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Total Synthesis of Phomactin A.†

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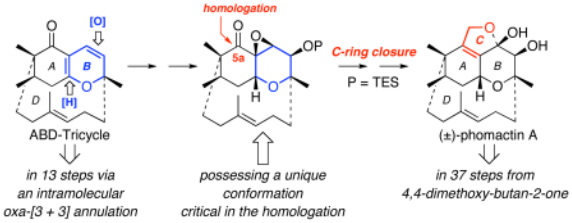
Abstract



A total synthesis of (±)-phomactin A is described to highlight the final completion of a complex natural product target that had commenced with an intramolecular *oxa*-[3 + 3] annulation strategy in the construction of the ABD-tricycle. These efforts reveal structural intricacies of this ABD-tricycle with an illustrative example being the conformational analysis that was ultimately critical for the C5a-homolgation.

In the last decade, phomactin A,[1–4] a structurally unique natural product isolated from the culture filtrate of a parasitic fungus *Phoma* sp. [SANK 11486] found on the shell of *Chinoecetes opilio*, has captured an impressive array of synthetic efforts.[5,6] Although possessing only modest inhibition against platelet-activating factor[7] [PAF] induced platelet aggregation [IC_{50} = 10 μM], phomactin A embodies a new class of PAF antagonists. The most active member is D and was synthesized by Yamada.[8] Phomactin A is the only known tetracycle [discounting epoxides] in the phomactin family with all other members lacking either the B-ring or C-ring. Thus, phomactin A represents structurally the most complex member. To date, two elegant total syntheses of (±)- and (+)-phomactin A were completed by Pattenden[9] and Halcomb,[10] respectively. Recently, Wulff[11] reported the synthesis of phomactin B2.

We approached[12] (±)-phomactin A with an intent to feature our intramolecular *oxa*-[3 + 3] annulation strategy[13–16] en route to ABD-tricycle **2**, which possesses a unique structural topology [Scheme 1].[17] We recently designed a 12-step asymmetric synthesis of the annulation precursor **3**[18] entailing Suzuki-Miyaura coupling of vinyl bromide **4** with the derivative of A-ring **5**, which was assembled from an asymmetric Diels-Alder cycloaddition[19,20] of **6**. We communicate here our total synthesis of (±)-phomactin A.

An immense amount of effort[17] was exerted to succeed in oxidizing the C3-3a olefin of ABD-tricycle **2** into its proper oxidation states. Ultimately only a singlet-oxygen Diels-Alder cycloaddition could be achieved selectively to give endo-peroxide **8**[21] [Scheme 2] without

†This paper is dedicated to Professor Bill Wulff on the very special occasion of his 60th birthday.

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Supporting Information Available: Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files are available for all new compounds and free of charge via Internet http://pubs.acs.org.

significant competition from [2 + 2] cycloaddition or ene reaction with the C3′-4′ olefin in D-ring or on the "belt." After failing an array of reductive protocols [i.e., Lindlar's [H], thiourea, or Ph_3P] to cleave the weak endo-peroxide bond, KOAc and 18-*c*-6 successfully opened the endo-peroxide bridge via a deprotonation pathway to give ene-dione **9**. Treatment of **9** with *p*-TsOH in MeOH isomerized the lactol motif to methyl ether **10**, proceeding through a vinyl oxocarbenium intermediate that was trapped by MeOH at C3a position.

We recognized that while the singlet-oxygen Diels-Alder cycloaddition sets up the desired stereochemistry for the C3-OH group, ring-opening of the endo-peroxide bond through the deprotonation pathway effectively destroyed this valuable stereochemical information. Consequently, with the knowledge of the "belt" blocking the bottom face, we chose a small hydride source such as $NaBH_4$ to reduce the C3 ketone in **10**, but only to attain a mixture of isomers with a 4:1 ratio in favor of the wrong alcohol diastereomer **11**-α. Surprisingly, when using L-Selectride™, we isolated only the desired isomer **11**-β. In hindsight, by examining the model of **10** [Figure 1– left side] , it would appear that the pseudo-axial C3a-OMe group likely plays a bigger role than the "belt" in the facial differentiation of the reduction. With a more bulky hydride, the C3a-OMe group was able to better prevent the hydride approaching from the top face.

Reduction at C8a was relatively less eventful. As shown in Scheme 3, capping of C3-OH in **11**-β with TESCl followed by demethylation with BBr_3 led to vinylogous ester **12**. However, no condition that we screened [i.e., L-Selectride™, CuI/LAH, or Na/IPA] was capable of reducing the vinylogous ester motif in a 1,4-manner. Realizing that vinylogous ester **12** may not be sufficiently electron deficient, we oxidized C3a-OH using Dess-Martin periodinane reagent, and an ensuing reduction effectively gave diketone **13**, which is isolable, but with extended reduction time at temperatures slightly greater than rt, hydroxy ketone **14** was obtained in 96% overall yield with completely selective reduction at C3a.

With hydroxy ketone **14**, we completed our efforts in transforming B-ring into its proper oxidation states, and a single-crystal X-ray structure of **14** [Figure 1 – right side] further affirms our success. However, we were concerned about the reactivity of the C5a carbonyl group because the challenge of C5a-homologation lies ahead. It became obvious that no reduction of the C5a carbonyl group in **10** had occurred when using L-Selectride™, and nor did $NaBH_4$ touch the C5a carbonyl group in **13**. While one could concede that reduction in **10** involved a vinylogous ester, lack of reduction in **13** was quite disconcerting.

Upon examination of the minimized Spartan™ model of **10** and X-ray structure of **14**, we found some unique conformational elements. In **10**, the α-Me group in the Aring [red] is pseudo-equatorial with the β-Me group [blue] being pseudo-axial, thereby blocking any incoming nucleophiles toward the C5a carbonyl group. On the other hand, hydroxy ketone **14** assumes a very different conformation with its AB-ring junction being both sp^3-hybridized instead of sp^2 as in **10**. In this case, the β-Me group [blue] is now pseudo-equatorial with the α-Me group [red] turning to occupy the pseudo-axial position, thereby hindering the attack of the C5a carbonyl group.

In contrast, the AB-ring junction of endo-peroxide **8** consists of sp^3-hybridized C8a and sp^2-hybridized C8b [Figure 2]. This set of hybridizations leads to yet another conformation in which the β-Me group [blue] remains pseudo-equatorial as in **14**, but the α-Me group [red] shifts away versus its respective position in **14**. We hoped that this minor shift would provide just enough opening to allow C5a to be accessible for homologation.

To test this hypothesis, we elected to construct enone **15** and epoxy ketone **16** for which both ring-junctions contain one sp^3- and one sp^2-hybridized carbon.[22] As shown in Scheme 4, after failing to eliminate the C3a-OH group via dehydrative protocols, we isolated sulfite **17** during

an attempt to chlorinate at C3a. A retro-Diels-Alder process in refluxing toluene would extrude SO_2 and afford the desired enone **15**. To our relief, we could add various one-carbon nucleophiles such as $ROCH_2Li$ [R = PBMB or MOM] to afford ene-diols **18a**/**b**, thereby succeeding what had appeared to be a daunting task in C5a-homologation. However, ene-diols **18a**/**b** were not useful for the total synthesis. Consequently, we prepared epoxy ketone **16**, but in three steps, because epoxidation of enone **15** would not take place unless the TES group was removed. Homologation of **16** via addition of MeLi followed by elimination gave vinyl epoxide **19**.

Nucleophilic ring-opening of vinyl epoxide **19** at C5 via a S_N2' pathway would have been truly welcome at this stage [Scheme 5]. Instead, a S_N1-like process occurred with H_2O adding at C8b with retention of stereochemistry when using $Mg(OTf)_2$ in wet CH_3CN,[23] leading to 1,2-diol **20** after re-silylating C3-OH. Allylic alcohol transposition using Dauben's protocol[24] led to epoxy diol **21**.[25,26] Subsequent treatment of **21** with Ph_3P-I_2[27] followed by Luche reduction of the enal intermediate **22** gave 1,4-diol **23**, which was confirmed through its X-ray structure.

After failing a number of approaches for constructing the C-ring using either enal **22** or 1,4-diol **23**, mainly due to our inability to consistently oxidize the C3a-OH group, we managed to first acrylate C5-OH. Subsequently, we found that oxidation of the C3a-OH group employing Dess-Martin periodinane reagent at a warmer temperature gave enone **25**. An ensuing de-protection sequence allowed for the formation of the lactol C-ring and the final completion of our total synthesis of (±)-phomactin A in 24 steps from ABD-tricycle **2**.

We have described a total synthesis of (±)-phomactin A that highlights the final completion of a complex natural product target that had commenced with an intramolecular *oxa*-[3 + 3] annulation strategy in the construction of an ABD-tricycle. Our efforts reveal structural intricacies of this ABD-tricycle with an illustrative example being the conformational analysis that was ultimately critical for the C5a-homolgation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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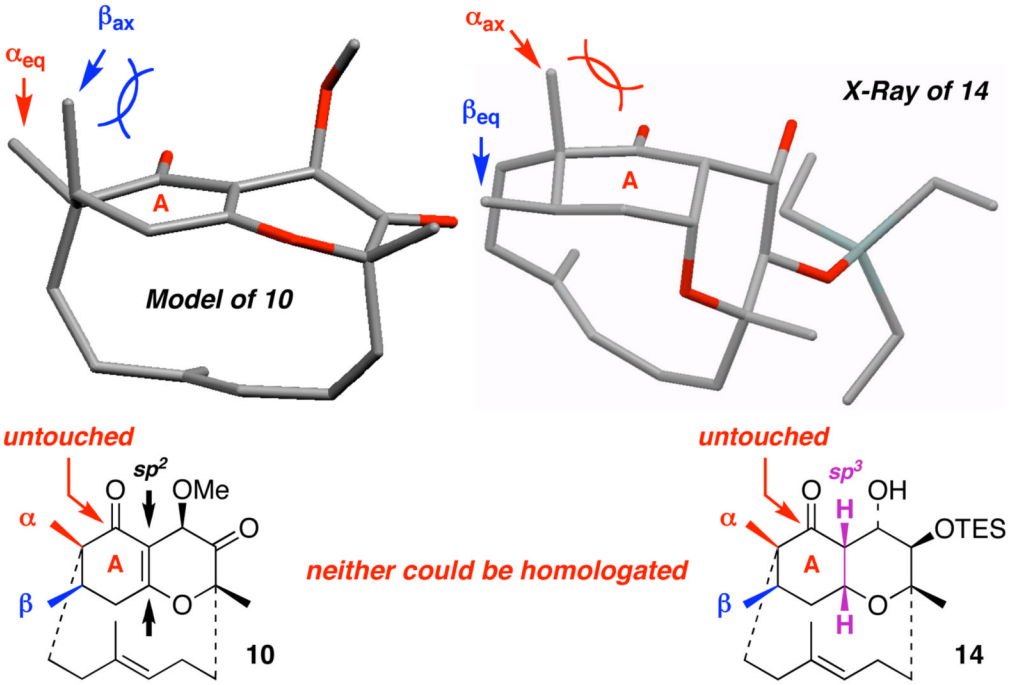


Figure 1.
Conformation Analysis for **10** and **14**.

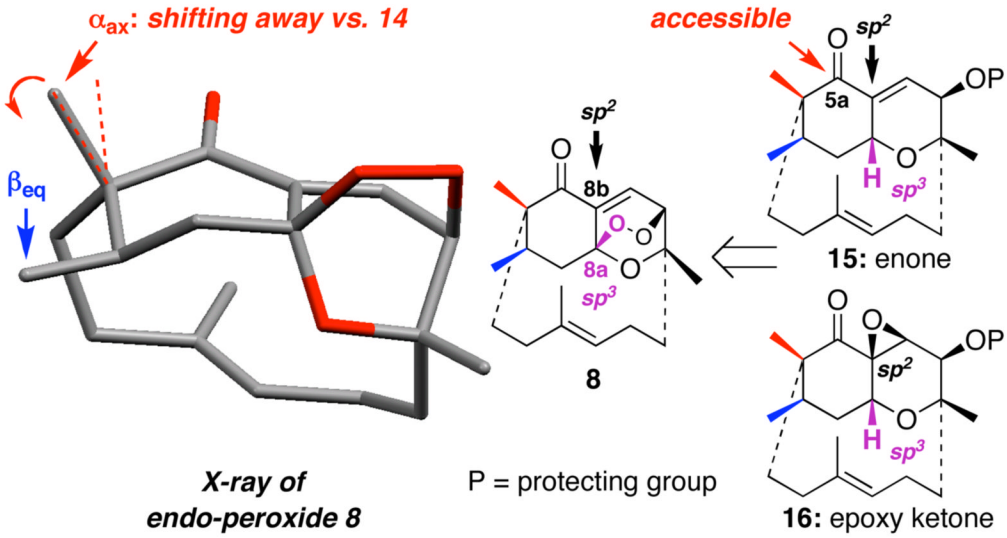
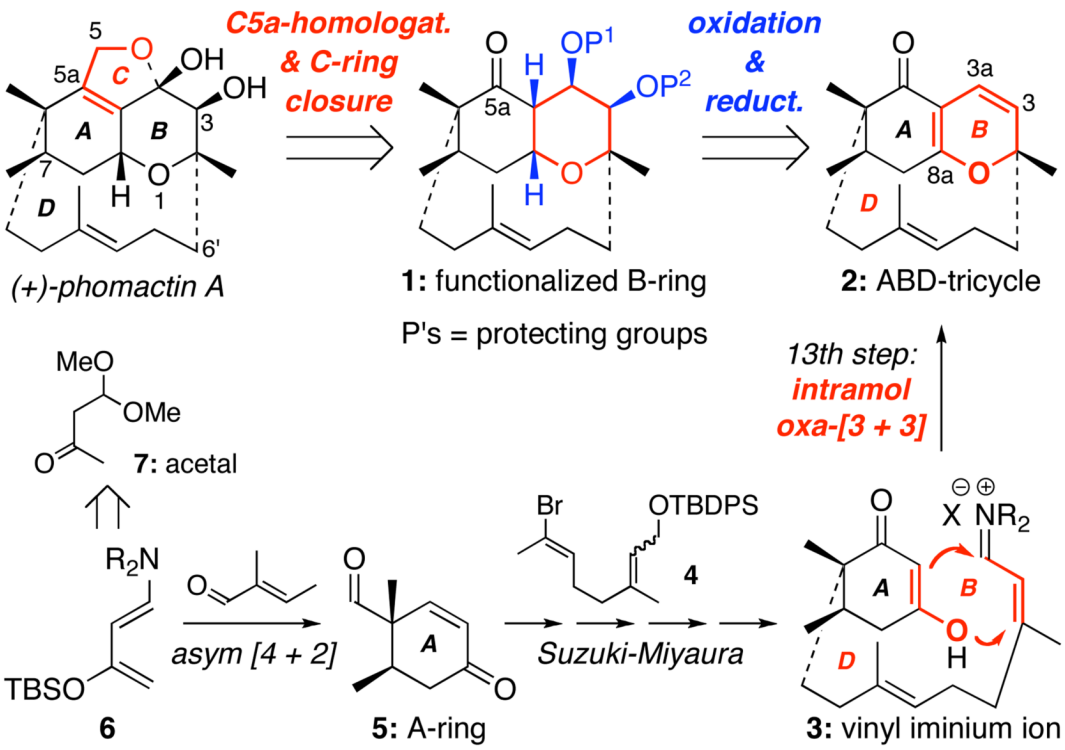
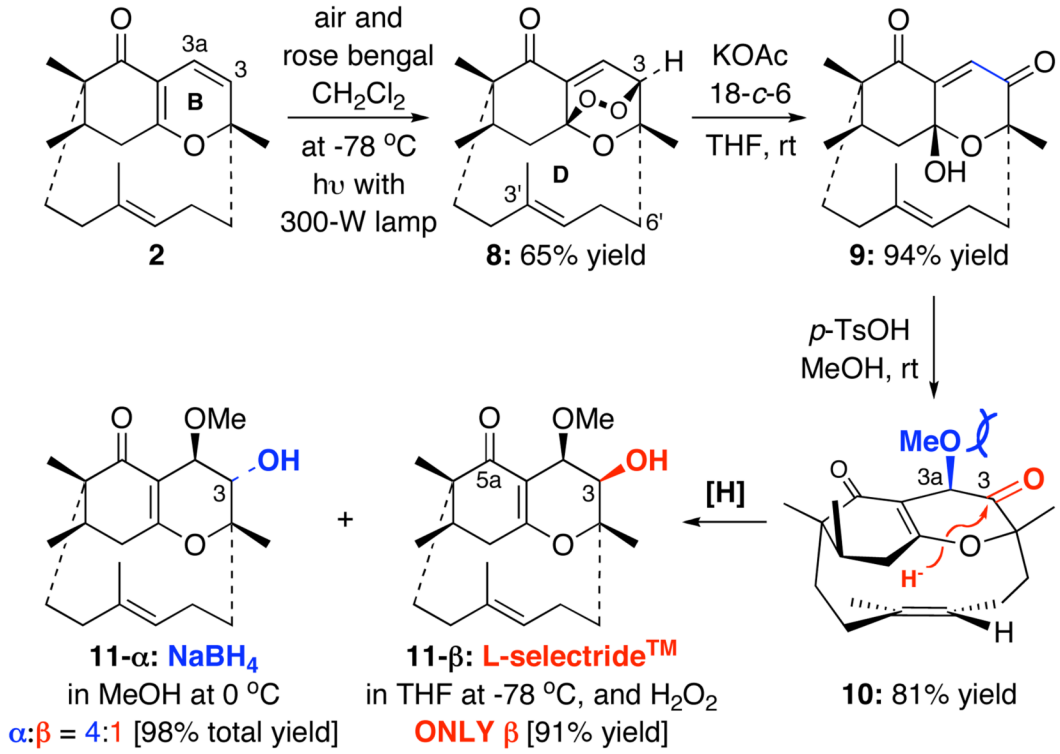


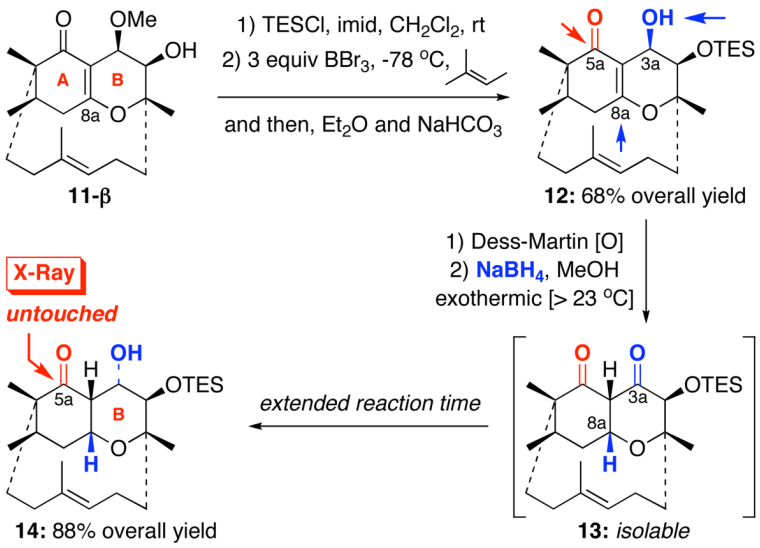
Figure 2.
Rationale for Choosing **15** and **16**.



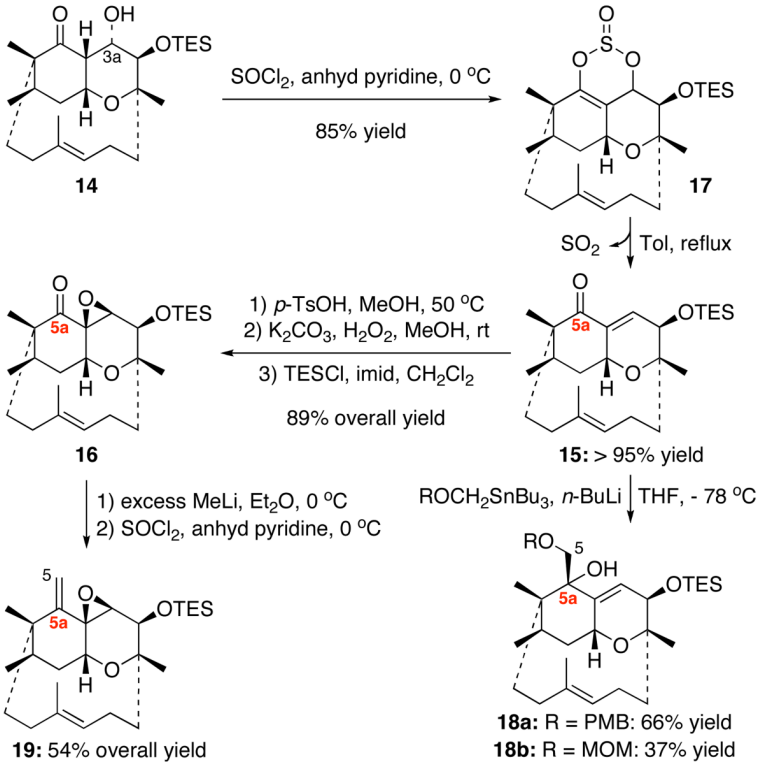
Scheme 1.
A Synthetic Plan Toward Phomactin A.



Scheme 2.
Oxidation of C3-3a Olefin: An Endo-Peroxide Route.

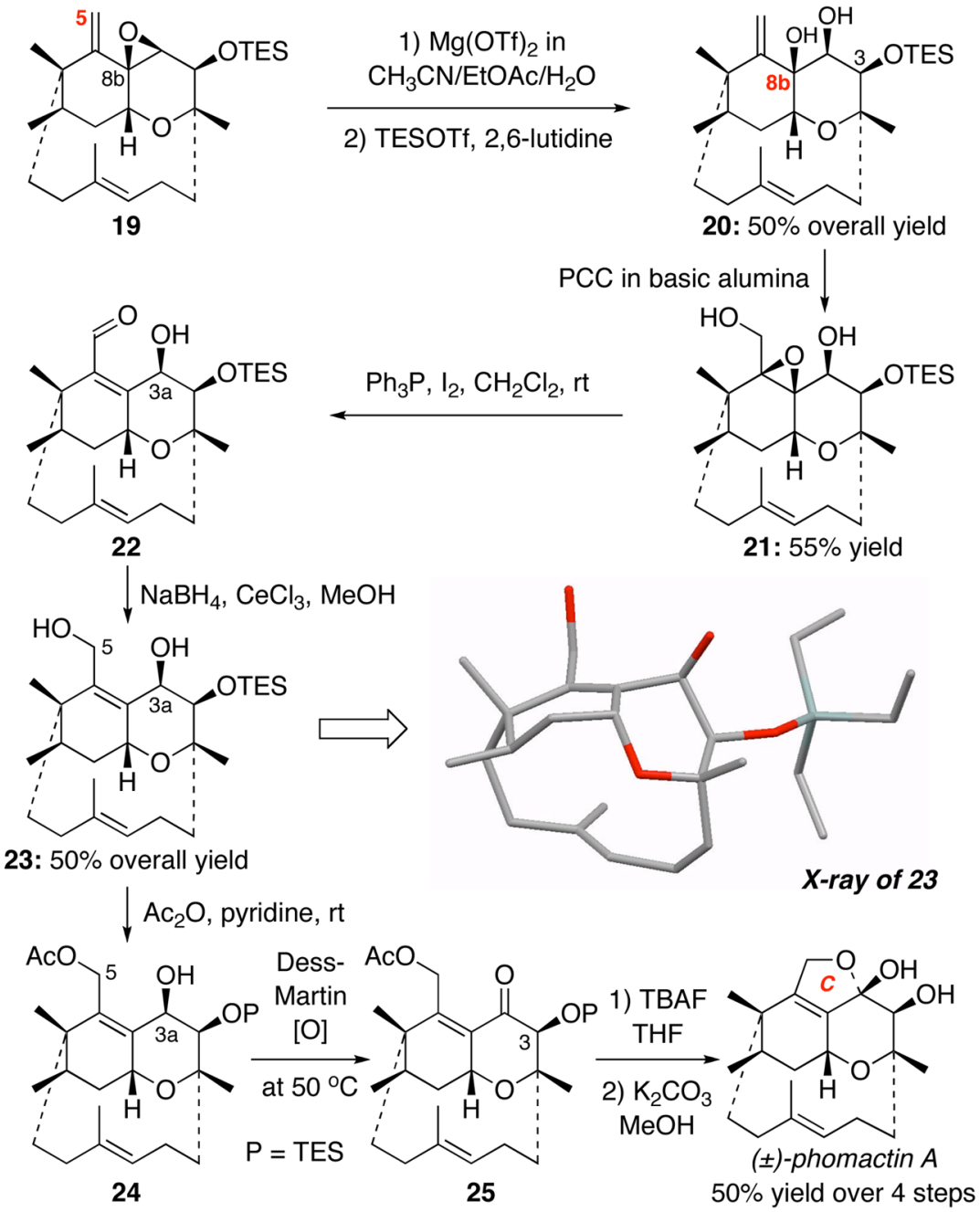


Scheme 3.
Reduction of C8a at the AB-Ring Junction.



Scheme 4.

C5a-Homologation of Enone **15** and Epoxy Ketone **16**.



Scheme 5.
Completing a Total Synthesis of (±)-Phomactin A.