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Efficient stereoselective syntheses of isopanepoxydone and panepoxydone: a re-assignment of relative configuration†

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Abstract

Recent efforts in our laboratories have resulted in efficient racemic syntheses of isopanepoxydone and panepoxydone, secondary metabolites isolated originally from the basidiomycete *Panus conchatus*. These synthetic efforts have led us to assign the structure of isopanepoxydone as that of **3** and re-assign the structure of panepoxydone as **2**.

Intrigued by recent reports describing the potent NF-κB inhibitory activity of cycloepoxydone (**1**) and panepoxydone (**2**),[1,2] two secondary metabolites isolated from fermentations of deuteromycete *45-93* and basidiomycete *conchatus* respectively,[1,3] we began developing efficient strategies for producing these and other congeners via total synthesis. Herein we describe the first total syntheses of isopanepoxydone (**3**) and panepoxydone (**2**), as well as the correction of the relative configuration for **2**.

Given long-range plans for detailed structure–activity relationship studies on several basidiomycete metabolites (e.g. **1**–**3**) and biologically relevant analogs, we are focusing on a synthetic strategy that utilizes the very versatile differentially protected vinyl bromides (**4**) as common intermediates (Scheme 1). As outlined in Scheme 2, the corresponding acetate (**8**) is readily prepared from TBS-protected bromoxone (**5**)[4] via reduction ($NaBH_4$, $CeCl_3$) and acylation (Ac_2O, DMAP). The chemical course of the reduction, which furnishes a 1:1 mixture of diastereomers,[5] was unambiguously established by deprotection and ^{13}C NMR analysis of the derived alcohols **9** and **10**. Thus, deprotection of the more polar isomer (**6**) furnishes the known asymmetric product (**9**),[6] whereas exposure of **7** to similar conditions produces the known symmetric diastereomer (**10**) (Scheme 3).[7]

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† It is with tremendous admiration, respect, and gratitude that we dedicate this paper to Professor Harry Wasserman on the occasion of his 80th birthday.

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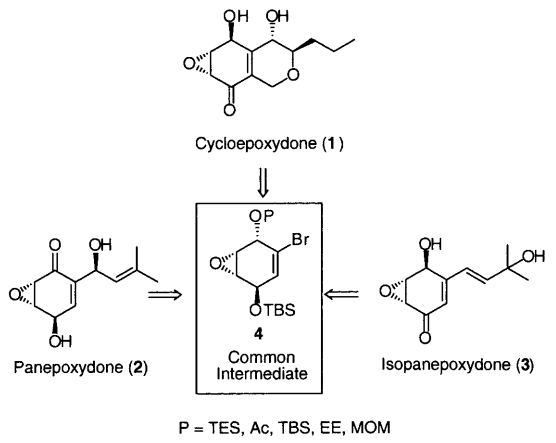
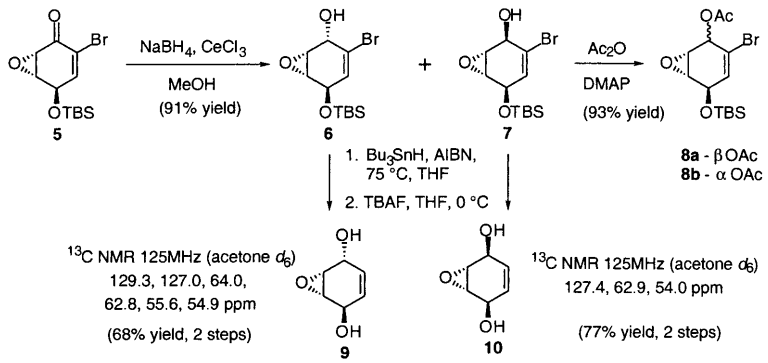
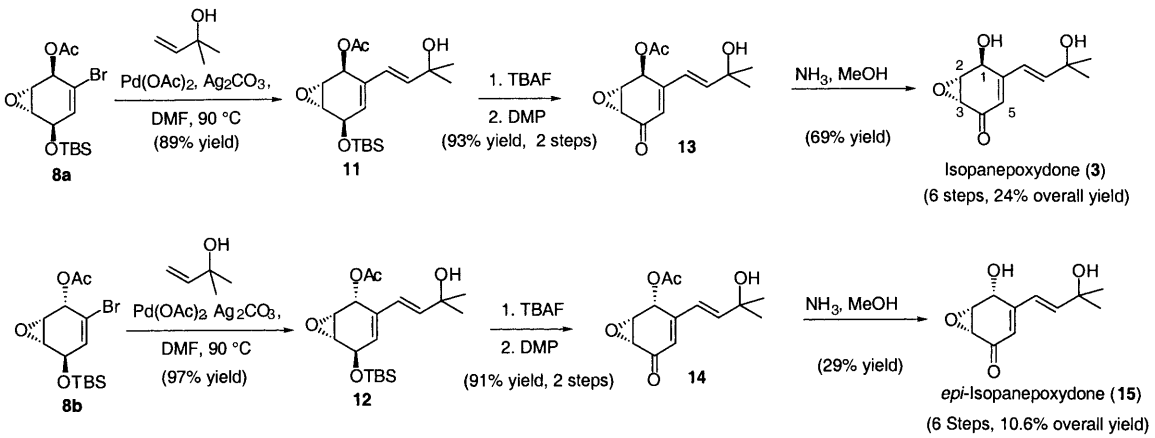


Scheme 1.



Scheme 2.



Scheme 3.

Although stereoselective access to intermediate **7** is important vis-á-vis syntheses of **1**–**3**, assigning the as yet unknown relative configuration of **3** required advancement of both **8a** and **8b** to the corresponding isopanepoxydone skeleton. To this end, coupling of **8a** and **8b** to 2-methyl-3-buten-2-ol under Heck conditions ($Pd(OAc)_2$, Ag_2CO_3) furnished **11** and **12**, respectively. Removal of the TBS protecting groups in **11** and **12** (TBAF) followed by Dess–Martin oxidation of the derived alcohols produces the moderately unstable acetates **13** and **14**.[8] Deacylation with methanolic ammonia furnished **3** and **15**.

As illustrated by the data in Table 1, the ^1H NMR chemical shift and coupling constant data obtained for **3** and **15** are only slightly discernible at high field (500 MHz) hence assigning relative configuration by comparison to the low field data (60 MHz) reported for the natural product did not seem prudent.[9] However, the physical properties of the two compounds suggest that the *anti* orientation of the epoxide and alcohol oxygens is conserved among panepoxydone, isopanepoxydone, and cycloepoxydone. Thus, in our hands compound **15** is an unstable oil which decomposes to aromatic materials within minutes at temperatures above 30–35°C. In contrast, **3** is a well-behaved white solid with a melting point similar to that reported for isopanepoxydone (118–120°C versus 123–124°C). Combined, these observations suggest that **15** would not have survived the isolation conditions described in the literature and hence the relative configuration of the natural product is as illustrated in **3**.[3]

Table 1
Relevant chemical shifts and coupling constants

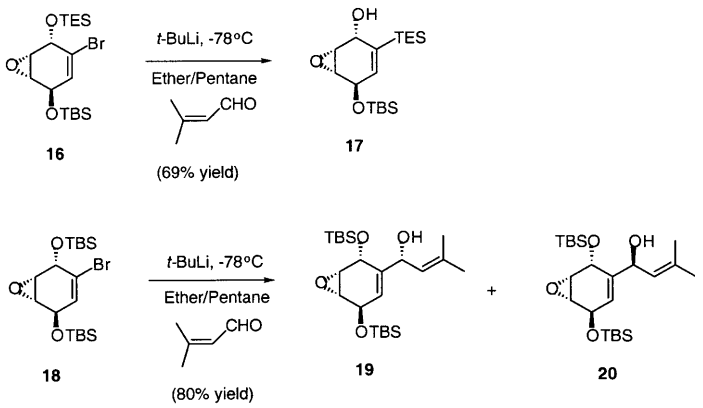
Proton	Chemical shift (ppm)[a]			Coupling constants (Hz)[b]		
	Nat. prod.	**3**	**15**	Nat. prod.	Synthetic **3**	Synthetic **15**
1	4.7	4.78	4.72	1/2 = 3	1/2 = < 1.5	1/2 = 3.1
2	3.9	3.77	3.81	2/3 = 4	2/3 = 3.9	2/3 = 4.1
3	3.5	3.43	3.42	3/5 = 2	3/5 = 2.0	3/5 = 3.0
5	5.9	5.86	5.89	5/1 = 1		

[a] Experiments were performed in DMSO-d_6 and chemical shift assignments were confirmed by a combination of HMBC and HETCOR $^1H/^{13}C$ correlated spectroscopy.

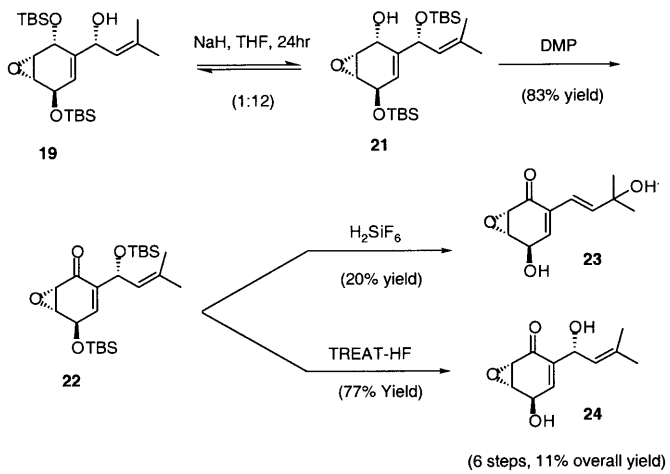
[b] Coupling constants were determined by selective homonuclear decoupling experiments.

We next turned toward advancing an existing intermediate to panepoxydone (**2**).[10] Halogen–metal exchange with **16** yielded only the product resulting from a retro-Brook rearrangement (**17**).[11] Similarly, treatment of **18** with *t*-BuLi in THF gave an analogous rearrangement. However, treatment of **18** with *t*-BuLi in ether/pentane afforded a 1.4:1 mixture of the allylic alcohols **19** and **20** (relative configuration established by X-ray crystallographic analysis of **20**). We initially sought to advance the major diastereomer **19** to panepoxydone as it contained the relative configuration described in the literature.[2,3,12] Treatment of **19** with NaH in THF over 24 hours generates a mixture of **19** and **21** (1:12).[13] Dess–Martin oxidation of **21** gives the bis-TBS ether **22**. Unfortunately, deprotection of **22** proved non-trivial. Attempts at deprotection with TBAF, TBAF–AcOH, TAS–F, $LiBF_4$, HF–pyridine, and KF–acetonitrile yielded only intractable mixtures of aromatic products. Mildly acidic conditions, including H_2SiF_6 and 2% HF–acetonitrile gave only low yields of the rearranged compound **23**. Finally, employment of

TREAT–HF with a modified work-up procedure gave **24**.[14] Interestingly, the spectral properties of **24** differed markedly from those of authentic panepoxydone, indicating that the relative configuration described in the literature is incorrect (Schemes 4 and 5).[15]

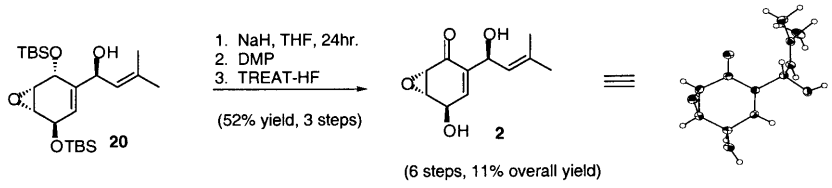


Scheme 4.



Scheme 5.

Advancement of the minor diastereomer **20** through the silyl migration, oxidation, and deprotection sequence gave, without incident, **2**, which has ^{1}H and ^{13}C properties identical to those of natural panepoxydone. In our hands, **2** was a white crystalline solid and thus single-crystal X-ray analysis was employed to provide unambiguous assignment of panepoxydone's relative configuration to that illustrated in **2** (Scheme 6).



Scheme 6.

In summary, isopanepoxydone (**3**) has been synthesized in six steps, 24% yield from **5**, and its relative configuration has been established by the comparison of spectroscopic and physical properties to those reported in the literature. Panepoxydone (**2**) has been prepared in six steps, 11% yield, from **5**, and its relative configuration has been reassigned by comparison with more recent, authentic spectroscopic data.[15]

Acknowledgements

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5. (a) The structure assigned to each new compound is in accord with its infrared and high-field ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) The syntheses reported herein are racemic; hence illustrations convey only relative configurational information.
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8. Although the structures of the decomposition products have not been fully delineated, these compounds appear by ^{1}H and ^{13}C NMR to undergo aromatization. Notably, **13** is easier to handle than **14**.
9. Assignment of structure by comparison of IR and UV data is equally dubious.
10. Attempts to functionalize **4** via carbonylative Stille coupling failed, as did all efforts to affect an allylic rearrangement of **11**.
11. Hoffman, R.; Brueckner, R. *Chem. Ber*. **1992**, *125*, 2731.
12. (a) Imagawa, Y.; Shima, S.; Hirota, A.; Sakai, H. *Agric. Biol. Chem*. **1979**, *43*, 2437. (b) Anderson, M. G.; Jarman, T. B.; Rickards, R. W. *J. Antibiot*. **1995**, *48*, 391.
13. Although normally a nuisance, others have used such migrations to their advantage using similar conditions (a) Molander, G. A.; Swallow, S. *J. Org. Chem*. **1994**, *59*, 7148. (b) Crich, D.; Ritchie, T. J. *Carbohydr. Res*. **1990**, *197*, 324.
14. (a) We employed a modified procedure to that described in the literature.[14b] Dilution of 30 mg of **24** in 2 mL dry acetonitrile followed by addition of 300 μL of commercial TREAT–HF solution in 100 μL aliquots over 48 hours, subsequent aqueous work-up with 5% $NaHPO_4$ and drying over $KHCO_3$ gave **26** in 77% yield. (b) Tius, M. A.; Hu, H.; Kawakami, J.; Busch-Petersen, J. *J. Org. Chem*. **1998**, *63*, 5971.
15. We are grateful to Professor Olov Sterner for providing us with 500 MHz ^{1}H and 125 MHz ^{13}C NMR data of authentic panepoxydone.