A Three-Component Coupling Approach to Cyclopentanoids

Barry M. Trost* and Anthony B. Pinkerton

Department of Chemistry, Stanford University, Stanford, California 94305

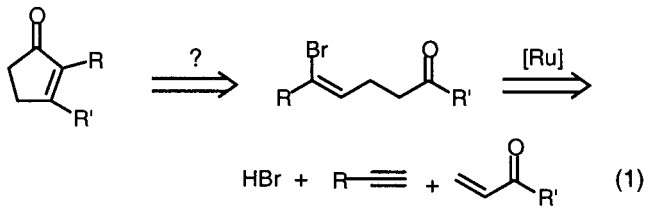
bmtrost@stanford.edu

Received June 12, 2001

A new approach to 2,3-disubstituted cyclopentenones has been developed. This approach consists of a two-step protocol involving the cyclization of a *Z*-vinyl bromide under Barbier type conditions to form a cyclopentenol, which is then oxidatively rearranged to generate the cyclopentenone. The *Z*-vinyl bromide is in turn derived from a ruthenium catalyzed three-component coupling of an alkyne, an enone, and a HBr equivalent. A range of 2,3-disubstituted cyclopentenones has been generated, including short syntheses of jasmone and dihydrojasmone. Further applicability of this strategy is shown in the total syntheses of tetrahydrodicranenone B, rosaprostol, and a selective COX-2 inhibitor.

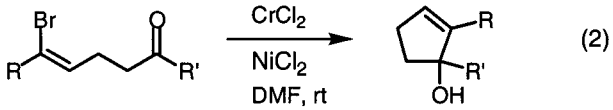
Introduction

Cyclopentanoid natural products, such as the jasmonates[1] and prostaglandins,[2] are a diverse and biologically significant class of compounds in which there has been considerable interest. Because of these and other natural products and pharmaceuticals containing cyclopentyl structures there has been intense development of methodology to construct such moieties.[3,4] Cyclopentenones are particularly useful precursors for the synthesis of various cyclopentyl compounds due to the versatility of their functionality. Because of this versatility, there have been many methods for their synthesis, including more classical methods such as the aldol reaction,[5] as well as newer methods such as the Nazarov cyclization,[6] the Pauson−Khand reaction,[7] and other methods.[8] This paper discusses the development of a synthesis of cyclopentenones from *Z*-vinyl bromides, which in turn are derived from a ruthenium catalyzed three-component coupling as illustrated in Scheme 1.[10] The general retrosynthetic idea is shown in eq 1. Thus, cyclopentenones then would derive from three simple building blocks: an enone, an alkyne, and the equivalent of HBr using a bromide salt and water as a surrogate.



(1)

Cyclopentenol Formation. We initially examined the cyclization of *Z*-vinyl bromides, with a 1,5 juxtaposition between the vinyl bromide moiety and the carbonyl group, to give cyclopentenols (eq 2). The prospect of using



(2)

a lithium−halogen exchange with an organolithium was unappealing due to concerns of chemoselectivity. A Barbier type protocol looked more promising. The conditions of Nozaki and Kishi involving $CrCl_2$ and $NiCl_2$ were most appealing because of their mildness.[11] Their

(1) For a recent review, see: Beale, M. H.; Ward, J. L. *Nat. Prod. Rep.* **1998**, 533.

(2) *The Synthesis of Prostaglandins*; Mitra, A.; J. Wiley-Interscience: New York, 1977. *Prostaglandin Synthesis*; Bindra, J. S., Bindra, R.; Academic Press: London, 1977.

(3) For a few recent references, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026. Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 5547. Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. Yamamoto, Y.; Matsumi, D.; Hattori, R.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 3224. Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 2178. Taber, D. F.; Yu, H.; Incarvito, C. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 13285. Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998**, *120*, 10782. Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637, 7641.

(4) For some reviews, see: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. Geis, O.; Schmalz, H. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164. Schore, N. E. In *Comprehensive Orgnometallic Chemistry II*; Abel, E. W., Stone, F. G., Wilkinson, G., Eds.; Elsevier: New York, 1995; Vol. 12, p 703. Padwa, A.; Krumpe, K. E. *Tetrahedron.* **1992**, *48*, 5385.

(5) Wenkert, E.; Greenberg, R. S.; Raju, M. S. *J. Org. Chem.* **1985**, *50*, 4681. Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 2614.

(6) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 6.3, pp 752−781. Chenard, B. L.; Van Zyl, C. M.; Sanderson, D. R. *Tetrahedron Lett.* **1986**, *27*, 2801. Hiyama, T.; Shinoda, M.; Tsukanaka, M.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1010. Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.

(7) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 9.1, pp 1037−1062. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026. See also: Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 5547. Negishi, E.-I. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 9.5, pp 1163−1183.

(8) Büchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021. Hayakawa, Y.; Yokoyama, K.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1799. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

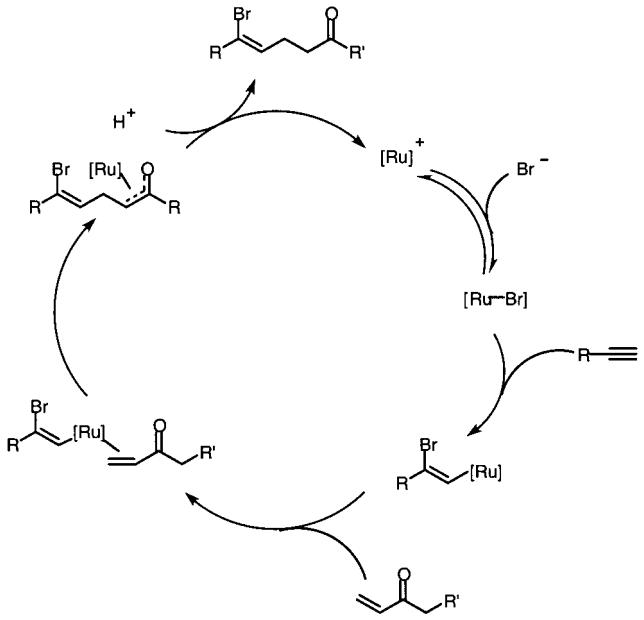
(9) A portion of this work has been published: Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601. See also: Trost, B. M.; Pinkerton, A. B. *Tetrahedron Lett.* **2000**, *41*, 9627.

(10) Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360.

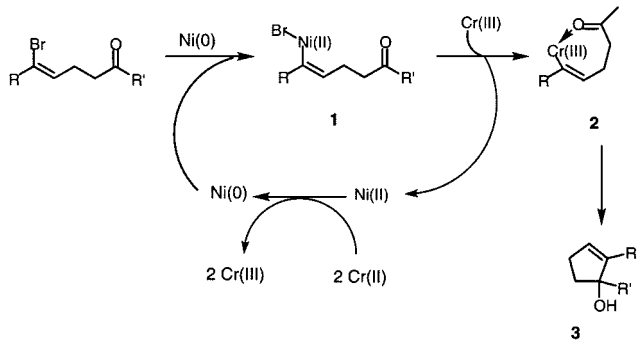
(11) (a) For a review, see: Cintas, P. *Synthesis* **1992**, 248. (b) For a recent intramolecular example and representative procedure, see: Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.

10.1021/jo010593b CCC: $20.00
Published on Web 10/13/2001

Scheme 1. A Ru-Catalyzed Three-Component Coupling



Scheme 2. Proposed Mechanism for the Nozaki–Kishi Reaction

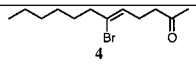
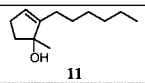
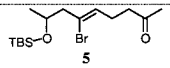
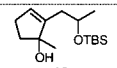
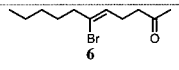
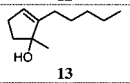
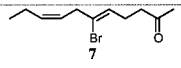
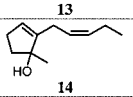
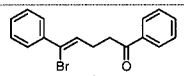
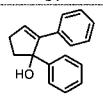
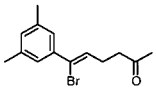
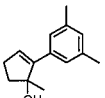
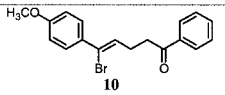
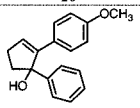


reported failure in intermolecular reactions with ketones seemed ominous; however, the prospect that such an acceptor might be better if the reaction were intramolecular induced us to at least try the experiment despite our reservations. In contrast to the intermolecular reaction, the corresponding intramolecular reaction was found to work well in these studies. A recent report using a bipyridyl-based ligand to give efficient intermolecular reaction with ketones has been disclosed,[12] but this was not necessary in our intramolecular case.

The proposed mechanism for this reaction is shown in Scheme 2. As shown in the scheme, nickel(0) inserts into the vinyl halide bond to form vinyl nickel **1**. This then transmetalates to chromium(III) to give vinyl chromium **2**, which attacks the carbonyl group to form cyclopentenol **3**. The nickel(II) is reduced by chromium(II) to reform the nickel(0) and chromium(III). One of the reasons that the ketone substrate may be more reactive in this case is potential coordination as depicted in **2**.

As shown in Table 1, the intramolecular Nozaki–Kishi cyclization works quite well with a range of substrates under quite standard conditions. Thus, no optimization was performed. Saturated aliphatic compounds (entries 1 and 3) can be used as substrates, as well as olefins (entry 4). Silyl-protected alcohols (entry 2) are compatible. Steric hindrance on the vinyl partner is tolerated (entries 5–7), as well as on the ketone portion (entries 5 and 7). It should be noted that these cyclopentenol products are quite sensitive, and even mild acid (for example deuteriochloroform that has not been basified) will lead to elimination to the cyclopentadiene. However, they can be subjected to silica gel chromatography with no apparent decomposition.

Table 1. Formation of Cyclopentenols from *Z*-Vinyl Bromides

Entry	Vinyl Halide	Z/E	Product	Yield (%)
1	 **4**	5.6/1	 **11**	70
2	 **5**	6.0/1	 **12**	64[a]
3	 **6**	4.1/1	 **13**	74
4	 **7**	4.2/1	 **14**	74
5	 **8**	--[b]	 **15**	83
6	 **9**	--[b]	 **16**	75
7	 **10**	--[b]	 **17**	60[c]

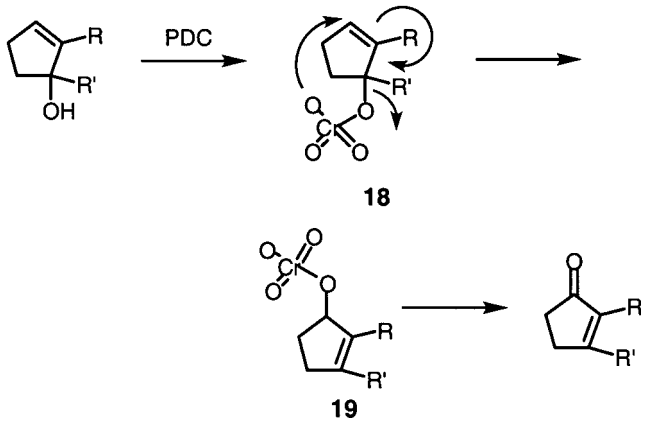
[a] i. A 1:1 diastereomeric ratio of cyclopentenols was obtained. ii. A 23% yield of the dehalogenated olefin was also obtained, as a mixture of isomers. [b] Exclusively the *Z*-isomer. [c] Trace amounts of dehalogenated olefin were observed, along with 20% unreacted starting material.

In all cases with *Z*/*E* mixtures, some of the dehalogenated *E* olefin (which cannot cyclize) is observed. However, only in the case of entry 2 was a substantial amount of the dehalogenated *E* olefin obtained. This could be due to the bulky O-TBS group slowing the cyclization, as indeed a mixture of *E* and *Z* dehalogenated olefin was seen. This steric effect is seen in entry 7, where a lower yield of cyclopentenol was obtained. However, in this case the lower yield could also be attributable to the instability of this compound due to the electron rich aromatic ring. The mildness of the reaction conditions is clearly indicated by the ability to form such products at all considering their extremely sensitive nature, especially in the cases of entries 5 and 7.

In general, the cyclopentenols were characterized by the appearance of an alcohol stretch at approximately 3400 cm^{-1} in the IR spectrum. Furthermore, there was the appearance of a characteristic olefin resonance at ~δ 5.5 in the proton NMR and olefin signals at ~δ 150 and ~δ 130 as well as the tertiary alcohol carbon (~δ 85) in the carbon NMR spectra. Finally, elemental analysis confirmed the elemental composition and the lack of bromine.

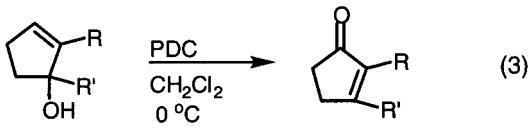
(12) Chen, C. *Synlett* **1998**, 1311. See also: Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.

Scheme 3. Proposed Mechanism for the Oxidative Rearrangement



Oxidative Rearrangement of Cyclopentenols To Give Cyclopentenones. After formation of the cyclopentenols, we investigated the oxidative rearrangement of the cyclopentenols to give cyclopentenones. As described in the literature, chromium oxidations such as those using pyridinium dichromate (PDC) in methylene chloride[13] typically effect this transformation. The mechanism proposed for this reaction is the initial formation of the chromate ester **18** from the tertiary alcohol followed by allylic rearrangement to the chromate ester of the secondary alcohol (**19**). Typical fragmentation of the resultant chromate ester delivers the ketone (Scheme 3).

Following the literature method, the reactions were run according to eq 3, and the results are summarized in Table 2. As shown in the table, good yields are obtained in all cases. In general an excess of PDC (1.5−2 equiv) was employed.



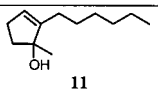
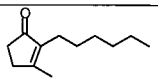
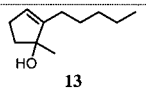
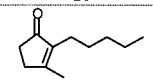
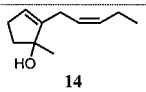
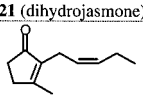
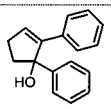
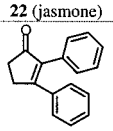
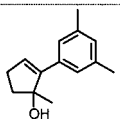
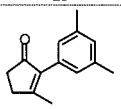
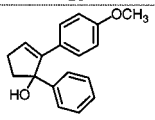
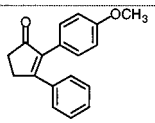
(3)

The cyclopentenones were readily characterized by the disappearance of an alcohol stretch in the IR spectrum and the appearance of an enone stretch at approximately 1700 cm $^{-1}$. The carbon NMR spectra showed signals indicative of an enone at ~δ 210, 170, and 140.

This process represents a novel and convergent method of five-membered ring synthesis that we felt could be developed into a general entry into cyclopentanoid natural products. Table 2, entries 2 and 3, illustrate the synthesis of dihydrojasmone and jasmone, respectively. We turned our attention to illustrating this potential more fully.

Total Synthesis of Cyclopentanoid Compounds. For our first target, we chose tetrahydrodicranenone B (**26**),[14,15] a cyclopentenone fatty acid isolated from the Japanese moss *Leucobryum scabrum* that shows antimicrobial and antihypertensive properties. Earlier syntheses of tetrahydrodicranenone B used five-membered ring precursors such as methyl jasmonate or 6-methoxyindanone. Scheme 4 illustrates a retrosynthetic analysis that derives from this newly developed cyclopentenone synthesis.

Table 2. Synthesis of Cyclopentenones

Entry	Cyclopentenol	Product	Yield (%)
1	 **11**	 **20**	63
2	 **13**	 **21** (dihydrojasmone)	70
3	 **14**	 **22** (jasmone)	74
4	 **15**	 **23**	83
5	 **16**	 **24**	68
6	 **17**	 **25**	72

The first subunit synthesized was the known[16] enyne **29**. Starting from *cis*-2-penten-1-ol (**31**), the alcohol was mesylated in high yield under standard conditions. This was followed by a copper(I)-mediated displacement[17] by trimethylsilylacetylene to give the TMS-protected enyne **33**, albeit as a 3:1 mixture of the desired product and the regioisomer resulting from S_N2' addition (determined by NMR spectroscopy). Lowering the amount of copper iodide used (from 1 equiv) eventually raised the ratio to 9:1, but at the expense of yield (for example, using 10% copper iodide, a 9:1 ratio was obtained, but only in 40% yield). Thus, the 3:1 mixture was used in subsequent steps. The silyl group was removed using TBAF buffered with acetic acid (when only TBAF was employed, extensive isomerization to the conjugated product was seen) to give the volatile enyne **29**, which was isolated by extraction into pentane followed by careful removal of the pentane via distillation (Scheme 5). Attempts to remove the silyl group under conditions to facilitate purification, such as sonicating **33** with aqueous KF in a variety of solvents were unsuccessful.

Enone **30** was synthesized in a very straightforward manner from commercially available azelaic acid monomethyl ester. The acid was converted to the acid chloride under standard conditions and then subjected without

(13) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. Majetich, G.; Song, J.-S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030. Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.

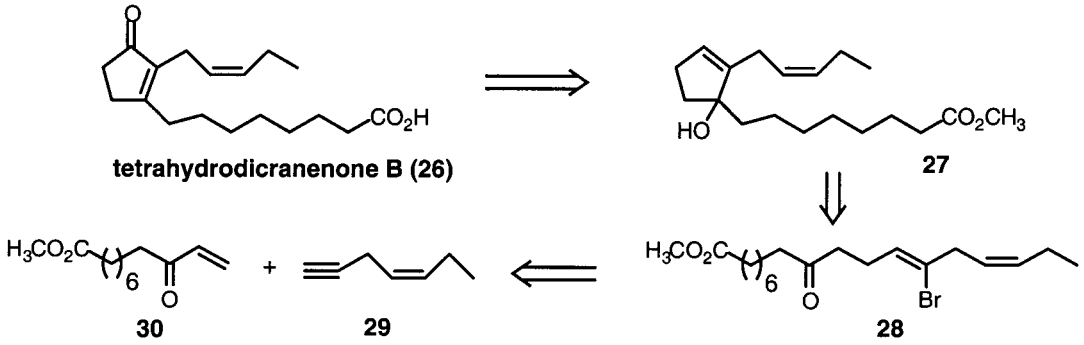
(14) Sakai, K.; Fujimoto, T.; Yamashita, M.; Kondo, K. *Tetrahedron Lett.* **1985**, *26*, 2089. Ichikawa, T.; Namikawa, M.; Yamada, K.; Sakai, K.; Kondo, K. *Tetrahedron Lett.* **1983**, *24*, 337.

(15) For syntheses, see: Ichikawa, T.; Namikawa, M.; Yamada, K.; Sakai, K.; Kondo, K. *Tetrahedron Lett.* **1983**, *24*, 337. Moody, C. J.; Roberts, S. M.; Toczek, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1292.

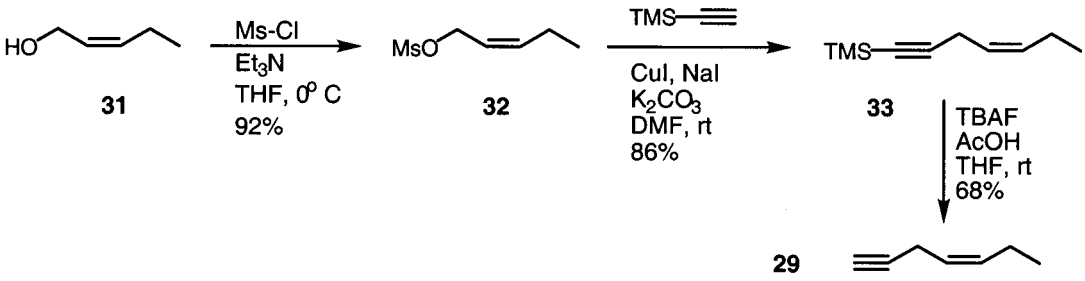
(16) Billington, D. C.; Blandon, P.; Helps, I. M.; Pauson, P. L.; Thomson, W.; Willison, D. *J. Chem. Res.* **1988**, *10*, 2601.

(17) Lapitskaya, M. A.; Vasiljeva, L. L.; Pivnitsky, K. K. *Synthesis* **1993**, 65. A method employing Bu_4NCl instead of NaI gave similar results, see: Jeffrey, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1992**, *33*, 5757.

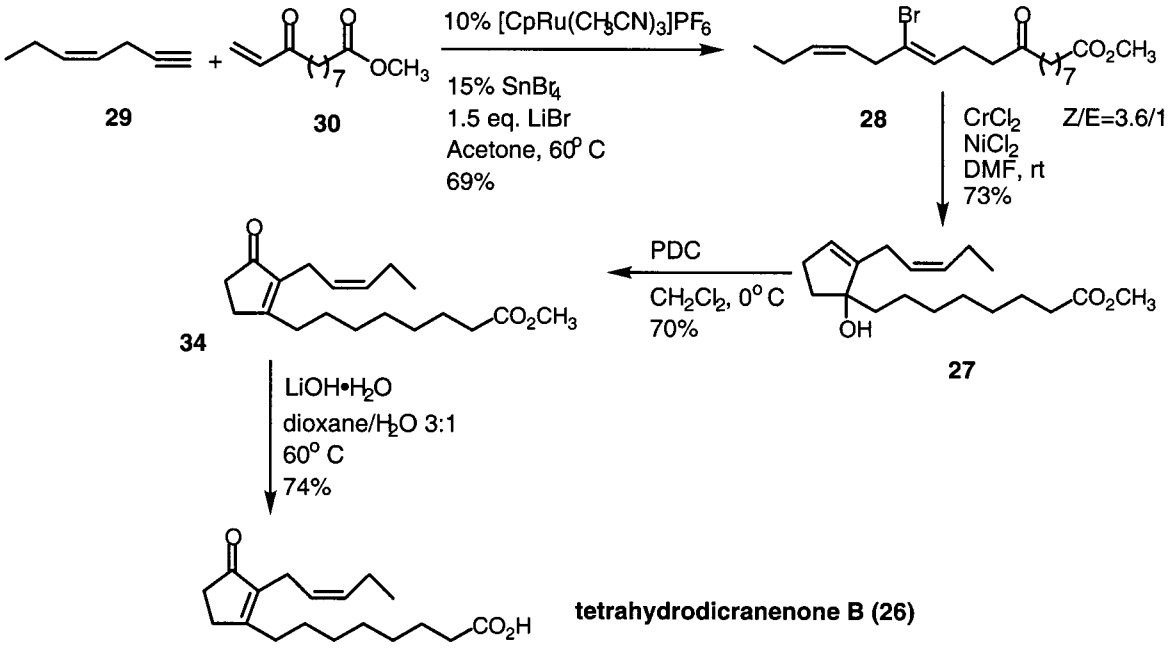
Scheme 4. Retrosynthetic Analysis of Tetrahydrodicranenone B



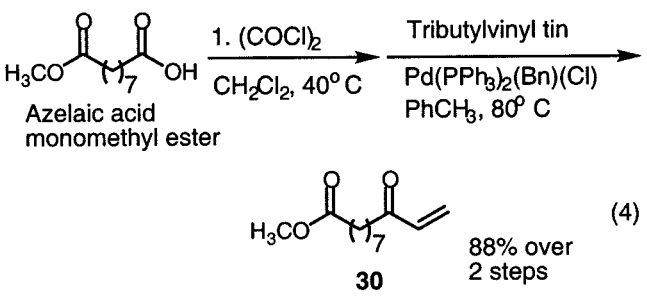
Scheme 5. Synthesis of Enyne 29



Scheme 6. Synthesis of Tetrahydrodicranenone B



purification to a Stille coupling[18] with tributylvinyl tin to give enone **30** in an 88% yield over two steps (eq 4).

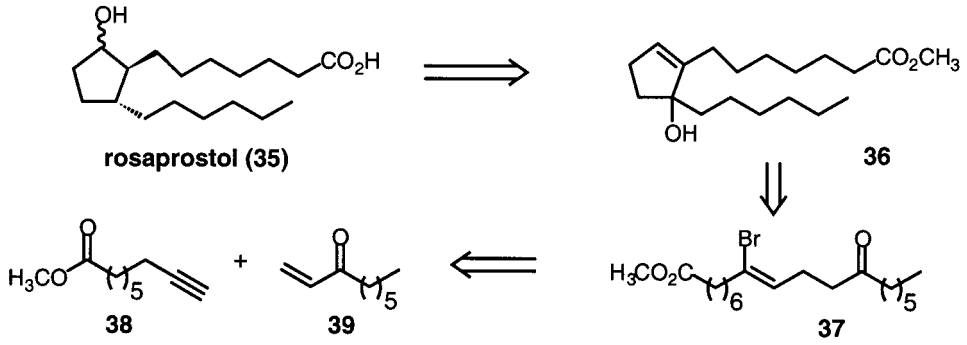


(4)

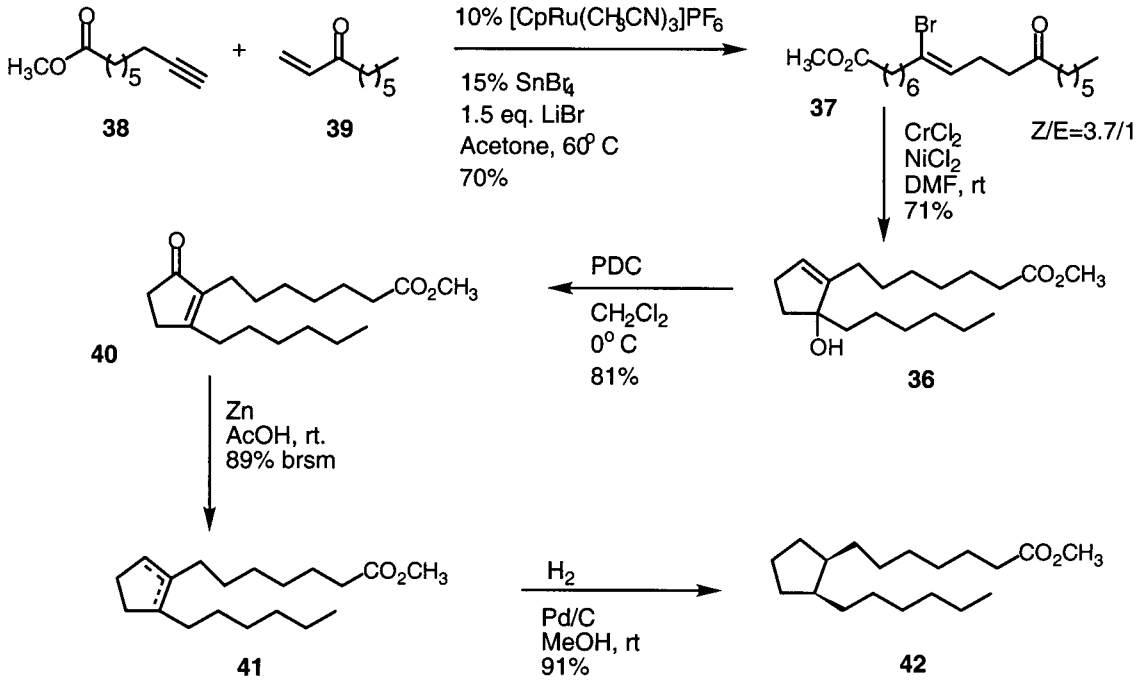
With the two subunits in hand, the stage was set for formation of the key vinyl bromide intermediate **28** (see Scheme 6). Subjecting the two subunits to our standard conditions[10] gave bromide **28** in 69% yield with a *Z*/*E* ratio of 3.6/1, values which are consistent with our earlier work. The use of $(CH_3)_4NBr$ in place of LiBr gave a *Z*/*E* ratio of 8.0/1, but in a yield of only 28%. Thus, the 3.6/1 mixture was used. The vinyl bromide was then reacted under Nozaki–Kishi conditions[11] to give an intramolecular cyclization yielding 73% of cyclopentenol **27**. Some of the dehalogenated cis olefin was observed, presumably coming from the *E*-vinyl bromide. The allylic alcohol was oxidatively rearranged[13] to give the cyclopentenone **34**

(18) For a representative procedure, see: Darwish, I. S.; Patel, C.; Miller, M. J. *J. Org. Chem.* **1993**, *58*, 6072. For a review, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998.

Scheme 7. Retrosynthesis of Rosaprostol



Scheme 8. Synthesis of Vinyl Bromide 37 and Cyclization



in 70% yield. All that remained for completion of the synthesis was hydrolysis of the ester to the acid, which proceeded in 74% yield using lithium hydroxide in a dioxane/water mixture, to give tetrahydrodicranenone B. The spectral data of this synthetic sample were consistent with those of the natural product.

We chose the cyclopentanol rosaprostol (**35**),[19] an antiulcer drug, as our next target. Marketed as the sodium salt under the name Rosal, it displays gastric antisecretory activity devoid of many of the side effects of other prostanoids. Earlier syntheses of rosaprostol have been reported from several groups.[20] Scheme 7 depicts the retrosynthetic analysis based on this new strategic concept. It is to be noted that rosaprostol is a diastereomeric mixture at the hydroxyl-bearing carbon.

The two subunits necessary for vinyl bromide formation were synthesized in a simple fashion. Fischer esterification of commercially available 8-nonynoic acid provided a quantitative yield of alkynoate **38**. Enone **39** was made from heptanoic acid using the acid chloride formation/Stille coupling procedure as described in eq 4 and is a known compound made in a similar fashion.[21]

The two subunits were coupled under our standard conditions[10] to form vinyl bromide **37** in 70% yield with a *Z*/*E* ratio of 3.7/1 (see Scheme 8). The vinyl bromide was the reacted under Nozaki−Kishi conditions[11] to give a 71% yield of cyclopentenol **36**, with traces of the dehalogenated *E* olefin also observed. At this point, **36** was oxidatively rearranged following the known procedure[13] to give the cyclopentenone **40** in 81% yield. Initial attempts to reduce the enone using zinc/acetic acid[22] gave instead deoxygenated products **41** (as a mixture of double bond isomers), which could be further reduced using catalytic hydrogenation to give the *cis*-disubstituted cyclopentane **42**.

Altering the route to rosaprostol, reduction of the olefin of the cyclopentenone **40** was accomplished using catalytic hydrogenation over Pd/C to give cyclopentanone **43**

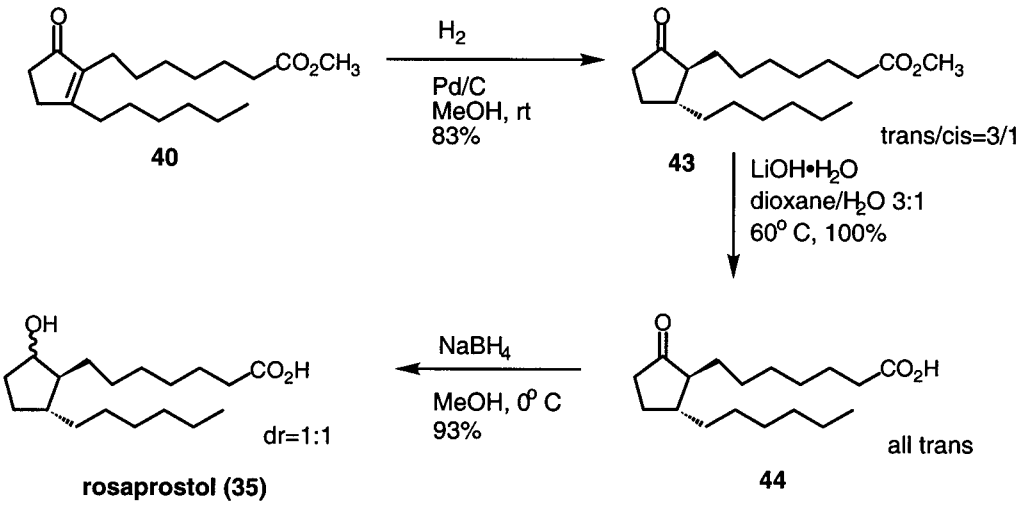
(19) Valcavi, U.; Caponi, R.; Brambilla, A.; Palmira, M.; Minoja, F.; Bernini, F.; Musanti, R.; Fumagalli, R. *Arzneim-Forsch.* **1982**, *32*, 657. Foschi, D.; et al. *Prostaglandins Leukotrienes Med.* **1984**, *15*, 147.

(20) Mikolajczyz, M.; Zurawinski, R. *J. Org. Chem.* **1998**, *63*, 8894. Tanimori, S.; Kainuki, T.; Nakayama, M. *Biosci. Biotech. Biochem.* **1992**, *56*, 1807. Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175. Valcavi, U. *Chem. Abstr.* **1976**, *85*, 32512q. Valcavi, U.; Innocenti, S.; Bosone, E.; Farina, P.; Marotta, V.; Zabban, G. B. Eur. Pat. Appl. EP 155,392; *Chem. Abstr.* **1986**, *104*, 168263c.

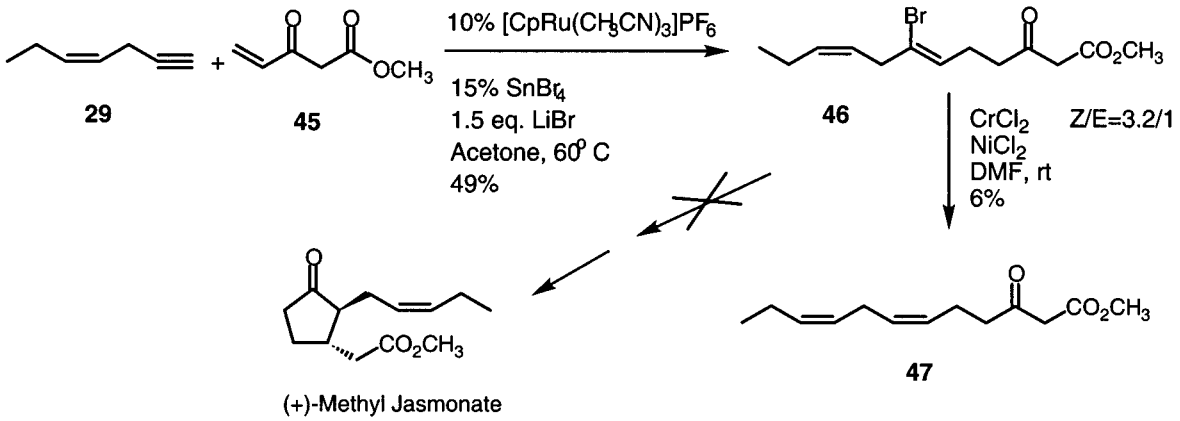
(21) Galatsis, P.; Millan, S. D.; Faber, T. *J. Org. Chem.* **1993**, *58*, 1215. Nakahira, H.; Ryu, I.; Ikebe, M.; Oku, Y.; Ogawa, A.; Kambe, N.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1992**, *57*, 17.

(22) Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152. Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781.

Scheme 9. Completion of the Synthesis



Scheme 10. Approach to Methyl Jasmonate



in 83% yield as a 3/1 *trans*/*cis* mixture (Scheme 9). This ratio was determined by NMR spectroscopic analysis of the methine signal α to the carbonyl group at δ 2.34−2.29. This ratio was, in the end, irrelevant since the next step, base-catalyzed hydrolysis of the ester, gave rapid equilibration to the trans substituted acid **44** in quantitative yield. To complete the synthesis, the cyclopentanone was reduced with sodium borohydride following the published procedure[20] to give a 1:1 mixture of the *cis*−*trans* and *trans*−*trans* products whose spectral properties were consistent with literature values.

We next turned to the cyclopentanone natural product methyl jasmonate. Methyl jasmonate is an extremely important factor in plant development, as well as a cell-signaler in the defense response of plants. It is also commercially valuable as a fragrance. Because of this it has been the subject of many synthetic efforts.[23]

Our approach to methyl jasmonate focused (as did the previous synthesis) on the generation of a cyclopentenone followed by reduction to the cyclopentanone. This required the coupling of the previously described alkyne **29** with Nazarov's reagent **45**, whose synthesis employed the method of Zibuck.[24] This compound was quite unstable and could not be stored longer than several days.

Nazarov's reagent and the enyne **29** were then reacted under our standard vinyl bromide conditions to form vinyl bromide **46** in a modest 49% yield as a 3.2/1 *Z*/*E* mixture (Scheme 10). This moderate yield is most likely due to the instability of Nazarov's reagent to the Lewis acidic conditions. Unfortunately, none of the desired cyclopentenol was obtained from the Nozaki−Kishi reaction. Rather, only a low yield of the dehalogenated *E*-olefin **47** was obtained. The acidity of the β-ketoester is a likely culprit for the failure of the Nozaki−Kishi version of the Barbier reaction. It is also possible that the initial adduct is unstable to a retro aldol reaction. Nevertheless, the success of employing the Nazarov reagent in the three component coupling is most gratifying.

The last target chosen was the diarylcyclopentenone **48**, which was developed by Merck as a potent and selective inhibitor of the COX-2 enzyme[25] and is structurally related to the osteoarthritis medication Vioxx (Figure 1).

Our synthetic strategy for cyclopentenone **48** focused on preparation of the requisite vinyl bromide followed by cyclization then oxidation. The necessary precursors, alkyne **49** and enone **50**, were synthesized in a simple fashion. The enone **50** was accessed in one pot from the commercially available acid **51** by first converting it to the acid chloride and then subjecting it to a Stille type cross-coupling as before (eq 5). Interestingly, attempts to perform the Stille cross-coupling with the sulfone

(23) See ref 1.
(24) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717.
(25) Zhao, D.; Xu, F.; Chen, C.-Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J.; Black, C.; Ouimet, N.; Prasit, P. *Tetrahedron* **1999**, *55*, 6001.

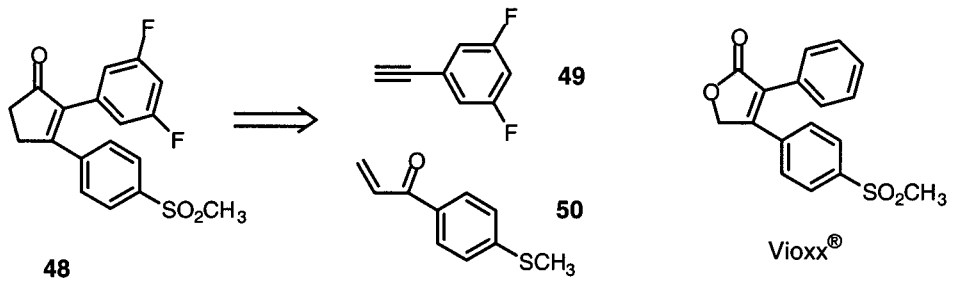
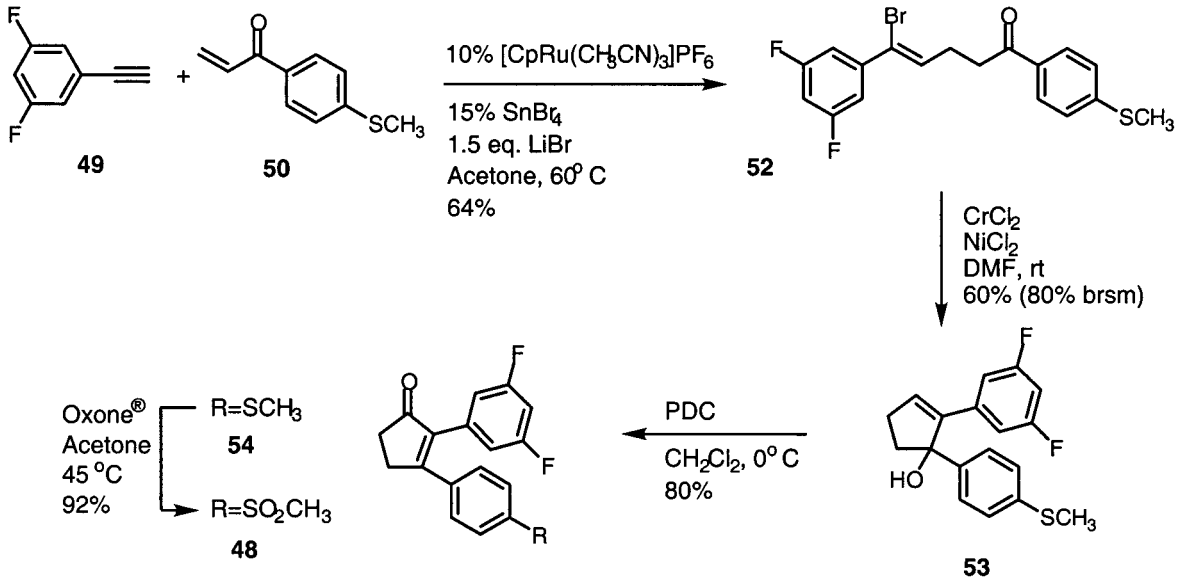
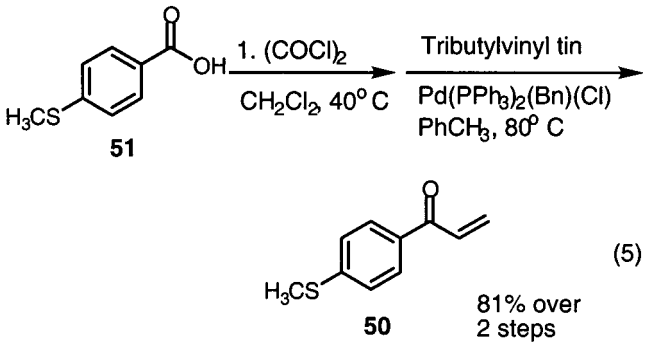


Figure 1. Selective COX-2 inhibitors.

Scheme 11. Completion of the Synthesis



(instead of the sulfide), to avoid an oxidation step later in the synthesis, gave only decomposition products. The known alkyne **49** was synthesized following the published procedure[26] in 68% yield for the two-step protocol of Sonogashira coupling and desilylation.



The synthesis of the COX-2 inhibitor **48** was then completed as shown in Scheme 11.[9] Alkyne **49** and enone **50** were reacted under the standard vinyl bromide conditions to form vinyl bromide **52** in 64% yield as exclusively the *Z*-isomer, a selectivity that has been seen with other aryl acetylenes.[9] Following the standard Nozaki–Kishi protocol, vinyl bromide **52** was then cyclized to cyclopentenol **53** in 60% yield (80% based on recovered starting material). This compound was found to be quite unstable (decomposing after several hours), probably due to the donating ability of the *S*-methyl group on the aryl ring. This additional destabilization makes the alcohol even more prone to eliminate to form the cyclopentadiene.

However, if cyclopentenol **53** was reacted immediately with pyridinium dichromate, cyclopentenone **54** could be formed in good yield (80%). At this point, our synthesis intercepts the previously published synthesis of this compound. All that remained was to oxidize the sulfide to the sulfone, which proceeded under the published conditions[25] using Oxone in acetone to give the target compound in 92% yield.

Conclusion

In conclusion, we have developed a general two-step procedure for the synthesis of 2,3-disubstituted cyclopentenones from vinyl bromides, which, in turn, are readily available from the Ru-catalyzed three-component coupling. The ease of access of both enones[27] and alkynes make this a very straightforward method. Therefore, this reaction compares quite favorably to the known methods of cyclopentenone synthesis, especially convergent methods such as the Pauson–Khand reaction and is a clear improvement over more linear approaches to cyclopentenones. Several limitations do exist, of course, mainly the ability to construct only 2,3-disubstituted cyclopen-

(26) Crisp, G. T.; Flynn, B. L. *J. Org. Chem.* **1993**, *58*, 6614. See also: Neenan, T. X.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 2489.

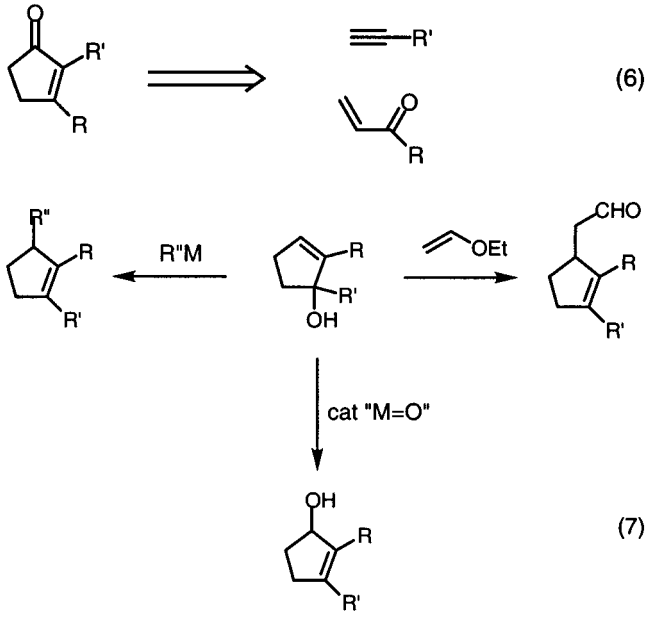
(27) For some other methods of enone synthesis, see: Floyd, J. C. *Tetrahedron Lett.* **1974**, *15*, 2877. Kim, B. M.; Guare, J. P.; Hanifin, C. M.; Arford-Bickerstaff, D. J.; Vacca, J. P.; Ball, R. G. *Tetrahedron Lett.* **1994**, *35*, 5153.

tenones rather than a full range of substitution patterns. Furthermore, some functional groups would not be tolerated under the Nozaki−Kishi reaction and the oxidative rearrangement, for example free alcohols.

However, the power of this approach has been exemplified by the rapid synthesis of the natural product tetrahydrodicranenone B, as well as the pharmaceutical agents rosaprostol and 2-(3,5-difluorophenyl)-3-(4-methanesulfonylphenyl)cyclopent-2-enone. A synthesis of tetrahydrodicranenone B was accomplished in a seven-step procedure from simple precursors (*cis*-2-penten-1-ol and azelaic acid monomethyl ester) in 14% overall yield. This compares very well with the other synthesis of this compound, which started with most of the carbons and required excessive functional group manipulation, especially oxidations and reductions.

Rosaprostol was synthesized in seven linear steps in 31% overall yield from simple precursors, 8-nonynoic acid and hexanoic acid. Although there are several other quite efficient syntheses and high-yielding syntheses of rosaprostol, our synthesis represents a more convergent approach as opposed to the rather linear approaces. Finally, COX-2 inhibitor **48** was synthesized in five linear steps from known compounds in a 30% overall yield. Although the Merck synthesis for this compound is very short and high yielding, and thus our synthesis offers no major advantage besides simpler starting materials, it is a much more flexible synthesis of this type of compound considering the wide range of different side chains that can be incorporated.

In conclusion, then, 2,3-disubstituted cyclopentenones can now be analyzed retrosynthetically as in eq 6. It should be noted that the cyclopentenols are also useful intermediates for a host of other transformations such as allylic couplings and Claisen rearrangements as well as simple allylic transposition of the OH group (eq 7). Thus, this new strategy can offer a general approach to a diverse range of five-membered ring targets.



Experimental Section

Preparation of 1-(4-Methylthiophenyl)propenone (50). To a solution of 4-(methylthio)benzoic acid (400 mg, 2.4 mmol) in CH_2Cl_2 was added oxalyl chloride (640 mg, 0.42 mL, 4.8 mmol). The reaction was heated to 40° C for 2 h, and then the volatile materials were removed in vacuo. The acid chloride was then redissolved in toluene (20 mL) and tributylvinyl tin (837 mg, 0.77 mL, 2.64 mmol) followed by palladium(II) bistriphenylphosphinebenzyl chloride (1.6 mg, 0.01mol %) were added. The mixture was heated to 80 ºC for 4 h and then cooled to room temperature. The toluene was evaporated by rotary evaporation and the crude mixture subjected directly to chromatography on silica gel (4/1 petroleum ether/ethyl ether) to give 348 mg product (81% over two steps).

White solid, mp = 54−56 °C. R_f = 0.38 (4/1 petroleum ether/ethyl ether). IR (neat): 1657, 1605, 1589 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.8, 2H), 7.28 (d, J = 8.3, 2H), 7.15 (dd, J = 17.1, 10.8, 1H), 6.43 (dd, J = 17.1, 1.7, 1H), 5.90 (dd, J = 10.5, 1.7, 1H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.7, 146.0, 133.5, 132.0, 129.8, 129.1, 125.0, 14.8. Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.51; H, 5.70; S, 18.13.

Preparation of 5-Bromo-5-(3,5-difluorophenyl)-1-(4-methylsulfanylphenyl)pent-4-en-1-one (52). The alkyne **49** (111 mg, 0.80 mmol) and the vinyl ketone **50** (150 mg, 0.84 mmol) in acetone (reagent grade, not distilled) (1.6 mL) was added to $[CpRu(CH_3CN)_3]PF_6$ (34.9 mg, 0.08 mmol), stannic bromide (52.5 mg, 0.12 mmol), and lithium bromide (104.3 mg, 1.20 mmol) in a pressure tube. The tube was capped and then heated to 60 °C with stirring for 2 h. The reaction was then cooled to room temperature and chromatographed directly on silica gel (8/1 petroleum ether/ethyl ether) to give 204 mg product (64%).

Viscous yellow oil. R_f = 0.35 (8/1 petroleum ether/ethyl ether). IR (neat): 1682, 1622 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.6, 2H), 7.26 (d, J = 8.6, 2H), 7.05 (dd, J = 8.6, 2.3, 2H), 6.73 (tt, J = 8.7, 2.3, 1H), 6.44 (t, J = 7.1, 1H), 3.16 (t, J = 7.1, 2H), 2.77 (q, J = 7.1, 2H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.6, 162.5 (dd, J = 248.9, 12.8), 146.1, 142.6 (t, J = 9.6), 132.8, 132.4, 128.4, 124.9, 123.6, 110.5 (dd, J = 20.3, 6.4), 103.6 (t, J = 25.1), 36.5, 27.0, 14.7. Anal. Calcd for $C_{15}H_{15}BrF_2OS$: C, 54.42; H, 3.87; S, 8.07. Found: C, 54.25; H, 3.95; S, 8.21.

Preparation of 2-(3,5-Difluorophenyl)-1-(4-methylsulfanylphenyl)cyclopent-2-enol (53). Chromium(II) chloride (154 mg, 1.25 mmol) and nickel(II) chloride (65 mg, 0.5 mmol) were weighed out in a flask in a drybox and placed under argon. To this flask was added a solution of the vinyl bromide substrate **52** (100 mg, 0.25 mmol) in DMF (2 mL) and the reaction stirred overnight at room temperature. The crude reaction mixture was then applied directly to a silica gel column (3/1 petroleum ether/ethyl ether) to give 48 mg of product (60%) as well as 12 mg of unreacted starting material (20%). This product was found to be very unstable and needed to be reacted in the next step very quickly in order to prevent decomposition.

Colorless oil. R_f = 0.28 (3/1 petroleum ether/ethyl ether). IR (neat): 3453 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.1, 2H), 7.19 (d, J = 8.3, 2H), 6.88 (dd, J = 9.0, 1.7, 2H), 6.58 (tt, J = 8.8, 2.3, 1H), 6.50 (t, J = 2.7, 1H), 2.69−2.62 (m, 1H), 2.54−2.51 (m, 2H), 2.47 (s, 3H), 2.39−2.33 (m, 1H), 2.14 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5 (dd, J = 246.7, 13.9), 142.3 (t, J = 9.0), 136.7, 133.8, 128.4, 126.5, 125.3, 124.9, 109.7 (dd, J = 20.3, 6.0), 102.5 (t, J = 25.6), 87.4, 45.7, 29.3, 15.7. HRMS: Calcd for $C_{18}H_{16}CF_2OS$: 318.0890. Found: 318.0888.

Preparation of 2-(3,5-Difluorophenyl)-3-(4-methylsulfanylphenyl)cyclopent-2-enone (54). To a solution of the cyclopentenol **53** (15 mg, 0.047 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added pyridinium dichromate (86 mg, 0.236 mmol). The reaction was stirred for 1 h, ether (20 mL) was added, and the mixture was filtered through a pad of Celite. The solvent was then evaporated by rotary evaporation, and the residue was purified by silica gel chromatography (3/1 petroleum ether/ethyl ether) to give 12 mg of product (80%).

White solid, mp=124−126 °C. R_f = 0.28 (3/1 petroleum ether/ethyl ether). IR (neat): 1698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 9.0, 2H), 7.15 (d, J = 8.8, 2H), 6.78−6.75 (m, 3H), 3.06−3.04 (m, 2H), 2.72−2.70 (m, 2H), 2.49 (s,

3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.3, 168.8, 163.0 (dd, J = 261.0, 12.0), 142.5, 137.8, 136.1 (t, J = 11.0), 130.8, 128.4, 125.4, 112.4 (d, J = 19.2), 103.4 (t, J = 25.1), 34.6, 29.4, 14.9. This compound has been previously described, and the data are consistent.[25]

Preparation of 2-(3,5-Difluorophenyl)-3-(4-methanesulfonylphenyl)cyclopent-2-enone (48). Following the literature procedure,[25] oxone (34 mg, 0.11 mmol) was added to a solution of **54** (12 mg, 0.038 mmol) in acetone/water 9/1 (1 mL). The reaction was heated to 45 °C and stirred for 2 h at this temperature. The reaction was then cooled to room temperature, filtered through a plug a Celite, and then concentrated in vacuo to give 12 mg of **48** (92%).

White solid, mp = 153−154 °C. R_f = 0.28 (3/1 petroleum ether/ethyl ether). IR (neat): 1704 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.8, 2H), 7.52 (d, J = 8.5, 2H), 6.82 (tt, J = 8.9, 2.4, 1H), 6.77−6.72 (m, 2H), 3.12−3.10 (m, 5H), 2.81−2.79 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.1, 166.8, 163.8 (dd, J = 249.6, 19.5), 141.6, 140.4, 139.8, 134.5 (t, J = 9.7), 128.7, 127.8, 112.4 (dd, J = 26.7, 9.7), 104.1 (t, J = 24.6), 44.3, 34.7, 29.9.

This compound has been previously described, and the data are consistent.[25]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California—San Francisco, supported by the NIH Division of Research Resources. A.B.P. thanks Abbott Laboratories, Glaxo-Wellcome, the ACS Division of Organic Chemistry (sponsored by Bristol-Myers Squibb), and Eli Lilly for fellowship support.

Supporting Information Available: Experimental details for all reactions as well as characterization data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO010593B