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Simultaneous Synthesis of Both Rings of Chromenes via a Benzannulation/*o*-Quinone Methide Formation/Electrocyclization Cascade

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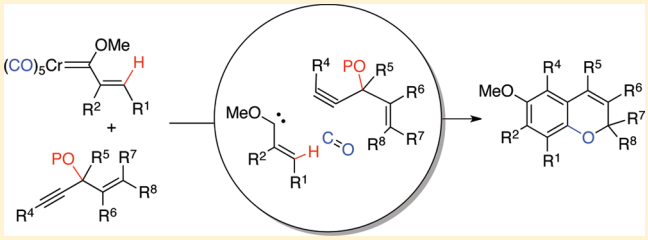
Supporting Information

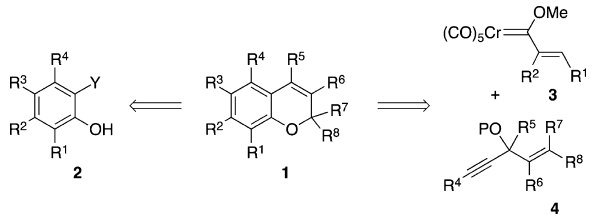
ABSTRACT: A new route to the chromene ring system has been developed which involves the reaction of an α,β-unsaturated Fischer carbene complex of chromium with a propargyl ether bearing an alkenyl group on the propargylic carbon. This transformation involves a cascade of reactions that begins with a benzannulation reaction and is followed by the formation of an *o*-quinone methide, and finally results in the emergence of a chromene upon an electrocyclization. This reaction was extended to provide access by employing an aryl carbene complex. This constitutes the first synthesis of chromenes in which both rings of the chromene system are generated in a single step and is highlighted in the synthesis of lapachenole and vitamin E.



1. INTRODUCTION

As a consequence of its appearance in compounds with a broad spectrum of biological activity, the chromene ring system (**1** in Scheme 1) has been identified as one of the privileged scaffolds

Scheme 1



for drug discovery[1] and thus for combinatorial libraries.[2] Nearly all of the methods for the synthesis of chromenes involve the closure of the pyran ring on a substrate containing a preformed phenol unit of the type **2**. Recent representative methods include Claisen rearrangement[3] or electrophile-induced cyclization of aryl propargyl ethers,[4] palladium-catalyzed[5] and selenium-mediated[2a] cyclization of 2-butenylphenols, ring closing metathesis,[6] cyclization of salicylaldehydes with enamines,[7] Wittig olefination,[8] Petasis reaction of salicylaldehydes[9] and the reaction of salicylaldehydes with vinyltrifluoroborates,[10] palladium-catalyzed oxidative cyclization of aryl-3-butenyl ethers,[11] ene,[12] and Baylis–Hillman[13] reactions of salicylaldehydes, ylide-induced annulation,[14] enolization of vinylquinones,[15] cyclization onto 3,4-epoxy alcohols,[16] the reactions of phenols with α,β-unsaturated aldehydes,[17] the oxa-Michael-aldol/Henry reaction of salicylaldehydes,[18] and the dehydrative cyclizations of 2-(1-hydroxy-2-propenyl)phenols.[19] Of all the methods of the myriad, to the best of our knowledge, there is not a single one in which both rings of the chromene core are constructed at the same time. We report here an efficient method for the preparation of chromenes in which both rings of the chromene unit are generated from the reaction of the carbene complex **3** and the alkoxyenyne **4** in a benzannulation/*o*-quinone methide formation/electro-cyclization cascade.

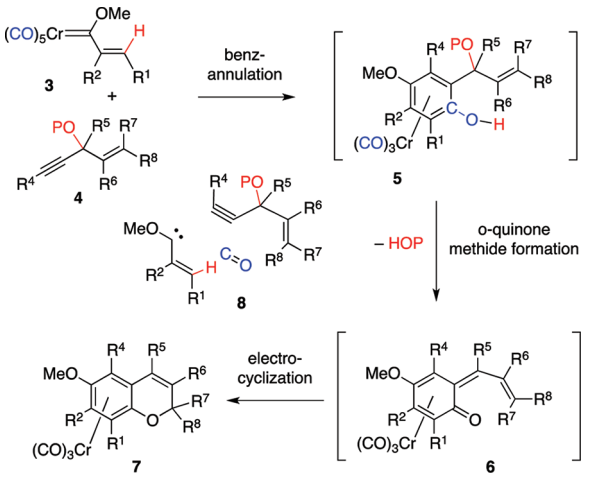
The anticipated events in the transformation of carbene complex **3** and alkoxyenyne **4** into a chromene are the benzannulation to give the phenol complex **5**,[20] the elimination of an alcohol to generate the *o*-quinone methide complex **6**,[21,22] and finally an electrocyclization to give the chromene chromium tricarbonyl complex **7**[23] (Scheme 2). The chromene oxygen in **7** has as its origin one of the carbon monoxide ligands of the carbene complex, and the overall integration of the pieces is indicated diagrammatically in the assembly **8**.

In previous studies we had shown that the reaction of alkenyl carbene complexes would react with propargyl ethers of the type **10** with a tethered alkene unit to generate hexahydrodibenzopyrans of the type **11**.[21] Significant yields of **11** were only observed if the reaction was performed in the presence of Hünig's base that presumably aided in the elimination of the propargyl oxygen unit from the benzannulated product **12** to generate the *o*-quinone methide complex **13**. The intramolecular Diels–Alder reaction that concludes the cascade must have occurred via the intermediate **13** with an *E*-alkene such that the trans-stereochemistry of **11** is established. This in turn requires that during *o*-quinone methide formation the alkyl group moves away from the phenol unit in **12** to establish the E-stereochemistry in the *o*-quinone methide. This was a source of concern in the original planning of the chromene synthesis in

Received: November 12, 2011
Published: December 16, 2011

   dx.doi.org/10.1021/ja210655g | *J. Am. Chem.Soc.* 2012, 134, 1357–1362

Scheme 2



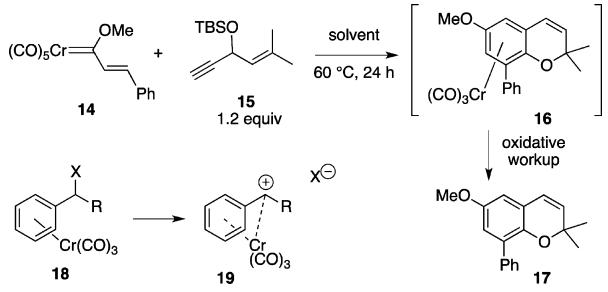
Scheme 2, since the ultimate electrocyclic ring closure would require the Z-configuration of the alkene in the *o*-quinone methide unit.

2. CHROMENES FROM ALKENYL CARBENE COMPLEXES

In our initial foray into exploring the cascade process in Scheme 2, we chose to examine the reaction of the *trans*-styrenyl carbene complex **14** and the siloxyenyne **15**. The first reaction was carried out in toluene with 5 equiv of Hünig's base, and the reaction mixture was subjected to oxidation with ferric chloride DMF complex to remove the metal from the product and to simplify purification. This reaction gave a 35% yield of chromene **17**, but the yield could be improved to 62% yield if the base was excluded (Table 1, entries 1 vs 2). This was a surprise since we had previously found that *o*-quinone methide formation was facilitated by the presence of a base (Scheme 3).[21] The more facile elimination in the present case may be related to the fact that a chromium tricarbonyl unit in an arene complex can stabilize a benzylic cation (**19** in Table 1).[24] Substitution reactions on the chromium tricarbonyl complex of benzyl chloride are 10^5 times faster than on benzyl chloride itself.[24a] The benzylic cation **19** (R = alkenyl) derived from alkoxyenyne **15** would be both benzylic and allylic rather than just benzylic (R = alkyl) as in previous reactions, where the base was employed to effect *o*-quinone methide formation which was presumably initiated via base-induced deprotonation in phenol complexes of the type **12** (Scheme 3).[21] The fact that base is not needed in the present case could be explained if *o*-quinone methide formation could be initiated by a chromium-induced loss of an alkoxide in the complex **5** (Scheme 2).

A survey of different solvents for this reaction shown in Table 1 found that acetonitrile was the optimum for this particular reaction and had the additional advantage that an oxidative workup was not needed since the solvent was capable of completely displacing the metal from the product under the reaction conditions. Ceric ammonium nitrate was too strong an oxidant since neither the chromene complex **16** nor the chromene **17** could be detected in the crude reaction mixture. In the absence of an oxidative workup, a mixture of **16** and **17** was obtained from which **16** could not be purified since it slowly oxidizes to **17** in air. The chromium tricarbonyl arene complex **21** derived from the *trans*-2-butenyl carbene complex

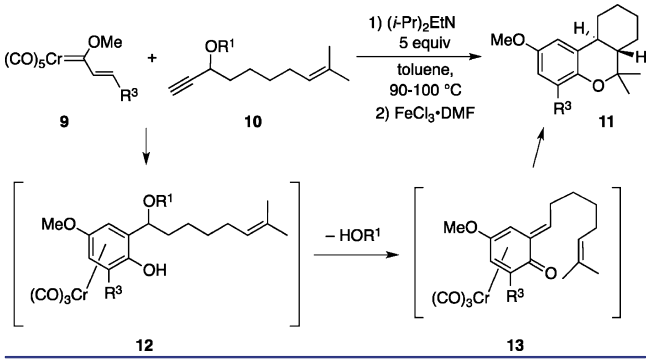
Table 1. Optimization of Chromene Formation from Chromium Carbene Complex 14[a]



entry	solvent	oxidative workup	% yield **17**[b]
1[c,d]	toluene	$FeCl_3$·DMF	35
2[c]	toluene	$FeCl_3$·DMF	62
3	benzene	$FeCl_3$·DMF	74
4	hexane	$FeCl_3$·DMF	70
5	THF	$FeCl_3$·DMF	65
6	MeCN	none	95
7	CH_2Cl_2	$FeCl_3$·DMF	76
8	CH_2Cl_2	CAN	nd[e]
9	CH_2Cl_2	none	nd[f]

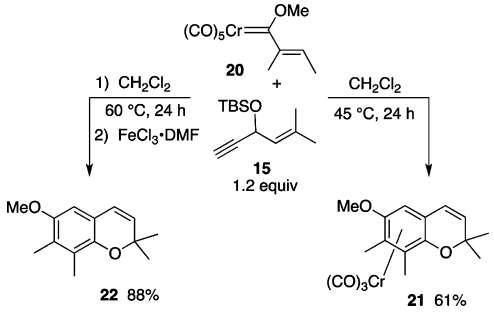
[a]Unless otherwise specified, all reactions were run at 0.03 M in **14** with 1.2 equiv of **15** at 60 °C for 24 h and worked up with 7.5 equiv of the indicated oxidant (if employed). [b]Isolated yield after chromatography on silica gel. All yields are the average of two runs except for entry 7; nd = not determined. [c]Reaction performed at 80 °C for 24 h. [d]Reaction performed with 5 equiv of $(i\text{-Pr})_2$EtN. [e]TLC indicated the absence of **16** and **17** and the presence of compounds more polar than either. [f]A mixture of **16** and **17** from which **16** could not be separated to purity due to its slow and continuous decomposition to **17**.

Scheme 3



20 was much more stable to loss of the metal and could be isolated in 61% yield after purification by chromatography on silica gel (Scheme 4). The corresponding chromene **22** could

Scheme 4

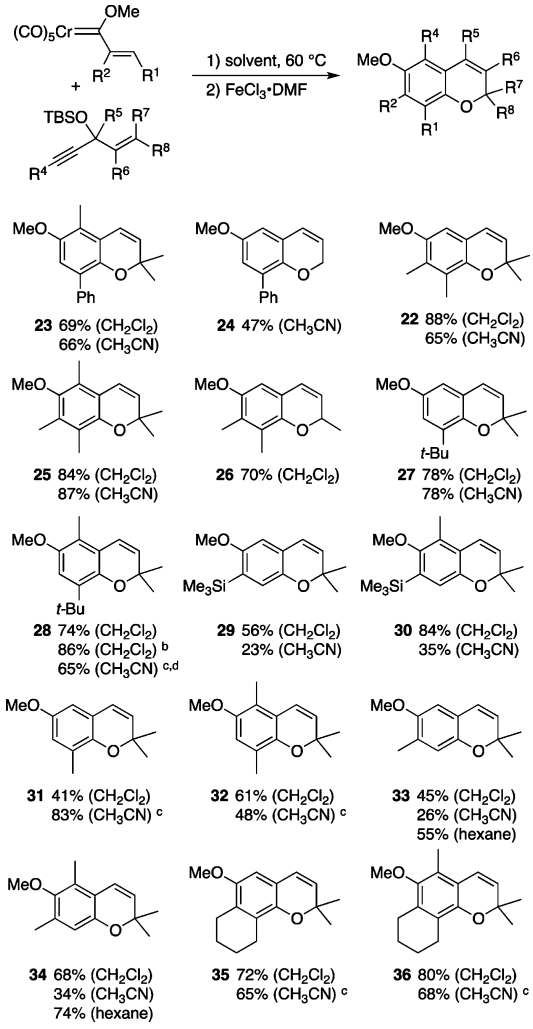


dx.doi.org/10.1021/ja210655g | J. Am. Chem.Soc. 2012, 134, 1357–1362

be obtained free of the metal in 88% yield if an oxidative workup with $FeCl_3$·DMF complex was employed.

The formation of chromenes from α,β-unsaturated carbene complexes and alkoxyenynes is efficient for a number of substituent patterns and with substituents of varying sizes (Table 2). It should be noted that alkoxyenynes with an internal alkyne function ($R^4 \neq H$) gave a single regioisomer of the chromene, specifically, that in which the R^4 substituent is ortho to the methoxy group in complex **5** in Scheme 2.[20] Most of the cases examined involved chromenes in which the sp^3 ethereal carbon of the chromene bears two substituents, but we were particularly pleased to note that chromenes with either one (**26**) or no substituents (**24**) could also be generated. The concern was that alkoxyenynes with either one or both of the substituents R^7 and R^8 as hydrogen would fail since the cation **19** would be less stable. While this was not the case, the fact that the yield of **24** is lower than **17** and that the yield of **26** is lower than **22** suggests the substitution pattern in cation **19** may play some role in this reaction. While Hünig's base was detrimental (Table 1), it was found that the yield of **28** could be slightly improved if the reaction was performed in the presence of 10 equiv of aniline, but the generality of this effect was not examined.

Table 2. Chromene Synthesis via Carbene Complexes and Alkoxyenynes[a]



[a]Unless otherwise specified, all reactions were run at 0.03 M in carbene complex in the indicated solvent with 1.2 equiv of the enyne at 60 °C for 24 h. If oxidation was used, it was carried out with 7.5 equiv of $FeCl_3$-DMF complex. All yields are isolated yields after chromatography on silica gel. [b]Reaction performed with 10 equiv of aniline. [c]Oxidative workup not used. [d]Isolation after treatment of crude reaction mixture with trifluoromethane sulfonic acid.

In many of the reactions, the solvents CH_2Cl_2 and CH_3CN were found to give similar yields of the chromenes. However, for carbene complexes that only had a substituent in the α-position (R^2), CH_2Cl_2 was superior to CH_3CN as solvent (**29**, **30**, **33**, and **34**). In the case of the chromenes **33** and **34**, which are obtained from the carbene complex with R^2 = methyl, the best solvent was found to be hexane. While the source of these differences is not fully appreciated, α,β-unsaturated carbene complexes that do not have a substituent at the β-carbon tend to be less stable as a result of a tendency to undergo polymerization.[25a] While the reactions in CH_3CN do not need an oxidative workup to remove the chromium tricarbonyl group from the chromene, these reactions produce $(CO)_5Cr(CH_3CN)$ which slowly air oxidizes and which can coelute with the chromene product. Therefore, many of the reactions in CH_3CN also utilized the $FeCl_3$·DMF complex in an oxidative workup to prevent $(CO)_5Cr(CH_3CN)$ from complicating product isolation.[25b]

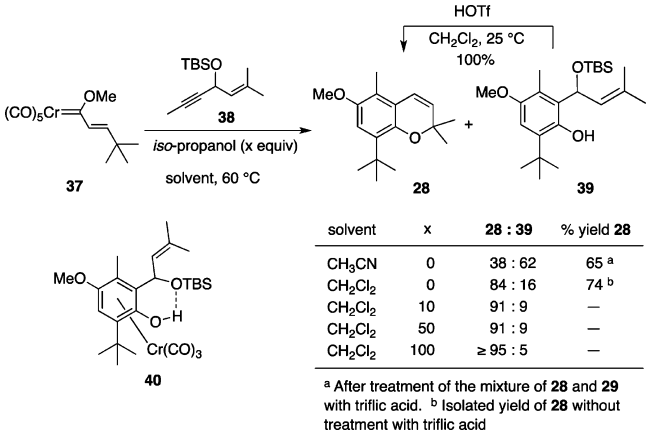
A side-product was isolated from the reaction of the *trans-t*-butyl alkenyl carbene complex **37** with the enyne **38**. The phenol **39** is the major product for the reaction in acetonitrile formed in a 3:2 ratio over the chromene **28**. Clearly, this product is the result of the failure of the *o*-quinone methide to form. Nonetheless, phenol **39** can be quantitatively converted to the chromene **28** by treatement with triflic acid. The yield given for chromene **28** in acetonitrile that is indicated in Table 2 involved treatment of the crude reaction mixture with triflic acid before purification. A possible explanation for the partial failure of *o*-quinone methide formation in these reactions is that the H-bonding indicated in structure **40** prevents the proper anti-orientation of the benzylic oxygen with respect to the chromium for the assisted elimination to generate a benzylic cation of the type **19** (Table 1). The role of *t*-butyl group in this process may be related in some fashion to the orientation of the chromium tricarbonyl group relative to the arene carbons.[26] As a test, this reaction was repeated in the presence of increasing amounts of isopropanol which was added to dissrupt the H-bonding, and indeed, at 100 equiv no detectable amount of **39** was observed. Acetonitrile would not be expected to disrupt this H-bonding since the pK_a of protonated acetonitrile has been reported to be −10.[27] Instead, the role of the acetonitrile in favoring the phenol product **39** is suspected of being related to its ability to displace the chromium tricarbonyl from the benzannulated product before it has the chance to completely ionize the benzylic oxygen.

3. NAPHTHOPYRANS FROM ARYL CARBENE COMPLEXES

The benzannulation/*o*-quinone methide formation/electrocyclization cascade of an aryl carbene complex with a propargyl enyne has the potential for providing access to 2*H*-benzo[*h*]-chromenes (naphthopyrans) **43** in a single step (Scheme 6). The 2*H*-benzo[*h*]chromene core **45** is quite common and occurs in a large number of natural and unnatural products.[28] One of the simplest members is the natural product lapachenole **46** which has been isolated from different sources,

dx.doi.org/10.1021/ja210655g | J. Am. Chem.Soc. 2012, 134, 1357−1362

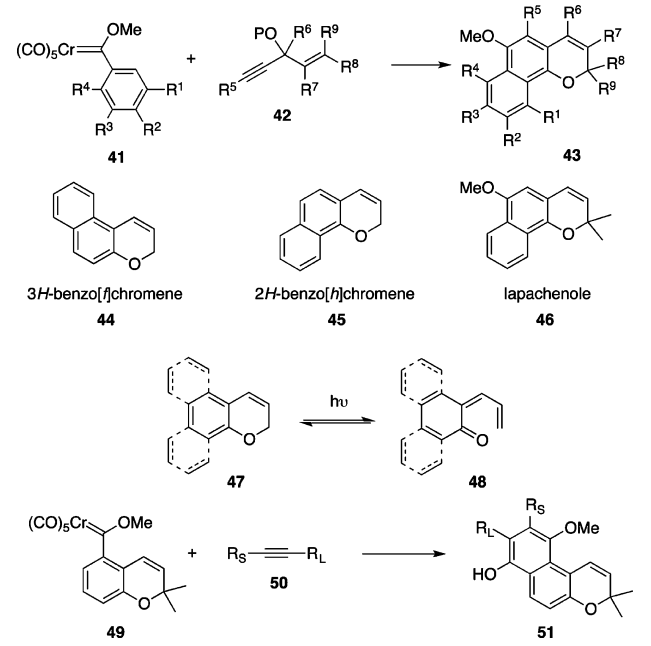
Scheme 5



solvent	x	28 : 39	% yield 28
CH_3CN	0	38 : 62	65 [a]
CH_2Cl_2	0	84 : 16	74 [b]
CH_2Cl_2	10	91 : 9	—
CH_2Cl_2	50	91 : 9	—
CH_2Cl_2	100	≥ 95 : 5	—

[a] After treatment of the mixture of **28** and **29** with triflic acid. [b] Isolated yield of **28** without treatment with triflic acid

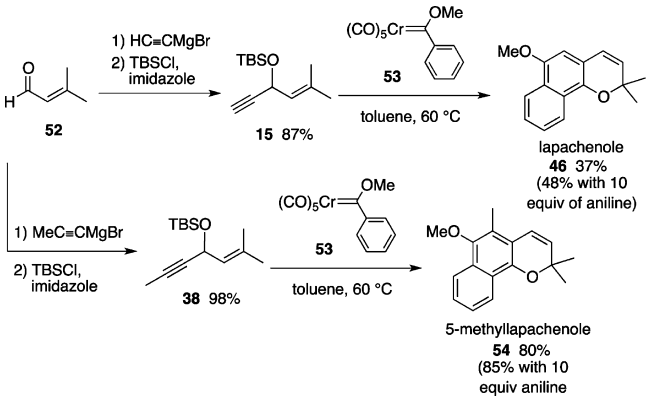
Scheme 6



including *Avicennia rumphiana*.[29] This compound has been used as a fluorescent photoaffinity label[30] and has been shown to have cancer chemopreventitive activity.[29] It occurs in *Tabebuia heptaphylla* which is the source of the Paraguayan traditional medicine "tayï pytá" used in the treatment of wounds, cancer, and inflammations.[31] Both 2*H*-benzo[*h*]-chromenes **45**[30] and 3*H*-benzo[*f*]chromenes **44**[32] are of interest for their photochromic properties which are associated with photoinduced electrocyclic ring opening to *o*-quinone methides. We have previously reported an approach to 3*H*-benzo[*f*]chromenes via the simple benzannulation reaction of a chromene carbene complex and an alkyne.[33] This approach required the preparation of the chromene carbene complex **49** which was accomplished in six steps from *o*-methoxybenzaldehyde. The proposed route to 2*H*-benzo[*h*]chromenes would potentially be much more efficient since aryl carbene complex of the type **41** can be prepared in one step from the corresponding aryl bromide or iodide in good to excellent yields.

The key reaction for the synthesis of lapachenole via the benzannulation/*o*-quinone methide formation/electrocyclization cascade is that of carbene complex **53** and enyne **15** (Scheme 7). This reaction only produced the natural product in

Scheme 7

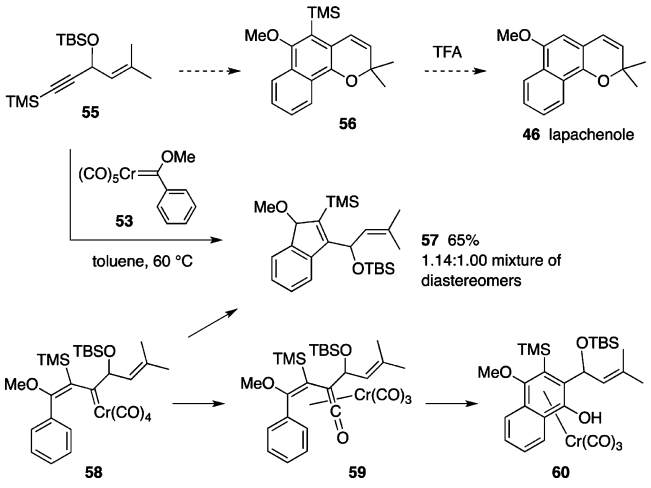


37% yield, but it was found that the yield could be improved slightly to 48% if the reaction was performed in the presence of 10 equiv of aniline. Despite the moderate yield, it represents a very short synthesis of lapachenole: Two steps from bromobenzene or two to three steps from the commercially available prenal.[34] No significant by-products were observed to form along with the desired product lapachenole. Collection of other fractions from the silica gel column yielded a complexed mixture of compounds, none of which were predominate or separable. This is suggestive of incorporation of multiple units of the enyne, and this has been observed in other reactions to produce phenols, trisubstituted benzenes or oligomers.[35] Previous experience suggests that if this was the case, improved yields could be achieved by contolling concentration. However, in the present case, there was not a great response in the yield to changes in the concentration. The yield was 37% at 0.035 M and, while this fell as expected when the concentration was increased (26% at 0.1 M), it also fell when the concentration was reduced (31% at 0.005 M). If multiple insertions of alkyne **15** containing a terminal alkyne function are responsible for the moderate yields of lapachenole, then increased yields would be expected for similar reactions with internal alkynes. Indeed, the synthesis of 5-methyllapachenole **54** was possible with a much higher yield (85%) than lapachenole.

An alternative approach to lapachenole **46** that has the potential to be more efficient is the reaction of the carbene complex **53** with the enyne **55** bearing an internal alkyne as the trimethylsilylated analog of enyne **15** (Scheme 8). In analogy with enyne **38** bearing an internal alkyne, the product from the reaction of enyne **55** would be expected to be the naphthopyran **56** from which the trimethylsilyl group could be removed by protonolysis to give lapachenole **46**. However, it was found that the reaction of the silylated enyne **55** gave the indene product **57** rather than the expected naphthopyran **56**. The indene **57** was isolated in 65% yield as a 1.14:1.0 mixture of diastereomers and was the only product that was observed that was mobile on TLC. This type of five-membered ring cyclized product is perhaps the most common of the many side products that have been observed in the benzannulation reaction.[20] There is a tendency to see increased amounts of five-membered ring products with increased steric bulk of the two acetylene substituents. Mechanistically, this reaction should occur by initial insertion of the alkyne function

dx.doi.org/10.1021/ja210655g | *J. Am. Chem.Soc.* 2012, 134, 1357–1362

Scheme 8

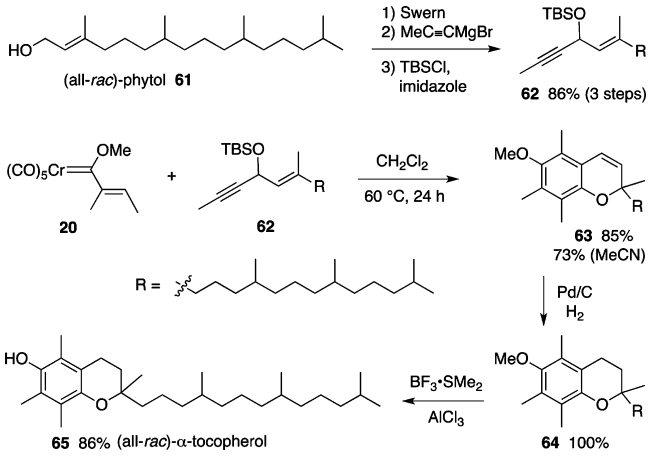


of **55** into the metal-carbene bond in carbene complex **53** to give the vinyl carbene complexed intermediate **58**. The subsequent events normally would be migratory insertion of a CO ligand to give the chromium complexed vinyl ketene **59** and then electrocyclic ring closure to give the phenol chromium tricarbonyl complex **60**. Apparently, in the case of the vinyl carbene complexed intermediate **58**, there is a preference for direct cyclization to **57** rather than CO insertion to give **59**. The reasons for this are not clear, but one might expect that it may be related to the increase in bond angles for the sp^2 carbons of **58**, as cyclization occurs to give a five-membered ring and the associated decrease in strain energy as the large substituents move further apart.

4. SYNTHESIS OF VITAMIN E VIA THE BENZANNULATION/*O*-QUINONE METHIDE FORMATION/ELECTROCYCLIZATION CASCADE

As an illustration of the utility of the benzannulation induced cascade in the synthesis of chromenes, we undertook the synthesis of vitamin E outlined in Scheme 9.[36,37] The most

Scheme 9



commercially important form of vitamin E is (all-*rac*)-α-tocopherol **65** which is a mixture of eight stereoisomers.[37] The synthesis begins with a Swern oxidation of commercially available (all-*rac*)-phytol **61** followed by reaction of the α,β-unsaturated aldehyde with propynyl Grignard and then protection of the alcohol as a TBS ether to give the key enyne **62**. The chromene **63** is generated in 85% yield directly from the reaction of carbene complex **20** and the internal alkyne **62**. Reduction of the double bond is quantitative, and cleavage of the methyl ether with $BF_3{\cdot}SMe_2$ complex and aluminum chloride gives vitamin E in 73% overall yield from the carbene complex **20**.

5. CONCLUSIONS

The formation of chromenes from the reaction of a chromium carbene complex with a 3-siloxypent-4-en-1-yne has been shown to proceed via an initial benzannulation reaction that produces a chromium tricarbonyl complexed phenol. Spontaneous loss of a silanol generates an *o*-quinone methide that undergoes a six-electron electrocyclic ring closure to the chromene. The reaction is general giving good to high yields of a variety of 4-alkoxychromenes with mono- and di-substituted alkenyl carbene complexes and mono-, di-, and trisubstituted 3-silyloxypent-4-en-1-ynes. The primary product of the reaction is a chromium tricarbonyl complexed chromene that can be isolated but is typically stripped of the metal either by ligand exchange with acetonitrile as solvent or by workup with an oxidizing agent. The reaction can also be extended to aryl carbene complexes for the synthesis of 2-*H*-benzo[*h*]-chromenes, and this process was employed in the synthesis of lapachenole and 5-methyllapachenole. The benzannulation/*o*-quinone methide formation/electrocyclization cascade was featured in a synthesis of vitamin E in which both rings of vitamin E were generated in a single step.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

This work was supported by NSF grant CHE-0750319 and the National Institute of General Medical Sciences (GM094478).

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