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A formal total synthesis of dictyostatin

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ABSTRACT

A convergent formal synthesis of the antimitotic macrolide dictyostatin has been achieved. The C11–C26 fragment of dictyostatin was prepared via convergent assembly of the central deoxypropionate motif utilizing a site- and stereoselective titanium-mediated reductive cross-coupling and an asymmetric hydrogenation of the resulting stereodefined 1,3-diene.

1. Introduction

(−)-Dictyostatin (**1**, Fig. 1), an antimitotic macrolide, was first isolated in 1994 by Pettit and co-workers from a Maldives marine sponge[1,2] and subsequently from a Caribbean sponge (*Corallistidae* sp.) by Wright and co-workers in 2003.[3,4] The 22-membered macrolactone has been shown to exhibit potent anticancer properties, similar or superior to its open-chain analogue discodermolide (**2**).[4] Displaying a Taxol-like mechanism of action by binding to tubulin and inducing microtubule assembly, dictyostatin inhibits human cancer cell proliferation at nanomolar concentrations (ED_{50} 0.38 nM, P338 leukemia cells).[5] Importantly, both discodermolide and dictyostatin retain activity against multi-drug resistant cell-lines as they do not bind to P-glycoprotein, a principal mediator of taxane resistance.[6] With the withdrawal of discodermolide from clinical development in 2005,[7] interest in dictyostatin has increased, particularly as the natural supply is extremely scarce.

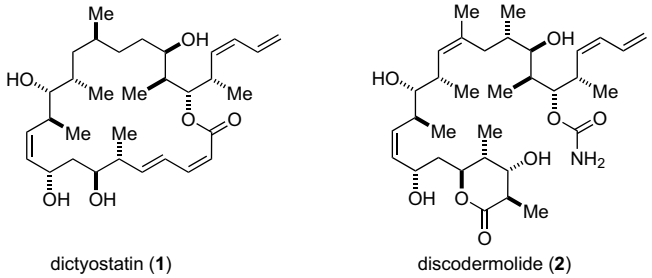

Figure 1. Dictyostatin and discodermolide.

Following the isolation of dicytostatin, its planar structure was determined to include 11 stereogenic centers, a *cis*-1,2-disubstituted olefin, an endocyclic 2*Z*,4*E*-dienoate and a pendant *Z*-diene.[1] Relative stereochemical assignment was later reported through the use of extensive high field NMR studies and molecular modeling,[5] with the absolute stereochemistry proposed based on a common biogenesis for dictyostatin and discodermolide.[8] Concurrent total syntheses by the Paterson[9] and Curran groups[10] in 2004 confirmed the proposed structure of dictyostatin, in which the 10 stereocenters that are shared with discodermolide have the same absolute configuration. Following these initial synthetic efforts, the significant therapeutic potential of dictyostatin has led several groups to target its synthesis in addition to several related analogues.[11–13]

Efficient construction of the functionalized deoxypropionate-containing fragment of dictyostatin (C11–C26) persists as a challenging synthetic goal.[13,14] In an extension of our prior work on the convergent assembly of trisubstituted (*E*,*E*)-1,3-dienes,[15] we anticipated that the C11–C26 subunit of dictyostatin (**3**) could arise from the regio-, stereo-, and chemoselective cross-coupling of homopropargylic ether **5** with terminal alkyne **6** (Scheme 1). From the resulting polyene, hydroxyl-directed reduction[16] of the central diene was expected to set the remote C16 stereocenter en route to triol **3**, an intermediate in the synthesis of dictyostatin reported by Paterson and co-workers.[9]

Targeting the synthesis of dictyostatin through an unconventional C16–C17 bond construction, we sought to expand the utility of our alkyne–alkyne cross-coupling methodology in the context of complex polyketide synthesis. In this case, sequential reductive cross-coupling and hydroxyl-directed reduction was expected to provide a means for the convergent stereoselective synthesis of deoxypropionates.

2. Results and discussion

2.1. Titanium-mediated cross-coupling

As depicted in Scheme 2, preparation of terminal alkyne fragment **6** commenced from the known homoallylic alcohol **7**,[17]

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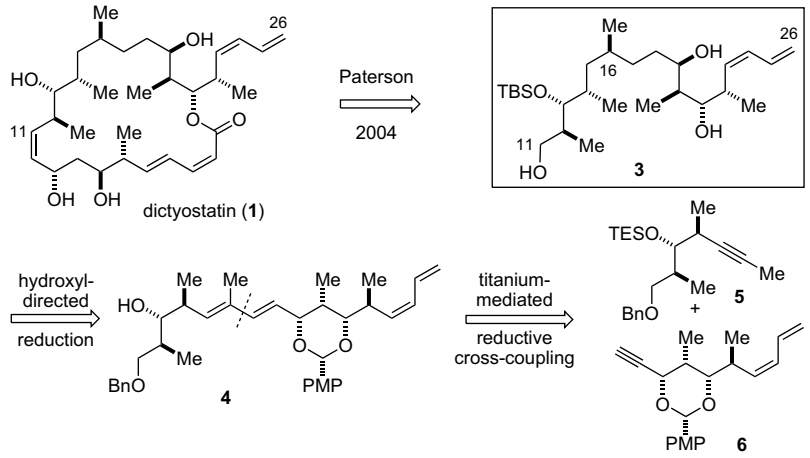
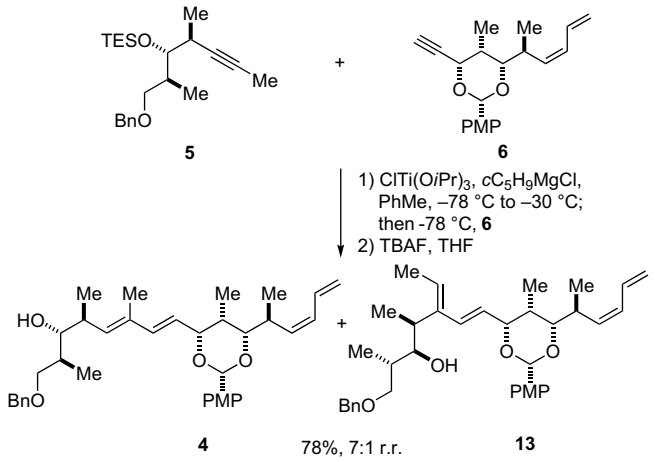


Scheme 1. Retrosynthesis of dictyostatin **1**: application of a titanium-mediated cross-coupling/hydroxyl-directed reduction sequence.

accessed in four steps from commercially available (2*S*)-3-hydroxy-2-methyl-propionate. Oxidation with DDQ followed by site-selective opening of the PMP acetal (DIBALH)[18] and protection of the primary alcohol (TBDPSCl, imid.) provided the homoallylic ether **8** in 80% overall yield. Oxidative cleavage of the terminal olefin (OsO_4, NMO, then $NaIO_4$) afforded aldehyde **9**, which was employed in a double asymmetric addition reaction with TMS–acetylene[19] to deliver propargyl alcohol **10** in 89% yield (d.s.=5:1). Oxidative formation of the corresponding PMP acetal (DDQ), followed by desilylation with TBAF and oxidation[20] supplied aldehyde **11**. Finally, allylation with (*E*)-γ-trimethylsilylallylboronic ester **12** and base-induced Peterson elimination (KH, THF) provided the stereodefined 1,3-(*Z*)-diene **6** in 64% yield as a single isomer.[21] Confirmation of the desired *syn–syn* stereochemistry was established using NOE analysis.

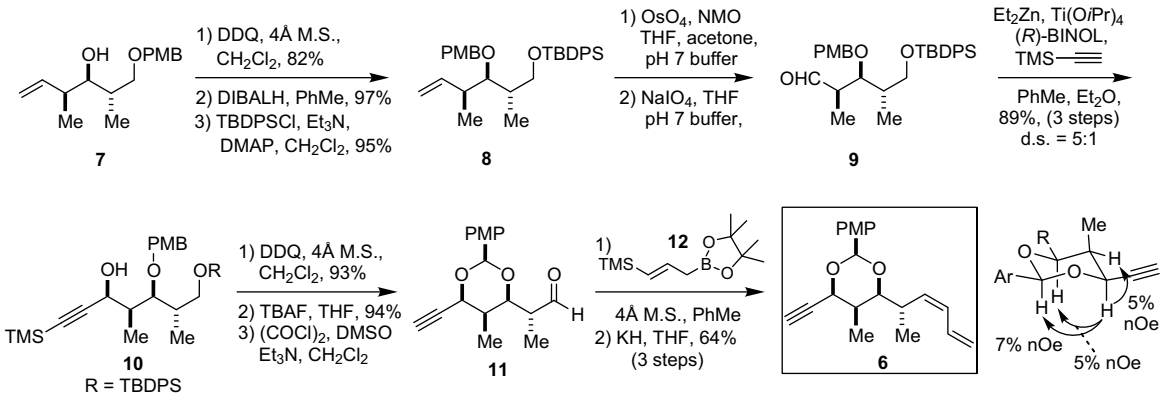
Reductive cross-coupling of **5** (available from well established propargylation chemistry)[22] with **6** ($ClTi(O\textit{i}\text{-}Pr)_3$, $c\text{-}C_5H_9MgCl$, PhMe), followed by desilylation (TBAF, THF) provided the 1,3-diene **4** in 78% yield as a 7:1 mixture of regioisomers (Scheme 3).[23] We were delighted to observe both regioselectivity for the formation of the desired product (**4**), as well as high levels of chemoselectivity in this reductive cross-coupling reaction; competitive reaction of the preformed titanium–alkyne complex of **5** with the 1,3-(*Z*)-diene of **6** was not observed. With a suitable convergent coupling reaction established, we set out to investigate the site- and stereoselective functionalization of the central (*E*,*E*)-diene of **4** using substrate-directed hydrogenation.[16,24]



Scheme 3. Titanium-mediated reductive cross-coupling in the preparation of tetraene **4**.

2.2. Hydroxyl-directed hydrogenation

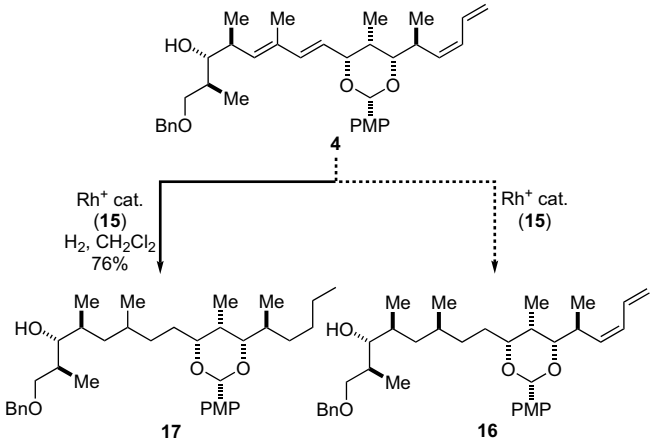
Numerous studies have demonstrated the ability of proximal hydroxyl groups to influence the stereochemical course of transition metal-catalyzed olefin hydrogenation reactions.[25] Despite significant precedent for hydroxyl-directed hydrogenation of allylic and homoallylic alcohols with either the cationic iridium catalyst, $Ir(COD)(py)(PCy_3)PF_6$ (Crabtree's catalyst, **14**)[26,27] or the cationic



Scheme 2. Synthesis of terminal alkyne coupling partner **6**.

rhodium catalyst [Rh(nbd)(dppb)]BF_4 (**15**),[28,29] to the best of our knowledge, hydroxyl-directed reduction of 1,3-dienes has not been reported. As such, we set out to investigate chemo- and stereoselective directed reduction of the central diene of **4** with the intent to: (1) extend the utility of our reductive cross-coupling reaction of alkynes in organic synthesis, (2) provide access to the C11–C26 fragment of dictyostatin, and (3) add to the body of literature associated with directed hydrogenation methodology (Scheme 1).

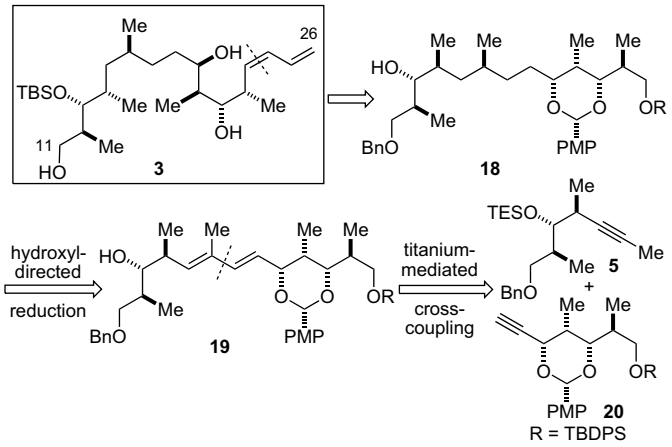
Initial attempts aimed at the selective functionalization of tetra-ene **4** using the cationic rhodium catalyst [Rh(nbd)(dppb)]BF_4 (**15**) in CH_2Cl_2 at 700 psi led to complete reduction of both the central and terminal diene, with **17** isolated in 76% yield (Scheme 4). Efforts to modify the reaction conditions to achieve site-selectivity in the reduction included varying temperature (−78 °C to 23 °C), H_2 pressure (1 atm to 700 psi), and use of either the rhodium catalyst **15** or Crabtree's iridium catalyst **14**.[26] In all cases, site-selective hydrogenation of the central trisubstituted diene was not possible. Therefore, despite the success of our reductive cross-coupling process to deliver tetra-ene **4** in a regio- and chemoselective manner, limitations in site selective hydroxyl-directed hydrogenation led us to redesign our synthetic route.



Scheme 4. Hydroxyl-directed reduction of polyene **4**.

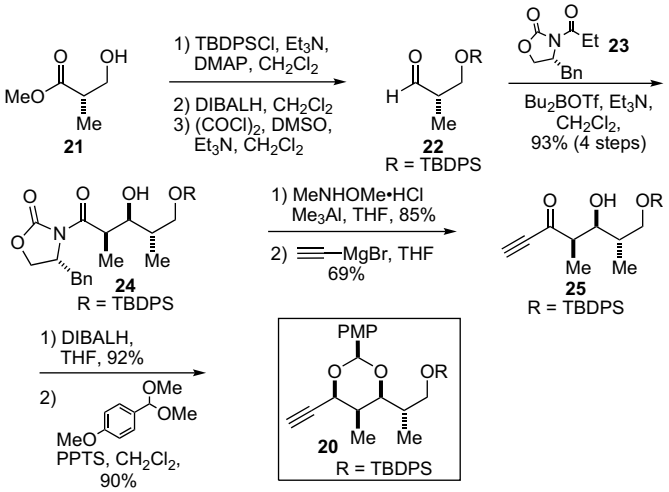
2.3. Revised route

To avoid the site selectivity problems observed in our attempted directed hydrogenation, we targeted hydroxyl-directed hydrogenation of **19**, a substrate that lacks the terminal (*Z*)-diene found in dictyostatin. Employing a titanium-mediated reductive cross-coupling reaction, **19** was thought to derive from the union of alkyne **5** with the terminal alkyne **20** (Scheme 5).



Scheme 5. Revised retrosynthetic analysis for the C11–C26 fragment of dictyostatin.

Through an efficient eight-step sequence, terminal alkyne **20** was prepared in an overall 45% yield from the commercially available (2*S*)-3-hydroxy-2-methyl-propionate (**21**). As shown in Scheme 6, the auxiliary-controlled enolborane *syn*-aldol reaction[30] with aldehyde **22** provided known aldol adduct **24** in 93% yield.[31] Conversion to the Weinreb amide[32] followed by ynone formation gave acetylenic ketone **25**. Diastereoselective reduction (DIBALH, THF) then afforded a *syn*-diol (92%, ≥20:1 d.s.),[33] which was protected as its corresponding PMP acetal (**20**).



Scheme 6. Synthesis of terminal alkyne fragment **20**.

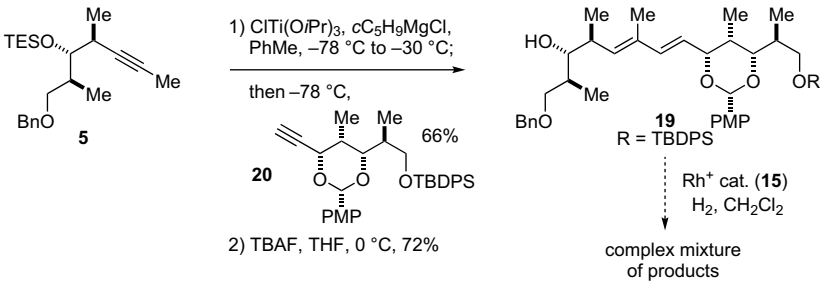
As expected, regioselective reductive cross-coupling of internal alkyne **5** with terminal alkyne **20** provided a functionalized 1,3-diene in 66% isolated yield (r.r.≥20:1; Scheme 7). Selective desilylation (TBAF, THF) then delivered the secondary carbinol **19** in 72% yield.

While we were pleased to have secured a convergent and stereoselective synthesis of **19**, all attempts to accomplish a stereoselective directed hydrogenation of this substrate were unsuccessful. In fact, only inseparable mixtures of products were obtained on exposure of **19** to either hydrogenation catalyst (**14** or **15**; CH_2Cl_2, 700 psi H_2).

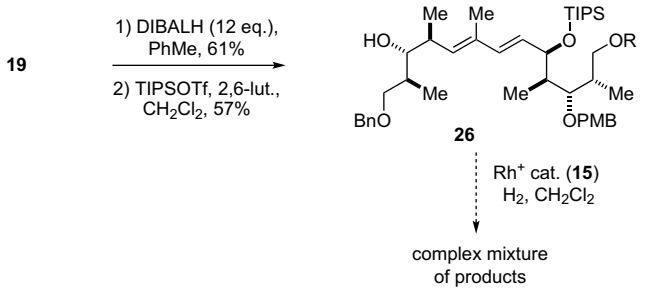
2.4. Exploring hydroxyl-directed reduction

Based on the lack of literature precedent for hydroxyl-directed hydrogenation of conjugated dienes, we set out to further investigate this type of reduction in the context of polyketide synthesis. Various directing groups have been shown to participate in the catalytic reduction of *endo*- or *exo*-cyclic olefins (including ethers, esters and amides).[24] As such, we were concerned that the allylic acetal in substrate **19** may competitively coordinate to the cationic rhodium catalyst and adversely affect selectivity in the reduction. Therefore, the Lewis basic dienylic PMP acetal of **19** was converted to the corresponding TIPS ether **26** (Scheme 8). Unfortunately, attempted hydrogenation of **26** was similarly unsuccessful, as exposure to the cationic Rh catalyst **15** and 750 psi H_2 led once again to an inseparable mixture of products.

In an attempt to dissect the problems that we were experiencing in directed hydrogenation of 1,3-dienes, we focused our attention on a substrate lacking some of the molecular complexity associated with the C11–C26 fragment of dictyostatin. As illustrated in Scheme 9, directed reduction of diene **27** proceeded with low selectivity, providing a separable mixture of four products in 85% yield: two fully-saturated diastereomers (**29** and **30**), as well as (*E*)- and (*Z*)-olefin isomers (**31** and **32**, respectively; **29:30:31:32**=2:1:1:1).[34]



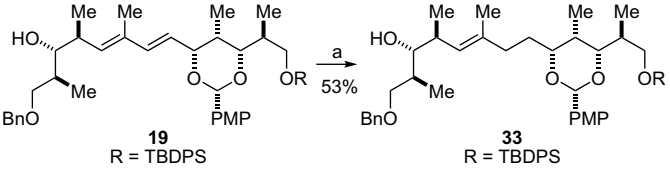
Scheme 7. Regioselective titanium-mediated cross-coupling and hydroxyl-directed reduction sequence.



Scheme 8. Preparation of diene **21** and subsequent hydroxyl-directed reduction.

The non-selective reduction of **27** suggested that olefin isomerization was partially responsible for the mixture of products observed in our attempted hydrogenation reactions toward a dictyostatin synthesis. Although isomerization is known to occur in rhodium-catalyzed hydroxyl-directed reductions of allylic alcohols at low H_2 pressures,[25] olefin isomerization of homoallylic alcohols where allylic and homoallylic stereogenic centers are present has not been reported.[29] To confirm that the conjugated diene was responsible for the low levels of selectivity observed in the reduction of **27**, we studied the directed hydrogenation of homoallylic alcohol **28**.[35] Interestingly, use of the cationic rhodium catalyst **15** resulted in a highly selective hydrogenation, in this case delivering **29** as essentially a single diastereomer in 88% yield.

Based on these findings, a potential synthetic solution to the problems associated with advancing our conjugated diene-containing substrates to the northern fragment of dictyostatin could include partial hydrogenation of the trisubstituted diene followed by directed hydrogenation of the remaining trisubstituted olefin. While standard hydrogenation catalysts (i.e., Pd/C, PtO_2, $RhCl(PPh_3)_3$) typically led to nonselective reduction of **19**, the chiral ruthenium catalyst $Ru(OAc)_2[(R)\text{-BINAP}]$[36] provided the desired intermediate **33** as the major product (50 °C, 1450 psi, 6 days, 53% yield; Scheme 10). Unfortunately, the long reaction time (6 days) and high pressure required to generate **33** in only modest yield were seen as a barrier to material throughput and an alternative pathway to establish this central deoxypropionate unit was pursued.

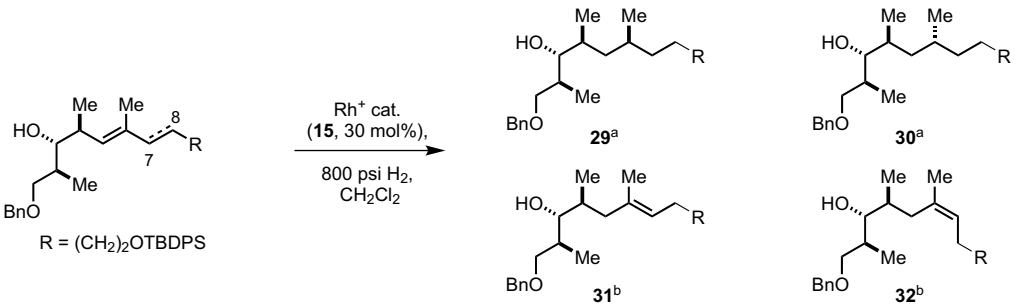


a) Reaction conditions: $Ru(OAc)_2[(R)\text{-BINAP}]$, 1450 psi H_2, 50 °C, 6 d

Scheme 10. Partial hydrogenation of **19**.

2.5. Asymmetric hydrogenation

Recently, the Burgess group has highlighted the utility of the chiral iridium carbene catalyst **34** (Fig. 2) in diastereoselective hydrogenation reactions leading to deoxypropionate architecture.[37,38] As shown in Scheme 11, catalyst control provided a pathway for conversion of the homoallylic alcohol **35** to either the *anti* or *syn* isomer (in 9:1 and 4:1 selectivity, respectively).[38] In a related series of experiments, the 1,3-diene **37** was selectively reduced to deliver either the *anti,syn* stereoisomer (d.s.=11:1) with D-**34**, or the *syn,syn* isomer (d.s.=3:1) with



	yield (%)	ratio (**29**:**30**:**31**:**32**)
27 C7-C8: C=C	85	2:1:1:1
28 C7-C8: C-C	88	≥20:1 (**29**:all others)

a = stereochemistry at C6 assigned based on literature precedent for diastereoselectivity: see Ref. 29.
b = olefin stereochemistry determined by nOe analysis: see Supplementary data.

Scheme 9. Hydroxyl-directed reduction of diene **27** versus homoallylic alcohol **28**.

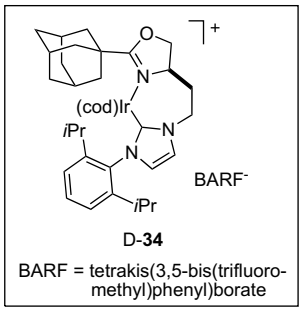
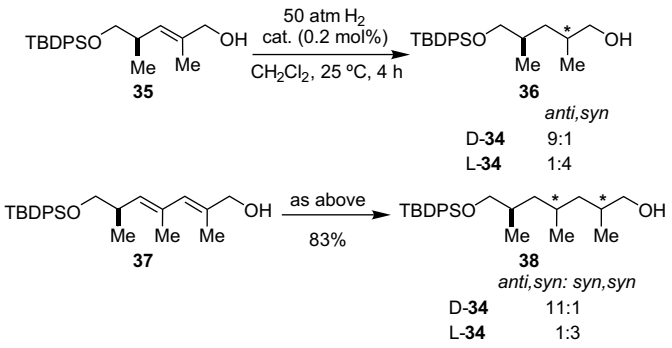


Figure 2. Burgess' iridium carbene–oxazoline complex.



Scheme 11. Asymmetric hydrogenation reactions of allylic and dienylic alcohols with **34** leading to deoxypropionates.

L-**34**. Based on these observations, we shifted our attention to the application of the Burgess catalyst to our synthetic problem.

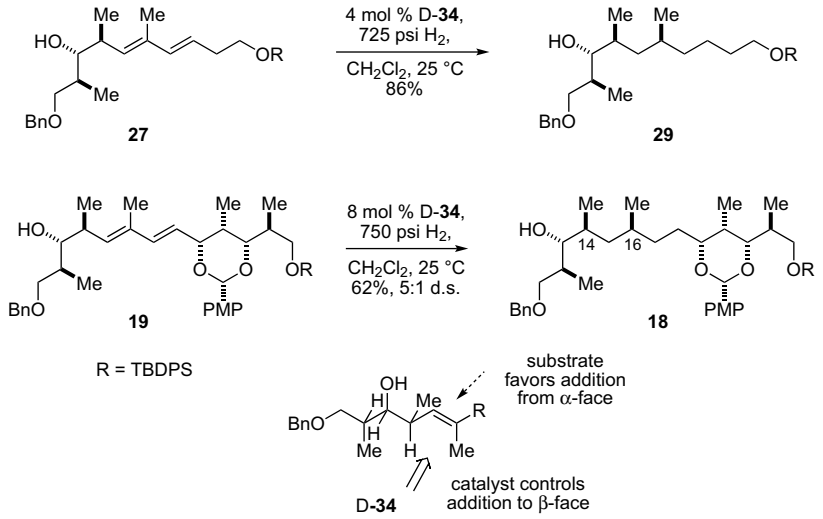
Hydrogenation of diene **27** with catalyst D-**34** resulted in the formation of **29** in 86% yield (4 mol % D-**34**, 725 psi, CH_2Cl_2, 3 h, Scheme 12).[39] Notably, products related to olefin isomerization or incomplete reduction were not observed. Encouraged by this result, we subjected our fully functionalized fragment **19** to related reduction conditions (8 mol % D-**34**, 750 psi H_2, CH_2Cl_2). To our delight, we isolated the desired deoxypropionate **18** in 62% yield (d.s.=5:1)[40] accompanied by a minor product resulting from deprotection of the PMP acetal.[41]

At this point, rigorous stereochemical assignment of C16 was not possible. Considering the intrinsic facial selectivity of **19** dictated by minimization of 1,3-allylic strain,[42] hydrogenation under substrate control[43] was anticipated to favor production of the undesired *anti* diastereomer. As such, selection of D-**34** was based on the desire to accomplish a stereoselective functionalization in which catalyst control would dominate over the inherent substrate-based selectivity (Scheme 12).[38] Success in related mismatched double asymmetric hydrogenation reactions reported by Burgess (Scheme 11) led to our optimistic assignment of the C14–C16 *syn* stereochemical relationship in the major product (**18**). Our tentative assignment was one that would require conversion to dictyostatin in order to confirm the C16 stereochemistry resulting from this asymmetric hydrogenation.

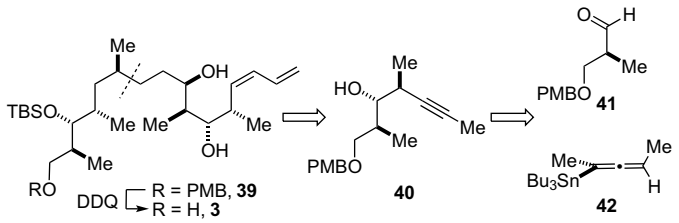
2.6. Completion of a formal synthesis of dictyostatin

Planning on a late stage deprotection of the C11 alcohol, we opted to exchange the benzyl ether protecting group on the internal alkyne component for a PMB ether (**40**, Scheme 13), a decision that was anticipated to facilitate deprotection in the presence of the terminal diene (i.e., **39**→**3**). This strategic consideration required a slight modification of our original synthetic pathway to the stereodefined internal alkyne coupling partner.[22] The often harsh Lewis acidic conditions required for propargylation of aldehydes with allenylsilanes (i.e., $TiCl_4$)[44] were expected to be incompatible with aldehyde **41**. As such, we opted to employ the related organometallic reagent **42**, as chiral allenylstannanes are known to undergo propargylation with chiral aldehydes under more mild reaction conditions ($BF_3\cdot OEt_2$, $MgBr_2\cdot OEt_2$).[45,46]

Toward this end, the double asymmetric[43] propargylation reaction of α-chiral aldehyde **41** with allenylstannane **42** ($MgBr_2\cdot OEt_2$, CH_2Cl_2) afforded the homopropargylic alcohol **40** in 79% yield (d.s.≥20:1). Following TES-protection of the homopropargylic alcohol, titanium-mediated reductive cross-coupling with terminal alkyne **20** afforded the (*E*,*E*)-1,3-diene in 65% yield with 7:1 regioselection (entry 1, Table 1). Subsequent selective desilylation of the TES ether (TBAF or HF·py) provided **44** in only moderate yields (43–60%), prompting us to examine the cross-coupling of terminal alkyne **20** with **40**, a substrate bearing an unprotected C13 hydroxy group.[15] Unfortunately, repeated attempts to accomplish this cross-coupling reaction led to mixtures of products in which the desired diene **44** was isolated in ≤23% yield. While the origin of this poor efficiency remains unclear, we opted to investigate the related reductive cross-coupling of TMS-ether **45**. To our delight, regioselective coupling of **45** with the terminal alkyne **20** provided the trisubstituted 1,3-diene in 76% isolated yield (r.r.≥20:1). Selective deprotection under mild conditions (K_2CO_3, MeOH) then delivered the fully functionalized substrate **44** in 71% yield.



Scheme 12. Diastereoselective hydrogenation reactions of dienes **27** and **19** with Burgess' catalyst.

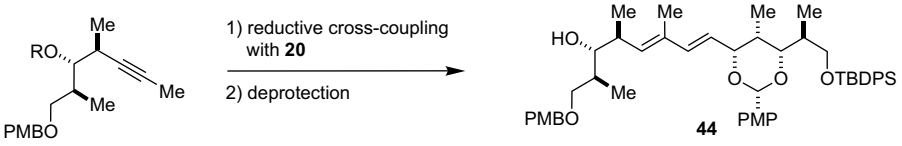


Scheme 13. Revised strategy for the preparation of **3**.

steps). Following oxidation with Dess–Martin periodinane,[48] installation of the terminal diene was achieved through the standard protocol used previously in the syntheses of discodermolide[49] and dictyostatin.[9,10,12] Accordingly, Nozaki–Hiyama–Kishi allylation[50] with 1-bromo-1-trimethylsilyl-2-propene provided a mixture of *anti*-β-hydroxysilanes (**48**), which upon treatment with KH underwent 1,2-*syn*-elimination[51] to provide the (*Z*)-diene **49** in 67% yield over the three-step sequence.

Completion of the formal total synthesis of dictyostatin was accomplished in two additional steps. Deprotection of the PMP acetal

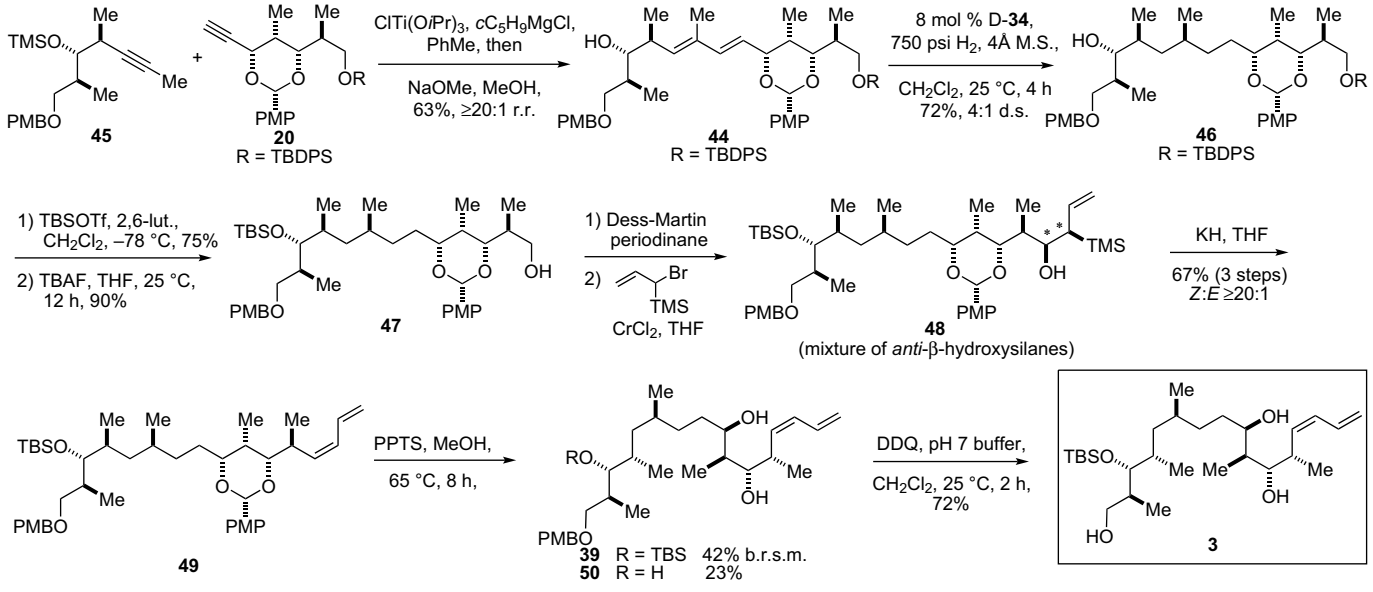
Table 1



Entry	Internal alkyne	Cross-coupling yield	Deprotection yield
1	R=TES (**43**)	65% (7:1 r.s.)	43–60% (TBAF or HF·py)
2	R=H (**40**)	≤23%	n/a
3	R=TMS (**45**)	76% (≥20:1 r.r.)	71% (K_2CO_3, MeOH)

Seeking to take advantage of the lability of the TMS ether, we next examined conditions for a one-pot cross-coupling/deprotection sequence. Following titanium-mediated reductive cross-coupling, successful removal of the TMS-ether was possible using a variety of acidic or basic conditions in the work-up (1 N HCl, TBAF or K_2CO_3), with NaOMe in MeOH providing the highest yield of diene **44** (63%, Scheme 14).

under acidic conditions (PPTS, MeOH) provided diol **39** in 42% yield accompanied by triol **50** in 23% yield. Finally, removal of the PMB ether with DDQ afforded the desired fragment **3** (72% yield), which was previously converted to dictyostatin over nine steps.[9] Comparison of our ^1H and ^{13}C NMR data to that provided by Paterson and co-workers verified the identity of triol **3** and confirmed the validity of this tita-



Scheme 14. Completion of a formal total synthesis of dictyostatin.

Next, asymmetric reduction employing the Burgess iridium carbene–oxazoline catalyst D-**34** provided the deoxypropionate fragment **46** in 72% yield (d.s.=4:1, separable by HPLC). The problematic partial deprotection of the PMP acetal previously observed in the reduction of **19**, presumably due to the Lewis acidic nature of the cationic iridium catalyst, was circumvented through the addition of 4 Å molecular sieves to the reaction mixture.[47] Subsequent protection with TBSOTf and selective removal of the TBDPS ether (TBAF, THF) provided the primary alcohol **47** (73% yield over two

nium-mediated cross-coupling/asymmetric reduction process for the convergent assembly of the C11–C26 fragment of dictyostatin.

3. Conclusion

In our planned synthesis of the C11–C26 fragment of dictyostatin, we targeted an unconventional bond construction for the convergent assembly of the central deoxypropionate motif. This strategy, based on initial application of a titanium-mediated

reductive cross-coupling reaction between an internal alkyne and terminal alkyne followed by stereoselective hydrogenation of the resulting 1,3-diene, led to the successful completion of a formal total synthesis of dictyostatin. Our initial investigations demonstrated notable chemoselectivity in the titanium-mediated reductive cross-coupling reaction (**5**+**6**→**4**); however, limitations associated with site- and stereoselective hydroxyl-directed hydrogenation ultimately prohibited the use of this pathway to dictyostatin. In the search to avoid the problems associated with selective hydrogenation, we arrived at a solution that: (1) employed a reductive cross-coupling reaction of a simplified terminal alkyne coupling partner to obviate the need for site-selective hydrogenation (removal of the terminal (*Z*)-diene), and (2) embraced a catalyst-controlled diastereoselective hydrogenation to establish the stereodefined central deoxypropionate. Overall, through investigations culminating in a formal total synthesis of dictyostatin, we have demonstrated the utility of our titanium-mediated reductive cross-coupling between an internal and terminal alkyne for the convergent assembly of deoxypropionate architecture.

4. Experimental section

4.1. General

All reactions were conducted in flame-dried glassware under nitrogen using anhydrous solvents. Toluene was distilled from sodium/benzophenone ketyl or passed through and activated alumina column followed by a copper column before using. Diethyl ether and tetrahydrofuran were passed through an activated alumina column. Et_3N was distilled from calcium hydride immediately prior to use. Ti(O*i*-Pr)$_4$ was used after distillation of the commercially available reagent. ClTi(O*i*-Pr)$_3$ was purchased as a 1 M solution in hexanes from Aldrich® and was used without further analysis or purification. All other commercially available reagents were used as received.

4.2. Titanium-mediated cross-coupling

4.2.1. (2S,3R,4S,5E,7E)-8-((2R,4R,5S,6S)-6-((S)-1-(tert-Butyldiphenylsilyloxy)propan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-1-(4-methoxybenzyloxy)-2,4,6-trimethylocta-5,7-dien-3-ol, ***44***

To a −78 °C solution of alkyne **45** (4.36 g, 12.5 mmol) in 80 mL of PhMe were added sequentially 19.0 mL of ClTi(O*i*-Pr)$_3$ (1.0 M in hexanes, 18.8 mmol) and 19.0 mL of *c*-C_5H_9MgCl (2.0 M in Et_2O, 37.5 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black while warming slowly to −30 °C over 1 h. The reaction mixture was stirred at −30 °C for 1 h and then cooled to −78 °C. Terminal alkyne **20** (4.63 g, 8.8 mmol) in 10 mL of PhMe was added slowly dropwise via a gas-tight syringe and warmed to −30 °C over 1 h. After stirring at −30 °C for 1 h, the reaction mixture was concentrated in vacuo to ca. 10 mL, and 50 mL of NaOMe (0.5 M in MeOH, 25.0 mmol) was added. The mixture was stirred at room temperature for 24 h and poured into 100 mL of H_2O. The aqueous layer was extracted with Et_2O (3×50 mL), and the combined organics were washed with satd $NaHCO_3$ solution (1×80 mL), brine (1×80 mL), and dried over anhydrous Na_2SO_4. Purification using silica gel chromatography (10% EtOAc/hexanes) provided 4.42 g (63%) of **44** as a clear, colorless oil: $[\alpha]_{589}^{20}$ −7.1° (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4H), 7.42–7.33 (m, 6H), 7.25–7.21 (m, 4H), 6.89–6.85 (m, 4H), 6.30 (d, *J*=16.1 Hz, 1H), 5.62 (dd, *J*=16.1, 5.7 Hz, 1H), 5.50 (s, 1H), 5.41 (d, *J*=9.8 Hz, 1H), 4.49–4.48 (m, 1H), 4.46 (A of AB, *J*=11.7 Hz, 1H), 4.39 (B of AB, *J*=11.4 Hz, 1H), 3.96 (dd, *J*=9.5, 4.1 Hz, 1H), 3.92 (dd, *J*=10.1, 1.9 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (dd, *J*=9.5, 2.5 Hz, 1H), 3.58 (dd, *J*=9.1, 3.8 Hz, 1H), 3.37 (dd, *J*=9.1, 5.4 Hz, 1H), 3.31 (dd, *J*=12.0, 6.0 Hz, 1H), 3.23 (d, *J*=5.7 Hz, 1H), 2.61–2.54 (m, 1H), 1.91–1.82 (m, 2H), 1.70–1.68 (m, 1H), 1.69 (d, *J*=0.95 Hz, 3H), 1.06 (s, 9H), 1.04 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 3H), 1.01 (d, *J*=7.3 Hz, 3H), 0.98 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 159.4, 136.4, 135.8, 135.60, 135.56, 133.94, 133.90, 131.9, 131.7, 129.9, 129.5, 129.4, 127.6, 127.5, 125.6, 113.9, 113.5, 101.1, 82.0, 80.5, 80.0, 77.2, 73.9, 73.3, 64.8, 55.34, 55.30, 36.8, 36.7, 35.7, 34.2, 26.9, 19.4, 15.5, 15.0, 12.5, 12.4, 6.3; IR (thin film, NaCl) 3494, 2962, 2931, 2857, 1615, 1515, 1457, 1362, 1250, 1112, 1034, 824, 757, 703 cm^{-1}; LRMS (EI, Na) calcd for $C_{50}H_{66}O_7SiNa$ *m*/*z* 829.45 (M+Na); observed *m*/*z* 829.4 (M+Na)$^+$.

4.3. Asymmetric hydrogenation

4.3.1. (2S,3R,4S,6S)-8-((2R,4R,5S,6S)-6-((S)-1-(tert-Butyldiphenylsilyloxy)propan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-1-(4-methoxybenzyloxy)-2,4,6-trimethyloctan-3-ol, ***46***

To a Schlenk flask containing **44** (660 mg, 0.82 mmol) in 5 mL of dry CH_2Cl_2 was added D-**34** (100 mg, 0.065 mmol). The resulting solution was degassed by three cycles of freeze–pump–thaw and transferred via cannula to a flame-dried glass liner equipped with a rubber septum containing activated 4 Å molecular sieves (30 mg, powder). The glass liner was quickly transferred to a Parr bomb hydrogenator, which was flushed with H_2 for 1 min without stirring. The reaction mixture was then stirred rapidly at 750 psi. After 4 h, the crude reaction mixture was transferred to a short silica gel column and eluted with 10%→20% EtOAc/hexanes to provide 475 mg (72%) of **46** as a viscous, clear and colorless oil (d.s.=4:1 by ^{1}H NMR). A small sample was further purified by HPLC [EtOAc/hexanes: 13% (28 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] to obtain **46** as a single diastereomer: $[\alpha]_{589}^{20}$ +13.3° (*c* 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4H), 7.42–7.38 (m, 1H), 7.36–7.33 (m, 5H), 7.26–7.20 (m, 4H), 6.88–6.84 (m, 4H), 5.45 (s, 1H), 4.47 (A of AB, *J*=11.4 Hz, 1H), 4.43 (B of AB, *J*=11.7 Hz, 1H), 3.96 (dd, *J*=9.5, 4.4 Hz, 1H), 3.84 (dd, *J*=10.1, 1.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80–3.76 (m, 1H), 3.66 (dd, *J*=9.5, 2.5 Hz, 1H), 3.57 (dd, *J*=8.8, 4.1 Hz, 1H), 3.48–3.44 (m, 2H), 3.39 (ddd, *J*=8.8, 2.5, 2.5 Hz, 1H), 1.99–1.84 (m, 2H), 1.73–1.49 (m, 6H), 1.46–1.41 (m, 1H), 1.15–1.07 (m, 2H), 1.05 (s, 9H), 1.04 (d, *J*=7.3 Hz, 3H), 0.93 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.6 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 3H), 0.81 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 159.3, 135.60, 135.56, 134.0, 133.9, 131.9, 129.9, 129.5, 129.40, 129.36, 127.6, 127.5, 127.4, 113.9, 113.5, 101.1, 81.9, 80.9, 78.6, 77.2, 76.2, 73.2, 64.9, 55.34, 55.27, 41.7, 36.8, 36.0, 32.5, 32.1, 30.00, 29.99, 29.97, 26.9, 19.4, 13.6, 12.8, 12.4, 5.9; IR (thin film, NaCl) 3496, 2959, 2932, 2856, 1615, 1516, 1463, 1361, 1249, 1113, 1035, 825, 757, 704, 505 cm^{-1}; LRMS (EI, Na) calcd for $C_{50}H_{70}O_7SiNa$ *m*/*z* 833.48 (M+Na); observed *m*/*z* 834.0 (M+Na)$^+$.

4.4. Completion of a formal synthesis

4.4.1. (2S,3R,4S,6S,9R,10S,11S,12S,Z)-3-(tert-Butyldimethylsilyloxy)-2,4,6,10,12-pentamethylhexadeca-13,15-diene-1,9,11-triol, ***3***

Diol **39** (17 mg, 0.029 mmol) was dissolved in 330 μL of CH_2Cl_2 and 83 μL of pH 7 buffer. To the solution, DDQ (7 mg, 0.032 mmol) was added and the resulting dark green mixture was stirred at room temperature. After 1 h, an additional 7 mg (0.032 mmol) of DDQ was added. The mixture was stirred for 30 min, quenched with satd $NaHCO_3$ solution (1 mL), and extracted with CH_2Cl_2 (3×1 mL). The combined extracts were washed with satd $NaHCO_3$ solution (1 mL) and dried over anhydrous Na_2SO_4. Purification using flash column chromatography (10%→30% EtOAc/hexanes) provided 14 mg (95%) of **3** as a clear, colorless oil. Analytically pure **3** was obtained using HPLC [EtOAc/hexanes (30%, 9 mL/min) on a Microsorb (Si 80-120-C5 F310135) column, refractive index detector]. The spectral data obtained for **3** was identical in all respects to that provided by Paterson and co-workers:[9] $[\alpha]_{589}^{20}$ −12.3° (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (ddd, *J*=16.7, 10.4, 10.4 Hz, 1H), 6.20 (t, *J*=11.0 Hz, 1H), 5.29–5.23 (m, 2H), 5.18 (d,

J=10.1 Hz, 1H), 3.77 (app. t, J=5.4 Hz, 1H), 3.60 (d, J=4.7 Hz, 2H), 3.48–3.45 (m, 2H), 2.86–2.78 (m, 1H), 1.89–1.82 (m, 1H), 1.76–1.69 (m, 3H), 1.57–1.46 (m, 4H), 1.36 (ddd, J=13.2, 7.9, 4.7 Hz, 1H), 1.09–1.04 (m, 1H), 0.95 (d, J=7.3 Hz, 3H), 0.95 (d, J=6.9 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H), 0.92 (s, 9H), 0.91 (d, J=7.3 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3, 131.9, 131.8, 119.0, 81.0, 80.6, 66.1, 41.3, 38.0, 37.0, 36.3, 35.3, 32.4, 32.2, 30.4, 26.1, 20.5, 18.2, 16.6, 16.2, 15.4, 4.1, −3.9, −4.1; IR (thin film, NaCl) 3374, 2958, 2929, 2856, 1616, 1517, 1457, 1379, 1258, 1030, 836, 773 cm^{-1}; HRMS (EI, Na) calcd for $C_{27}H_{54}O_4SiNa$ m/z 493.36891 (M+Na); observed m/z 493.36919 $(M+Na)^+$.

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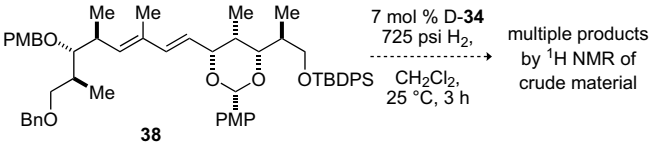
Supplementary data

Complete experimental details for all preparative procedures along with spectral data for all products are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.073.

References and notes

1. Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1111–1112.
2. Pettit, G. R.; Cichacz, Z. A. In *Chem. Abstr.*, Vol. WO 5430053, 1995, p 733500.
3. Wright, A. E.; Cummins, J. L.; Pomponi, S. A.; Longley, R. E.; Isbrucker, R. A. In PCT Int. Appl. Vol. WO 0162239, 2001.
4. Isbrucker, R. A.; Cummins, J.; Pomponi, S. A.; Longley, R. E.; Wright, A. E. *Biochem. Pharmacol.* **2003**, *66*, 75–82.
5. Paterson, I.; Britton, R.; Delgado, O.; Wright, A. E. *Chem. Commun.* **2004**, 632–633.
6. Madiraju, C.; Edler, M. C.; Hamel, E.; Raccor, B. S.; Balachandran, R.; Zhu, G. Y.; Giuliano, K. A.; Vogt, A.; Shin, Y. S.; Fournier, J. H.; Fukui, Y. H.; Bruckner, A. M.; Curran, D. P.; Day, B. W. *Biochemistry* **2005**, *44*, 15053–15063.
7. Novartis, A.G. Annual Report, File no. 1-15024, Form 20-F, Jan 28, 2005, p 42.
8. Shin, Y.; Choy, N.; Balachandran, R.; Madiraju, C.; Day, B. W.; Curran, D. P. *Org. Lett.* **2002**, *4*, 4443–4446.
9. Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629–4633.
10. Shin, Y.; Fournier, J. H.; Fukui, Y.; Bruckner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4634–4637.
11. O'Neil, G. W.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 5340–5341; Fukui, Y.; Bruckner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, *8*, 301–304; Shin, Y.; Fournier, J. H.; Balachandran, R.; Madiraju, C.; Raccor, B. S.; Zhu, G.; Edler, M. C.; Hamel, E.; Day, B. W.; Curran, D. P. *Org. Lett.* **2005**, *7*, 2873–2876; Shin, Y.; Choy, N.; Balachandran, R.; Madiraju, C.; Day, B. W.; Curran, D. P.; Curran, P. *Org. Lett.* **2002**, *4*, 4443–4446; Paterson, I.; Gardner, N. M. *Chem. Commun.* **2007**, 49–51; Jägel, J.; Maier, M. E. *Synlett* **2006**, 693–696; Baba, V. S.; Das, P.; Mukkanti, K.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 7927–7930; Moura-Letts, G.; Curran, D. P. *Org. Lett.* **2007**, *9*, 5–8.
12. Ramachandran, P. V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157–160.
13. Prusov, E.; Rohm, H.; Maier, M. E. *Org. Lett.* **2006**, *8*, 1025–1028; Dilger, A. K.; Gopalsamuthiram, V.; Burke, S. D. *J. Am. Chem. Soc.* **2007**, *129*, 16273–16277.
14. O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253–4256; Sharon, O.; Monti, C.; Gennari, C. *Tetrahedron* **2007**, *63*, 5873–5878; Monti, C.; Sharon, O.; Gennari, C. *Chem. Commun.* **2007**, 4271–4273.
15. Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005**, *7*, 5111–5114.
16. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
17. Francavilla, C.; Chen, W. C.; Kinder, F. R. *Org. Lett.* **2003**, *5*, 1233–1236; Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359.
18. Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201–202.
19. Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197–3199.
20. Tidwell, T. T. *Org. React.* **1990**, *39*, 297–572.
21. Jieh Shyh Tsai, D.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751–2752.
22. Shimp, H. L.; Hare, A.; McLaughlin, M.; Micalizio, G. C. *Tetrahedron* **2008**, *64*, 3437–3445.
23. Regioisomeric ratio (r.r.) was determined by ^{1}H NMR analysis of the product mixture after flash column chromatography. Regioisomers **4** and **13** were separable by HPLC: see Supplementary data for details.
24. Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.
25. Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866–3868.
26. Crabtree, R. H.; Felkin, H.; Fillebeenkhan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183–195.
27. Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072–1073; Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681–682.
28. Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348–350; Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637–4640.
29. Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005–6008.
30. Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77–82; Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
31. Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1787–1798.
32. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993; Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
33. Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009–3012.
34. See Supplementary data for experimental details on the preparation of diene **27**.
35. See Supplementary data for experimental details on the preparation of homoallylic alcohol **28**.
36. Takaya, H.; Ohta, T.; Inoue, S. i.; Tokunaga, M.; Masato, K.; Noyori, R. *Org. Synth.* **1995**, *72*, 74–85.
37. Perry, M. C.; Cui, X. H.; Powell, M. T.; Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113–123.
38. Zhou, J. G.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131.
39. Diastereoselectivity could not be determined due to overlapping peaks in the crude ^{1}H NMR spectrum.
40. Diastereomer **18** was separable by HPLC: see Supplementary data for details.
41. As the chiral iridium catalyst does not require a coordinating functional group, we also examined the hydrogenation with the protected homoallylic ether **38**. Although **38** was completely consumed upon exposure to D-**34** (725 psi H_2, CH_2Cl_2, 3 h), significant amounts of products resulting from PMP deprotection and low levels of diastereoselectivity (ca. 1.3:1) were observed.



42. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
43. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.
44. Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870–3878; Buckle, M. J. C.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2383–2386; Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630–633.
45. Marshall, J. A.; Wang, X. *J. Org. Chem.* **1992**, *57*, 1242–1252.
46. Belardi, J. K.; Micalizio, G. C. *Org. Lett.* **2006**, *8*, 2409–2412.
47. Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, *350*, 979–983.
48. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
49. Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 377–380; Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498–500.
50. Cintas, P. *Synthesis* **1992**, 248–257; Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1992**, *33*, 4761–4762; Andringa, H. H.; Heuskloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1987**, *336*, C41–C43.
51. Ager, D. *Org. React.* **1990**, *38*, 1–223.