JOC*Article*

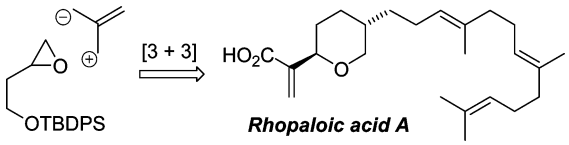
Investigation of an Organomagnesium-Based [3 + 3] Annelation to Pyrans and Its Application in the Synthesis of Rhopaloic Acid A

Julien C. R. Brioche,[†] Katharine M. Goodenough,[†] David J. Whatrup,[‡] and Joseph P. A. Harrity*,[†]

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, United Kingdom, and GlaxoSmithKline Research and Development, Tonbridge, Kent, TN11 9AN, United Kingdom

j.harrity@sheffield.ac.uk

Received December 8, 2007



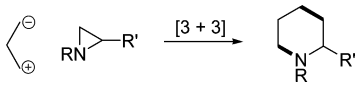
A stepwise [3 + 3] annelation reaction has been developed that allows access to pyrans from epoxides. This process involves the addition of an allylmagnesium reagent, itself readily prepared from methallyl alcohol, and a Pd-catalyzed cyclodehydration reaction. The potential of this process to be employed in natural product synthesis has been exemplified by its use in the preparation of rhopaloic acid A.

Introduction

Recent studies within our laboratories have focused on the development of [3 + 3] annelation processes to functionalized piperidines.[1] As outlined in Scheme 1, our key strategy was to exploit aziridines, readily prepared in enantiomerically enriched form, as three-atom components in an annelation process with an appropriate conjunctive reagent. To date, we have employed Trost's Pd-TMM reagent,[2] the Büchi Grignard,[3] and an allylmagnesium reagent derived from the double deprotonation of methallyl alcohol.[4]

In an effort to broaden the scope of this strategy, we turned our attention to the synthesis of functionalized pyrans via the [3 + 3] annelation of epoxides. Pyrans are a common motif to many natural products, in particular those of a marine source.[5] Not surprisingly therefore, a significant number of methods have been developed for the synthesis of these compounds. Assembly of the six-membered ring by [4 + 2] approaches has received

SCHEME 1



widespread attention;[6] in contrast however, the employment of a formal [3 + 3] strategy has been much less generally explored. Nonetheless, techniques based on addition of 4-hydroxy-2-pyrones to enals and Sakurai−Prins sequences have been reported.[7] Moreover, we were intrigued by a report from Klumpp and co-workers that demonstrated that Grignard reagent **2** reacted with epoxides to produce pyrans after in situ Pd-catalyzed cyclization.[8] This reagent is closely related to the organomagnesium reagent **4** that we had employed in the synthesis of piperidines (Scheme 2). In the context of the preparation of these organomagnesium reagents, **2** is prepared in two steps[9] while **4** can be accessed in one pot by double

[†] University of Sheffield.

[‡] GlaxoSmithKline Research and Development.

(1) For reviews of [3 + 3] approaches to heterocycle systems see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23.

(2) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596. (b) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286.

(3) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089.

(4) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993.

(5) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(6) Tietze, L. F.; Kettschau, G.; Gewert, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19.

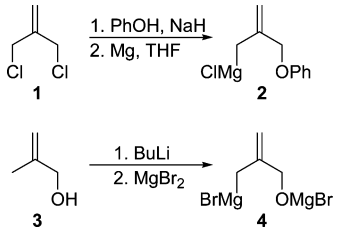
(7) (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888. (b) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (c) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Wei, L.-L.; Sklenicka, H. M.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729. (d) Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.

(8) van der Louw, J.; van der Baan, J. L.; Out, G. J. J.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 9901.

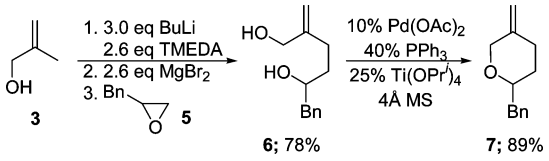
(9) van der Louw, J.; van der Baan, J. L.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 6087.

10.1021/jo702620e CCC: $40.75 © 2008 American Chemical Society
Published on Web 02/07/2008

SCHEME 2



SCHEME 3



deprotonation of methallyl alcohol and transmetalation with magnesium bromide (Scheme 2). We set out to investigate the suitability of Grignard reagent **4** for the formation of pyrans and report herein the scope and limitations of this technique.[10] Furthermore, we demonstrate the employment of this methodology in the total synthesis of rhopaloic acid A.

Results and Discussion

In our preliminary studies, we opted to prepare pyrans from epoxides using conditions that had been developed for the analogous transformation of aziridines to piperidines.[4] Accordingly, as outlined in Scheme 3, treatment of methallyl alcohol **3** with an excess of BuLi in the presence of TMEDA followed by addition of $MgBr_2$ provided a Grignard reagent that underwent addition to 2-benzyloxirane **5** to provide the corresponding diol **6** in 78% yield. Furthermore, we were delighted to find that cyclocondensation could be achieved directly, without prior activation of the allylic alcohol,[11] by Pd-catalysis to provide pyran **7** in high yield.

While we were pleased that the potential of the annelation reaction with in situ generated Grignard reagent **4** had been verified, a significant limitation was the requirement for 5 equiv of this Grignard reagent. A similar requirement was observed in our earlier studies on the addition of **4** to aziridines. It was apparent to us that one reason for the requirement of excess Grignard was an overestimation of the concentration of **4** during titration of this reagent. Specifically, the use of 3.0 equiv of BuLi meant that a full equivalent of butylmagnesium species remained after transmetalation and that this would account for some of the active Grignard reagent as assessed by titration. We were aware that Trost's procedure for the double deprotonation of **3** required 2.6 equiv of BuLi[12] and wondered if this could be further reduced without a significant deleterious effect on the deprotonation process. Accordingly, as outlined in Scheme 4, the employment of 2.1 equiv each of 10 M BuLi and TMEDA resulted in formation of a red gum after stirring at room temperature for 24 h. Removal of the ethereal solution by cannula and addition of fresh ether and freshly prepared $MgBr_2$ resulted in the formation of a white precipitate that was

SCHEME 4

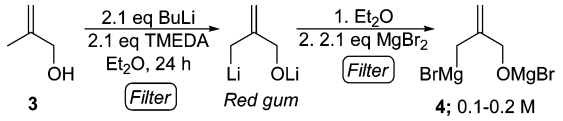
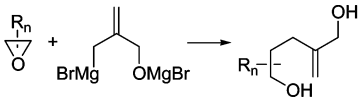
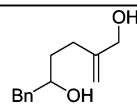
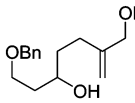
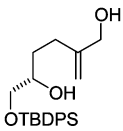
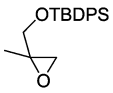
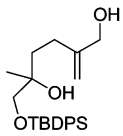
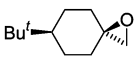
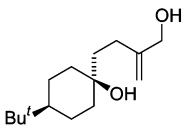
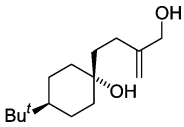


TABLE 1. Addition of Grignard 4 to Epoxides



entry[a]	epoxide	addition product	yield
1	 **5**		**6;** 76%
2	 **8**		**9;** 74%
3	 **10**		**11;** 82%
4[b]	 **12**		**13;** 75%
5	 **14** (2.5:1; *cis*:*trans*)		**15a;** 66%
			**15b;** 21%

[a] Conditions: 1.5 equiv of Grignard added to a THF solution of epoxide. [b] 2.5 equiv of Grignard used in this case.

removed from the Grignard reagent by cannula filtration. Titration of the resulting solution generally provided a concentration of active reagent of around 0.1−0.2 M, providing an estimated yield for formation of **4** of 20−40%, over two steps.

With the Grignard reagent in hand, we turned our attention to the study of its addition to epoxides. As outlined in Table 1, we were delighted to find that the organomagnesium reagent underwent smooth addition to a range of epoxides. *Moreover, only 1.5 equiv of reagent was generally required to achieve complete conversion of each epoxide substrate*. As outlined in entries 1−3, 2-alkyl epoxides underwent smooth addition to provide the corresponding diols in high yield. Moreover, we demonstrated that 2,2-disubstituted epoxides could be transformed to the corresponding diols under these conditions (entries 4 and 5).

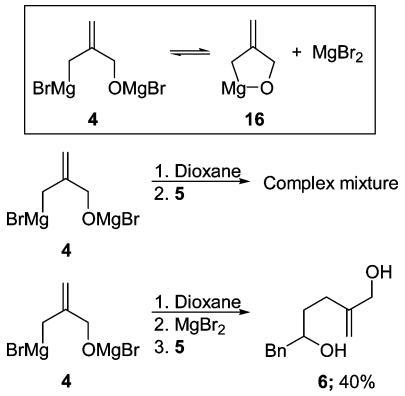
We had assumed in our studies that the organomagnesium reagent had the formula **4**; however, it occurred to us that the

(10) For a preliminary report of this work see: Brioche, J. C. R.; Goodenough, K. M.; Whatrup, D. J.; Harrity, J. P. A. *Org. Lett.* **2007**, *9*, 3941.

(11) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000.

(12) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

SCHEME 5

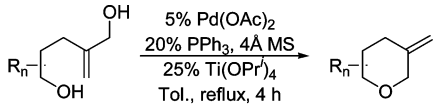


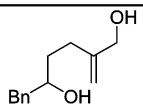
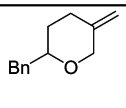
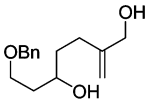
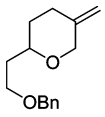
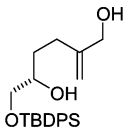
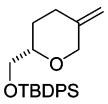
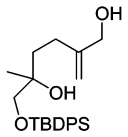
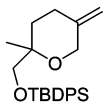
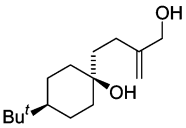
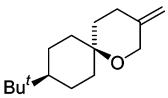
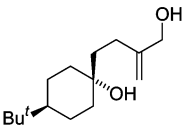
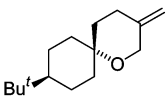
reactive reagent could well be the cyclic organomagnesium alkoxide **16** formed by the Schlenk equilibrium as outlined in Scheme 5.[13] In an effort to further clarify this issue, we opted to drive the equilibrium toward the cyclic organomagnesium reagent **16**. Accordingly, treatment of the Grignard reagent with dioxane resulted in precipitation of the $MgBr_2$·dioxane adduct. The organomagnesium reagent was removed by cannula filtration and added to epoxide **5**. A complex mixture of products resulted from which the diol **6** could not be isolated. In contrast, however, addition of freshly prepared $MgBr_2$ to this organomagnesium reagent followed by addition of epoxide **5** provided the corresponding diol **6** in 40% yield. These experiments suggest that $MgBr_2$ is essential for successful addition of the doubly deprotonated methallyl alcohol to epoxides; however, it is not clear whether the reaction involves Grignard reagent **4**, or is the result of a $MgBr_2$-promoted addition of cyclic magnesium alkoxide **16**.

We next turned our attention to the Pd-catalyzed cyclization reaction and our results are summarized in Table 2. We were delighted to find that the Pd/Ti-catalyzed cyclodehydration proceeded efficiently for a range of diols to provide the corresponding pyrans in high yield (entries 1−3). Tertiary alcohol substrates proved to be a disappointing exception as these provided the corresponding pyrans in low yield (entries 4−6). In these cases, dimerization via allylic alcohol dehydration proceeded in favor of the cyclization, presumably because of steric hindrance surrounding the tertiary-alcohol moiety.

The Ti-promoted cyclodehydration process was first reported for the coupling of allylic alcohols and anilines[11] and so we were intrigued by the applicability of this process for ether formation, in particular with regard to the role of $Ti(OPr^i)_4$. As outlined in Table 3, preliminary control experiments indicated that the inclusion of the Ti-Lewis acid significantly promotes this cyclization (entry 1), and poor conversions of **9** to **17** were observed in its absence, even after prolonged reaction times (∼20% after 24 h). We therefore assumed that the Lewis acid was simply assisting the removal of the hydroxyl group; to our surprise, however, the corresponding acetate[14] also failed to undergo cyclization in the absence of $Ti(OPr^i)_4$ (entry 2). In contrast, cyclization of **22** proceeded smoothly within 2 h in the presence of 25 mol % of Lewis acid. Therefore, while it is likely that $Ti(OPr^i)_4$ does assist removal of OH in the cyclodehydration, we believe that it has a significant role in addition of the alcohol moiety to the putative intermediate Pd π-allyl complex, presumably via formation of a soft Ti-alkoxide nucleophile.[15]

TABLE 2. Pd-Catalyzed Cyclization



entry[a]	diol	pyran	yield
1	 **6**		**7;** 82%
2	 **9**		**17;** 85%
3	 **11**		**18;** 83%
4	 **13**		**19;** 38%
5	 **15a**		**20;** 23%
6	 **15b**		**21;** 34%

To assess the applicability of this methodology in the stereoselective synthesis of target compounds, we opted to

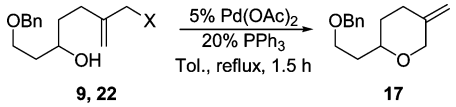
The studies outlined in Table 3 also provided a solution to the low-yielding cyclization of compounds **13** and **15a**,**b**. Specifically, the competing dimerization reaction was readily obviated in each case by acetylation of the allylic alcohol as outlined in Scheme 6.

(13) For a recent example of the preparation and use of cyclic magnesium alkoxides see: Fleming, F. F.; Gudipati, S.; Vu, V. A.; Mycka, R. J.; Knochel, P. *Org. Lett.* **2007**, *9*, 4507.

(14) Compound **22** was prepared from **9** in 76% yield (Ac_2O, Et_3N, cat. DMAP), see the Experimental Section for details.

(15) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931.

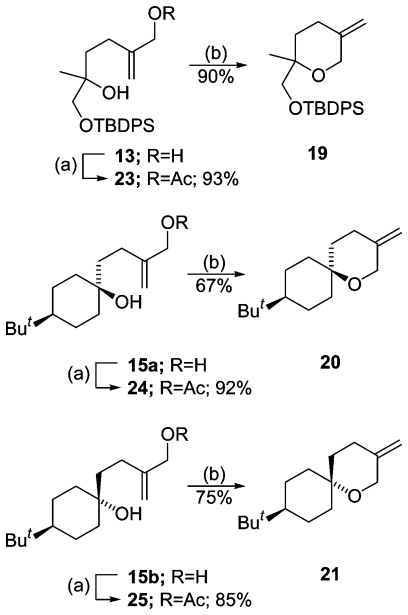
TABLE 3. Role of $Ti(OPr^i)_4$ in the Cyclodehydration



9, 22 **17**

entry	X	$Ti(OPr^i)_4$ loading (mol %)	yield (%)
1	OH; **9**		<5
2	OAc; **22**		<5
3	OAc; **22**	25	86

SCHEME 6[a]



[a] Reagents and conditions: (a) Ac_2O, Et_3N, cat. DMAP; (b) 5% $Pd(OAc)_2$, 20% PPh_3, 25% $Ti(OPr^i)_4$.

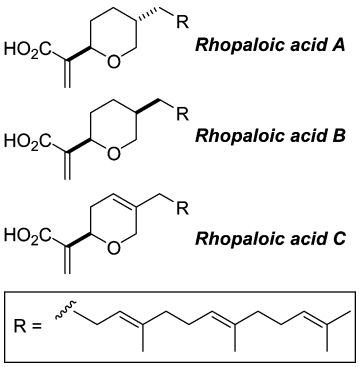
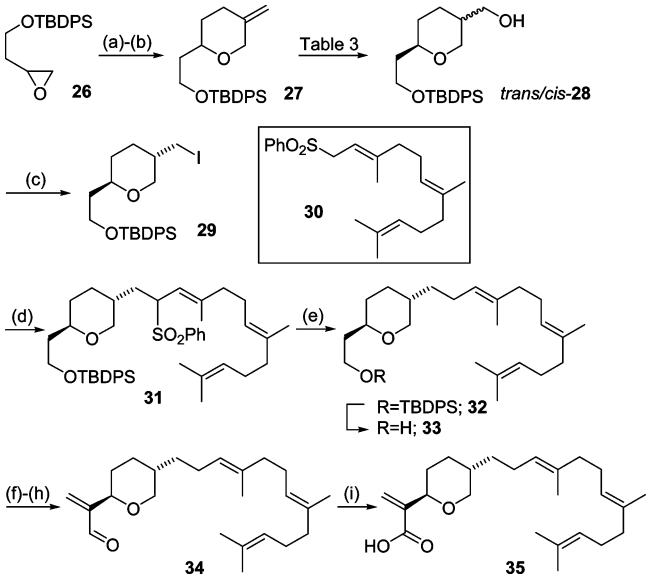


FIGURE 1. Rhopaloic acids.

exploit the [3 + 3] annelation in the synthesis of the rhopaloic acids. The rhopaloic acids (Figure 1) are a class of novel norsesterterpenes that were first isolated from the marine sponge *Rhopaloeides* sp. by Ohta and Ikegami,[16] and subsequently also from *Hippospongia* sp. by Andersen and co-workers.[17] These

SCHEME 7[a]



[a] Reagents and conditions: (a) **4**, THF, 79%; (b) 5% $Pd(OAc)_2$, 20% PPh_3, 25% $Ti(OPr^i)_4$, toluene, reflux, 86%; (c) I_2, imid., PPh_3, THF, rt, 92%; (d) 30, LDA, DMPU, THF, −78 °C; (e) 10% $PdCl_2$(DPPF), $LiEt_3BH$, THF, rt, 70% over two steps; (f) TBAF, THF, rt, 98%; (g) Swern; (h) CH_2NMe_2I, Et_3N, CH_2Cl_2, rt, 66% over two steps; (i) NaH_2PO_4, NaO_2Cl, 2-methyl-2-butene, $^tBuOH/H_2O$, rt, 80%.

compounds exhibit potent inhibition of the gastrulation of starfish embryos, in vitro cytotoxicity toward human myeloid K-562 cells, human MOLT-4 leukemia cells, and murine L1210 cells, and RCE protease inhibitory activity. The interesting biological activity of these compounds coupled with the paucity of material available from their natural sources has inspired some significant synthetic effort toward these molecules. Specifically, Snider developed a short synthesis of racemic rhopaloic acid A that also provided minor quantities of rhopaloic acid B methyl ester.[18] Additionally, enantioselective syntheses of rhopaloic acid A have been reported by Ogasawara[19] and Ohkata.[20] The former required some 30 steps from an enantiomerically pure dioxabicyclo-[3.2.1]octane while the latter, shorter synthesis featured an inefficient pyran-forming cyclization (30−40% yield). We hoped to develop a new approach to the rhopaloic acids that would deliver short, stereoselective routes to this family of compounds[21] and turned our attention to the synthesis of rhopaloic acid A.

As shown in Scheme 7, addition of the Grignard **4** to epoxide **26** and subsequent cyclization proceeded without incident to provide pyran **27** in good overall yield. Functionalization of the exomethylene group in **27** would set the stage for elaboration of this intermediate to each member of the rhopaloic acids. Therefore, we opted to investigate the diastereoselectivity of various hydroboration protocols at this stage and our results are highlighted in Table 4. Preliminary studies were discouraging and poor selectivity was observed when bulky monoalkylboranes were employed (entries 1 and 2). Employment of Evans' Rh-

(16) (a) Ohta, S.; Uno, M.; Yoshimura, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 2265. (b) Yanai, M.; Ohta, S.; Ohta, E.; Ikegami, S. *Tetrahedron* **1998**, *54*, 15607.

(17) Craig, K. S.; Williams, D. E.; Hollander, I.; Frommer, E.; Mallon, R.; Collins, K.; Wojciechowicz, D.; Tahir, A.; Van Soest, R.; Andersen, R. J. *Tetrahedron Lett.* **2002**, *43*, 4801.

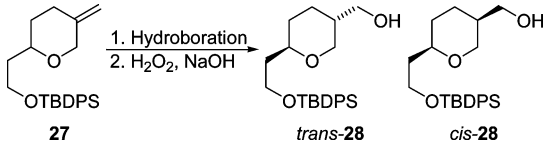
(18) Snider, B. B.; He, F. *Tetrahedron Lett.* **1997**, *38*, 5453.

(19) Kadota, K.; Ogasawara, K. *Heterocycles* **2003**, *59*, 485.

(20) (a) Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Chem. Commun.* **1997**, 1887. (b) Takagi, R.; Sasaoka, A.; Nishitani, H.; Kojima, S.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 925.

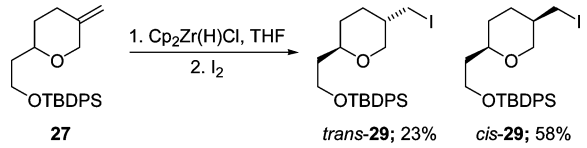
(21) For a recent enantioselective synthesis of related hippospongic acid A and lead references see: Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.

TABLE 4. Diastereoselective Hydroboration



entry[a]	borane	yield (%) (trans:cis)
1	ThexylBH$_2$	92 (1:2)
2	Bu^{t}Pr^{i}CHBH$_2$	93 (1:1)
3	HBC at 5% RhCl(PPh$_3$)$_3$	88 (1:3)
4	9-BBN	96 (3:1)

SCHEME 8



catalyzed hydroboration methodology was moderately diastereoselective, but was found to favor the cis-diastereomer.[22] Surprisingly, however, the use of 9-BBN successfully overturned the diastereoselectivity to favor the desired *trans*-**28** in high yield.[23] Conversion of *trans*-**28** to the iodide **29** proceeded in excellent yield and allowed us to separate the trans/cis-diastereomers. At this stage, we took the opportunity to examine the hydrozirconation of alkene **27** as a direct means to obtain iodide **29**. Treatment of **27** with Schwartz's reagent followed by addition of iodine provided a 2.5:1 mixture of diastereomers in favor of the cis-iodide (Scheme 8). While this approach predominantly generated the wrong diastereomer for the synthesis of rhopaloic acid A, it provides a more direct means for accessing rhopaloic acid B by this strategy.[10]

We next opted to install the farnesyl chain by alkylation of iodide **29** with sulfone **30**. This reaction proceeded efficiently; however, sulfone **31** was found to be contaminated by some unreacted **30** and so the crude material was subjected to Pd-catalyzed reduction to provide **32** in good overall yield. Finally, conversion of the protected 2-hydroxyethyl chain to the required α,β-unsaturated acid was carried out by cleavage of the silyl ether with TBAF followed by Swern oxidation, Mannich methylenation, and Pinnick oxidation.

Conclusion

We have developed a stepwise annelation route to pyrans from epoxides that employs addition of a readily prepared Grignard reagent **4** and a Pd-catalyzed cyclodehydration reaction. The potential of this process to be employed in natural product synthesis has been exemplified by its use in the preparation of rhopaloic acid A.

(22) This result was obtained with use of aged catalyst. The employment of freshly prepared Wilkinson's catalyst resulted in a significantly slower reaction, albeit with better levels of selectivity. For a mechanistic study and lead references see: Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679.

(23) Complementary diastereofacial selectivities in catalyzed and non-catalyzed alkene hydroboration reactions are well documented. For a discussion see: Burgess, K.; van der Donk, W. A.; Jarstfer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 6139.

Experimental Section

Experimental procedures and characterization data for compounds **6**, **7**, **9**, **11**, **17**, **18**, **26**, **27**, **29**, and **30** have been described previously.[10]

Procedure for the Synthesis of Grignard Reagent 4. To *n*-BuLi (15 mL, 10 M, 2.1 equiv) at 0 °C were added anhydrous ether (114 mL) and TMEDA (22.6 mL, 2.1 equiv). After the solution was cooled at −78 °C, methallyl alcohol **3** was added dropwise (6.40 mL, 1 equiv) and the reaction was stirred at −78 °C for 1 h. The bath was then removed and the resulting mixture was vigorously stirred for 24 h. After this time, stirring was stopped for 30 min and the solvent was removed via cannula filtration. Anhydrous ether (100 mL) was added to the remaining orange solid and the suspension was cooled to 0 °C. At this point, a solution of freshly prepared $MgBr_2$ [prepared from magnesium (3.9 g, 2.1 equiv) and dibromoethane (13.8 mL, 2.1 equiv) in ether (58 mL)] was transferred quickly via cannula to the suspension. After addition, the bath was removed and the suspension was vigorously stirred for 30−45 min. At this stage, the stirring was stopped and the Grignard solution was separated from colorless solid via cannula. The Grignard solution was stored at 0 °C under argon.

Representative Procedure for the Addition of 4 to Epoxides: 6-(*tert*-Butyldiphenylsilyloxy)-5-methyl-2-methylenehexane-1,5-diol (13). To a solution of Grignard **4** (17.0 mL, 0.11 M, 1.87 mmol) was added a solution of epoxide **12** (244 mg, 0.75 mmol) in THF (7.5 mL) via cannula at rt and the reaction was stirred for 2 h. The crude residue was purified by flash chromatography (60:40; petroleum ether/EtOAc) to give the desired product **13** as a colorless solid (224 mg, 75%). Mp 100−101 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74−7.55 (4H, m), 7.50−7.32 (6H, m), 5.01 (1H, br), 4.86 (1H, br), 4.07 (2H, br), 3.48 (2H, d, J = 2.0 Hz), 2.45 (1H, br), 2.22−1.98 (2H, m), 1.84−1.48 (3H, m), 1.17 (3H, s), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 135.7, 133.1, 130.0, 127.9, 109.3, 72.8, 70.9, 66.2, 36.5 (2C), 27.0, 23.3, 19.5; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3345 (br), 3071 (w), 3050 (w), 2931 (s), 2858 (s), 1651 (w), 1589 (w), 1742 (m), 1428 (s), 1391 (m), 1362 (m), 1307 (w), 1188 (w), 1112 (s), 1030 (m), 1008 (m), 931 (m), 905 (m), 822 (s), 740 (s), 702 (s), 614 (s), 504 (s), 490 (s); HRMS (ES) m/z [M + Na]$^+$ calcd for $C_{24}H_{34}O_3NaSi$ 421.2175, found 421.2177.

***cis*- and *trans*-4-*tert*-Butyl-1-(3-(hydroxymethyl)but-3-enyl)-cyclohexanol (15a and 15b).** To a solution of Grignard **4** (15 mL, 0.10 M, 1.5 mmol) was added a solution of epoxide **14** (168 mg, 1.0 mmol) in THF (10 mL) via cannula at rt and the reaction was stirred for 2 h. The crude residue was purified by flash chromatography to give compounds **15a**/**b** as separable colorless solids, **15a** (160 mg, 66%) and **15b** (50 mg, 21%). **15a**: Mp 92−94 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.98 (1H, br), 4.85 (1H, br), 4.06 (2H, br), 2.23−2.09 (2H, m), 1.76−1.64 (2H, m), 1.64−1.46 (4H, m), 1.39−1.19 (4H, m), 1.00−0.75 (1H, m), 0.84 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.7, 109.6, 70.8, 66.0, 48.1, 42.0, 37.5, 32.5, 27.7, 26.5, 22.5; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3307 (br), 2932 (s), 2040 (m), 1435 (m), 1360 (w), 1292 (w), 1234 (w), 1148 (w), 1068 (w), 1012 (s), 925 (m), 901 (w), 887 (w), 616 (w); [M]$^+$ calcd for $C_{15}H_{28}O_2$ 240.2089, found 240.2093. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.77; H, 11.60. **15b**: Mp 108−110 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.02 (1H, br), 4.91 (1H, br), 4.11 (2H, br), 2.21−2.08 (2H, m), 1.90−1.78 (2H, m), 1.75−1.61 (4H, m), 1.45−1.23 (2H, m), 1.17−0.96 (3H, m), 0.85 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.7, 109.7, 72.4, 66.2, 47.8, 39.0, 34.4, 32.4, 27.8, 26.3, 24.6; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3201 (br), 2935 (s), 2860 (m), 1452 (s), 1364 (s), 1289 (w), 1265 (w), 1197 (w), 1131 (w), 1089 (m), 1070 (m), 1034 (m), 1019 (s), 990 (w), 928 (w), 890 (m), 734 (m); HRMS (ES) m/z [M]$^+$ calcd for $C_{15}H_{28}O_2$ 240.2089, found 240.2100. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.87; H, 11.45.

Representative Procedure for the Pd-Catalyzed Cyclodehydration. *tert*-Butyl-(2-methyl-5-methylenetetrahydropyran-2-yl-

methoxy)diphenylsilane (19). A round-bottomed flask containing molecular sieves 4 Å (46 mg) was flame dried under vacuum and cooled under a nitrogen atmosphere. To this was added palladium acetate (3.5 mg, 0.016 mmol), triphenylphosphine (16.45 mg, 0.063 mmol), and anhydrous toluene (1 mL). The suspension was stirred for 10 min, and a solution of allylic alcohol **13** (125 mg, 0.31 mmol) in anhydrous toluene (2 mL) was transferred via cannula to the reaction mixture. Titanium isopropoxide (24 μL, 0.078 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. After cooling to rt, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the pyran **19** as a clear oil (45 mg, 38%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73−7.62 (4H, m), 7.48−7.33 (6H, m), 4.87−4.61 (2H, m), 4.13 (1H, d, J = 13.0 Hz), 4.00 (1H, d, J = 13.0 Hz), 3.61 (1H, d, J = 9.5 Hz), 3.54 (1H, d, J = 9.5 Hz), 2.43−2.15 (2H, m), 1.85−1.63 (2H, m), 1.32 (3H, s), 1.08 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.6, 135.8, 133.7, 129.8, 127.8, 108.4, 74.0, 69.7, 66.2, 33.4, 27.7, 27.0, 20.9, 19.5; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3071 (s), 3050 (s), 2931 (s), 2857 (s), 1656 (m), 1589 (m), 1472 (s), 1428 (s), 1390 (m), 1362 (m), 1278 (w), 1270 (w), 1221 (m), 1189 (m), 1112 (s), 1062 (s), 1000 (m), 998 (m), 939 (w), 898 (m), 862 (m), 824 (m), 740 (m), 701 (m), 624 (m), 504 (m); HRMS (EI) m/z [M]$^+$ calcd for $C_{24}H_{32}O_2Si$ 380.2171, found 380.2167.

***cis*-9-*tert*-Butyl-3-methylene-1-oxaspiro[5.5]undecane (20).** Following the representative procedure, a solution of allylic alcohol **15a** (100 mg, 0.42 mmol) in anhydrous toluene (3.5 mL) was transferred via cannula to a suspension of molecular sieves 4 Å (65 mg), $Pd(OAc)_2$ (4.7 mg, 0.021 mmol), PPh_3 (22.0 mg, 0.084 mmol), and anhydrous toluene (1.0 mL). Titanium isopropoxide (32 μL, 0.10 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. Pyran **20** was isolated as a clear oil (22 mg, 23%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.77−4.69 (2H, m), 4.0 (2H, s), 2.37−2.27 (2H, m), 2.12−2.00 (2H, m), 1.58−1.45 (4H, m), 1.40−0.90 (5H, m), 0.85 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 145.0, 108.3, 71.0, 65.3, 48.5, 38.5, 34.5, 32.6, 27.9, 27.8, 22.1; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 2939 (s), 2867 (s), 2838 (s), 1477 (m), 1442 (m), 1364 (m), 1284 (w), 1212 (w), 1158 (w), 1140 (w), 1090 (m), 1063 (s), 1038 (m), 1012 (w), 982 (w), 926 (w), 895 (m), 876 (m), 810 (w); HRMS (EI) m/z [M]$^+$ calcd for $C_{15}H_{26}O$ 222.1984, found 222.1990.

***trans*-9-*tert*-Butyl-3-methylene-1-oxaspiro[5.5]undecane (21).** Following the representative procedure, a solution of allylic alcohol **15b** (80 mg, 0.33 mmol) in anhydrous toluene (3.0 mL) was transferred via cannula to a suspension of molecular sieves 4 Å (50 mg), $Pd(OAc)_2$ (3.7 mg, 0.016 mmol), PPh_3 (17.3 mg, 0.066 mmol), and anhydrous toluene (1.0 mL). Titanium isopropoxide (25 μL, 0.08 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. Pyran **21** was isolated as a clear oil (25 mg, 34%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.78−4.69 (2H, m), 4.10 (2H, s), 2.33−2.23 (2H, m), 2.11−1.98 (2H, m), 1.80−1.60 (4H, m), 1.40−1.23 (2H, m), 1.15−0.98 (3H, m), 0.85 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 145.0, 108.2, 73.0, 65.8, 48.1, 35.5 (2C), 32.4, 32.0, 27.7, 24.0; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 2939 (s), 2867 (s), 2838 (s), 1477 (m), 1442 (m), 1364 (m), 1284 (w), 1212 (w), 1158 (w), 1140 (w), 1090 (m), 1063 (s), 1038 (m), 1012 (w), 982 (w), 926 (w), 895 (m), 876 (m), 810 (w); HRMS (EI) m/z [M]$^+$ calcd for $C_{15}H_{26}O$ 222.1984, found 222.1980.

Representative Procedure for Allylic Alcohol Acetylation: 7-(Benzyloxy)-5-hydroxy-2-methyleneheptyl Acetate (22). In a flame-dried flask was dissolved allylic alcohol **9** (50 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (4 mL). The solution was cooled to 0 °C and triethylamine (56 μL, 0.40 mmol), DMAP (1.5 mg), and acetic anhydride (19 μL, 0.20 mmol) were added sequentially. The cool bath was removed and the reaction stirred at rt for 1 h. The reaction was quenched with aqueous HCl solution (1 M) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (60:40; petroleum ether/EtOAc) to give **22** as a clear oil (45 mg, 76%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.21 (5H, m), 5.01 (1H, br), 4.95 (1H, br), 4.50 (4H, s), 3.88−3.77 (1H, m), 3.76−3.58 (2H, m), 3.04 (1H, br), 2.34−2.00 (2H, m), 2.06 (3H, s), 1.80−1.68 (2H, m), 1.67−1.54 (2H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.9, 143.9, 138.0, 128.6, 127.9, 127.8, 112.4, 73.5, 71.1, 69.3, 67.0, 36.5, 35.3, 29.3, 21.0; IR (film, cm^{-1}) 3460 (s), 3089 (m), 3031 (m), 2939 (s), 2863 (s), 1739 (s), 1654 (m), 1496 (w), 1452 (s), 1373 (s), 1235 (s), 1029 (s), 909 (m), 739 (m), 699 (m), 607 (w); HRMS (EI) m/z [M]$^+$ calcd for $C_{17}H_{24}O_4$ 292.1675, found 292.1681.

6-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-5-methyl-2-methylenehexyl Acetate (23). Following the representative procedure, allylic alcohol **13** (100 mg, 0.250 mmol) in anhydrous CH_2Cl_2 (3.5 mL) was treated with triethylamine (70 μL, 0.502 mmol), DMAP (1.5 mg), and acetic anhydride (35 μL, 0.376 mmol). The crude residue was purified by flash chromatography (60:40; petroleum ether/EtOAc) to give **23** as a clear oil (102 mg, 93%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76−7.61 (4H, m), 7.52−7.32 (6H, m), 5.03 (1H, br), 4.95 (1H, br), 4.53 (2H, br), 3.50 (2H, br), 2.46 (1H, br), 2.22−1.99 (2H, m), 2.07 (3H, s), 1.82−1.54 (2H, m), 1.18 (3H, s), 1.10 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.7, 144.2, 135.7, 133.1, 130.0, 127.9, 112.0, 72.5, 70.9, 67.0, 36.4, 27.2, 27.0, 23.3, 21.0, 19.4; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3482 (m), 3072 (m), 3050 (m), 2933 (s), 2859 (s), 1745 (s), 1655 (m), 1590 (w), 1472 (m), 1428 (m), 1375 (m), 1238 (m), 1113 (m), 1030 (m), 909 (m), 822 (m); HRMS (EI) m/z [M + Na]$^+$ calcd for $C_{26}H_{36}O_4NaSi$ 463.2281, found 463.2273.

***cis*-4-(4-*tert*-Butyl-1-hydroxycyclohexyl)-2-methylenebutyl Acetate (24).** Following the representative procedure, allylic alcohol **15a** (84 mg, 0.354 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with triethylamine (98 μL, 0.707 mmol), DMAP (2 mg), and acetic anhydride (50 μL, 0.530 mmol). The crude residue was purified by flash chromatography (80:20; petroleum ether/EtOAc) to give **24** as a clear oil (92 mg, 92%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.98 (1H, br), 4.92 (1H, br), 4.51 (2H, s), 2.18−2.08 (2H, m), 2.06 (3H, s), 1.73−1.62 (2H, m), 1.61−1.48 (4H, m), 1.36−1.23 (5H, m), 0.87−0.87 (1H, m), 0.83 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.9, 144.5, 112.1, 70.5, 67.0, 48.0, 42.0, 37.5, 32.5, 27.6, 26.8, 22.5, 21.0; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3480 (s), 2941 (s), 2868 (s), 2844 (s), 1744 (s), 1653 (m), 1478 (m), 1445 (m), 1392 (m), 1366 (s), 1315 (w), 1235 (s), 1143 (w), 1095 (w), 1029 (m), 988 (w), 960 (w), 926 (m), 914 (m); HRMS (EI) m/z [M]$^+$ calcd for $C_{17}H_{30}O_3$ 282.2195, found 282.2193.

***trans*-4-(4-*tert*-Butyl-1-hydroxycyclohexyl)-2-methylenebutyl Acetate (25).** Following the representative procedure, allylic alcohol **15b** (150 mg, 0.624 mmol) in anhydrous CH_2Cl_2 (9 mL) was treated with triethylamine (173 μL, 1.25 mmol), DMAP (4 mg), and acetic anhydride (88 μL, 0.94 mmol). The crude residue was purified by flash chromatography (80:20; petroleum ether/EtOAc) to give **25** as a clear oil (150 mg, 85%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.98 (1H, br), 4.93 (1H, br), 4.51 (2H, s), 2.15−1.96 (2H, m), 2.04 (3H, s), 1.85−1.50 (6H, m), 1.42−1.21 (2H, m), 1.09−0.87 (4H, m), 0.80 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.8, 144.5, 112.1, 71.9, 67.0, 47.6, 38.8, 34.3, 32.3, 27.7, 26.5, 24.5, 20.9; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3436 (s), 2941 (s), 2867 (s), 1743 (s), 1653 (m), 1458 (m), 1392 (m), 1366 (s), 1233 (s), 1126 (w), 1084 (w), 1032 (m), 984 (w), 960 (w), 926 (m), 916 (m); HRMS (ES) m/z [M + Na]$^+$ calcd for $C_{17}H_{30}O_3Na$ 305.2093, found 305.2098.

Representative Procedure for Pd-Catalyzed Allylic Acetate Cyclization: *tert*-Butyl(2-methyl-5-methylenetetrahydropyran-2-ylmethoxy)diphenylsilane (19). In a flame-dried flask was dissolved $Pd(OAc)_2$ (2.6 mg, 0.011 mmol) and PPh_3 (11.5 mg, 0.044 mmol) in anhydrous toluene (0.8 mL) and the solution was stirred for 10 min at rt. A solution of allylic acetate **29** (88 mg, 0.20 mmol) in anhydrous toluene (1.2 mL) was transferred via cannula to the suspension. Titanium isopropoxide (15 μL, 0.035 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. After cooling to rt, direct purification by chromatography on silica gel provided

the desired product **26** as a clear oil (69 mg, 90%). The product showed identical spectroscopic data to that outlined earlier.

***cis*-9-*tert*-Butyl-3-methylene-1-oxaspiro[5.5]undecane (20).** Following the representative procedure, a mixture of $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and PPh_3 (14.9 mg, 0.057 mmol) in anhydrous toluene (1.0 mL) was treated with a solution of **30** (80 mg, 0.28 mmol) in anhydrous toluene (1.9 mL) and titanium isopropoxide (21 μL, 0.07 mmol). Purification by chromatography on silica gel provided the desired product **27** as a clear oil (42 mg, 67%). The product showed identical spectroscopic data to that outlined earlier.

***trans*-9-*tert*-Butyl-3-methylene-1-oxaspiro[5.5]undecane (21).** Following the representative procedure, a mixture of $Pd(OAc)_2$ (5.0 mg, 0.022 mmol) and PPh_3 (23.1 mg, 0.088 mmol) in anhydrous toluene (1.5 mL) was treated with a solution of **31** (125 mg, 0.44 mmol) in anhydrous toluene (3.5 mL) and titanium isopropoxide (32.5 μL, 0.11 mmol). Purification by chromatography on silica gel provided the desired product **27** as a clear oil (74 mg, 75%). The product showed identical spectroscopic data to that outlined earlier.

7-(*tert*-Butyldiphenylsilyloxy)-2-methyleneheptane-1,5-diol. To a solution of Grignard **4** (10 mL, 0.14 M, 1.4 mmol) was added a solution of epoxide **26** (304 mg, 0.93 mmol) in THF (4 mL) via cannula at rt and the reaction was stirred for 2 h. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate) to give the title compound as a clear oil (293 mg, 79%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70−7.63 (4H, m), 7.48−7.33 (6H, m), 5.06−5.01 (1H, m), 4.92−4.88 (1H, m), 4.09 (2H, br), 3.99−3.78 (3H, m), 3.50 (1H, br), 2.33−1.94 (3H, m), 1.84−1.54 (4H, m), 1.04 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.0, 135.7, 133.1, 133.0, 130.0, 127.9, 109.7, 71.5, 66.1, 63.6, 38.5, 35.7, 29.0, 26.9, 19.1; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3354 (br), 3071 (w), 3050 (w), 2932 (s), 2858 (s), 1652 (w), 1472 (m), 1428 (s), 1390 (m), 1361 (m), 1112 (s), 1085 (s), 1029 (m), 900 (m), 823 (m), 737 (m), 702 (s), 688 (m), 614 (m), 504 (s); HRMS (ES) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{35}O_3Si$ 399.2355, found 399.2371.

Preparation of *cis*- and *trans*-(6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)tetrahydro-2*H*-pyran-3-yl)methanol (28). In a round-bottomed flask under a nitrogen atmosphere was dissolved **27** (650 mg, 1.7 mmol) in anhydrous THF (2 mL). To this solution was added dropwise, at rt, 9-BBN (0.5 M in THF, 4.40 mL, 2.20 mmol). The reaction was stirred at rt for 18 h, cooled to 0 °C, and quenched with NaOH (1 M, 3.4 mL, 3.4 mmol) and H_2O_2 (1 M, 0.4 mL, 3.4 mmol). The reaction was then stirred for 3 h at rt, and after this time saturated aqueous NH_4Cl solution was added to the solution and the product extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (60:40; petroleum ether/EtOAc) to give a mixture of cis:trans **28** as a yellow oil (608 mg, 90%, 3:1 trans/cis ratio). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80−7.57 (4H, m, trans/cis-isomers), 7.52−7.28 (6H, m, trans/cis-isomers), 4.06 (0.75 H, ddd, J = 11.0, 4.0, 2.5 Hz, trans-isomer), 3.95 (0.25 H, d, J = 12.0 Hz, *cis*-isomer), 3.89−3.33 (5.25 H, m, trans/cis-isomers), 3.13 (0.75H, t, J = 11.0 Hz, trans-isomer), 1.91−1.19 (8H, m, trans/cis-isomers), 1.06 (9H, s, trans/cis-isomers); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 135.7, 134.2, 134.1, 129.6, 127.7, 74.8, 74.7, 71.0, 68.5, 65.1, 63.4, 60.5, 60.3, 39.2, 39.0, 36.0, 31.5, 27.9, 27.0, 26.8, 24.6, 19.4; FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3377 (br), 3071 (m), 2930 (s), 2857 (s), 1472 (m), 1428 (s), 1389 (m), 1361 (m), 1212 (w), 1186 (w), 1112 (s), 1088 (s), 1007 (m), 974 (w), 940 (w), 910 (w), 863 (w), 823 (m), 788 (w), 736 (s), 702 (s), 613 (m), 505 (s); HRMS (ES) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{34}O_3NaSi$ 421.2175, found 421.2177.

Hydrozirconation Route to *trans*/*cis*-*tert*-Butyl(2-(5-(iodomethyl)tetrahydro-2*H*-pyran-2-yl)ethoxy)diphenylsilane (29). To a solution of pyran **27** (100 mg, 0.26 mmol) in anhydrous THF (2.2 mL) under nitrogen atmosphere was added in one portion $Cp_2Zr(H)Cl$ (203 mg, 0.79 mmol). The reaction was stirred at room temperature for 20 h. After this time, a solution of I_2 (264 mg, 1.04 mmol) in anhydrous THF (3.5 mL) was added via cannula at 0 °C to the reaction mixture. The reaction was then warmed to rt over 1 h, diluted with 70 mL of EtOAc, and washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (99:1; petroleum ether/EtOAc) to give the desired products as yellow oils *trans*-**29** (31 mg, 23%) and *cis*-**29** (78 mg, 58%). Satisfactory spectroscopic data were obtained for these compounds.[10]

***tert*-Butyldiphenyl(2-((2*R**,5*S**)-5-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)tetrahydro-2*H*-pyran-2-yl)ethoxy)silane (32).** Farnesyl sulfone **30** (62 mg, 0.18 mmol) was dissolved in anhydrous THF (550 μL) and DMPU (200 μL) and cooled to −78 °C. A 330 μL sample of a freshly prepared LDA solution (from 200 μL of DIPA, 710 μL of 1.9 M nBuLi in 1.45 mL of THF) was added to the sulfone and the resulting bright orange solution was stirred for 1 h at −78 °C. A solution of *trans*-**29** (105 mg, 0.20 mmol) in anhydrous THF (350 μL) was added dropwise. The reaction was stirred an additional 1 h at −78 °C, and then the cold bath was removed and the reaction stirred for another 3−4 h. The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution. The aqueous solution was extracted three times with ether, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil residue was purified via flash chromatography on silica gel (90:10; petroleum ether/EtOAc) to give an inseparable mixture (105 mg) of the desired product **31** and farnesyl sulfone.

The obtained mixture (105 mg) was dissolved in anhydrous THF (1.6 mL) and $PdCl_2$(dppf) (13.2 mg, 0.018 mmol) was added. Super Hydride (1 M in THF, 540 μL, 0.54 mmol) was added dropwise at 10 °C to the orange solution, the cold bath removed, and the reaction stirred at rt for 6 h. The reaction was quenched carefully at 0 °C with saturated aqueous NH_4Cl solution. The resulting aqueous layer was extracted with ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by flash chromatography on silica gel (98:2; petroleum ether/EtOAc) to give the desired product **32** as a yellow oil (74 mg, 70% over two steps). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73−7.63 (4H, m), 7.45−7.34 (6H, m), 5.18−5.04 (3H, m), 3.91 (1H, ddd, J = 11.0, 4.0, 2.0 Hz), 3.86−3.69 (2H, m), 3.50−3.37 (1H, m), 3.00 (1H, t, J = 11.0 Hz), 2.15−1.85 (11H, m), 1.76−1.69 (4H, m), 1.66−1.55 (10H, m), 1.30−1.10 (6H, m), 1.06 (9H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 135.7, 135.3, 135.1, 134. 3, 134.1, 131.3, 129.9, 127.7, 124.5, 124.4, 124.3, 74.6, 73.6, 60.6, 39.8, 39.4, 35.7, 32.8, 32.1, 30.7, 29.8, 27.0, 26.9, 26.7, 25.8, 25.1, 19.4, 17.8, 16.1 (2C); FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3174 (w), 3049 (w), 2928 (s), 2855 (s), 1472 (m), 1446 (m), 1428 (m), 1384 (m) 1361 (w), 1261 (w), 1213 (w), 1188 (w), 1112 (s), 1088 (s), 1007 (w), 940 (w), 823 (m), 736 (m), 701 (s), 613 (m), 504 (s); HRMS (ES) *m*/*z* [M]$^+$ calcd for $C_{39}H_{58}O_2Si$ 586.4206, found 586.4194.

2-((2*R,5*R**)-Tetrahydro-5-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)-2*H*-pyran-2-yl)ethanol (33).** To a solution of **32** (135 mg, 0.23 mmol) in anhydrous THF (2.5 mL) was added dropwise TBAF (1 M in THF, 350 μL, 0.36 mmol). The reaction was stirred at rt for 20 h and quenched with H_2O. The aqueous layer was extracted two times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (80:20; petroleum ether/EtOAc) to give the desired product **33** as yellow oil (78 mg, 98%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.15−5.02 (3H, m), 3.93 (1H, ddd, J = 11.0, 4.0, 2.0 Hz), 3.77 (2H, t, J = 5.0 Hz), 3.52−3.39 (1H, m), 3.03 (1H, t, J = 11.0 Hz), 2.94−2.76 (1H, br), 2.13−1.80 (10H, m), 1.77−1.04 (21H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 135.4, 135.0, 131.3, 124.5, 124.3 (2C), 78.4, 73.6, 61.6, 39.8 (2C), 38.1, 35.4, 32.7, 31.9, 30.3, 26.8, 26.7, 25.8, 25.0, 17.8, 16.1 (2C); FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 3391 (br), 2919 (s), 2850 (s), 1448 (m), 1382 (m), 1223 (w), 1092 (s), 1059 (m), 890 (w), 853 (w); HRMS (ES) *m*/*z* [M]$^+$ calcd for $C_{23}H_{40}O_2$ 348.3028, found 348.3033.

2-((2*R,5*R**)-Tetrahydro-5-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)-2*H*-pyran-2-yl)acrylaldehyde (34).** To a solution of oxalyl chloride (23 μL, 0.26 mmol) in anhydrous CH_2Cl_2 (380 μL) was added dropwise at −78 °C a solution of DMSO (37 μL, 0.52 mmol) in CH_2Cl_2 (380 μL). The reaction was stirred at −78 °C for 20 min. A solution of **33** (45 mg, 0.13 mmol) in CH_2Cl_2 (330 μL) was added dropwise at −78 °C for 15 min and the reaction mixture was stirred for 1 h at −78 °C. Et_3N (128 μL, 0.91 mmol) was added dropwise and the reaction was stirred for a further hour. The reaction was quenched with brine and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the corresponding aldehyde as a yellow oil. The crude residue (37 mg, 83% crude) was dissolved in anhydrous CH_2Cl_2 (1.8 mL) and Eschenmoser's salt (98 mg, 0.53 mmol) and Et_3N (300 μL, 2.13 mmol) were added. The reaction was stirred at rt for 20 h. The reaction was quenched with a solution of $NaHCO_3$ and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (99:9:1 petroleum ether/EtOAc/Et_3N) to give the desired product **34** as a yellow oil (30 mg, 66% over two steps). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (1H, s), 6.55−6.51 (1H, m), 6.05 (1H, s), 5.14−5.04 (3H, m), 4.13 (1H, d, J = 9.5 Hz), 4.02 (1H, ddd, J = 11.0, 4.0, 2.0 Hz), 3.13 (1H, t, J = 11.0 Hz), 2.15−1.78 (12H, m), 1.67 (3H, s), 1.62−1.55 (1H, m), 1.60 (9H, s), 1.30−1.04 (4H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 193.4, 151.7, 135.4, 135.1, 133.8 (2C), 124.5, 124.3 (2C), 74.0, 73.8, 39.8 (2C), 35.5, 32.6, 32.2, 30.4, 26.9, 26.8, 25.8, 25.0, 17.8, 16.1 (2C); FTIR (CH_2Cl_2, ν_{max} cm^{-1}) 2919 (s), 2850 (s), 1694 (s), 1448 (m), 1378 (m), 1352 (w), 1292 (w), 1250 (w), 1094 (s), 1049 (w), 951 (w), 902 (w), 840 (w), 668 (w), 665 (w), 550 (w); HRMS (ES) m/z $[M]^+$ calcd for $C_{24}H_{38}O_2$ 358.2871, found 358.2888.

Rhopaloic A (35). To a solution of aldehyde **35** (29 mg, 0.08 mmol) in ^{t}BuOH/H_2O (5:1, 4.0 mL) was added 2-methyl-2-butene (2M in THF, 2.5 mL, 4.85 mmol), NaH_2PO_4 (58.2 mg, 0.48 mmol), and $NaClO_2$ (80%, 55 mg, 0.485 mmol). The reaction was stirred at rt for 2 h, brine was added, and the reaction mixture was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (gradient starting with 100:0 and ending with 60:40 petroleum ether/EtOAc) to give the desired product as a yellow oil (24 mg, 80%). The compound showed satisfactory spectral data:[16a] ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.38 (1H, br), 5.91 (1H, br), 5.12−5.07 (3H, m), 4.12 (1H, d, J = 11.0 Hz), 4.06 (1H, ddd, J = 11.0 4.0, 1.5 Hz), 3.17 (1H, t, J = 11.0 Hz), 2.11−1.91 (12H, m), 1.68 (3H, d, J = 1.0 Hz), 1.64−1.57 (1H, m), 1.60 (9H, s), 1.38−1.30 (1H, m), 1.27−1.12 (3H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.8, 141.0, 135.6, 135.1, 131.4, 127.1, 124.5, 124.3, 124.2, 76.2, 74.1, 39.9, 39.8, 35.3, 32.6, 32.1, 30.4, 26.9, 26.7, 25.8, 25.0, 17.8, 16.2 (2C); HRMS (ES) m/z $[M]^+$ calcd for $C_{24}H_{38}O_3$ 374.2820, found 374.2807.

Acknowledgment. We are grateful to GlaxoSmithKline and the University of Sheffield for financial support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702620E