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Evolution of a Synthetic Approach to CP-263,114

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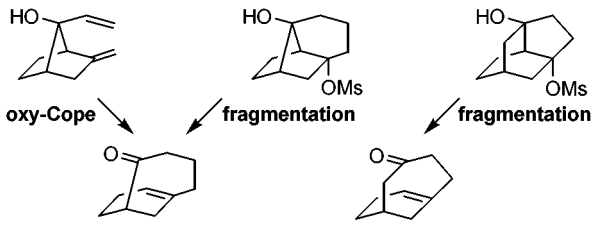
ABSTRACT



Three different approaches to the carbocyclic core of CP-263,114 are presented that illustrate a strategic evolution from an oxy-Cope rearrangement to variants of the Wharton fragmentation.

An intriguing combination of complex structure and biological activity has resulted in a great deal of attention being focused on the nonadrides CP-263,114 (phomoidride B, Figure 1) and CP-225,917 (phomoidride A). Since their isolation in 1995,[1] numerous reports have appeared describing syntheses,[2] approaches,[3] and biosynthetic investigations.[3o]

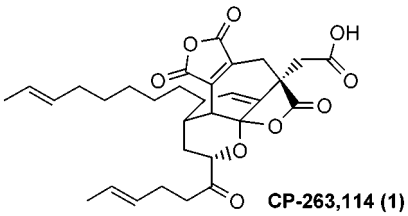


Figure 1.

As has been elegantly demonstrated by Clive and Leighton, the 1,5-diene unit present in the phomoidride core can be envisioned to arise via a Cope rearrangement of an appropriately functionalized [2.2.1] bicycle.[4] In an effort that began prior to these reports, we too were seduced by this disconnection, which in the forward sense would allow assembly of both the quaternary center and bridgehead olefin in a single potentially late-stage step. Uncertain of feasibility, we took a conservative first step by addressing the rearrange-

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(2) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1676. (c) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829. (c) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424. (d) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825. (e) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509.

(3) (a) Sgarbi, P. W.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157. (b) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737. (c) Armstrong, A.; Critchley, T. J.; Mortlook, A. A. *Synlett* **1998**, 552. (d) Frontier, A. J.; Danishefsky, S. J.; Koppel, G. A. *Tetrahedron* **1998**, *54*, 12721. (e) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890. (f) Clive, D. L. J.; Sun, S.; He, X.; Zhang, J.; Gagliardini, V. *Tetrahedron Lett.* **1999**, *40*, 4605. (g) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215. (h) Clive, D. L. J.; Zhang, J. *Tetrahedron* **1999**, *55*, 12059. (i) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337. (j) Crimmins, M. T.; Hauser, E. B. *Org. Lett.* **2000**, *2*, 281. (k) Clive, D. L. J.; Sun, S.; Gagliardini, V.; Sano, M. K. *Tetrahedron Lett.* **2000**, *41*, 6259. (l) Bio, M. M.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 2905. (m) Yoshimitsu, T.; Yanagisawa, s.; Nagaoka, H. *Org. Lett.* **2000**, *2*, 3751. (n) Devaux, J.,-F.; O'Neil, S. V.; Guillo, N.; Paquette, L. A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 490. For biosynthetic studies, see: (o) Spencer, P.; Agnelli, F.; Williams, H. J.; Keller, N. P.; Sulikowski, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 420.

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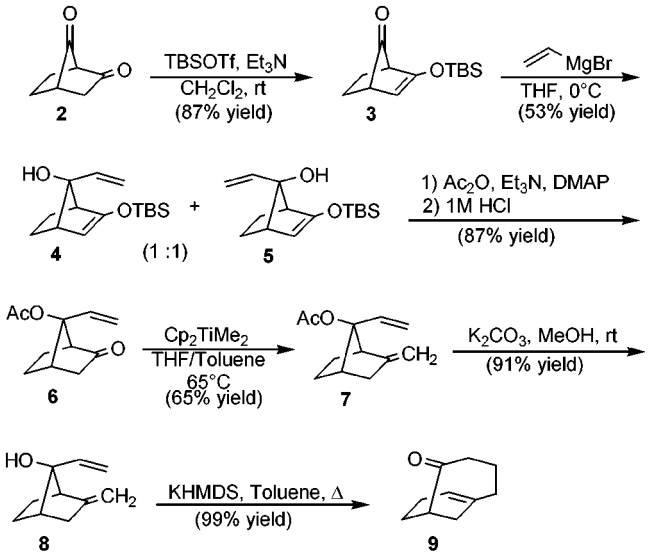
ment question in the simplified model substrate **8**. As illustrated in Scheme 1 assembly of **8** commenced via

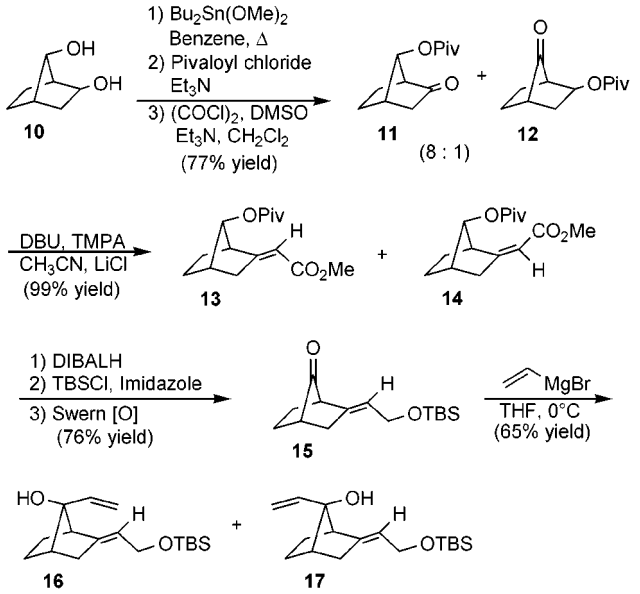
Scheme 1



protection of diketone **2** followed by addition of vinylmagnesium bromide to the derived ketone **3**. The resultant mixture of allylic alcohols (**4** and **5**) was separated and the desired adduct (**4**) was deprotected to ketone **6** which was, in turn, methylenated to **7** using the Petasis reagent.[5] Methanolysis of **7** afforded the desired diene **8**, which was found to undergo an anion-accelerated oxy-Cope rearrangement in refluxing toluene to yield **9**.

Although encouraging, the somewhat forcing conditions required to convert **8** to **9** led us to explore a more heavily functionalized oxy-Cope substrate (i.e. **16**, Scheme 2). As illustrated, our point of departure to this material was known diol **10**, which was advanced via a stannylene-mediated selective pivaloation and oxidation sequence to **11**.[6] Homologation of **11** employing the Masamune−Roush modification of the Horner−Wadsworth−Emmons reaction[7] furnished enoates **13** and **14** (2:1, respectively) which were separated and advanced.[8] Exhaustive reduction of **13** followed by protection and oxidation furnished ketone **15** in high yield. Addition of vinylmagnesium bromide to **15** yielded a 3:1 mixture of **16** and **17**[9] and set the stage for exploring the oxy-Cope chemistry. Interestingly, with **16** as substrate we were unable to effect the desired rearrangement under either thermal or anion-accelerated conditions.[10] In

Scheme 2



light of this failure we began to consider alternative approaches and soon recognized that the same net result could be achieved in a stepwise fashion by first constructing the norbornane-based tricyclic system **18** and then unveiling the desired bicyclic core structure (**9**) via a Wharton fragmentation (Figure 2).[11]

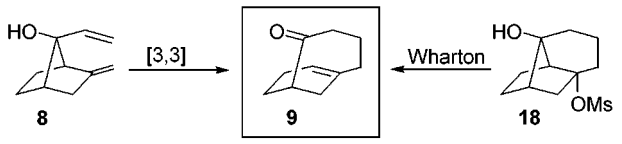


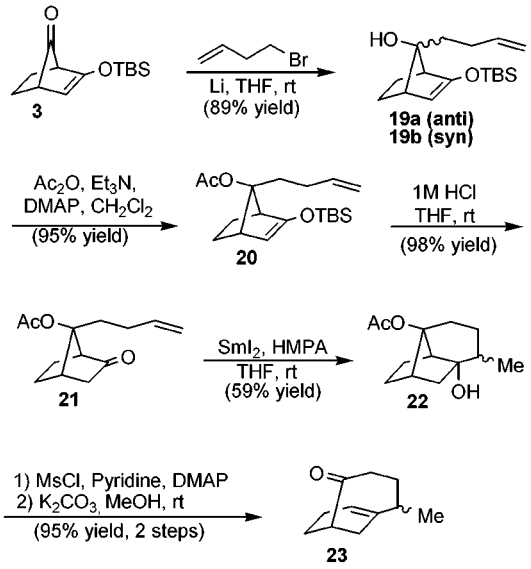
Figure 2.

In exploring the fragmentation approach, we chose a conservative path and first explored the reactivity of model substrate **22**. As in our initial Cope study, this approach was initiated with ketone **3**, which upon addition of 1-lithio-3-butene furnished a 1:1 mixture of alcohols **19** in good yield (Scheme 3). The desired addition product (**19a**) was protected as its acetate (**20**) and silyl deprotected to yield ketone **21**. In efforts to complete the tricyclic core via radical cyclization methods,[12] we met with little to no success using tin hydride but eventually found that ketone **21** smoothly undergoes cyclization to **22** upon exposure to samarium diiodide in the presence of HMPA.[13]

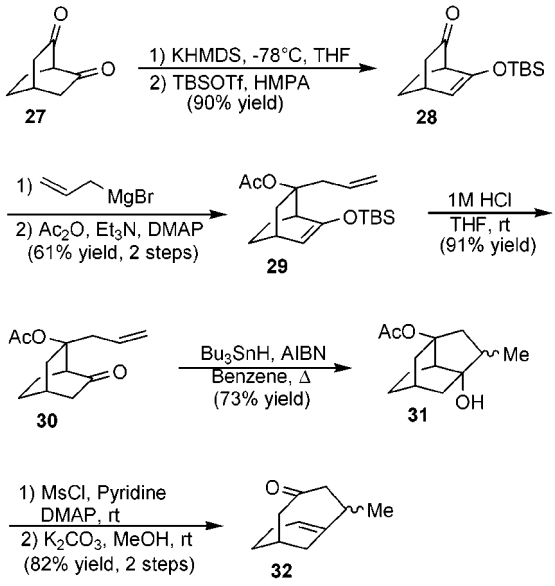
Mesylation of the tertiary alcohol in the derived mixture of diastereomers followed by methanolysis of the acetate

(4) Both Clive[3a,f,h,k] and Leighton[3e,l] have demonstrated successfully the use of an oxy-Cope rearrangement in assembling the phomoidride ring system.
(5) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(6) Pivaloyl chloride furnished a mixture of **11** and **12** in a 8:1 ratio, while benzoyl chloride gave a 3:1 mixture and acetyl chloride a 1:1 mixture of the corresponding benzoates and acetates.
(7) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron lett* **1984**, *25*, 2183.
(8) Although not shown in Scheme 2, enoate **14** was also carried through the same sequence (see Supporting Information).
(9) The structures of **16** and **17** were determined using NOE.
(10) This observation was also made by Clive.[3h]
(11) Caine, D. *Org. Prep. Proc. Int.* **1988**, *20*, 1.
(12) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939.
(13) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

Scheme 3



Scheme 4



resulted in an exceedingly facile fragmentation reaction to furnish **23** in near quantitative yield.[14]

Pleased with the successful Wharton fragmentation, we began exploring approaches to a fully elaborated norbornane-based core. We soon encountered several limitations in both the assembly and advancement of these scaffolds; however, in the course of our efforts we recognized that fragmenting an isomeric variant of the norbornane system (i.e., **25**) would serve as an alternative means of accessing the phomoidride core (Figure 3). Importantly, the isotwistane[15] scaffold (**25**)

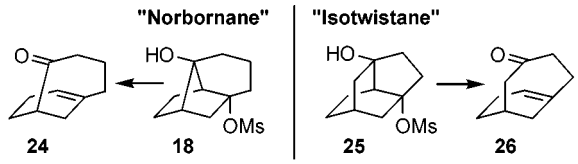


Figure 3.

appeared an ideal candidate since the bicyclo[2.2.2]core could be assembled efficiently by employing the Diels−Alder reaction.

Again proceeding in a conservative manner, we explored the reactivity of a model fragmentation substrate (**31**). These efforts commenced with known diketone **27**[16] (Scheme 4) which was converted to its mono silyl enol−ether **28**. Addition of allylmagnesium bromide to **28** favored the desired addition product in a 3:1 ratio. The addition products were separated, and the tertiary alcohol of the desired diastereomer was treated with acetic anhydride to furnish acetate **29**. Silyl deprotection of **29** produced **30**, which upon ketyl radical cyclization (Bu_3SnH) furnished isotwistane **31** as a mixture of diastereomers.[17] The resulting alcohol (**31**) was then derivatized as the corresponding mesylate and subjected to methanolysis. To our delight these mild conditions were again sufficient to initiate an in situ fragmentation that produced **32** in high yield.

Having demonstrated the feasibility of using a Wharton fragmentation to construct the CP-263,114 core, we next sought to explore construction of the quaternary center (Scheme 5). Our goal was to install this center using a 5-exo-trig ketyl radical cyclization similar to that employed in accessing **31**. This would require a modified allylic side chain, which we believed could be accessed by simply changing the nucleophile in the addition to ketone **28** from allyl- to propargyl-Grignard. In the event, we found that addition of propargylmagnesium bromide to ketone **28** gave only the desired addition product **33**. Acetylation under standard conditions followed by deprotection furnished **35**, a compound whose structure was confirmed by X-ray crystallographic analysis.

As illustrated in Scheme 5, alkyne **35** was envisioned as a superb precursor on the basis of the elegant work by Gabriele and co-workers,[18] who have shown that terminal alkynes are capable of undergoing an oxidative dicarbonylation to alkyl- or arylmaleic esters. In the event, exposure of alkyne **35** to Gabriele's dicarbonylation conditions produced the corresponding maleate **36** in excellent yield. Subsequent treatment of **36** with samarium diiodide resulted

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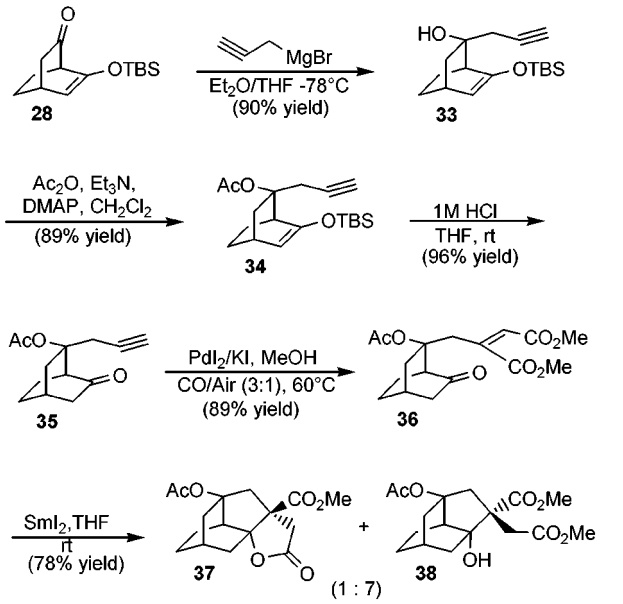
(15) Tricyclo[4.3.1.$0^{3,7}$]decane.

(16) Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, *23*, 1499.

(17) Structure confirmed by X-ray crystallographic analysis.

(18) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, C. P. *J. Chem Soc., Perkin Trans. 1* **1994**, 83.

Scheme 5



in a very facile 5-exo cyclization of the incipient ketyl radical. Unfortunately, the resultant mixture was dominated by the undesired diastereomer (**38**, >7:1). Interestingly, the desired cyclization product was produced as the corresponding lactone (**37**).

In summary, exploratory investigations into applying an anion-accelerated oxy-Cope rearrangement to the construction of the CP-263,114 skeleton were met with limited success but inspired a more efficient approach based upon the Wharton fragmentation of an intermediate tricyclic scaffold. This fragmentation was successfully implemented from both a norbornane and isotwistane system. From a synthetic standpoint, the latter is believed to be more attractive, since the bicyclo[2.2.2]octane skeleton can be constructed easily using Diels−Alder protocols. These studies also illustrated the possibility of assembling quaternary centers similar to those found in the phomoidrides via ketyl radical cyclizations into maleic ester moieties. As described in the accompanying Letter, subsequent work has focused on developing an efficient means of accessing an isotwistane scaffold suitable for advancement to phomoidrides A and B.[19]

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Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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