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Approach to the synthesis of the C1–C11 and C14–C18 portion of Leucascandrolide A†‡

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An asymmetric synthesis of the C1 to C11 and C14 to C18 fragments of the macrocyclic portion of the antibiotic Leucascandrolide A was achieved in 21 total steps from an achiral dienoate. The key 4-hydroxy-2,5-pyran portion of the natural product was established by oxy-Michael cyclization of a 5,7,9,11-tetraol intermediate, which in turn was established by an iterative asymmetric-hydration of dienoates. Alternative strategies for establishing the polyol stereochemistry were explored.

Introduction

As part of humankind's continuous search for unique biologically active structures from the deep blue sea, Leucascandrolide A (**1**) was discovered in the Coral Sea off the northeastern coast of New Caledonia.[1] In 1996, Pietra reported the isolation of the macrocyclic lactone from the calcareous sponge *Leucascandra caveolata*. A combination of 2D-NMR and Mosher ester analysis was used to assign the absolute and relative stereochemistry of the macrocyclic natural product. In addition to its novel structure, interest in Leucascandrolide A was further peaked by discovery that it possessed potent anticancer and antifungal activity, with IC_{50} value against the human KB (70 nM) and P388 (350 nM) cell lines and activity against *Candida albicans*.[1] As is often the problem associated with marine natural products isolated from sponges, as opposed to the bacteria that most likely produce it, Leucascandrolide A no longer appears to be available from the same sponge.[2] These factors have inspired synthetic organic chemist to pursue the total synthesis of Leucascandrolide A (Fig. 1).

A mere four years after its isolation, the first total synthesis of Leucascandrolide A was completed by Leighton.[3] Since the Leighton synthesis there have been 10 other total[4] and 11 formal syntheses.[5] More recently, Kozmin was able to show that Leucascandrolide A inhibits oxidative phosphorylation *via* interaction with cytochrome bc_1 complex.[6] As part of a larger program aimed at the synthesis and SAR-study of anticancer agents that act by inhibition of ion transport, we became interested in the synthesis of Leucascandrolide A.

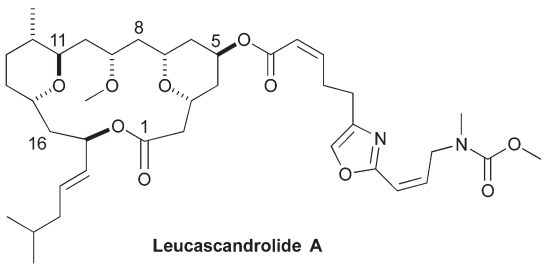

Fig. 1 Structure of Leucascandrolide A.

Retrosynthetically, we envisioned that the Leucascandrolide A macrocycle (**1**) could be derived by ring closing cross metathesis and reductive cyclization of diene **2** (Scheme 1). Compound **2** in turn could be derived from an *anti*-selective crotylation of aldehyde **3**. Aldehyde **3** could be prepared by an esterification of alcohol **4** and acid **5**. Carboxylic acid **5** could be derived from protected tetraol **6**, which could result from a diastereoselective allylation/cross metathesis of protected trihydroxy ester **7**.[7] Previously we have shown that esters such as **7** can be derived by the iterative asymmetric hydration of dienoates like **8**.[8] The β-hydroxy enone **4** was also envisioned as ultimately arising from an asymmetric hydration of a dienoate. Herein we describe our latest efforts aimed at the synthesis of the C1 to C11 and C14 to C18 containing fragment of Leucascandrolide A, aldehyde **3**.

Results and discussion

Our synthetic efforts aimed at Leucascandrolide A began with aldehyde **9** (Scheme 2), which we previously had shown could be made from the DibalH reduction of esters like **7**.[9] Exposure

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†This manuscript is dedicated to Barry M. Trost on the occasion of this 75th birthday.

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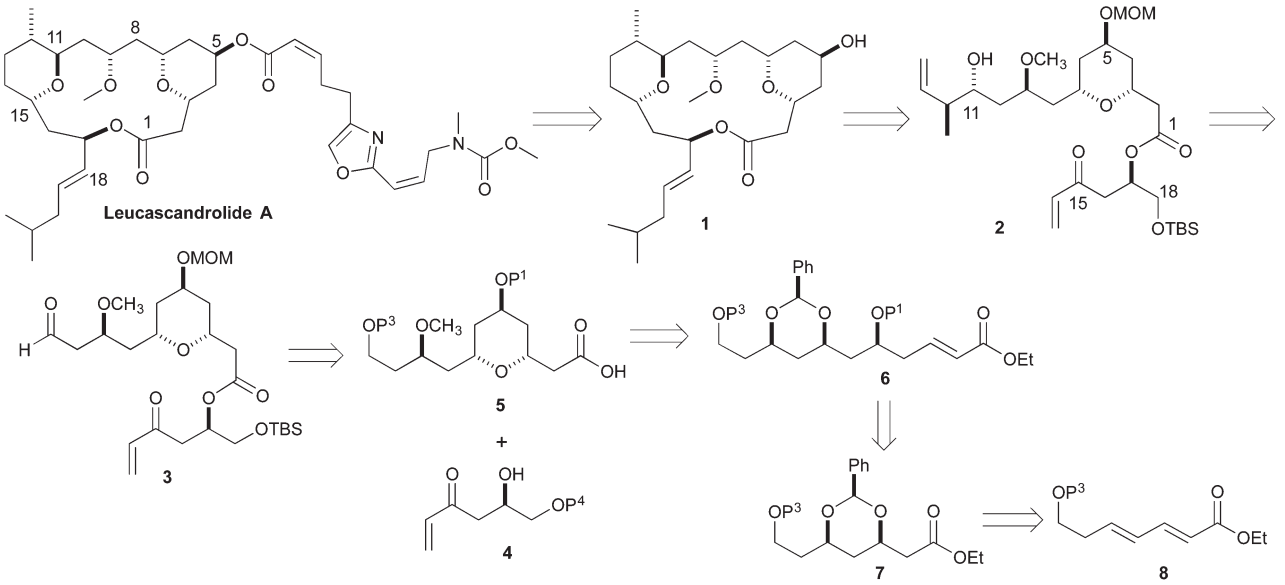
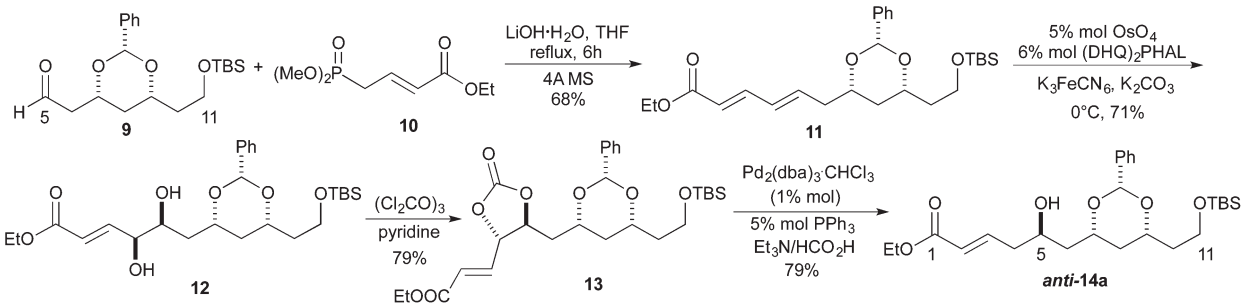


Scheme 1 Retrosynthesis of Leucascandrolide A.



Scheme 2 Os/Pd approach to protected triol.

of aldehyde **9** to the vinylogous Horner–Wadsworth–Emmons reagent **10** and LiOH as base gave the desired dienoate **11** (68%),[10] which could be converted into the desired *syn*/*anti*-1,3,5-triol by our three step asymmetric hydration protocol. Thus, treating the *E*,*E*-dienoate **11** to the typical Sharpless asymmetric dihydroxylation conditions (5% OsO_4, 6% $(DHQ)_2PHAL$, K_3FeCN_6, $MeSO_2NH_2$), provided diol **12** in good yield (71%) and as a single diastereomer.[11] Exposing diol **12** to a pyridine solution of triphosgene converted it into a cyclic carbonate **13** in good yield (79%). When cyclic carbonate **13** was exposed to our Pd-reduction conditions (HCO_2H/Et_3N, 1% $Pd_2(dba)_3{\cdot}CHCl_3$/5% PPh_3) it cleanly reacted to give the 5-hydroxy-1-enoate ***anti*-14a** in an excellent yield (79%).

Following a nearly identical procedure, we previously have shown that ***anti*-14b** (Table 1), with a C11 PMB-group, can be prepared from a dienoate like **8** (P^3 = PMB).[8] Similarly, the C5 diastereomer ***syn*-14b**, was also prepared from the same dienoate, by simply replacing the ligand in the Sharpless dihydroxylation to $(DHQD)_2PHAL$.

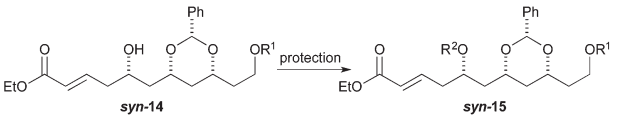
To our surprise, we found it difficult to protect the C5 alcohol of ***anti*-14a** with either a TBDPS-group or a benzyl-group (Table 1). The benzyl protection was similarly problematic, whether acidic or basic conditions were used. In contrast, we were able to react alcohol ***anti*-14b** with MOMCl to give MOM-ether ***anti*-15d** in a satisfactory yield (47%). To our delight, the C5 diastereomer ***syn*-14b** reacted under a similar procedure to give ***syn*-15d** in a similar yield (52%).

We surmised that the difficulty associated with the protection of the C5 hydroxyl group could be due to the acidity of the C4 position and the propensity of the substrate to undergo elimination to form dienoates **11**. Thus we decided to explore an alternative procedure (Scheme 3) for the synthesis of enoates, like ***syn*-15**. Specifically, we decided to pursue a route where the protection step occurred before the ester group was introduced. This revised route was envisioned to occur through an allylation, protection and cross-metathesis sequence.

The revised route began with the unselective allylation of aldehyde **9** with an allylic Grignard reagent (AllylMgCl). The Grignard addition occurred to give a mixture of diastereomeric homo-allylic alcohols ***syn*-16a** and ***anti*-16a** (1.2 : 1), which could be separated by silica gel chromatography. Fortunately,

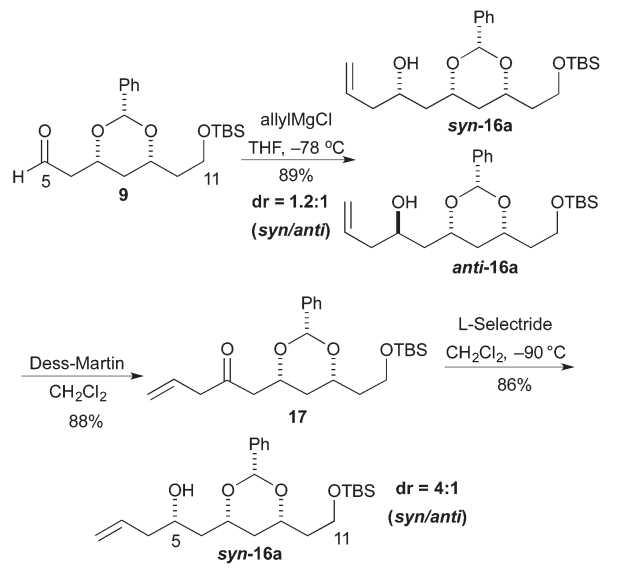
Table 1 Screening of protection groups on δ-hydroxyl enoate

Entry	SM	R^1	R^2	Yield (*anti*-15)
1[a]	***anti*-14a**	TBS	TBDPS	NR[e] (***anti*-15a**)
2[b]	***anti*-14a**	TBS	Bn	Low (***anti*-15b**)
3[c]	***anti*-14b**	PMB	Bn	Low (***anti*-15c**)
4[d]	***anti*-14b**	PMB	MOM	47% (***anti*-15d**)



Entry	SM	R^1	R^2	Yield (*syn*-15)
5[d]	***syn*-14b**	PMB	MOM	52% (***syn*-15d**)

Reaction conditions: [a] TBDPSCl (2 equiv.), imidazole (2.5 equiv.), DMF, 18 h. [b] Benzyl trichloroacetimidate (1.2 equiv.), TMSOTf, CH_2Cl_2. [c] BnBr (2 equiv.), NaH, TBAI, THF, 24 h. [d] MOMCl (4 equiv.), DMAP (3% equiv.), i-Pr_2NEt, CH_2Cl_2, 0 °C. [e] NR = no reaction.



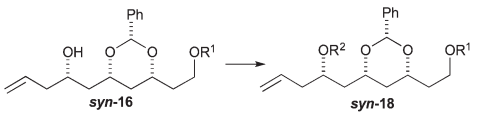
Scheme 3 Alternative synthesis of protected triol.

the diastereoselectivity for the formation of ***syn*-16a** could be improved by an oxidation/reduction sequence (Scheme 3).

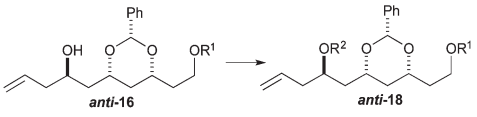
Thus, the mixture of alcohols ***syn*/*anti*-16a** was treated with the Dess–Martin reagent to give β,γ-unsaturated enone **17** in good yield (88%). Then reduction of enone **17** with L-selectride occurred to give the ***syn*-16a** as the major isomer. When the reaction was performed at −90 °C the maximal *syn*/*anti* ratio was achieved (>4 : 1).

To our delight we were able to protect both homo-allylic alcohols ***syn*-16a** and ***anti*-16a** with both the TBDPS and

Table 2 Screening of protection groups on homoallyic alcohol



Entry	SM	R^1	R^2	Yield (*syn*-18)
1[a]	***syn*-16a**	TBS	TBDPS	83% (***syn*-18a**)
2[b]	***syn*-16a**	TBS	Bn	48% (***syn*-18b**)
3[c]	***syn*-16b**	PMB	Bn	49% (***syn*-18c**)
4[d]	***syn*-16b**	PMB	MOM	87% (***syn*-18d**)



Entry	SM	R^1	R^2	Yield (*anti*-18)
5[a]	***anti*-16a**	TBS	TBDPS	78% (***anti*-18a**)
6[b]	***anti*-16b**	PMB	Bn	52% (***anti*-18c**)
7[d]	***anti*-16b**	PMB	MOM	85% (***anti*-18d**)

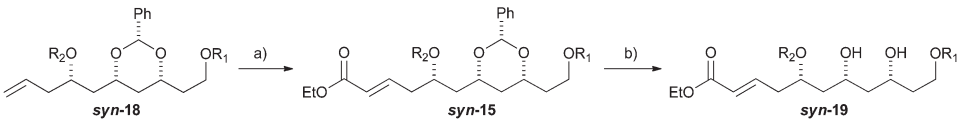
Reaction conditions: [a] TBDPSCl (2 equiv.), imidazole (2.5 equiv.), DMF, 18 h. [b] Benzyl trichloroacetimidate (1.2 equiv.), TMSOTf, CH_2Cl_2. [c] BnBr (2 equiv.), NaH, TBAI, THF, 24 h. [d] MOMCl (4 equiv.), DMAP (3% equiv.), i-Pr_2NEt, CH_2Cl_2, 0 °C.

Bn– ether groups, as well as the MOM-group. While the yields for the benzyl protection of either the *syn*- or *anti*-homoallylic alcohols were suboptimal, both TBDPS- and MOM-groups could be installed in excellent yields (78–87%), providing ample quantities ***syn*-18a** and ***syn*-18d** and ***anti*-18a** and ***anti*-18d** to pursue the cross metathesis protocol (Table 2).

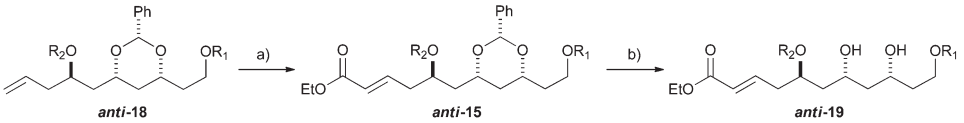
With an improved procedure for installing protecting groups at the C5 position in ***syn*-/*anti*-18**, we next investigated the cross metathesis of ***syn*-18** and ***anti*-18** to form ***syn*-15** and ***anti*-15** and the subsequent deprotection to form diols ***syn*-19** and ***anti*-19**. Treatment of ***syn*-18b–d** with ethyl acrylate and Grubbs II catalyst (1.5%) cleanly provided the desired enoates ***syn*-15b–d** in excellent yields (90–96%). Unfortunately, the primary TBS-groups were not compatible with the benzylidene deprotection conditions, whereas the PMB-group survived. The deprotection of the benzylidene group was accomplished by heating the enoates ***syn*-15c/d** in 80% aqueous acetic acid (60 °C) to provide the *syn*-diols ***syn*-19c/d** (72% and 80%). Following a similar procedure, the *anti*-diastereomer ***anti*-16d** was also converted into ***anti*-19d** (Table 3).

We next pursued the formation of the 2,6-*cis*-pyran ring. This was most easily accomplished under basic conditions. The addition of 1 equiv. of potassium *t*-butoxide to a −40 °C solution of ***syn*-19c** in THF, followed by warming to room temperature led to the formation of tetrahydropyran ***syn*-20c** (70%). Under similar condition ***syn*-19d** was converted into tetrahydropyran ***syn*-20d** (61%). These conditions produced tetrahydropyran ***syn*-21c** in 70% yield as a 6 : 1 ratio of *cis* and *trans* diastereomers, and tetrahydropyran ***syn*-21d** product in a

Table 3 Alternative route to diol **19**

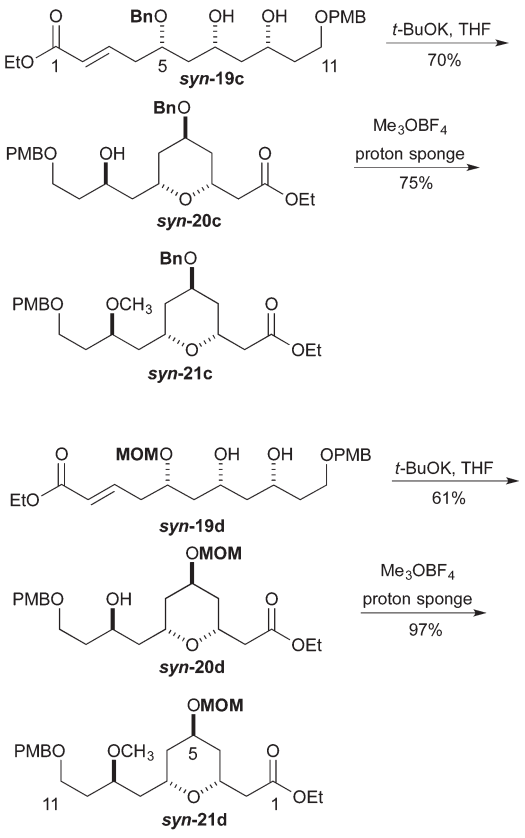


Entry	SM	R^1	R^2	Yield (***syn*-15**)	Yield (***syn*-19**)
1	***syn*-18b**	TBS	Bn	96% (***syn*-15b**)	NA[c] (***syn*-19b**)
2	***syn*-18c**	PMB	Bn	91% (***syn*-15c**)	72% (***syn*-19c**)
3	***syn*-18d**	PMB	MOM	90% (***syn*-15d**)	80% (***syn*-19d**)

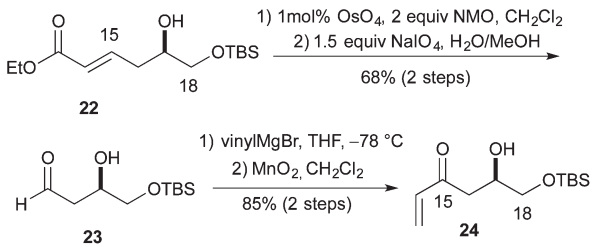


Entry	SM	R^1	R^2	Yield (***anti*-15**)	Yield (***anti*-19**)
4	***anti*-18a**	TBS	TBDPS	88% (***anti*-15a**)	low (***anti*-19a**)
5	***anti*-18b**	PMB	MOM	92% (***anti*-15d**)	71% (***anti*-19d**)

Reaction conditions: [a] Ethyl acrylate (2.5 equiv.), Grubbs II catalyst (1.5% equiv.), CH_2Cl_2, reflux, 4 h. [b] 80% acetic acid/H_2O, 60 °C, 4 h. [c] Not attempted.



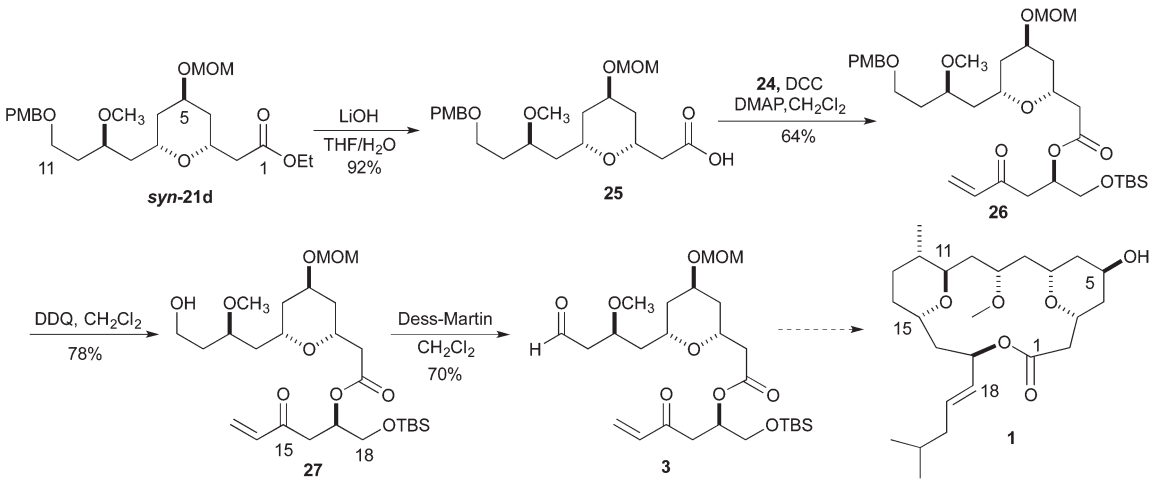
Scheme 4 Synthesis of tetrahydropyran.



Scheme 5 Synthesis of enone.

61% yield with a 7 : 1 ratio of *cis* to *trans* diastereomers. Formation of the methyl ether was accomplished using Me_3OBF_4 on ***syn*-20c** and ***syn*-20d** to produce the products ***syn*-21c** and ***syn*-21d** in excellent yields (75 and 97%, respectively) (Scheme 4). Turning to the synthesis of the C1 to C11 and the C14 to C18 portion of Leuscandrolide A, we undertook the synthesis of alcohol **24** from δ-hydroxy enoate **22**. Previously we have shown that **22** can be prepared by an asymmetric hydration of the corresponding dienoate.[8] The double bond of enoate **22** was oxidatively cleaved by a dihydroxylation (OsO_4/NMO)/diol cleavage ($NaIO_4$) sequence to form aldehyde **23**. Addition of vinylmagnesium bromide to the aldehyde **23** and manganese dioxide oxidation of the allylic alcohol completed the synthesis of enone **24** (Scheme 5).

To demonstrate the viability of the synthesis going forward, we chose to pursue the fragment coupling sequence with ester ***syn*-21d**. With the synthesis of enone **24** complete, the ester **26** was synthesized *via* a DCC coupling of the carboxylic acid of ester **25** and alcohol **24**. The hydrolysis of ester ***syn*-21d** was accomplished by treatment with LiOH in THF and H_2O. The conversion of the PMB-ether to the aldehyde began with a DDQ deprotection. Treatment of a dichloromethane solution of **26** with H_2O and DDQ produced the primary alcohol **27** in 78% yield. Oxidation of the primary alcohol **27** to the aldehyde **3** was accomplished with Dess–Martin reagent (Scheme 6).



Scheme 6 Completion of Leucascandrolide A fragment.

Conclusions

In conclusion we have shown the viability of the asymmetric hydration of dienoate for the synthesis of key chiral building blocks for the synthesis of a potential Leuscandrolide A precursor **2**. The further elaboration of this advanced intermediate is ongoing and will be reported in due course.

Acknowledgements

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Notes and references

1 M. D'Ambrosio, A. Guerriero, C. Debitus and F. Pietra, *Helv. Chim. Acta*, 1996, **79**, 51.

2 M. D'Ambrosio, M. Tato, C. Debitus and F. Pietra, *Helv. Chim. Acta*, 1999, **82**, 347.

3 K. R. Hornberger, C. L. Hamblett and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894.

4 (*a*) I. Paterson and M. Tudge, *Angew. Chem., Int. Ed.*, 2003, **42**, 343; (*b*) I. Paterson and M. Tudge, *Tetrahedron*, 2003, **59**, 6833; (*c*) Y. Wang, J. Janjic and S. A. Kozmin, *J. Am. Chem. Soc.*, 2002, **124**, 13670; (*d*) Y. Wang, J. Janjic and S. A. Kozmin, *Pure Appl. Chem.*, 2005, **77**, 1161; (*e*) A. Fettes and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2002, **41**, 4098; (*f*) A. Fettes and E. M. Carreira, *J. Org. Chem.*, 2003, **68**, 9274; (*g*) P. Wipf and J. T. Reeves, *Chem. Commun.*, 2002, 2066; (*h*) M. T. Crimmins and P. Siliphalvanh, *Org. Lett.*, 2003, **5**, 4641; (*i*) D. R. Williams, S. Patnaik and S. V. Plummer, *Org. Lett.*, 2003, **5**, 5035; (*j*) P. A. Evans and W. J. Andrews, *Angew. Chem., Int. Ed.*, 2008, **47**, 5426; (*k*) H. H. Jung, J. R. Seiders and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2007, **46**, 8464; (*l*) Q. Su, L. A. Dakin and J. S. Panek, *J. Org. Chem.*, 2007, **72**, 2; (*m*) Q. Su and J. S. Panek, *Angew. Chem., Int. Ed.*, 2005, **44**, 1223; (*n*) L. J. Van Orden, B. D. Patterson and S. D. Rychnovsky, *J. Org. Chem.*, 2007, **72**, 5784.

5 (*a*) M. T. Crimmins, C. A. Carroll and B. W. King, *Org. Lett.*, 2000, **2**, 597; (*b*) L. A. Dakin, N. F. Langille and J. S. Panek, *J. Org. Chem.*, 2002, **67**, 6812; (*c*) L. A. Dakin and J. S. Panek, *Org. Lett.*, 2003, **5**, 3995; (*d*) L. Ferrie, L. Boulard, F. Pradaux, S. Bouzbouz, S. Reymond, P. Capdevielle and J. Cossy, *J. Org. Chem.*, 2008, **73**, 1864; (*e*) L. Ferrie, S. Reymond, P. Capdevielle and J. Cossy, *Org. Lett.*, 2007, **9**, 2461; (*f*) D. J. Kopecky and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2001, **123**, 8420; (*g*) S. A. Kozmin, *Org. Lett.*, 2001, **3**, 755; (*h*) K. Lee, H. Kim and J. Hong, *Org. Lett.*, 2011, **13**, 2722; (*i*) D. R. Williams, S. V. Plummer and S. Patnaik, *Angew. Chem., Int. Ed.*, 2003, **42**, 3934; (*j*) D. R. Williams, S. V. Plummer and S. Patnaik, *Tetrahedron*, 2011, **67**, 5083; (*k*) P. Wipf and T. H. Graham, *J. Org. Chem.*, 2001, **66**, 3242; (*l*) J. S. Yadav, M. R. Pattanayak, P. P. Das and D. K. Mohapatra, *Org. Lett.*, 2011, **13**, 1710.

6 O. A. Ulanovskaya, J. Janjic, M. Suzuki, S. S. Sabharwal, P. T. Schumacker, S. J. Kron and S. A. Kozmin, *Nat. Chem. Biol.*, 2008, **4**, 418.

7 (*a*) C. M. Smith and G. A. O'Doherty, *Org. Lett.*, 2003, **5**, 1959; (*b*) M. Li and G. A. O'Doherty, *Org. Lett.*, 2006, **8**, 6087; (*c*) H. Guo, M. S. Mortensen and G. A. O'Doherty, *Org. Lett.*, 2008, **10**, 3149.

8 (*a*) T. J. Hunter and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 2777; (*b*) T. J. Hunter, Y. Wang, J. Zheng and G. A. O'Doherty, *Synthesis*, 2016, 1700; (*c*) S. D. Garaas, T. J. Hunter and G. A. O'Doherty, *J. Org. Chem.*, 2002, **67**, 2682; (*d*) M. Li and G. A. O'Doherty, *Org. Lett.*, 2006, **8**, 3987; (*e*) Y. Wang, Y. Xing, Q. Zhang and G. A. O'Doherty, *Chem. Commun.*, 2011, **47**, 8493.

9 (*a*) Y. Wang and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2013, **135**, 9334–9337; (*b*) T. J. Hunter and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 1049–1052.

10 (*a*) R. S. Burden and L. Crombie, *J. Chem. Soc. C*, 1969, 2477; (*b*) F. Bohlmann and C. Zdero, *Chem. Ber.*, 1973, **106**, 3779; (*c*) W. R. Roush, *J. Am. Chem. Soc.*, 1980, **102**, 1390; (*d*) D. A. Evans and D. M. Fitch, *J. Org. Chem.*, 1997, **62**, 454; (*e*) G. H. Posner, J. K. Lee, M. C. White, R. H. Hutchings, H. Dai, J. L. Kachinski, P. Dolan and T. W. Kensler, *J. Org. Chem.*, 1997, **62**, 3299; (*f*) A. G. M. Barrett, D. Hamprecht, A. J. P. White and D. J. Williams, *J. Am. Chem. Soc.*, 1997, **119**, 8608; (*g*) J. M. Takacs, M. R. Jaber, F. Clement and C. Walters, *J. Org. Chem.*, 1998, **63**, 6757; (*h*) M. Nazare and H. Waldmann, *Chem. – Eur. J.*, 2001, **7**, 3363; (*i*) M. Sun, Y. Deng, E. Batyreva, W. Sha and R. G. Salomon, *J. Org. Chem.*, 2002, **67**, 3575; (*j*) T. Tsuzuki, K. Tanaka, S. Kuwahara and T. Miyazawa, *Lipids*, 2005, **40**, 147; (*k*) R. Barth and J. Mulzer, *Angew. Chem., Int. Ed.*, 2007, **46**, 5791; (*l*) J. T. Markiewicz, D. J. Schauer, J. Lofstedt, S. J. Corden, O. Wiest and P. Helquist, *J. Org. Chem.*, 2010, **75**, 2061.

11 (*a*) H. Berker, M. A. Soler and K. B. Sharpless, *Tetrahedron*, 1995, **51**, 1345; (*b*) Y. Zhang and G. A. O'Doherty, *Tetrahedron*, 2005, **61**, 6337–6351. For synthetic application of this, see: (*c*) T. J. Hunter and G. A. O'Doherty, *Org. Lett.*, 2002, **4**, 4447; (*d*) Y. Xing and G. A. O'Doherty, *Org. Lett.*, 2009, **11**, 1107; (*e*) Md. M. Ahmed, M. S. Mortensen and G. A. O'Doherty, *J. Org. Chem.*, 2006, **71**, 7741; (*f*) Md. M. Ahmed and G. A. O'Doherty, *Tetrahedron Lett.*, 2005, **46**, 3015–3019; (*g*) Md. M. Ahmed, B. P. Berry, T. J. Hunter, D. J. Tomcik and G. A. O'Doherty, *Org. Lett.*, 2005, **7**, 745.