Organic Syntheses

Discussion Addendum for:

Allylic Oxidation Catalyzed by Dirhodium(II) Tetrakis[ε-caprolactamate] of *tert*-Butyldimethylsilyl-protected *trans*-Dehydroandrosterone

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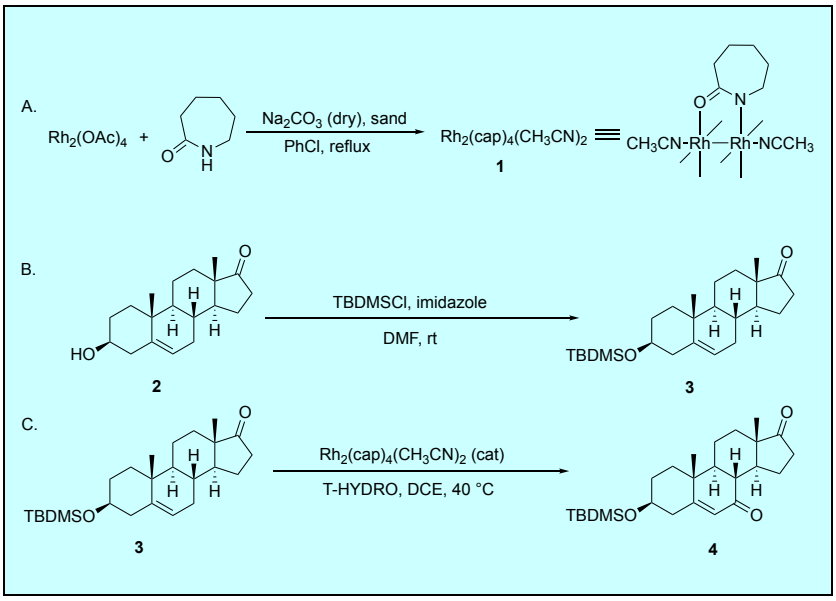
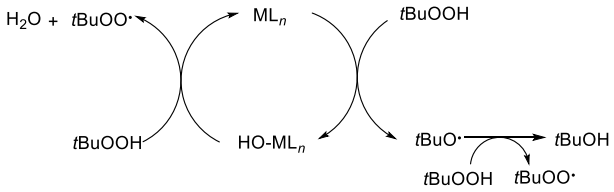
Original Article: Ratnikov, M. O.; Goldmann, P. L.; McLaughlin, E. C.; Doyle, M. P. Org.Synth. ***2012****, 89, 19–33.*



Allylic oxidation of alkenes, which converts an allylic methylene group to a carbonyl group,[2] is powerful methodology for the synthesis of unsaturated ketones.[3] Compared with more traditional oxidative reagents, such as stoichiometric oxidants selenium dioxide[4] and chromium(VI),[5] the mild *tert*-butyl hydroperoxide (TBHP) oxidant, when combined with select

transition metals, has advantages,[6] especially in large-scale reactions and natural product syntheses. Doyle and coworkers have developed an efficient and selective oxidative system using dirhodium(II) caprolactamate $Rh_2(cap)_4$ as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant.[7] Since this protocol was first reported for the allylic oxidation of cyclic alkenes, a variety of oxidative transformations, including benzylic oxidations,[8] propargylic oxidations,[9] oxidative reactions with phenols and aniline,[10] imine formation from secondary amines,[11] and oxidative Mannich reactions of *N*,*N*-dialkylanilines, have also been shown to be efficient.[12]

The success of TBHP as a selective oxidant is due to formation of the *tert*-butylperoxy radical (Scheme 1).[13] Although the initial reaction with the transition metal is O-O cleavage, the initially formed and more reactive *tert*-butoxy radical preferentially abstracts a hydrogen atom from TBHP at a near diffusion-controlled rate. The oxidized transition metal compound then undergoes reductive elimination with the formation of water and the *tert*-butylperoxy radical. In these reactions dirhodium caprolactamate appears to have an advantage over other transition metal complexes because of its low oxidation potential and high turnover rates.[14] A competing reaction for the *tert*-butylperoxy radical is dimerization that results in the production of dioxygen and di-*tert*-butyl peroxide.

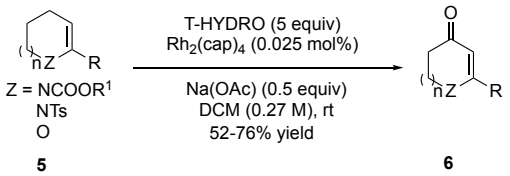


Scheme 1. Catalytic production of the *tert*-butylperoxy radical

At the time of our 2012 *Org. Synth.* report, allylic oxidations catalyzed by $Rh_2(cap)_4$ and TBHP focused on cyclic alkenes, including unsaturated steroids, and on electron-deficient acyclic alkenes. The applications of this powerful catalytic oxidative method to other substrates bearing allylic C-H bonds, especially in the total synthesis of natural products, are summarized in this Discussion Addendum.

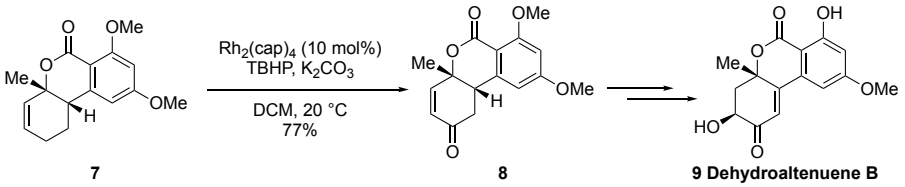
N-Substituted 2,3-dihydro-4-piperidones and substituted 4-pyranone compounds are important intermediates in natural products and drug candidates.[15] Allylic oxidations of cyclic enamides and enol ethers provide substituted piperidones and pyranones by $Rh_2(cap)_4$-catalyzed oxidations

using TBHP with NaOAc as the additive (Scheme 2).[16] Initial hydrogen atom abstraction produces a heteroatom-stabilized allylic radical, with ketone formation at the 4-position when R= aryl or alkyl and at the 2-position when R = H. Oxidation occurs under mild conditions with very low catalyst loading.



Scheme 2. Catalytic oxidation of cyclic enamides and enol ethers

Although many allylic oxidation methods have been reported, it is challenging to find the optimal methodology that provides the necessary chemo-, regio- and stereoselectivity for the synthesis of multifunctional natural products.[3b] The $Rh_2(cap)_4$-catalyzed TBHP allylic oxidation was employed for the synthesis of *dehydroaltenuene B*, which had been isolated from cultures of an unidentified freshwater aquatic fungal species from the Tubeufiaceae family.[17] In the first total synthesis of *dehydroaltenuene B* by the Barrett group,[18] the authors found that α, β -unsaturated ketone **8**, which was the key intermediate, could be obtained by TBHP allylic oxidation of fused cyclic alkene **7** in good yield (Scheme 3).

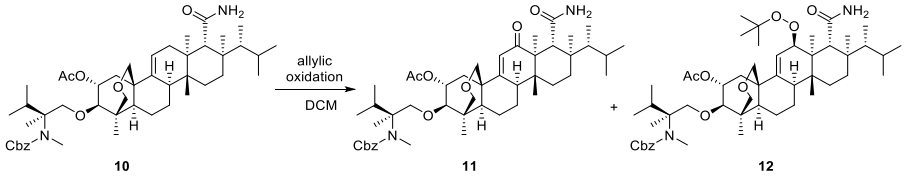


Scheme 3. Preparation of 8 in the total synthesis of dehydroaltenuene B

In the synthesis of antifungal glucan synthase inhibitors from *enfumafungin*, the allylic oxidation of amide **10** to enone **11** is one of the key steps.[19] The method first reported by Merck Research Laboratories and Scynexis Inc., required 45 equivalents of CrO_3 and 3,5-dimethylpyrazole (3,5-DMP) (Table 1, entry 1).[20] The yield of enone **11** decreased to 36% when CrO_3 and 3,5-DMP were reduced to 15 equivalents (Table 1, entry 2). Further optimization of this step with catalytic metal catalyst and TBHP or cumene hydroperoxide (CHP) demonstrated that the oxidation of **10** catalyzed by

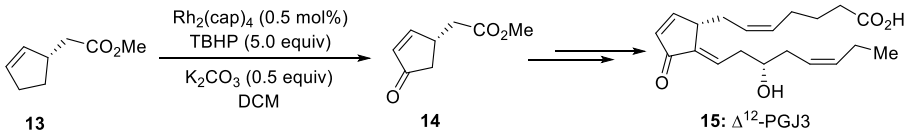
$Rh_2(cap)_4$ afforded enone **11** and *tert*-butylperoxy ether **12** (1.3 : 1), with a 30% isolated yield of enone **11**. The oxidation of amide **10** under Corey-Yu conditions[21] gave a similar result, which could be further optimized with a bulkier oxidant CHP (Table 1, entries 4-5).

Table 1. Allylic of amide 10 to enone 11



Entry	Catalyst	Additive	Oxidant	T(°C)	**11**:**12**	**11** (%)
1	-	3,5-DMP (45 equiv)	CrO_3 (45 equiv)	-25 to 15	-	85
2	-	3,5-DMP (15 equiv)	CrO_3 (15 equiv)	-25 to 15	-	36
3	$Rh_2(cap)_4$	K_2CO_3	TBHP	rt	1.3:1	30
4	$Pd(OH)_2/C$	K_2CO_3	TBHP	rt	1.3:1	34
5	$Pd(OH)_2/C$	K_2CO_3	CHP/TBHP (12/10 equiv)	0-5	6.6:1	64

Δ ^{12}-Prostaglandin J_3 (Δ ^{12}-PGJ_3) and analogs have been reported as potent and selective antileukemic prostaglandin compounds.[22] In the synthesis of Δ ^{12}-PGJ_3, Nicolaou and coworkers found that selective allylic oxidation could be achieved by the combination of $Rh_2(cap)_4$ and TBHP, which produced **14** in 48% yield, while other common conditions like SeO_2, *t*BuOOH/PDC, *t*BuOOH–bleach, and $Mn(OAc)_3$ with or without an O_2 atmosphere were generally inferior (Scheme 4).[23] The effects of ring sizes and side-chain functionalities on the oxidative reactions were also studied (Table 2). Substrates with side-chain electron withdrawing groups undergo direct allylic oxidation without migration of the double bond (Table 2, entries 1 and 2); however, formation of the more stable allylic radical produced transposed enones as the main or exclusive product when other cyclic alkenes were investigated (Table 2, entries 3-11).



13 **14** **15:** Δ^{12}-PGJ3

Scheme 4. Synthesis of enone 14 as the intermediate of Δ^{12}-PGJ$_3$

Table 2. Regioselective allylic oxidation of substituted cycloalkenes by (A) $Rh_2(cap)_4$ (0.5 mol%) and *t*BuOOH (5.0 equiv) or (B) $Mn(OAc)_3$ (20 mol%)) and *t*BuOOH (4.0 equiv)

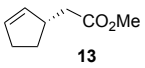
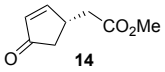
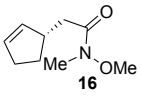
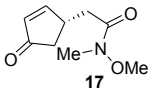
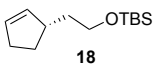
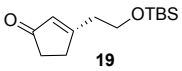
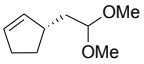
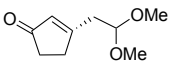
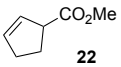
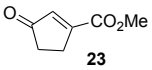
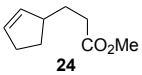
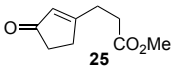
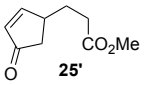
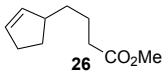
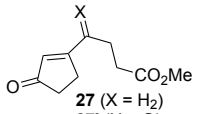
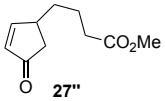
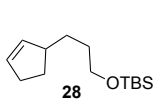
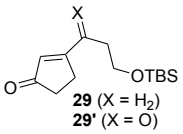
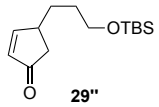
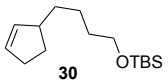
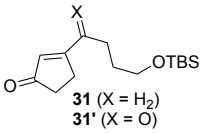
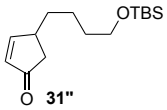
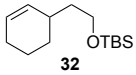
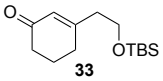
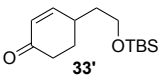
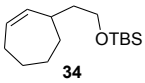
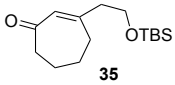
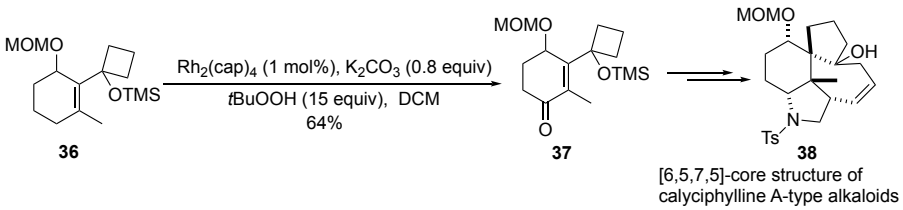
Entry	Substrate	Product(s)	Yield
1	 **13**	 **14**	**A**: 48 **B**: 35
2	 **16**	 **17**	**A**: 41 **B**: 37
3	 **18**	 **19**	**A**: 63 **B**: 61
4	 **20**	 **21**	**A**: 45 **B**: 39
5	 **22**	 **23**	**A**: 38 **B**: 47
6	 **24**	 **25**  **25'**	**A**: 26/13 **B**: 20/0
7	 **26**	 **27** (X = H_2) **27'** (X = O)  **27''**	**A**: 20/14/6 **B**: 22/6/8

Table 2 (continued)

8	 **28**	 **29** (X = H_2) **29'** (X = O)	 **29"**	**A**: 32/9/13 **B**: 6/7/11
9	 **30**	 **31** (X = H_2) **31'** (X = O)	 **31"**	**A**: 20/11/7 **B**: 21/9/11
10	 **32**	 **33**	 **33'**	**A**: 43/10 **B**: 34/11
11	 **34**	 **35**		**A**: 64 **B**: 27

Tu and coworkers developed an efficient synthesis route for the construction of the core structure of *calyciphylline A* type alkaloids **38** in which the precursor of key rearrangement step was synthesized by $Rh_2(cap)_4$-catalyzed allylic oxidation of a substituted cyclohexene (Scheme 5).[24] This transformation shows good tolerance of functional groups for this oxidative method.

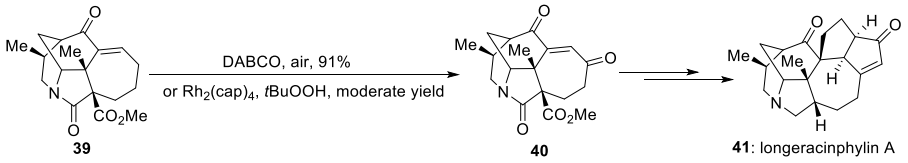


36 **37** **38**

Scheme 5. Synthesis of the rearrangement precursor 37

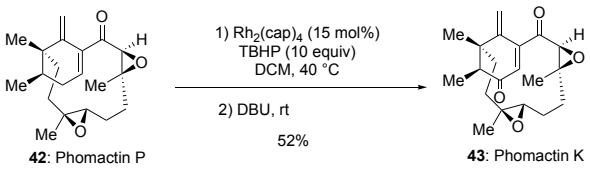
In the asymmetric total synthesis of *longeracinphyllin A* **41**, Li and coworkers found that the allylic oxidation of enone **39**, promoted by DABCO and air, furnished enedione **40** in 91% yield, presumably through enolate peroxidation and hydroxyl elimination (Scheme 6).[25] The author also

reported that $Rh_2(cap)_4$-catalyzed TBHP oxidation could also achieve this transformation, but yield of the reaction was moderate.



Scheme 6. Allylic oxidation of enone 39 to enedione 40

The Sarpong group reported the synthesis of a range of phomactin congeners via a common intermediate.[26] The allylic oxidation of phomactin P provided phomactin K in 52% yield (Scheme 7). Amazingly, in this process the exocyclic double bond and epoxide functional groups of phomactin P survive.



Scheme 7. Allylic oxidation of phomactin P to phomactin K

7α-Hydroxy-cholest-4-en-3-one has been reported as a biomarker for bile acid loss, irritable bowel syndrome, and other associated disorders and diseases. A key feature of the synthesis of this compound reported by the Yoshimoto group[27] involved two allylic oxidative reactions, the C-7 allylic oxidation of **44** to give **45** and the C-3 allylic oxidation of **46** to give **47** (Tables 3 and 4). In the C-3 allylic oxidation, use of $Rh_2(cap)_4$ as the catalyst with TBHP was competitive with those with CrO_3 or PCC oxidants (entries 1-2) or oxidations by TBHP catalyzed by other transition metal compounds (entries 3 and 6). However, $Co(OAc)_2$ and CuI were superior to $Rh_2(cap)_4$ as catalysts for the allylic oxidation of enone **47** (Table 4).

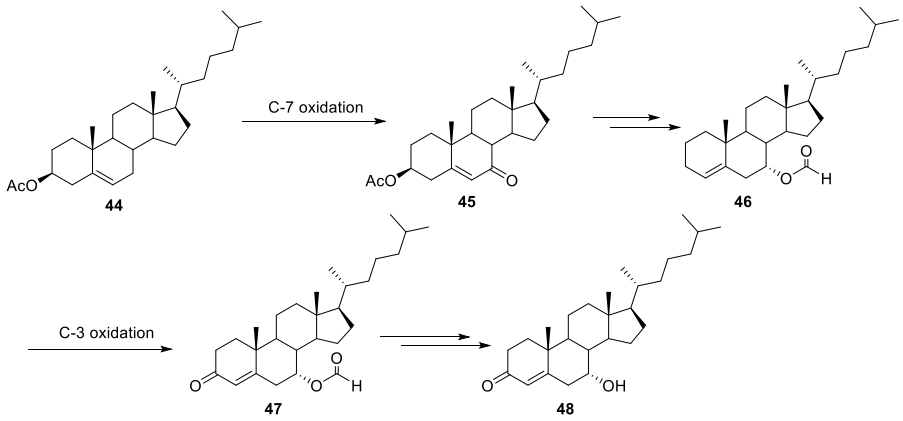


Table 3: Summary of C7-oxidation conditions[a]

Entry	Time	Metal	Solvent	Isolated yield of **45**
1	12 h	CrO_3/3,5-DMP	DCM	79%
2	36 h	PCC	Toluene	27%
3	20 h	$Co(OAc)_2$	CH_3CN	68%
4	24 h	$Rh_2(cap)_4$	DCE	71%
5	12 h	$Rh_2(cap)_4$	DCE	45%
6	20 h	CuI	CH_3CN	53%

[a]For entries 2–6: the metal was added to the solution of the starting material (**44**, 300 mg, 0.7 mmol) in indicated solvent (5–6 mL) in a 50 mL screw cap vial fitted with a rubber stopper. The reaction mixture was evacuated and backfilled with nitrogen. For entries 4–6: 1 mg of metal was used. For entry 3: 30 mg of $Co(OAc)_2$ tetrahydrate (0.12 mmol, 0.17 equiv) was used. For entry 2: 1.8 g of PCC (8.4 mmol, 12 equiv.) and 3.52 g of celite (58 mmol) were used (and stirred at reflux). Entries 3–6: the reaction temperature was 40°C, 1.5 mL (70% in water, v/v) of *tert*-butyl hydroperoxide (11 mmol, 15 equiv) was used.

Table 4: Summary of C3-oxidation conditions[a]

Entry	Time	Metal	Solvent	Isolated yield of **47**
1	12 h	CrO_3/3,5-DMP	DCM	56%
2	20 h	$Co(OAc)_2$	DCM	60%
3	24 h	$Rh_2(cap)_4$	DCE	33%
4	12 h	$Rh_2(cap)_4$	DCE	37%
5	20 h	CuI	DCM	58%

[a]For entries 2–5: *tert*-butyl hydroperoxide was used (0.15 mL, 1.1 mmol), reaction temperature was 40 °C, 5 mL of solvent was used. Entry 2: 105 mg of starting material (0.25 mmol), 10 mg of $Co(OAc)_2$ (0.04 mmol), gave 66 mg of product (0.15 mmol, 60%). Entry 3: 92 mg of starting material (0.22 mmol), 1 mg of $Rh_2(cap)_4$ used gave 31 mg of product (0.072 mmol, 33%). Entry 4: 130 mg of starting material (0.31 mmol), 1 mg of $Rh_2(cap)_4$ used gave 50 mg of product (0.12 mmol, 37%) and 8 mg of 27 (0.019 mmol, 6%). Entry 5: 83 mg of starting material (0.2 mmol), 1 mg of CuI used gave 50 mg of product isolated (0.12 mmol, 58%).

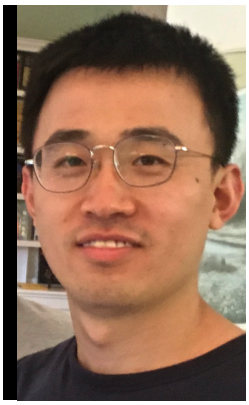
In summary, dirhodium(II) caprolactamate is a selective and efficient catalyst for TBHP oxidations of the allylic C-H bond. The method features high selectivity, low catalyst loading (usually 0.025 mol%-1 mol%), mild conditions, and a broad substrate scope. Substrates that enunciate $Rh_2(cap)_4$ limitations on allylic oxidations are acyclic olefins, whereas acyclic enones are applicable for this type of oxidation. The reagent's application to allylic oxidations in the total synthesis of natural products demonstrates its utility.

References

1. Department of Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249. Email: michael.doyle@utsa.edu. Financial support from the Welch Foundation (AX-1871) is gratefully acknowledged.
2. (a) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567–3571; (b) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845–866; (c) Moiseev, I. I.; Vargaftik, M. N. *Coord. Chem. Rev.* **2004**, *248*, 2381–2391; (d) Weidmann, V.; Maison, W. *Synthesis* **2013**, *45*, 2201–2221; (e) Chen, K.; Zhang, P.; Wang, Y.; Li, H. *Green Chem.* **2014**, *16*, 2344–2374.
3. (a) *Modern Oxidation Methods*, 2nd ed.; Backvall, J.-E., Eds.; Wiley-VCH: Weinheim, 2010; (b) Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421–1451.
4. (a) Rapoport, H.; Bhalerao, U. T. *J. Am. Chem. Soc.* **1971**, *93*, 4835–4840; (b) Rabjohn, N. *Org. React.* **1976**, *24*, 261–415; (c) Crich, D.; Zou, Y. *Org. Lett.* **2004**, *6*, 775–777.
5. (a) G. Canielli and G. Cardillo, Chromium oxidation in organic chemistry, Springer, Berlin, 1984; (b) Muzart, J. *Chem. Rev.* **1992**, *92*, 113–140.
6. (a) Caudle, M. T.; Riggs-Gelasco, P.; Gelasco, A. K.; Penner-Hahn, J. E.; Pecoraro, V. L. Inorg. Chem. **1996**, *35*, 3577–3584; (b) Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Liguori, L.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 3849–3857; (c) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, 33–34; (d) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233; (e) Shing, T. K. M.; Yeung, Y. Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151.
7. Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623.
8. Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167–5170.

9. McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317–4319.
10. Ratnikov, M. O.; Farkas, L. E.; McLaughlin, E. C.; Chiou, G.; Choi, H.; El-Khalafy, S. H.; Doyle, M. P. *J. Org. Chem.* **2011**, *76*, 2585–2593.
11. Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745–747.
12. Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649.
13. Ratnikov, M. O.; Doyle, M. P. *Mendeleev Commun.* **2014**, *24*, 187−196.
14. Doyle, M. P.; Ren, T. *Prog. Inorg. Chem.* **2001**, *49*, 113–168.
15. (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309-3362; (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2474; (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59* , 2953–2989.
16. Yu, Y.; Humeidi, R.; Alleyn, J. R.; Doyle, M. P. *J. Org. Chem.* **2017**, *82*, 8506–8513.
17. Jiao, P.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *J. Nat. Prod.* **2006**, *69*, 612–615.
18. Soorukram, D.; Qu, T.; Barrett, A. G. M. *Org. Lett.* **2008**, *10*, 3833–3835.
19. Zhong, Y. L.; Gauthier, D. R.; Shi, Y. J.; McLaughlin, M.; Chung, J. Y. L.; Dagneau, P.; Marcune, B.; Krska, S. W.; Ball, R. G.; Reamer, R. A.; Yasuda, N. *J. Org. Chem.* **2012**, *77*, 3297–3310.
20. (a) Greenlee, M. L.; Meng, D.; Mamai, A.; Fan, W.; Balkovec, J. M.; Peel, M.; Li, K. Antifungal agents. PCT Int. Appl. WO 2007126900, 2007. (b) Balkovec, J. M.; Boufford, F. A.; Tsu, B.; Dropinski, J.; Meng, D.; Greenlee, M. L.; Peel, M.; Fan, W.; Mamai, A.; Liu, H.; Li, K. Antifungal agents. PCT Int. Appl. WO 2007127012, 2007. (c) Balkovec, J. M.; Siliphaivanh, P.; Bouffard, F. A.; Peel, M. R.; Fan, W.; Mamai, A.; Dimick G.; Ray, S. M. Antifungal agents. PCT Int. Appl. WO 2009045311, 2009.
21. (a) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233. (b) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727–2730.
22. (a) Hegde, S.; Kaushal, N.; Ravindra, K. C.; Chiaro, C.; Hafer, K. T.; Gandhi, U. H.; Thompson, J. T.; van den Heuvel, J. P.; Kennett, M. J.; Hankey, P.; Paulson, R. F.; Prabhu, K. S. *Blood* **2011**, *118*, 6909 *Chem.-Eur. J.* **2016**, *22*, 8559–8570. 6919. (b) Kudva, A. K.; Kaushal, N.; Mohinta, S.; Kennett, M. J.; August, A.; Paulson, R. F.; Prabhu, K. S. *PLoS One* **2013**, *8*, e80622.
23. (a) Nicolaou, K. C.; Pulukuri, K. K.; Yu, R.; Rigol, S.; Heretsch, P.; Grove, C. I.; Hale, C. R. H; ElMarrouni, A. *Chem.-Eur. J.* **2016**, *22*, 8559–8570. (b) Nicolaou, K. C.; Heretsch, P.; ElMarrouni, A.; Hale, C. R. H.; Pulukuri, K. K.; Kudva, A. K.; Narayan, V.; Prabhu, K. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 10443–10447. (c) Nicolaou, K. C.; Pulukuri, K. K.; Rigol, S.; Heretsch,

P.; Yu, R.; Grove, C. I.; Hale, C. R. H.; ElMarrouni, A.; Fetz, V.; Brönstrup, M.; Aujay, M.; Sandoval, J.; Gavrilyuk, J. *J. Am. Chem. Soc.* **2016**, *138*, 6550−6560.
24. Shao, H.; Bao, W.; Jing, Z.-R.; Wang, Y.-P.; Zhang, F.-M.; Wang, S.-H.; Tu, Y.-Q. *Org. Lett.* **2017**, *19*, 4648–4651.
25. Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893–14896.
26. Kuroda, Y.; Nicacio, K. J.; da Silva, I. A., Jr.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A.; Sette, L.; Williams, D.; Andersen, R.; Jancar, S.; Berlinck, R.; Sarpong, R. *Nat. Chem.* **2018**, *10*, 938–945.
27. Offei, S. D.; Arman, H. D.; Yoshimoto, F. K. *Steroids*, **2019**, *151*, 108449.



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