.0, 8.0 Hz, 1 H), 2.66 (dd, *J*=5.0, 2.5 Hz, 1 H), 3.78 (s, 3 H), 4.76 (s, 1 H), 4.89 (m, 1 H), 4.97 (m, 1 H), 6.82 (d, *J*=9.0 Hz, 2 H), 6.89 (d, *J*=9.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.0, 18.1, 24.6, 25.4, 26.6, 36.5, 55.6, 63.3, 76.7, 103.3 (enol ether), 109.5, 114.3, 120.3, 148.7 (enol ether), 149.1, 149.3, 155.3, 210.6.

Cyclobutenone 50a*Z*. 23% yield, spectral data for **50a*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.56 (s, 3 H), 1.65 (s, 3 H), 1.82 (s, 3 H), 2.21 (q, *J*=7.5 Hz, 2 H), 2.69 (t, *J*=7.5 Hz, 2 H), 3.11 (s, 2 H), 3.79, (s, 3 H), 5.02 (m, 1 H), 5.23 (s, 1 H), 6.83 (d, *J*=9.0 Hz, 2 H), 6.91 (d, *J*=9.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(17.7, 18.6, 25.1, 25.6, 31.4, 50.0, 55.6, 99.4 (enol ether), 114.6, 119.7, 123.0, 133.4, 140.7, 148.9, 153.6 (enol ether), 155.7, 170.6, 188.2; IR (NaCl, thin film, cm^{-1}) 2965m, 1765s, 1455m, 1215m; MS (EI) *m/z* (relative intensity) 312 (M^+, 22), 269 (15), 227 (7), 215 (11), 201 (23), 189 (100), 173 (61), 161 (19), 147 (70), 135 (78), 124 (95), 109 (62), 91 (25), 84 (20), 69 (22), 55 (11), 49 (19); HRMS (EI) calcd for $C_{20}H_{24}O_3$ *m/z* 312.1725, found 312.1738: Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.54; H, 7.97.

Cyclobutenone 50a*E*. 11% yield, spectral data for **50a*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57 (s, 3 H), 1.66 (s, 3 H), 2.19 (q, *J*=8.0 Hz, 2 H), 2.31 (s, 3 H), 2.43 (t, *J*=8.0 Hz, 2 H), 3.09 (s, 2 H), 3.81, (s, 3 H), 4.86 (s, 1 H), 5.02 (m, 1 H), 6.86 (d, *J*=9.0 Hz, 2 H), 6.92 (d, *J*=9.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(17.7, 18.4, 24.7, 25.6, 29.7, 49.3, 55.7, 94.4 (enol ether), 114.6, 121.9, 122.7, 133.8, 140.7, 148.9, 156.3, 160.6 (enol ether), 168.5, 187.1.

Bicycloheptanone 49b*E*. 47% yield, spectral data for **49b*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (s, 3 H), 1.03 (s, 3 H), 1.88 (s, 3 H), 2.06–2.20 (m, 2 H), 2.30–2.40 (m, 1 H), 2.47 (dd, *J*=16.3, 7.5 Hz, 1 H), 2.69 (dd, *J*=5.0, 1.5 Hz, 1 H), 4.75 (s, 1 H), 4.88 (m, 1 H), 4.93 (m, 1 H), 7.00 (d, *J*=7.5 Hz, 2 H), 7.04 (t, *J*=7.5 Hz, 1 H), 7.31 (t, *J*=7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(17.5, 17.8, 24.5, 24.9, 27.3, 34.9, 62.8, 75.8, 104.1 (enol ether), 109.4, 118.6, 122.6, 129.4, 149.8, 155.4, 156.2 (enol ether), 208.9; IR (NaCl, thin film, cm^{-1}): 2947w, 1766s, 1591m, 1481s, 1217s, 1165m; MS (EI) *m/z* (relative intensity) 282 (M^+, 9), 254 (30), 239 (37), 211 (35), 188 (93), 173 (22), 161 (92), 146 (100), 131 (56), 119 (90), 105 (65), 91 (55), 77 (43), 69 (30), 55 (26); HRMS (EI) calcd for $C_{19}H_{22}O_2$ *m/z* 282.1620, found 282.1613: Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.76; H, 7.96.

Bicycloheptanone 49b*Z*. 24% yield, spectral data for **49b*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (s, 3 H), 1.16 (s, 3 H), 1.88 (s, 3 H), 2.06–2.20 (m, 2 H), 2.25–2.35 (m, 1 H), 2.42 (dd, *J*=16.3, 7.5 Hz, 1 H), 2.67 (dd, *J*=5.0, 1.5 Hz, 1 H), 4.87 (m, 1 H), 4.88 (s, 1 H), 4.97 (m, 1 H), 6.94 (d, *J*=7.5 Hz, 2 H), 7.04 (t, *J*=7.5 Hz, 1 H), 7.29 (t, *J*=7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(17.8, 18.0, 24.5, 25.3, 26.5, 36.6, 63.3, 76.8, 105.1, 109.5 (enol ether), 118.9, 122.5, 129.2, 148.9 (enol ether), 149.3, 155.0, 210.3.

Cyclobutenone 50b*E*. 5% yield, spectral data for **50b*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55 (s, 3 H), 1.64 (s, 3 H), 1.88 (s, 3 H), 2.20 (q, *J*=7.3 Hz, 2 H), 2.67 (t, *J*=7.3 Hz, 2 H), 3.09 (s, 2 H), 5.00 (m, 1 H), 5.34 (s, 1 H), 6.96 (d, *J*=7.5 Hz, 2 H), 7.06 (t, *J*=7.5 Hz, 1 H), 7.31 (d, *J*=7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(17.7, 18.7, 25.1, 25.6, 31.3,

50.0, 101.1, 118.1, 122.9, 123.0, 129.5, 132.8, 140.6, 152.7, 155.3, 171.1, 188.0; IR (NaCl, thin film, cm^{-1}): 3054s, 2986m, 1756s, 1490s, 1422s, 1220s; MS (EI) *m/z* (relative intensity) 282 (M^+, 7), 267 (2), 256 (2), 240 (3), 213 (5), 189 (100), 171 (25), 161 (15), 147 (54), 131 (12), 119 (18), 105 (17), 94 (42), 84 (6), 77 (15), 55 (8); HRMS (EI) calcd for $C_{19}H_{22}O_2$ *m/z* 282.1620, found 282.1624: Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.53; H, 7.98.

Cyclobutenone 50b*Z*. 11% yield, spectral data for **50b*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57 (s, 3 H), 1.66 (s, 3 H), 2.20 (q, J=7.5 Hz, 2 H), 2.32 (s, 3 H), 2.46 (t, J=7.5 Hz, 2 H), 3.11 (s, 2 H), 5.02 (m, 1 H), 5.02 (s, 1 H), 6.99 (d, J=7.5 Hz, 2 H), 7.13 (t, J=7.5 Hz, 1 H), 7.34 (t, J=7.0 Hz, 2 H).

Bicycloheptanone 49c*E*. 46% yield, spectral data for **49c*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (s, 3 H), 1.02 (s, 3 H), 1.85 (s, 3 H), 2.08–2.20 (m, 2 H), 2.30–2.40 (m, 1 H), 2.47 (dd, J=16.3, 8.0 Hz, 1 H), 2.69 (dd, J=5.0, 1.5 Hz, 1 H), 4.75 (s, 1 H), 4.84 (m, 1 H), 4.92 (m, 1 H), 6.89 (d, J=8.5 Hz, 2 H), 7.40 (d, J=8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 17.8, 24.5, 24.9, 27.4, 34.9, 62.9, 75.8, 104.7 (enol ether), 109.4, 115.1, 120.3, 132.4, 149.7, 155.3, 155.4 (enol ether), 208.7; IR (NaCl, thin film, cm^{-1}): 2954s, 1772s, 1483s, 1265s, 1226s; HRMS (EI) calcd for $C_{19}H_{21}O_2{}^{79}Br$ *m/z* 360.0725, found 360.0747. HRMS (EI) calcd for $C_{19}H_{21}O_2{}^{81}Br$ *m/z* 362.0706, found 362.0696.

Bicycloheptanone 49c*Z*. 23% yield, spectral data for **49c*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (s, 3 H), 1.13 (s, 3 H), 1.87 (s, 3 H), 2.02-2.20 (m, 2 H), 2.25-2.35 (m, 1 H), 2.40 (dd, J=16.3, 8.0 Hz, 1 H), 2.66 (dd, J=5.0, 1.5 Hz, 1 H), 4.75 (s, 1 H), 4.84 (m, 1 H), 4.92 (m, 1 H), 6.89 (d, J=8.5 Hz, 2 H), 7.40 (d, J=8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8, 17.9, 24.5, 25.3, 26.6, 36.4, 63.3, 76.7, 106.2 (enol ether), 109.5, 115.0, 120.4, 132.2, 148.9 (enol ether), 149.0, 154.2, 209.7.

Cyclobutenone 50c*Z*. 6% yield, spectral data for **50c*Z***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.57 (s, 3 H), 1.66 (s, 3 H), 1.88 (s, 3 H), 2.21 (q, J=7.1 Hz, 2 H), 2.64 (t, J=7.4 Hz, 2 H), 3.09 (s, 2 H), 5.00 (m, 1 H), 5.34 (s, 1 H), 6.84 (d, J=9.0 Hz, 2 H), 7.40 (d, J=9.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 18.6, 25.0, 25.6, 31.1, 50.0, 102.2 (enol ether), 115.3, 119.5, 122.8, 132.5, 133.0, 140.4, 152.1 (enol ether), 154.6, 171.3, 187.4; IR (NaCl, thin film, cm^{-1}): 2914s, 1755s, 1671s, 1585s, 1482s, 1220s; HRMS (EI) calcd for $C_{19}H_{21}O_2{}^{79}Br$ *m/z* 360.0725, found 360.0715. HRMS (EI) calcd for $C_{19}H_{21}O_2{}^{81}Br$ *m/z* 362.0706, found 362.0717.

Cyclobutenone 50c*E*. 3% yield, spectral data for **50c*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (s, 3 H), 1.67 (s, 3 H), 2.21 (q, J=8.0 Hz, 2 H), 2.31 (s, 3 H), 2.47 (t, J=7.0 Hz, 2 H), 3.12 (s, 2 H), 5.03 (s, 1 H), 5.03 (m, 1 H), 6.88 (d, J=9.0 Hz, 2 H), 7.44 (d, J=9.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 18.2, 24.7, 25.6, 29.8, 49.5, 97.3 (enol ether), 116.7, 122.1, 122.5, 132.7, 133.3, 142.0, 150.9 (enol ether), 154.3, 169.8, 186.8.

Bicycloheptanone 49d*E*. 43% yield, spectral data for **49d*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 3 H), 1.06 (s, 3 H), 1.87 (s, 3 H), 2.10-2.22 (m, 2 H), 2.33-2.41 (m, 1 H), 2.49 (dd, J=16.2, 7.6 Hz, 1 H), 2.72 (dd, J=5.0, 1.5 Hz, 1 H), 4.87 (d, J=2.1 Hz, 1 H), 4.93 (s, 1 H), 4.96 (s, 1 H), 7.07 (d, J=8.5 Hz, 2 H), 7.56 (d, J=8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 17.7, 24.5, 24.9, 27.4, 35.0, 63.0, 75.8, 107.4 (enol ether), 109.5, 117.6, 124.3 (q, J_{CF}=269.6 Hz), 124.4 (q, J_{CF}=32.5 Hz), 127.0 (q, J_{CF}=3.8 Hz), 149.6, 154.3, 159.4 (enol ether), 208.3; IR (NaCl, thin film, cm^{-1}): 2957brm, 1755s, 1631s, 1619s, 1325s, 1242s, 1168s, 1107s, 1066s; HRMS (EI) calcd for $C_{20}H_{21}O_2F_3$ *m/z* 350.1494, found 350.1509. Anal. Calcd for $C_{20}H_{21}O_2F_3$: C, 68.55; H, 6.04. Found: C, 68.50; H, 6.14.

Bicycloheptanone 49d*Z*. 22% yield, spectral data for **49d*Z***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3 H), 1.14 (s, 3 H), 1.92 (s, 3 H), 2.06–2.12 (m, 2 H), 2.25–2.35 (m, 1 H), 2.41 (dd, J=16.2, 7.6 Hz, 1 H), 2.67 (dd, J=5.0, 1.5 Hz, 1 H), 4.86 (m, 1 H), 4.88 (m, 1 H), 4.98 (s, 1 H), 7.01 (d, J=8.5 Hz, 2 H), 7.55 (d, J=8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 17.9, 24.5, 25.4, 26.6, 36.4, 63.3, 76.8, 107.8 (enol ether), 109.5, 118.3, 124.4 (q, J_{CF}=269.6 Hz), 124.5 (q, J_{CF}=32.5 Hz), 126.7 (q, J_{CF}=3.8 Hz), 148.7 (enol ether), 149.0, 157.9, 209.2.

Cyclobutenone 50d*E*. 3% yield, spectral data for **50c*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ (1.57 (s, 3 H), 1.65 (s, 3 H), 1.93 (s, 3 H), 2.21 (q, J=7.2 Hz, 2 H), 2.63 (t, J=7.2 Hz, 2 H), 3.08 (s, 2 H), 4.99 (m, 1 H), 5.48 (s, 1 H), 7.02 (d, J=8.5 Hz, 2 H), 7.56 (d, J=8.5 Hz, 2 H); HRMS (EI) calcd for $C_{20}H_{21}O_2F_3$ *m/z* 350.1494, found 350.1501.

Diketone 51. Enol ether **49** (0.2 mmol) was dissolved in 10 mL ether, 1.5 mL acetic acid, and 1.5 mL H_2O. The mixture was stirred at room temperature and monitored by TLC for completion of reaction (4–12 h). Upon completion of reaction, sat. aq. $NaHCO_3$ was added and the product was extracted with CH_2Cl_2. After drying with Na_2SO_4, filtration, and concentration, the crude diketone **51** was further purified by subjection to silica gel chromatography (25% EtOAc/hexanes) to give a colorless oil. Yields varied from 78–90%. Spectral data for **51**: R_f=0.15 (10% EtOAc/hexanes), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 3 H), 1.12 (s, 3 H), 2.08–2.23 (m, 2 H), 2.19 (s, 3 H), 2.29–2.36 (dddd, J=16.5, 10.0, 2.5, 2.5 Hz, 1 H), 2.38–2.43 (dd, J=16.0, 8.0 Hz, 1 H), 2.68 (dd, J=5.0, 1.5 Hz, 1 H), 2.69 (dd, J=53.0, 17.5 Hz, 2 H), 4.52 (d, J=2.5 Hz, 1 H), 4.88 (d, J=2.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.8, 24.1, 24.5, 28.3, 30.1, 34.9, 41.0, 63.2, 73.5, 108.3, 149.6, 206.5, 209.2; IR (NaCl, thin film, cm^{-1}): 2953m, 1771s, 1722m, 1361m; MS (EI) *m/z* (relative intensity) 206 (M^+, 10), 192 (12), 178 (36), 163 (29), 135 (95), 121 (60), 105 (75), 91 (100), 79 (74), 55 (55); HRMS (EI) calcd for $C_{13}H_{18}O_2$ *m/z* 206.1307, found 206.1312.

Isomerization of 51 to diketone 52. To a solution of 100 mg (0.49 mmol) diketone **51** in 15 mL absolute EtOH was added 400 mg 5% Pd on $BaCO_3$. Under an atmosphere of hydrogen, the mixture was stirred for 4 h at room temperature. The solvent then was evaporated and the resulting residue was subjected to silica gel chromatography (10% EtOAc/hexanes) to yield **52** a clear oil in 70% yield. Spectral data for **52**: R_f=0.15 (10% EtOAc/hexanes), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 3 H), 1.36 (s, 3 H),

1.64 (s, 3 H), 2.19 (s, 3 H), 2.60 (m, 3 H), 2.68 (d, J=19.2 Hz, 1 H), 2.93 (d, J=19.2 Hz, 1 H), 5.45 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 19.9, 24.7, 28.0, 31.1, 33.6, 42.4, 63.7, 67.7, 121.2, 140.0, 206.4, 206.8; IR (NaCl, thin film, cm^{-1}): 2950s, 1771s, 1710s, 1366m, 1165s; MS (EI) m/z (relative intensity) 206 (M^+, 40), 189 (11), 178 (12), 163 (30), 145 (25), 135 (80), 121 (100), 105 (70), 93 (80), 77 (55), 69 (55), 57 (60); HRMS (EI) calcd for $C_{13}H_{18}O_2$ m/z 206.1307, found 206.1310.

Acknowledgements

This work was supported by a grant from the National Institutes of Health (PHS-GM 33589).

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