ORGANIC LETTERS

2001
Vol. 3, No. 16
2435−2438

An Expeditious Approach toward the Total Synthesis of CP-263,114

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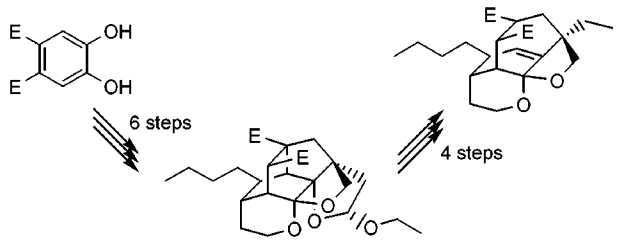
Received April 12, 2001

ABSTRACT

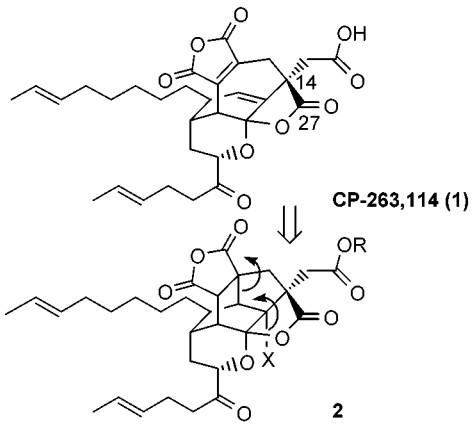


Assembly of the carbocyclic core of CP-263,114 has been accomplished efficiently and in high yield. Key steps include a phenolic oxidation/intramolecular Diels–Alder sequence, tandem radical cyclization, and the late-stage fragmentation of a densely functionalized isotwistane skeleton.

In the preceding Letter,[1] we described the evolution of a synthetic approach to CP-263,114 (**1**). On the basis of these efforts, our current retrosynthetic analysis focuses on the late-stage fragmentation of a heavily functionalized isotwistane ring system. Whereas our earlier efforts focused on a Wharton fragmentation,[1] in this series we hoped to achieve the same result via a carbon-based fragmentation (**2**, Scheme 1). Although the bicyclo[2.2.2]octane construct offers a variety of Diels−Alder disconnections, we were inspired by reports from Yates and Wessely and began by focusing on a tandem phenolic oxidation/intramolecular Diels−Alder sequence.[2,3]

To investigate the Yates chemistry, we prepared **5**, via a route that commenced with known ester **3**.[4] Alkylation of **3** with propargyl bromide set the stage for a Gabriele dicarbonylation reaction (Scheme 2)[5] that, followed by removal of the allyl group, furnished free phenol **5**. Wessely oxidation of **5** using lead(IV) acetate in acetic acid furnished only minuscule quantities of the desired orthoquinol oxidation product (**6**). However, after much experimentation, we found that Quinkert's modified Wessely conditions afforded an improved yield of oxidation products.[6] Thus, reaction of phenol **5** under these conditions furnished two products (**6** and **7**) in a 1:3 ratio, respectively. Heating of triene **6** in

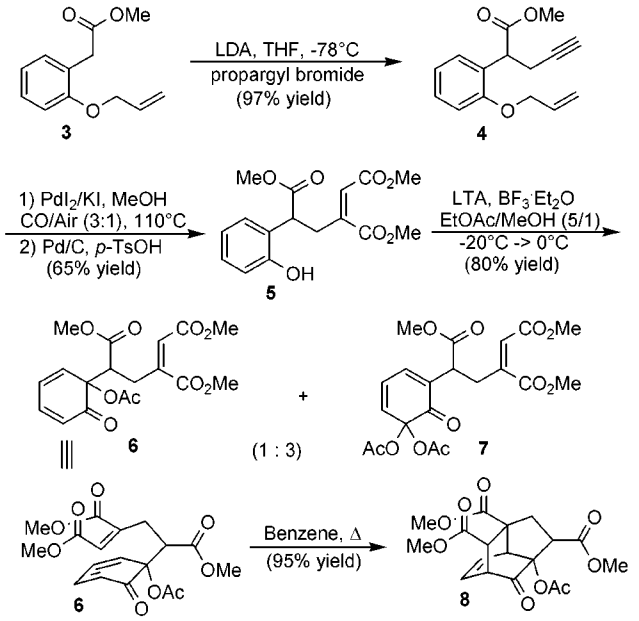
Scheme 1



(1) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431 and references therein.
(2) Wessely, F.; Sinwel, F. *Monatsch. Chem.* **1950**, *81*, 1053.
(3) Yates, P.; Maras, T. S. *Can. J. Chem.* **1988**, *66*, 1.
(4) Kunio, H.; Jun, A.; Kyoko, S.; Toshihiro, K. *J. Org. Chem.* **1994**, *59*, 203.
(5) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83.

10.1021/ol015979n CCC: $20.00
Published on Web 07/10/2001

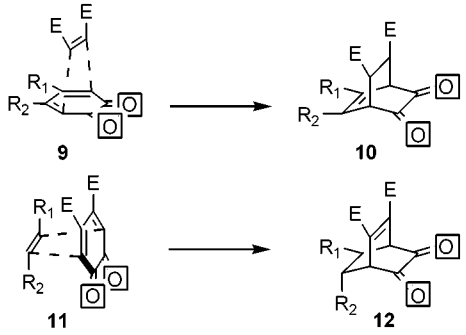
Scheme 2



benzene yielded **8**, thus completing construction of the isotwistane skeleton in only five steps from **3**.

Our inability to optimize the conversion of **5** to **6** beyond 20% isolated yield coupled with the inefficiencies associate with transforming the Diels−Alder-derived olefin into the *trans*-disposed side chains led us to explore alternative phenolic oxidations. Specifically, attention was turned to orthoquinone monoketals since the litereature suggests that these systems often are superior to those used in the Wessely-type oxidations.[7] In addition to altering the oxidation substrate, we focused on a different Diels−Alder disconnection (cf. **9** → **10** and **11** → **12**). As illustrated in Scheme 3, the latter of these two allows efficient access to the *trans*-

Scheme 3



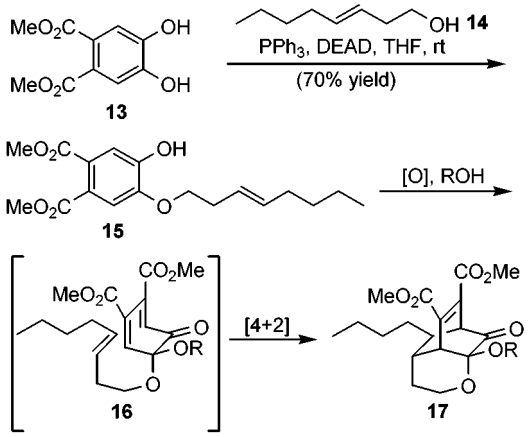
orientated side chains (i.e., R_1 and R_2) found in the natural product.

(6) Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Durner, G.; Zimmerman, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771.

(7) Quideau, S.; Pouysegu, L. *Org. Prep. Proc. Int.* **1999**, 617.

Our point of departure in the quinone monoketal approach was the known catechol **13**[8] (Scheme 4) which we desym-

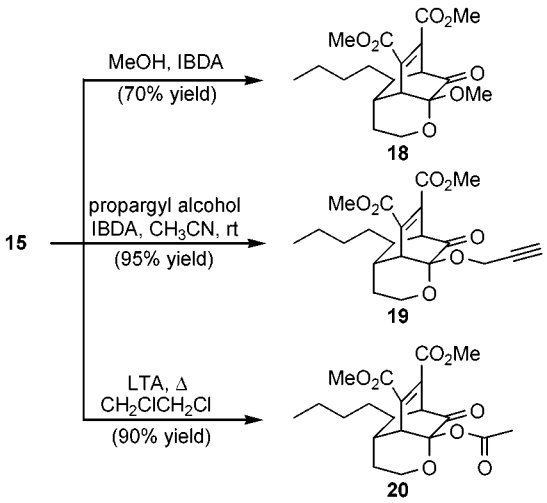
Scheme 4



metrized under Mitsunobu conditions with alcohol **14**[9] to furnish mono ether **15** in good yield. Our hope was that aromatic oxidation of **15** would be followed by trapping and intramolecular Diels−Alder reaction to furnish **17**, a compound poised for further advancement to the isotwistane and possessing the desired stereochemical relationship between the side chains.

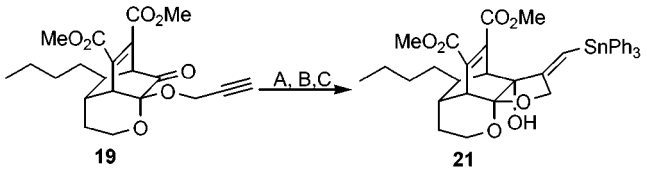
In the event, we were pleased to find that exposure of **15** to iodobenzene diacetate (IBDA) in methanol at room temperature resulted in the desired cascade reaction and provided **18** in good yield (Scheme 5). In employing more synthetically useful trapping reagents, we found that propargyl alcohol in acetonitrile provided the desired cycloadduct **19** in excellent yield. Moreover, the acid oxidation state found at C(27) in the natural product could be readily incorporated simply by changing the oxidizing agent from IBDA to lead(IV) acetate, to furnish **20** in high yield.

Scheme 5



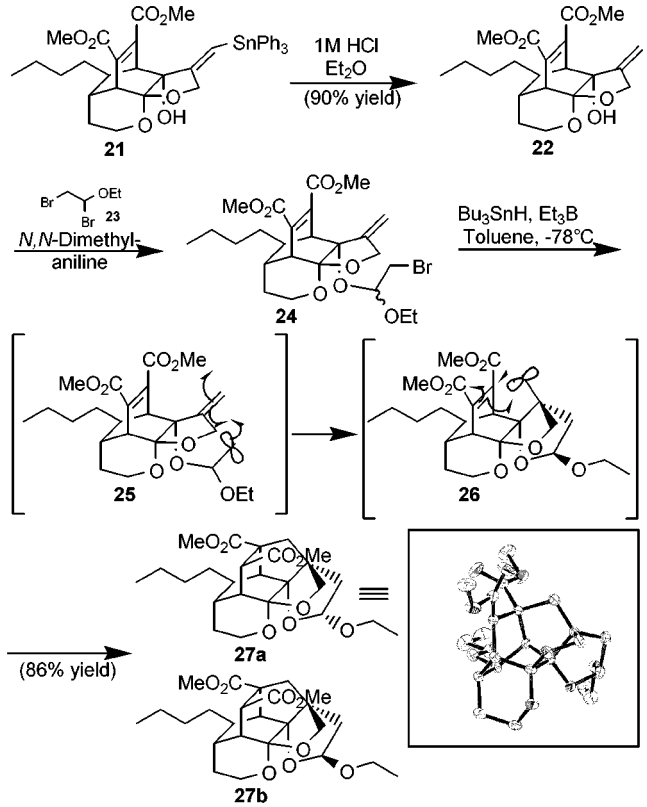
With these promising results in hand, we continued construction of the isotwistane skeleton. Treatment of **19** with triphenyltin hydride under the various reaction conditions afforded the desired cyclization product **21** (Scheme 6), the highest yield being achieved with triethylborane in toluene.[10] Stannane **21** was obtained in all cases as a single isomer, the structure of which was confirmed by X-ray crystallographic analysis.

Scheme 6



To complete the isotwistane core, we turned to Stork's bromoacetal method in hope of advancing tertiary alcohol **21** via the intramolecular tandem/radical cyclization sequence outlined in Scheme 7.[11] To this end, stannane **21** was protodestannylated with dry hydrochloric acid to furnish **22** which was efficiently converted to bromoacetal **24** by exposure to dibromoethyl ether **23** and *N*,*N*-dimethylaniline.

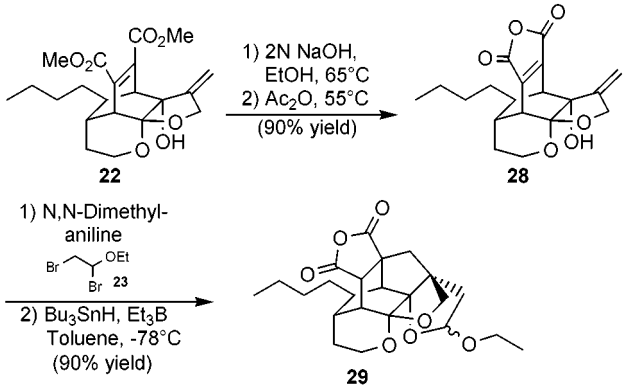
Scheme 7



To our delight, treatment of bromoacetal **24** with tributyltin hydride and triethylborane delivered **27** as a mixture of diastereomers in excellent yield for the two steps. Mechanistically, this transformation likely proceeds via initial formation of primary radical **25** followed by 5-exo-trig cyclization into the adjacent exocyclic olefin. A second cyclization event into the maleate followed by trapping of hydrogen from the less hindered face yields **27**. The acetal diastereomers (**27a** and **27b**) were separated, and the stereochemistry was confirmed via single-crystal X-ray analysis of **27a**.[12]

Curious as to functional group tolerance in the cyclization cascade, we explored preformation of the maleic anhydride unit found in the natural product (Scheme 8). Thus, hydrolysis and dehydration of maleate **22** with acetic anhydride provided maleic anhydride **28** in good yield. As before, derivatization as the corresponding bromoacetal was followed by exposure to Bu_3SnH and Et_3B. We were pleased to find that the radical cascade sequence again delivered a cyclization product (**29**) in excellent yield.

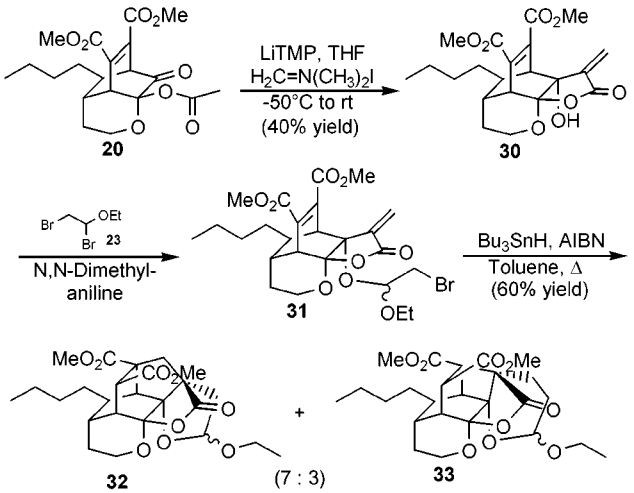
Scheme 8



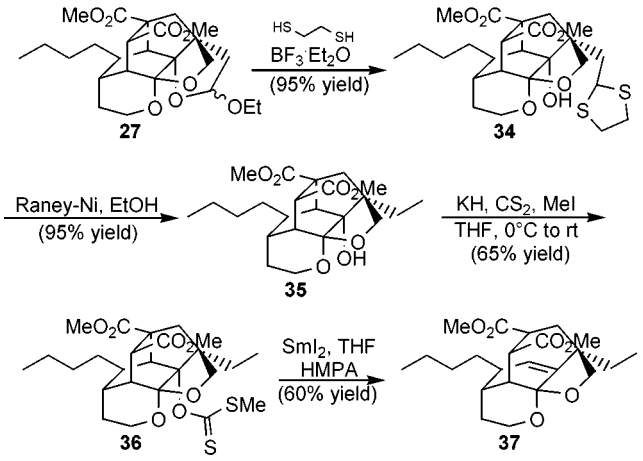
Having established an extremely efficient method for constructing the isotwistane core, we turned our attention to the acid oxidation state at C27 (Scheme 1).[13] Since we had already successfully incorporated an acetate moiety into the phenolic oxidation cascade by using $Pb(OAc)_4$ (i.e., **15** → **20**), our efforts focused on advancing the latter. In what proved to be a remarkable one-pot procedure, we discovered that simply exposing **20** to LiTMP and Eschenmoser's salt effects conversion to **30**, thus setting the stage for the tandem radical cascade.[14] As before, bromoacetal formation furnished

(8) Anderson, D. R.; Koch, T. H. *J. Org. Chem.* **1978**, *43*, 2726.
(9) Fujisawa, T.; Kurita, Y.; Kawashima, M.; Sato, T. *Chem. Lett.* **1982**, 1641.
(10) Nishida, A.; Takahashi, H.; Takeda, H.; Takada, N.; Yonemitsu, O. *J. Am. Chem. Soc.* **1990**, *112*, 902.
(11) Stork, G.; Biller, S. A.; Rychnovsky, S. D.*J. Am. Chem. Soc.* **1983**, *105*, 3741.
(12) **27a** and **27b** were subjected separately to Jones conditions, in which they both converged to the same lactone.
(13) Phomoidride numbering system as reported in the following: Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.
(14) Lansbury, P. T.; Zhi, B.-X. *Tetrahedron Lett.* **1988**, *29*, 5735.

Scheme 9



Scheme 10



31 (Scheme 9), and subsequent treatment of **31** with tributyltin hydride effected the cascade event. In contrast to previous substrates, the desired 5-exo-5-exo-trig product (**32**) was accompanied by a 6-endo-4-exo-trig product (**33**) (produced in a 7:3 ratio, respectively).

Having developed methods for installing both the anhydride unit and the appropriate oxidation level at C27, our attention turned to the critical fragmentation. Our initial explorations began with acetal mixture **27**, which was converted to dithiolane **34** using standard protocols. To facilitate analysis of the product mixture, the dithiolane was removed using Raney Ni to furnish **35**. Formation of *S*-methyl dithiocarbonate **36** was accomplished using an excess of potassium hydride in combination with carbon disulfide and methyl iodide as described by Barton.[15] To our delight, reaction of **36** with samarium diiodide in the presence of HMPA furnished the desired fragmentation **37** in 60% yield (Scheme 10).[16]

In summary, we have devised a short and efficient synthesis of an isotwistane core needed for the synthesis of the phomoidrides. The approach employs a phenolic oxidation/cycloaddition cascade followed by two substrate-controlled radical cyclizations. Additionally, installations of the anhydride moiety and the C(27) oxidation state have been addressed in parallel studies. Importantly, preliminary results show great promise for completing the phomoidride syntheses via fragmentation of the isotwistane core.

Acknowledgment. We acknowledge the support of this work by Bristol-Myers Squibb, Eli Lilly, Glaxo-Wellcome, Yamanouchi, and Zeneca through their Faculty Awards Programs and the Camille and Henry Dreyfus Foundation for a Teacher-Scholar Award. We thank Susan DeGala for securing the X-ray crystallographic analyses.

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.

OL015979N

(15) Barton, D. H. R.; Parekh, S. I.; Tse, C.-L. *Tetrahedron Lett.* **1993**, *34*, 2733.

(16) Ananthanarayan, T. P.; Gallagher, T.; Magnus, P. *Chem. Commun.* **1982**, 709.