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[4] For selected reviews, see: a) M. S. Lee, H. Nakanishi, M. Kahn, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 332 – 341; b) P. J. Edwards, M. Gardner, W. Klute, G. F. Smith, N. K. Terrett, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 321 – 331; c) C. D. Floyd, C. Leblanc, M. Whittaker, *Prog. Med. Chem.* **1999**, *36*, 91 – 168; d) S. Wilson, A. W. Czarnik, *Combinatorial Chemistry: Synthesis and Application*, Wiley, New York, **1997**, p. 314.

[5] For some recent examples, see: G. W. Plant, S. Woerly, A. R. Harvey, *Exp. Neurol.* **1997**, *143*, 287 – 299; M. Chatterjee, P. J. Smith, C. A. Townsend, *J. Am. Chem. Soc.* **1996**, *118*, 1938 – 1948; G. S. Jacob, *Front. Biomed. Biotechnol.* **1993**, *1*, 74 – 86.

[6] Anonymous in *Carbohydr. Chem. Vol. 30,* Royal Society of Chemistry, London, **1998**, pp. 123 – 140; J. Jurczak, *Prep. Carbohydr. Chem*. **1997**, 595 – 614.

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[9] Although, with such a mode of reaction as that shown in Scheme 1, one might expect *cis* delivery to the olefin, *trans* addition is also conceivable in certain cases. In the absence of a definitive mechanistic trend for this IBX-mediated reaction at the outset of this work, it was left to empirical observation to provide the answer as to the stereochemical outcome.

[10] The aryl moiety and nitrogen atom of the carbamate group are intimately involved in this IBX reaction, see Ref. [1f] for more details.[26]

[11] D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765 – 2768; S. Knapp, P. J. Kukkola , S. Sharma, *J. Org. Chem.* **1990**, *55*, 5700 – 5710.

[12] H. H. Baer, L. Siemsen, J. DaFaye, K. Burak, *Carbohydr Res.* **1984**, *134*, 49 – 61. The α- and β-isomers of this pyranose were separated after reaction with DBU and p-methoxyphenyl isocyanate (α-anomer used in Scheme 3; β-anomer used in entry 5, Table 1).

[13] Compounds **9** and **10** were derived from methyl-α-D-mannose pyranoside and methyl-β-D-galactose pyranoside, unpublished results.

[14] Compounds **11** and **12** were derived from *l*-arabinose, unpublished results..

[15] K. C. Nicolaou, C. K. Hwang, B. E. Marrow, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carrol, J. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3040 – 3054.

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[18] Compounds **18** and **19** were derived from ethyl *l*-lactate, unpublished results.

[19] A. W. Johnson, R. M. Smith, R. D. Guthrie, *J. Chem. Soc. Perkin Trans. 1* **1972**, *17*, 2153 – 2159; W. D. Weringa, D. H. Williams, J. Feeny, J. P. Brown, R. W. King, *J. Chem. Soc. Perkin Trans. 1* **1972**, *3*, 443 – 446.

[20] a) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **1983**, *24*, 5281 – 5284; b) H. Jin, J. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, *108*, 5644 – 5646.

[21] X. Lu, G. Zhu, S. Ma, *Chin. J. Chem.* **1993**, *11*, 267 – 271.

[22] Prepared in two steps from ethyl *l*-lactate by TBS protection (TBSCl, imidazole) and DIBAL reduction (toluene, $-78\,^{\circ}C$).

[23] J.-L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226 – 2227.

[24] For selected syntheses of *l*-vancosamine and derivatives thereof, see: a) T. T. Thang, F. Winternitz, *J. Chem. Soc. Chem. Commun.* **1979**, 153 – 154; b) I. Dyong, H. Friege, *Chem. Ber.* **1979**, *112*, 3273 – 3281; c) T. T. Thang, F. Winternitz, *Tetrahedron Lett.* **1980**, *21*, 4495 – 4498; d) H. I. Ahmad, J. S. Brimacombe, A. S. Mengech, L. C. N. Tucker, *Carbohydr. Res.* **1981**, *93*, 288 – 293; e) I. Dyong, H. Friege, H. Luftmann, H. Merten, *Chem. Ber.* **1981**, *114*, 2669 – 2680; f) G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *Tetrahedron Lett.* **1981**, *22*, 5073 – 5076; g) J. S. Brimacombe, A. S. Mengech, K. M. M. Rahman, L. C. N. Tucker, *Carbohydr. Res.* **1982**, *110*, 207 – 215; h) G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *J. Carbohydr. Chem.* **1983**, *2*, 225 – 248; i) Y. Hamada, A. Kawai, T. Shioiri, *Tetrahedron Lett.* **1984**, *25*, 5413 – 5414; j) F. M. Hauser, S. R. Ellenberger, *J. Org. Chem.* **1986**, *51*, 50 – 57; k) I. Dyong, J. Weigand, J. Thiem, *Liebigs Ann. Chem.* **1986**, 577 – 599; l) A. Klemer, H. Wilbers, *Liebigs Ann. Chem.* **1987**, 815 – 823; m) Y. Hamada, A. Kawai, T. Matsui, O. Hara, T. Shioiri, *Tetrahedron* **1990**, *46*, 4823 – 4846; n) R. Greven, P. Jutten, H.-D. Scharf, *Carbohydr. Res.* **1995**, *275*, 83 – 93; o) K. C. Nicolaou, H. J. Mitchell, F. L. van Delft, F. Rübsam, R. M. Rodríguez, *Angew. Chem.* **1998**, *110*, 1972 – 1974; *Angew. Chem. Int. Ed.* **1998**, *37*, 1871 – 1874.

[25] J. O. Hoberg, *Carbohydr. Res.* **1997**, *300*, 365 – 367.

[26] Extensive mechanistic studies dealing with the interactions of periodinanes with anilides will be reported in due course.

[27] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-142005. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Novel Reactions Initiated by Titanocene Methylidenes: Deoxygenation of Sulfoxides, *N*-Oxides, and Selenoxides**

K. C. Nicolaou,* Alexandros E. Koumbis, Scott A. Snyder, and Klaus B. Simonsen

Over the course of the past several years, sulfoxides have become an increasingly important functional group in organic synthesis, particularly as chirons in asymmetric synthesis.[1] As

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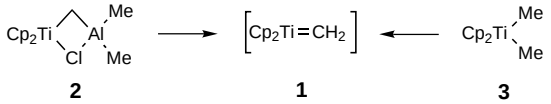
such, there has been an enduring interest among chemists in developing novel methods to effect the deoxygenation (or reduction) of sulfoxides to sulfides so that this functionality can be cleanly extruded from the molecule of interest once its presence is no longer required.[2] During the course of recent synthetic investigations, we uncovered a novel method to effect such a conversion with a titanocene methylidene complex **1** (Scheme 1), generated either from the Tebbe[3] or

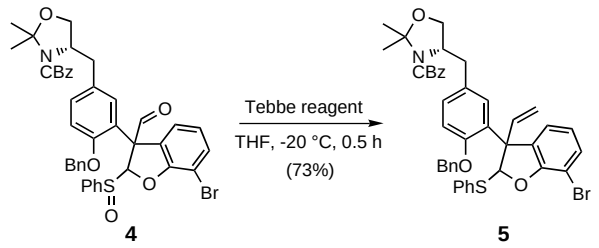


2 **1** **3**

Scheme 1. Generation of a titanocene methylidene complex **1** from the Tebbe (**2**) and Petasis (**3**) reagents. Cp = cyclopentyl.

Petasis[4] reagents (**2** and **3**, respectively). Herein we report the extension of this initial discovery to the deoxygenation of a wide range of highly functionalized sulfoxides, as well as the application of this novel methodology towards the reduction of *N*-oxides and selenoxides. Based upon these results, we propose an unprecedented carbene-initiated deoxygenation mechanism to account for our findings.

When we treated aldehyde **4** (Scheme 2) with an excess of Tebbe reagent (2.0 equivalents) at $-20^{\circ}C$, we observed not only the expected formation of the desired alkene, but also the



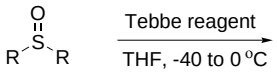
4 **5**

Scheme 2. Discovery of the sulfoxide to sulfide conversion in the presence of Tebbe reagent. CBz = benzyloxycarbonyl, Bn = benzyl.

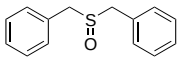
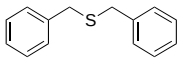
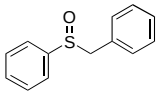
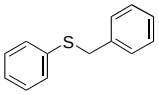
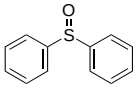
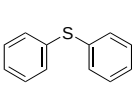
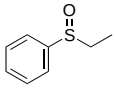
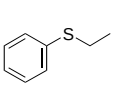
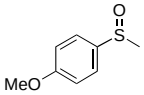
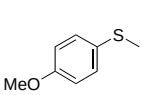
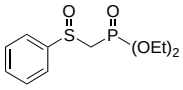
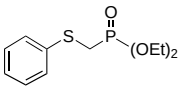
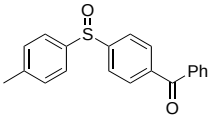
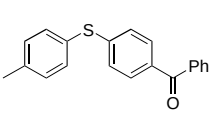
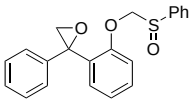
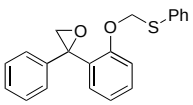
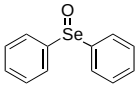
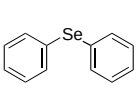
concomitant reduction of the sulfoxide group to the corresponding sulfide **5**. Although we were highly pleased with this serendipitous transformation, since we anticipated having to perform sulfoxide reduction later in our synthetic sequence, we were particularly struck by the mild conditions under which deoxygenation occurred while in the presence of numerous functionalities which survived the reaction conditions. Over the years, numerous methods have been developed to reduce sulfoxides to sulfides; however, many of these transformations require prolonged reaction times, harsh conditions, or reagents that are not readily available. Many other reported methods (see below), even if they do proceed under mild conditions with fair yields, have been explored only on a limited number of simple substrates.[5] In light of this information, we sought to explore the full utility and scope of our deoxygenation process using the Tebbe reagent.

As shown in Table 1, a wide range of diaryl, aryl – alkyl, and dialkyl sulfoxides were readily and rapidly reduced (< 3 hours) in good to excellent yields at low temperature. In particular, the reduction of dibenzylsulfoxide (entry 1)

Table 1. Conversion of sulfoxides into sulfides and the reduction of selenoxides.



(1)

Entry	Starting material	Product	Time [h]	Yield [%]
1			2	80
2			3	81
3			0.5	94
4			3	85
5			2	84
6			4	77
7			18	25
8			1	85
9			2	50
10			4	81

serves as a diagnostic measure of the utility of the reaction, since most methods either fail completely with this substrate or only provide poor yields of dibenzylsulfide.[6] Moreover, despite the high oxophilicity of titanocenes, sulfoxides were prefentially reduced by Tebbe reagent in the presence of both ketones (entry 8) and epoxides (entry 9).[7] We did find, however, that we could not effect selective reduction of sulfoxides in the presence of aldehydes, amides, or esters, with both sulfoxide deoxygenation and carbonyl methylenation occurring simultaneously. The only other sulfoxide substrate with which any difficulty was encountered was the sterically hindered di-*tert*-butyl sulfoxide (entry 7); after a prolonged reaction time, only a 25% isolated yield of product was obtained with recovery of a significant amount of unreacted starting material. Attempted reduction of diphenyl sulfone resulted in only the recovery of starting material, suggesting that the polarized nature of sulfoxides is critical for reactivity.

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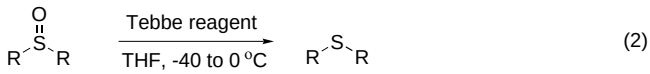
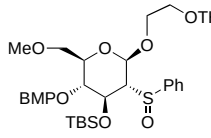
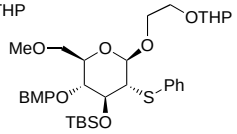
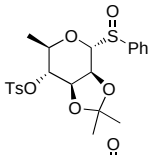
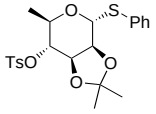
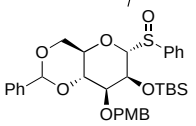
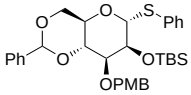
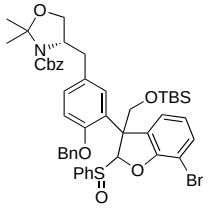
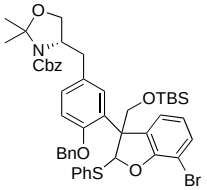
Although we found that phosphine oxides could not be deoxygenated with this protocol (neither triphenylphosphine oxide nor the phosphonate residue in entry 6 were reduced), diphenylselenoxide was readily reduced upon exposure to Tebbe reagent (entry 10).

With the scope of the reaction more clearly defined, we next sought to employ several advanced sulfoxide-containing synthetic intermediates to stringently test whether this methodology could be applied in the preparation of complex molecules (Table 2). In particular, due to their widespread use in carbohydrate chemistry, we attempted to chemoselectively reduce the sulfoxide group in several sugars. Gratifyingly, sugars containing a sulfoxide moiety in both the anomeric and the 2-position were smoothly reduced in high yield in the presence of various acetal, silyl, benzyl, THP, and tosyl protecting groups. The carbamate and aryl halide groups in entry 4 were also found to be inert under the reaction conditions. To the best of our knowledge, no other methodology currently exists where sulfur deoxygenation can occur in the presence of every one of these functional and/or protecting groups. As such, the highly selective nature of this reaction renders sulfoxides as a viable protecting group for thioethers in organic synthesis.

Table 2. Advanced examples of sulfide generation from sulfoxides.

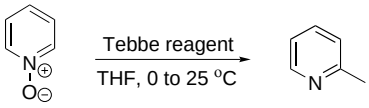


(2)

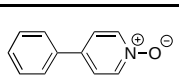
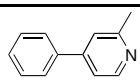
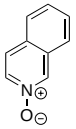
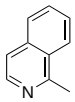
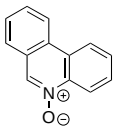
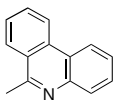
Entry	Starting material	Product	Time [h]	Yield [%]
1			3	79
2			1	76
3			0.5	84
4			1	83

Several other titanium-based reagents are known to effect the sulfoxide to sulfide conversion, such as $TiCl_4/LiAlH_4$,[6a] $TiCl_4/NaBH_4$,[8] $TiCl_4/Sm$,[9] $TiCl_4/NaI$,[10] $TiCl_3$,[11] $TiCl_2$,[12] $Cp_2Ti(CO)_2$,[13] Cp_2TiCl_2/iPrMgBr,[14] and a titanium–porphyrin complex;[15] for each of these reagent combinations, it is thought that either a low-valent Ti^{II} or Ti^{III} species is the active component, which effects deoxygenation by a redox pathway. In our case, however, since the titanocene methylidene **1** derived from Tebbe reagent is an active Ti^{IV} species, we hypothesized that sulfoxide reduction was occurring by a novel mode of action. To test this assumption, we explored the deoxygenation of pyridine *N*-oxides, a process which can be effected by several of the reagents listed above. Surprisingly, as shown in Table 3, when we subjected three different pyridine-derived *N*-oxides to Tebbe reagent, we observed the smooth formation of the corresponding 2-methylpyridines as opposed to just simple heterocycle deoxygenation. Interestingly, in the case of isoquinoline *N*-oxide (entry 2), the formation of solely one regioisomeric product was observed. Not only is this conversion of pyridine *N*-oxides to 2-methylpyridines entirely unprecedented, but this result also clearly indicates that the reaction follows a novel mechanism, different from those previously reported for titanium-mediated deoxygenation.

Table 3. Generation of 2-methylpyridines from pyridine *N*-oxides upon exposure to Tebbe reagent.



(3)

Entry	Starting material	Product	Time [h]	Yield [%]
1			2	83
2			2	90
3			2	87

To verify that a titanocene methylidene complex was indeed playing an active role in the deoxygenation process, as well as to exclude any possible role that an aluminum species derived from **2** might have in the reaction, we subjected diphenylsulfoxide, isoquinoline *N*-oxide, and diphenyl selenoxide to the Petasis reagent (**3**), readily prepared upon addition of methyl lithium to Cp_2TiCl_2.[16] Gratifyingly, as shown in Table 4, the reaction proceeded smoothly, albeit with longer reaction times at higher temperature, providing the same deoxygenated product in each case in high yield.

With these results in hand, the mechanism by which the titanocene methylidene exerts deoxygenation would appear to be a carbene-initiated process, as delineated in Scheme 3. For sulfoxides, initial oxygen coordination to titanium is followed by the formation of a metallacycle **8**, which then breaks down to reveal a sulfur-based ylide. Due to the inherent instability of species such as **9**, the nonstabilized ylide decomposes upon standing to provide the observed sulfide

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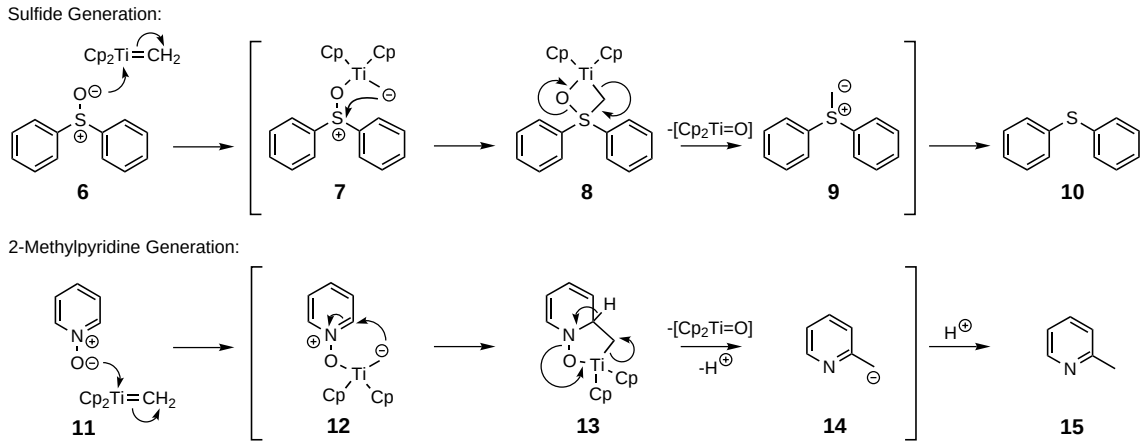
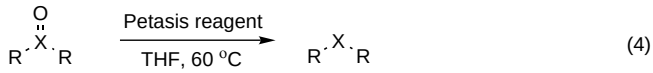
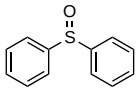
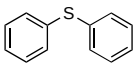
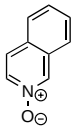
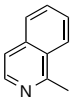
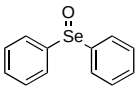
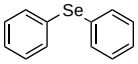


Scheme 3. Proposed carbene-based mechanisms to account for sulfur deoxygenation and 2-methylpyridine formation upon exposure to the Tebbe or Petasis reagents.

Table 4. Use of the Petasis reagent to effect sulfoxide, pyridine *N*-oxide, and selenoxide reductions.



(4)

Entry	Starting material	Product	Time [h]	Yield [%]
1			12	97
2			12	77
3			12	91

10.[17] In the pyridine *N*-oxide case, the same initial addition of oxygen to titanium is postulated to occur (to form intermediate **12**), but since the resultant alkyl anion cannot engage the nitrogen atom directly as in the sulfoxide case, it instead adds to the ortho position, forming a five-membered metallacycle in what is formally a 3+2 cycloaddition process. Once **13** has formed, hydrogen elimination results in the formation of **14** attended by the release of $Cp_2Ti{=}O$; ensuing proton capture generates the final 2-methylpyridine product **15**. In an additional experiment, the existence of intermediate **14** was confirmed by the incorporation of a single deuterium on the methyl group of **15** upon quenching the reaction with D_2O, as verified by ^1H NMR, ^{13}C NMR, and HRMS analyses.

In conclusion, we have discovered a novel methodology by which to deoxygenate sulfoxides and selenoxides as well as generate 2-methylpyridines from the corresponding *N*-oxides by an unprecedented carbene-initiated deoxygenation mechanism. Moreover, the mild conditions employed, as well as the wide range of both functional and protecting groups which have been successfully incorporated, now permits the use of sulfoxides as protecting groups and auxiliaries for complex synthetic substrates.

Experimental Section

All sulfoxides were prepared by oxidizing the precursor sulfide with *m*CPBA (1.0 equivalent) in CH_2Cl_2 at 0°C, with reaction completion typically observed within fifteen minutes. All *N*-oxides were prepared by the method of C. Copéret, H. Adolfsson, T.-A. V. Khuong, A. K. Yudin, K. B. Sharpless, *J. Org. Chem.* **1998**, *63*, 1740–1741. Diphenyl selenoxide was prepared as described by M. R. Detty, *J. Org. Chem.* **1980**, *45*, 274–279.

In a representative procedure, the sulfoxide (0.5 mmol) was dissolved in anhydrous THF (20 mL), cooled to −40°C, and then treated with Tebbe reagent (0.5 M in toluene, 0.55–0.75 mmol, 1.1–1.5 equivalents). The reaction mixture was allowed to slowly warm to 0°C if necessary, with reaction progress monitored by thin layer chromatography. Once the reaction reached completion, any excess Tebbe reagent was quenched by the addition of a few drops of 10% aqueous NaOH. The reaction mixture was then diluted with ether and, once bubbling ceased, $MgSO_4$ was added. Filtration of the solution through Celite, evaporation, and flash column chromatography furnished the pure product. In each case, the generated sulfide matched authentic material based on both thin layer chromatography and ^1H NMR analysis. For the pyridine *N*-oxide substrates, reactions were performed similarly, except the starting temperature was 0°C and the reaction was warmed to ambient temperature. For all reactions involving Petasis reagent, the reagents were refluxed for 12 hours.

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[7] Although the reaction with the epoxide derivative went to completion, difficulty in isolating the final product accounted for the lower yield compared to the other cases reported.

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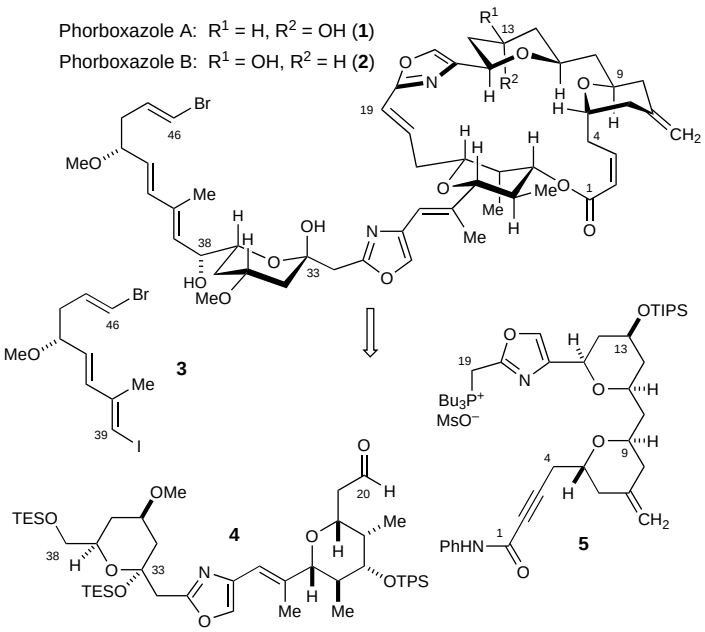


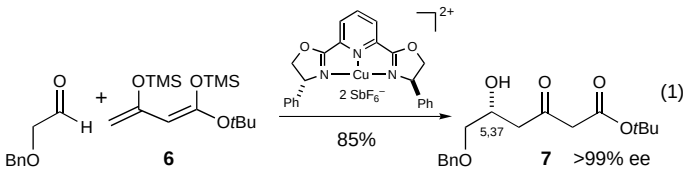
Scheme 1. Retrosynthetic analysis of phorboxazole B. (See ref. [5] for abbreviations.)

Asymmetric Synthesis of Phorboxazole B—Part I: Synthesis of the $C_{20}-C_{38}$ and $C_{39}-C_{46}$ Subunits**

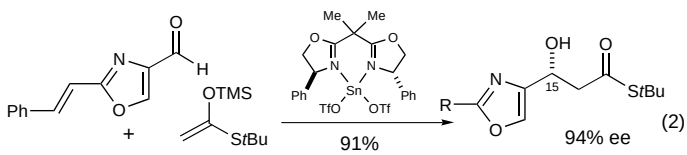
David A. Evans,* Victor J. Cee, Thomas E. Smith, Duke M. Fitch, and Patricia S. Cho

Phorboxazoles A (**1**) and B (**2**) are marine natural products isolated from a newly discovered species of Indian Ocean sponge (genus *Phorbas sp.*).[1] These substances are representatives of a new class of macrolides and are among the most cytostatic natural products known; they inhibit the growth of tumor cells at nanomolar concentrations (mean $GI_{50} = 1.58 \times 10^{-9}$ M).[2] As a result, phorboxazoles A and B have been selected by the National Cancer Institute for in vivo antitumor trials.[1b] The unique structure and impressive biological activity of these molecules have led to widespread efforts to synthesize these substances,[3] and a total synthesis of phorboxazole A has recently been reported.[3u] In this and the following communication[4] we describe our work culminating in the synthesis of phorboxazole B.

The synthesis plan (Scheme 1) calls for an early disconnection of the C_{38}–C_{39} bond to provide the triene side chain **3**, which allows the remainder of the molecule to be divided into fragments of roughly equal complexity. Disconnection through the C_{19}–C_{20} *E* olefin and macrolactone moieties provides the $C_{20}-C_{38}$ core fragment **4** and the C_1-C_{19} bispyran fragment **5**. The distinctive features of this plan include a Wittig reaction to form the C_{19}–C_{20} olefin, macrolactonization of a C_1-C_{38} seco acid, and late-stage incorporation of the fully functionalized triene side chain. The utilization of our recently developed Cu^{2+}-catalyzed enantioselective aldol reaction[6] [Eq. (1)] provides the foundation for the synthesis of two of



the polyacetate regions of the molecule (C_4-C_9 and $C_{33}-C_{38}$), while an enantioselective stannous triflate catalyzed aldol reaction has been employed to assemble the $C_{13}-C_{19}$ oxazole-containing subunit [Eq. (2) where R = 2-phenylethene].[4]



The synthesis of the polypropionate region of the central core fragment **4** began with the addition of the (*E*)-boron enolate of **9**[7] to the known aldehyde **8**,[8] which delivered the desired *anti* aldol adduct in 97% yield (94:6 *dr*) (Scheme 2).[9, 10] Subsequent hydroxyl-directed reduction[11] of the C_{24} ketone provided *anti* diol **10**, which was isolated in 81% yield as a single diastereomer after crystallization.[12] Cyclization of **10** under basic conditions (cat. DBU, CH_2Cl_2) followed by in situ

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