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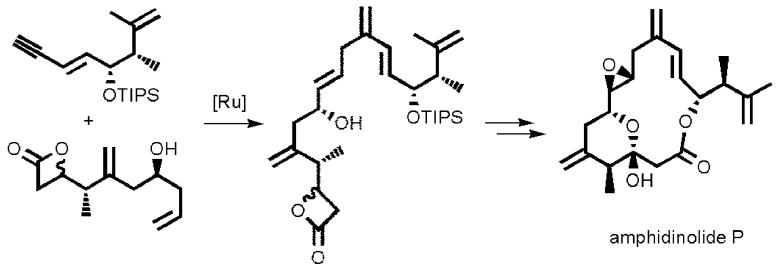

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Ru-Catalyzed Alkene−Alkyne Coupling. Total Synthesis of Amphidinolide P

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Abstract: A coordinatively unsaturated ruthenium complex catalyzed the formation of a carbon−carbon bond between two judiciously chosen alkene and alkyne partners in good yield, and in a chemo- and regioselective fashion, despite the significant degree of unsaturation of the substrates. The resulting 1,4-diene forms the backbone of the cytotoxic marine natural product amphidinolide P. The alkene partner was rapidly assembled from (*R*)-glycidyl tosylate, which served as a linchpin in a one-flask, sequential three-components coupling process using vinyllithium and a vinyl cyanocuprate. The synthesis of the alkyne partner made use of an unusual anti-selective addition under chelation-control conditions of an allyltin reagent derived from tiglic acid. In addition, a remarkably *E*-selective E_2 process using the azodicarboxylate−triphenylphosphine system is featured. Also featured is the first example of the use of a β-lactone as a thermodynamic spring to effect macrolactonization. The oxetanone ring was thus used as a productive protecting group that increased the overall efficiency of this total synthesis. This work was also an opportunity to further probe the scope of the ruthenium-catalyzed alkene−alkyne coupling, in particular using enynes, and studies using various functionalized substrates are described.

Introduction

Within the past decade, marine microorganisms have become an important source of biologically active substances. Unicellular eukaryotes known as dinoflagellates produce some of the most structurally complex and most toxic substances known to man such as brevetoxin, ciguatoxin, okadaic acid, and saxitoxin, all of which are increasingly the source of human intoxication.[1] Although 90% of these organisms are planktons, a number of photosynthetic dinoflagellates take up residence within other organisms as symbiotic partners. In 1986, the group of Kobayashi isolated a novel macrolide, named amphidinolide A, from a strain of laboratory-cultured symbiotic dinoflagellates of the genus *Amphidinium sp.*, which are found inside the cells of the Okinawan flatworm *Amphiscolops sp.*[2] New members of this structurally varied class of compounds have been continually discovered by the group of Kobayashi ever since, and close to 40 amphidinolides have been isolated.[3] These macrolides have all demonstrated antineoplastic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cells in vitro. Although most of them have an IC_{50} in the low micromolar range, amphidinolide N displays subpicomolar activity against these two cell lines.[3c] The biological activity of these compounds, along with their very limited availability and challenging structures, has made them popular targets for total synthesis. Numerous strategies have been disclosed,[4] and several amphidinolides have succumbed to total synthesis.[5] A common feature to the vast majority of amphidinolides is the presence of one, or more commonly, several, *exo*-methylene units. We envisioned that the ruthenium-catalyzed alkene−alkyne coupling reaction developed in our laboratories[6] would provide a tool to develop convergent syntheses of these compounds (the proposed mech-

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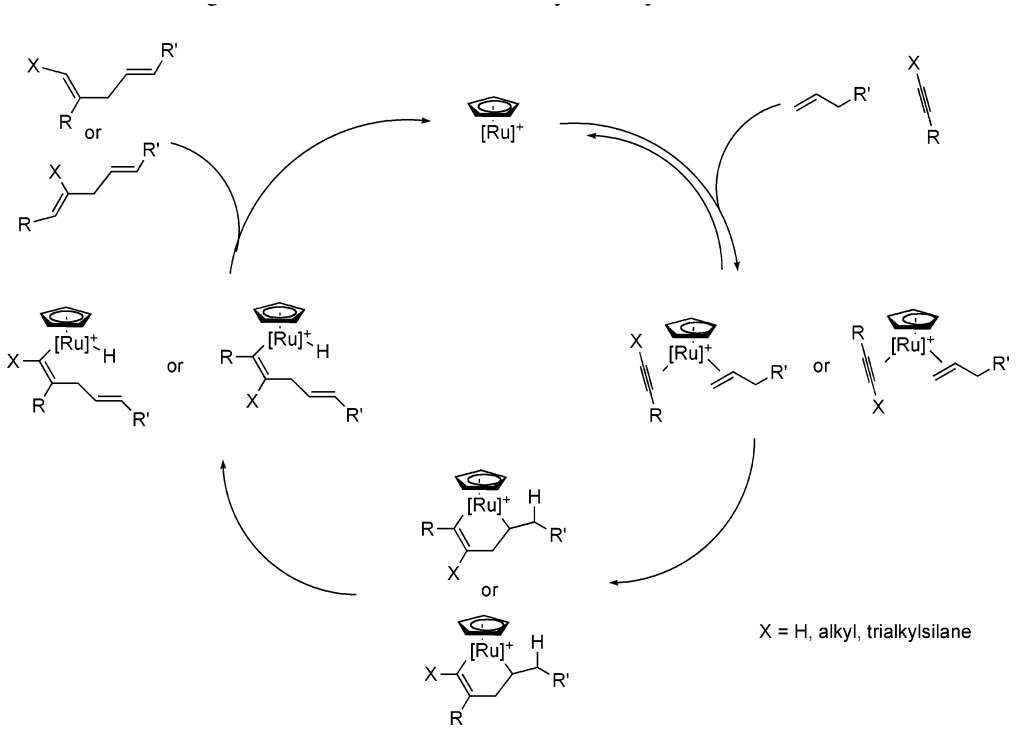
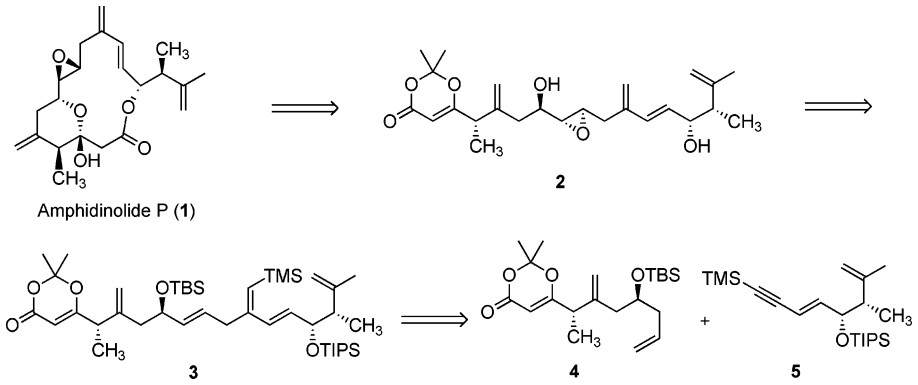


Figure 1. Proposed catalytic cycle for the ruthenium-catalyzed alkene−alkyne coupling reaction.

Scheme 1. Initial Retrosynthetic Analysis



anism is shown in Figure 1). Reciprocally, total synthesis of judiciously chosen members of this family would provide a stringent test for the chemoselectivity of this reaction and an opportunity for further development. We have successfully applied it, both inter- and intramolecularly, to the synthesis of amphidinolide A.[5e,f] We now report in full details our efforts which led to the completion of the synthesis of amphidinolide P.[5c] Amphidinolide P (**1**), which was isolated by Kobayashi in a yield of 0.0002%, exhibits cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells in vitro ($IC_{50} = 4.0$ and 14.6 μM, respectively).[7] The structure and relative configuration of amphidinolide P was determined by extensive ^1H NMR and ^{13}C NMR studies and molecular mechanics calculations. These studies revealed a backbone consisting of a 15-membered macrolactone with three *exo*-methylene units, one hemiketal forming a tetrahydropyran moiety, an epoxide moiety, and seven chiral centers. The proposed structure and relative configuration of **1** was confirmed by total synthesis.[5d]

Our initially envisioned retrosynthetic analysis is depicted in Scheme 1. Amphidinolide P (**1**) was anticipated to derive from precursor **2** via a thermal macrocyclization.[8] Although β-ketoesters also undergo thermal macrocyclization (via the same acylketene intermediate),[5d,9] the dioxenone can be conveniently carried through multiple synthetic steps. We therefore initially envisioned **4** as the desired alkene addition partner. An intriguing feature of **1**, and of **2** by extension, is the presence

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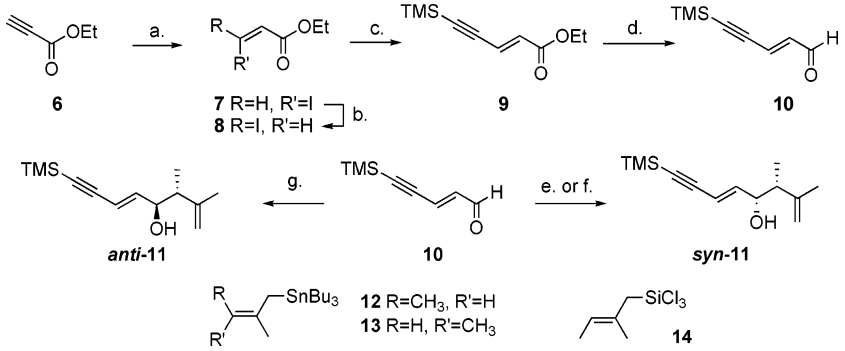
Scheme 2. Synthesis of Racemic Enyne Systems[a]



[a] Reagents and conditions: (a) 1.5 equiv of NaI, AcOH, 70 °C, 13 h, *Z*/*E* > 49:1; (b) 0.01 equiv of HI(aq), benzene, 1.7 M, 80 °C, 8 h, *E*/*Z* 16:1; (c) 1.1 equiv of trimethylsilylacetylene, 0.005 equiv of CuI, 0.01 equiv of $Pd(PPh_3)_2Cl_2$, Et_3N, 50 °C, 13 h, 81% (3 steps); (d) 1.1 equiv of DIBAL-H, toluene, −95 °C, 1 h, 70%; (e) 1.1 equiv of $BF_3{\cdot}Et_2O$, 1.3 equiv of **12**, CH_2Cl_2, −78 °C, 5 min, quant, syn/anti 2.6:1; (f) 1.1 equiv of $BF_3{\cdot}Et_2O$, 1.3 equiv of **13**, CH_2Cl_2, −78 °C, 5 min, quant, syn/anti 6.5:1; (g) 1.0 equiv of HMPA, 2.0 equiv of **14**, CH_2Cl_2, −78 °C, 12 h, 23%, syn/anti 1:19.

of an *exo*-methylene unit in conjugation with an olefin, forming a 1,3-diene moiety. Synthesis of this moiety by a ruthenium-catalyzed alkene−alkyne coupling reaction would therefore require enyne **5**. This type of substrate had never been investigated before, and it was unclear at the onset of this project what the outcome would be. As shown in Figure 1, the alkyne partner can adopt two orientations in the cationic ruthenium(II) complex, leading to either a linear or a branched 1,4-diene product (although the alternative orientation of the alkene may also lead to a ruthenacycle, syn-β-hydrogen elimination would in this case most likely be precluded for geometrical reasons). Our results have shown that as the size of R increases, the branched-to-linear ratio decreases, indicating that steric interaction between the alkene and alkyne is an important factor in determining the regioselectivity of the reaction. On the basis of steric factors, the enyne was therefore expected to largely favor the formation of the desired branched product. However, on electronic grounds, one might expect that attack of the ruthenium at the terminal carbon of the alkyne would be less favorable since the conjugated olefin reduces the polarization of the triple bond. Conversely, we have shown that increasing the polarization of the triple bond, by appending a trimethylsilyl group at the terminal carbon, improved the branched-to-linear product ratio.[6b] On the basis of these considerations, TMS−alkyne **5** was envisioned to be the desired addition partner. Herein we disclose a detailed account of our studies, leading to a synthesis of amphidinolide P.

Results and Discussion

Synthesis of the Alkyne Coupling Partner. Several routes toward alkyne **5** were investigated in the course of this project. We envisioned that **5** could be the product of the allylation of the corresponding aldehyde, as depicted in Scheme 2. The required aldehyde **10** was prepared by an unusual partial reduction of known ester **9**.[10] The reaction of allyltin reagent **12** and **13** (obtained in two steps from commercially available angelic acid methyl ester and tiglic acid, respectively)[11] with aldehyde **10** in the presence of a stoichiometric amount of $BF_3{\cdot}Et_2O$ provided *syn*-**11** in quantitative yield, as a 2.6:1 and 6.5:1 mixture of diastereomers, respectively. Given literature precedents, the major diastereomer was assumed to be the syn isomer. This was confirmed by a selective synthesis of *anti*-**11**.[12] Various enantioselective versions of the allylation reactions shown in Scheme 2 have been reported. Addition of allyltin reagents to aldehydes, which proceed through open transition states, are usually syn-selective.[13] An exception to this trend was discovered by Yamamoto and co-workers, who showed that methallyl- and crotyltrialkyltin reagents react with aldehydes in the presence of AgOTf-BINAP to give the anti adduct, irrespective of the geometry of the starting material.[14] However, to the best of our knowledge, the use of trialkyl-(β-methylcrotyl)stannane has not been reported in this process. The reaction of **10** and **12** in the presence of 20 mol % AgOTf-(*R*)-Binap at −20 °C, according to Yamamoto's procedure,[14b] was attempted. Unfortunately, the reaction was prohibitively slow, and only minute traces of product could be detected. Warming the mixture to room temperature did not afford any further conversion. Yamamoto reported good yields with both crotyltributyltin and methallyltributyltin,[14b] and it appears that substitution at both the β- and γ-position is detrimental to the reactivity of the allylmetal reagent. We found however that **13** reacted with aldehyde **10** in the presence Yamamoto's CAB catalyst[15] to afford scalemic ***syn*-11**. Without optimization, the reaction proceeded in 80% yield and 5:1 syn/anti ratio. Conversion of the mixture into the *O*-methyl mandelate esters,[16] and 500 MHz ^{1}H NMR spectroscopy analysis indicated a 6.5:1 enantiomeric ratio (e.r.) for the syn isomer and 2:1 e.r. for the anti isomer. This was not a viable route however, since, as one would anticipate, inversion of stereochemistry at the alcohol carbon using Mitsunobu conditions resulted in intractable mixtures of S_N2' and elimination products, as well as the desired product.

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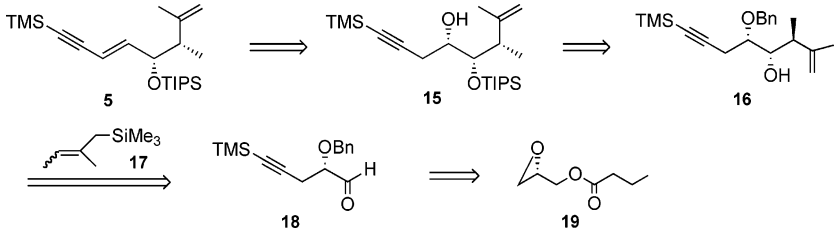
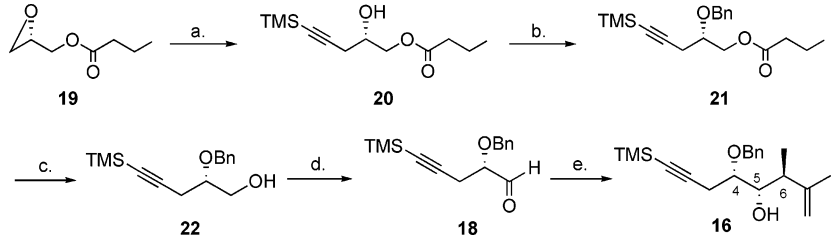
Scheme 3 Substrate-Controlled Approach to Alkyne **5**



Scheme 4. Synthesis of Alcohol **16**[a]



[a] Reagents and conditions: (a) added to 1.3 equiv of lithium acetylide, 1.3 equiv of $AlMe_3$, then 1.3 equiv of $BF_3{\cdot}Et_2O$ added, ether, −78 °C, 0.5 h; (b) 2.0 equiv of benzyl-2,2,2-trichloroacetimidate, 0.2 equiv of TfOH, dioxane, 24 °C, 0.5 h; (c) 1.3 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (d) 2.0 equiv of oxalyl chloride, 4.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, −78 °C to 0 °C, 71% (4 steps); (e) 1.0 equiv of $SnCl_4$, 2.0 equiv of **17**, CH_2Cl_2–pentane 1:1, −110 °C, 15 min, 77%, 9:1 d.r. at *C*-6.

The stereochemistry of the allylation product can usually be dictated by the geometry of the starting allylmetal reagent when the reaction goes through closed transition states, and axial−axial interactions in a Zimmermann−Traxler transition state become the controlling factor. This has been shown to be the mode of reaction of allyltrichlorosilanes in the presence of nucleophilic catalysts.[17] Again, to the best of our knowledge, the use of trichloro-(β-methylcrotyl)silane (**14**) has not been reported in this process. Although trichlorosilanes, *including* β-substituted crotylsilane,[17c,e] are known to be relatively stable, off-the-shelf compounds, **14** appeared to be an exception. The isolation of **14** proved to be problematic, and it showed poor intrinsic stability, as decomposition was noted after overnight storage at −15 °C under argon. Given the difficulties we encountered with the preparation and handling of this compound, we did not pursue the asymmetric synthesis of *anti*-**11** using this reagent. Instead, we decided to investigate a substrate-controlled approach to the allylmetal addition problem, as depicted in Scheme 3. This idea was based on previous results disclosed by Mikami et al., who found that the addition of trimethyl-(β-methylcrotyl)silane to scalemic α-benzyloxypropionaldehyde under chelation-control conditions afforded the unusual anti product in excellent selectivities, regardless of the geometry of the starting silane reagent.[18]

The optimized synthesis of **16** is described in Scheme 4. Use of the aluminum ate-complex derived from lithium trimethylsilylacetylide[19] resulted in a quantitative yield for the addition reaction to commercially available (*S*)-glycidyl butyrate (**19**) in the presence of $BF_3{\cdot}Et_2O$. The benzyl protection of alcohol **20** using benzyl-2,2,2-trichloroacetimidate in mixtures of CH_2Cl_2–hexane[20] was quite sluggish, and we found that dioxane was an excellent solvent for this reaction, giving clean and complete conversion within 15 min, in the presence of 20 mol % of trifluoromethanesulfonic acid and using crude, freshly prepared acetimidate.[21] DIBAL-H deprotection of the crude ether **21** gave alcohol **22**, which was essentially clean. No purification of the intermediates was found to be necessary, and after a Moffat−Swern oxidation, aldehyde **18** was isolated in 71% yield over the four steps. This aldehyde was stable to chromatography on silica gel. A Kumada coupling between a 7:3 isomeric mixture of 2-bromo-2-butene and trimethylsilylmagnesium chloride, using a modified literature procedure, gave the silane **17** in 52% yield as a 1:1 mixture of diastereomers.[15a] We initially conducted the reaction at −78 °C in neat CH_2Cl_2, and a 42% yield of product was obtained. As judged from 500 MHz ^1H NMR spectroscopy analysis, only traces of nonchelation product was detected, and the product resulting from chelation control (**16**) was isolated as a 6:1 mixture, epimeric at *C*-6. The 4,5-syn-5,6-anti relationship for the major product was tentatively assigned on the basis of the coupling constants for *H*-6, *H*-5, *H*-4, (dq, *J* 9.0, 7.0), (dd, *J* 9.0, 2.0), (ddd, *J* 8.0, 6.0, 2.0), respectively. This assignment was later supported by NOE studies on a cyclopentane derivative (vide infra). The corresponding signals for the minor diastereomer were masked, but the two methyl doublets, as well as one benzylic hydrogen doublet, were resolved and could be integrated. With the use of a CH_2Cl_2–pentane mixture, the temperature could be lowered to −110 °C, and we found that using 2 equiv of silane and 1 equiv of $SnCl_4$ in a 1:1 mixture of CH_2Cl_2–pentane, the product could be isolated in 77% yield and 9:1 diastereomeric ratio (d.r.).

The alcohol was protected as the TIPS ether to give **23** in good yield, and the two diastereomers were separated at this stage. Cleavage of the benzyl group with lithium di-*tert*-butylbiphenylide resulted in the partial migration of the TIPS group. Both BCl_3 and transfer hydrogenation gave complex mixtures. Various Lewis acids were tested, and they all

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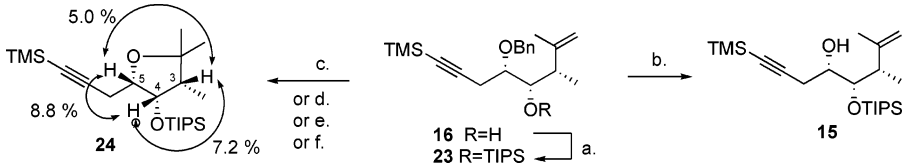
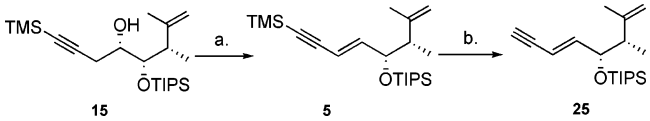
Scheme 5. Debenzylation of Alkyne **16**[a]



[a] Reagents and conditions: (a) 3.0 equiv of TIPSOTf, 4.0 equiv of 2,6-lutidine, CH_2Cl_2, 24 °C, 6 h, 82%; (b) 2.0 equiv of DDQ, dichloroethane−buffer (pH 7) 9:1 v/v, reflux, 45 min, 82%; (c) 1.3 equiv of 9-Br-9-BBN, CH_2Cl_2, −78 °C, 5 min, 59%; (d) 1.3 equiv of 9-I-9-BBN, CH_2Cl_2, −78 °C, 5 min, 75%; (e) 1.3 equiv of $FeCl_3$, CH_2Cl_2, 0−24 °C, 30 min, 39%; (f) 2.0 equiv of $SnCl_4$, CH_2Cl_2, 0 °C, 30 min, complete conversion.

Scheme 6. Conversion of Alcohol **15** to Alkene **5**[a]



[a] Reagents and conditions: (a) 3.0 equiv of PPh_3, 3.0 equiv of diisopropyl azodicarboxylate, toluene, 80 °C, 20 min, 75%, *E*/*Z* 8:1; (b) 1.0 equiv of K_2CO_3, MeOH, 24 °C, 2 h, 96%.

promoted rapid cyclization to give the tetrahydrofuran derivative **24** (Scheme 5).

This facile process is precedented,[22] and could be due to the presence of traces of water in the solvent, or of protic acid in the commercial solution of Lewis acid. Hydrochloric acid has been shown to promote this reaction,[23] and although it has been found that the $CeCl_3 \cdot 7H_2O$/NaI system was an efficient cyclization promoter,[24] this might also be due to the presence of Brønsted acid. In the event, although analysis of the ^{1}H NMR spectrum of tetrahydrofuran derivative **24** was ambiguous (*H*-3, qd, *J* 7.5, 4.5; *H*-4, dd, *J* 4.5, 4.0; *H*-5, ddd, *J* 8.0, 5.5, 4.0) with regard to the relative stereochemistry, NOEs of 5.0% (*H*-3 irradiation) and 4.1% (*H*-5 irradiation) were measured between *H*-3 and *H*-5 (Scheme 5). Although NOEs between *H*-4 and *H*-3, and *H*-4 and *H*-5 are less diagnostic in a five-membered ring, the large values observed (7.2% and 8.8%, respectively) also pointed to an all-syn arrangement in **24**, consistent with a (chelation-controlled) anti-selective silane addition, and this was in agreement with Nakai's precedent.[18] Eventually, we found that the use of an excess of DDQ in a boiling mixture of dichloroethane and aqueous buffer (pH 7) rapidly cleaved the benzyl ether to give alcohol **15** in excellent yields (82−86%) (Scheme 5). This easy oxidation might be facilitated by the inductive effect of the neighboring silyl ether.

Initial elimination attempts focused on converting alcohol **15** into the sulfonate derivative, followed by base-promoted elimination. DBU-promoted elimination of the mesylate derivative afforded the alkene **5** in 60% yield, albeit in an unacceptable 1.6:1 *E*/*Z* ratio. An attempt to improve this ratio by making the triisopropylbenzenesulfonyl derivative failed, as the alcohol was too unreactive toward trisyl chloride. We turned our attention to the use of the azodicarboxylate−triphenylphosphine system. We were pleased to find that DIAD−PPh_3 (3 equiv) in toluene at 80 °C gave a clean reaction to afford **5** in 83% yield (Scheme 6) and a very satisfying 9:1 *E*/*Z* ratio (*E* isomer: 2 d, δ 5.70 and 6.09, *J* 16.0, 5.0 and 16.0, 2.0; *Z* isomer: 1 d, δ 5.49, *J* 11.0 and 1 dd, δ 5.89, *J* 11.0, 9.0). The two isomers were inseparable, and traces of starting material remained. Extended reaction time afforded no further conversion. Neither higher temperatures nor the use of *tert*-butyl azodicarboxylate had any effect on the selectivity and conversion. On scale-up, those conditions reliably afforded **5** in 75−83% yield and 8−9:1 *E*/*Z* ratios. We therefore had access to alkyne **5** in eight steps and 32% overall yield from commercially available (*S*)-glycidyl butyrate (**19**). The TMS group could be removed using standard conditions in 96% yield, to give alkyne **25**.

Synthesis of the Alkene Coupling Partner. We initially envisioned that alkene **4** could be prepared using the sequence outlined in Scheme 7. The chirality in this fragment could be introduced using an asymmetric allylation reaction, and this chiral center could be used to induce additional asymmetry. Alkyloxy-directed aldol reactions between propionate-derived silylketene acetals and β-alkoxyaldehydes have been described and shown to proceed with good simple diastereoselectivity, to give 1,2-syn products, and high levels of 1,3-induction to give predominantly the 2,4-anti-diastereomer.[25] Although there has been no reported precedent for the use of silyl dienolates derived from *ethyl* dioxenone in this process, the substrate-controlled reaction of a silyl dienolate derived from *methyl* dioxenone with a β-alkoxyaldehyde was recently disclosed (it proceeded stereorandomly).[26]

We studied this unprecedented reaction with racemic **28a**[27] and **28b**.[28] Silylketene acetal **27** was prepared following a known procedure,[29] as a 1.6:1 mixture of isomers, starting from 6-ethyl-2,2-dimethyl-[1,3]-dioxin-4-one.[30] Although Sato et al. reported that the *Z* isomer was the major product of the reaction,[29] NOE studies established that the *E* isomer was the major product in our hands.[31]

Treatment of **27** and the TBS-protected aldehyde **28b** with $TiCl_4$ as Lewis acid in dichloromethane at −78 °C resulted in decomposition of the starting material (Table 1, entry 1). Applying the same conditions to the reaction of the PMB-protected aldehyde **28a** resulted in cleavage of the benzyl group (entry 3), and the diols could be obtained in good yield in a 2.6:1 ratio for the 2,4-anti/syn diastereomers, which could be separated by column chromatography. The 2,4-anti product was found to be a 4:1 diastereomeric mixture, favoring the desired

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(24) Marrota, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* **2002**, *4*, 4451.
(25) (a) Reetz, M.; Kessler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.
(26) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722.
(27) Racemic aldehyde **28a** was prepared by dihydroxylation, followed by oxidative cleavage of known PMB-protected hepta-1,6-dien-4-ol: Shepherd, J. N.; Na, J.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 4558.
(28) Racemic aldehyde **28b** was prepared in four standard steps (allylation, TBS protection, DDQ-mediated PMB cleavage, and Moffat−Swern oxidation) from known 3-(4-methoxy-benzyloxy)-propionaldehyde: Oka, T.; Marai, A. *Tetrahedron* **1998**, *54*, 1.
(29) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435.
(30) (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. (b) Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848.
(31) See the Supporting Information for details.

Scheme 7. Retrosynthetic Analysis for the Preparation of **4**

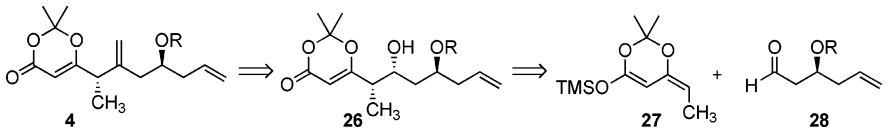
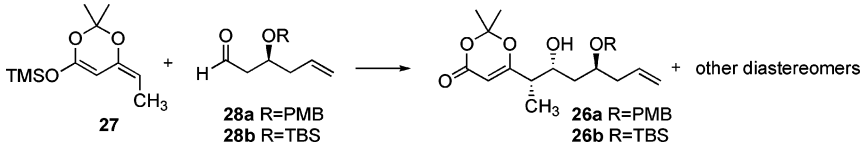


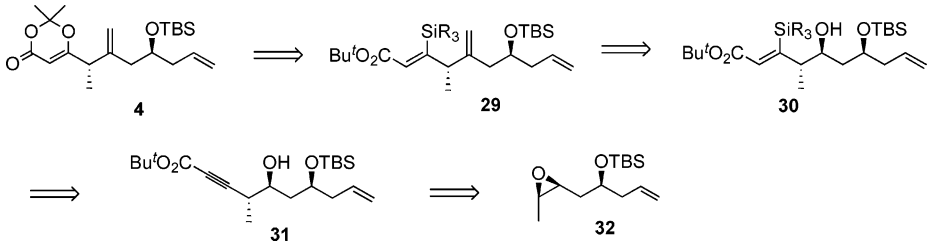
Table 1. Addition of Silylketene Acetal **27** to Aldehydes **28a** and **28b**



entry	R	*E*/*Z* ratio **27**	lewis acid	solvent	2,4-anti/syn[a]	1,2-anti/syn[b]	yield[c]
1	TBS	1.6:1	$TiCl_4$	CH_2Cl_2			decomp
2	TBS	1.6:1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	2:1	1:1	78%
3[d]	PMB	1.6:1	$TiCl_4$	CH_2Cl_2	2.6:1	1:4[e]	61%
4	PMB	1.6:1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	1.7:1	1:1	76%
5	PMB	1.6:1	$TiCl_2(O^iPr)_2$	CH_2Cl_2	3.4:1	1:1.3	80%
6	PMB	1.6:1	$TiCl_2(O^iPr)_2$	toluene	7.5:1	1:1	89%
7	PMB	10:1	$TiCl_2(O^iPr)_2$	CH_2Cl_2	3:1	2:1	75%
8	PMB	10:1	$TiCl_2(O^iPr)_2$	toluene	8:1	3:1	73%
9	PMB	1:2	$TiCl_2(O^iPr)_2$	CH_2Cl_2	4:1	1:1.4	80%
10	PMB	1:2	$TiCl_2(O^iPr)_2$	toluene	5:1	1.1:1	72%

[a] All four diastereomers were inseparable; the ratio was determined by integration of the PMB benzylic protons, which gave one AB system for each pair of 2,4-anti and 2,4-syn diastereomers. [b] Determined by integration of the protons of the methyl α to the hydroxyl, which gave one doublet for each pair of 1,2-anti and 1,2-syn diastereomers. [c] Combined yield of all diastereomers. [d] Loss of the PMB group was observed. [e] The 2,4-anti/syn diastereomers were separable; the 1,2-anti/syn ratio is given for the desired 2,4-anti product.

Scheme 8. Retrosynthetic Analysis for a Hydrosylilation-Based Approach to Dioxenone **4**



syn isomer. The yield of the desired product was however unacceptably low, and we sought to improve on this result. Use of $BF_3{\cdot}Et_2O$ resulted in very poor selectivities (entries 2 and 4). The switch to $TiCl_2(O^iPr)_2$ gave cleaner reactions, with no PMB deprotection and improved 2,4-anti/syn ratios. Although the four diastereomers were inseparable, only two AB systems were observed for the methylene group of the PMB ether, which corresponded to each pair of 2,4-anti and 2,4-syn diastereomers, and these could be integrated. Likewise, the 1,2-anti/syn diastereomeric ratio was determined by integration of proton signals of the methyl group in the α position of the hydroxyl group, which gave only two doublets corresponding to each pair of 1,2-anti and 1,2-syn diastereomers.[31] Replacing dichloromethane with toluene consistently improved the 2,4-anti selectivity (entries 6 vs 5, 8 vs 7, 10 vs 9). However, 1,2-anti/syn ratios were poor, and we therefore investigated whether modifying the isomeric ratio for **27** could lead to improved results. When a 10:1 mixture was used, the 1,2-anti/syn ratio increased (entries 7 and 8). It was possible to obtain a 1:2 *E*/*Z* solution of **27** from a 10:1 *E*/*Z* solution by treating **27** with iodine in dichloromethane. Unfortunately, no major improvement of the 1,2-anti/syn ratio could be observed using this 1:2 *E*/*Z* solution of **27** (entries 9 and 10). The use of simple esters and thioesters instead of the dioxenone did not provide any satisfactory solution,[32] nor did the use of chiral Lewis acids.[29] Thus, we abandoned this route.

Capitalizing on a hydrosilylation reaction developed in our laboratories,[33] a different approach to dioxenone **4** was envisioned using alkyne **31** (Scheme 8). Oxidation of the vinylsilane **29** to the corresponding ketone could lead to dioxenone **4**. We hoped that a regioselective addition to epoxide **32** would afford alkyne **31**.

Epoxide **32** was prepared as depicted in Scheme 9. Klunder et al. reported that Grignard reagents reacted chemoselectively with *p*-toluenesulfonic acid glycidyl ester (**34**) in the presence of Li_2CuCl_4, although they reported incomplete conversions for this reaction.[34] Commercially available *Z*-1-bromoprop-1-ene (**33**) could be converted at room temperature (r.t.) without apparent loss of stereochemistry to the corresponding Grignard reagent,[35] which reacted with **34** in the presence of Li_2CuCl_4

(32) Use of a 1:5 *E*/*Z* mixture of silylketene acetal derived from ethyl propionate in the presence of $TiCl_2(O^iPr)_2$ in toluene gave a 2.5:1 1,2-anti/syn ratio and a better than 10:1 2,4-anti/syn ratio. Use of a 1:6 *E*/*Z* mixture of silylketene acetal derived from *tert*-butyl thiopropionate in the presence of $TiCl_2(O^iPr)_2$ in dichloromethane gave a 1:1 1,2-anti/syn ratio and an 8:1 2,4-anti/syn ratio. In both cases, alternative conditions gave higher 1,2-anti/syn ratio.

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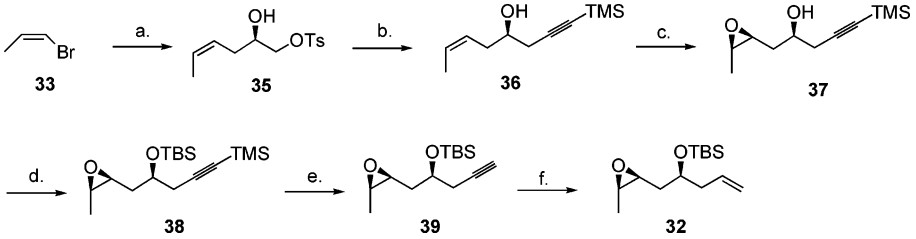
(34) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.

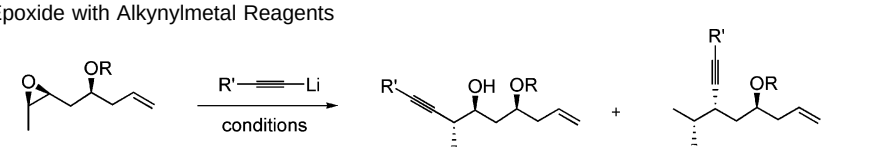
(35) Kant, J. *J. Org. Chem.* **1993**, *58*, 2296 and references therein.

Scheme 9. Synthesis of Epoxide **32**[a]



[a] Reagents and conditions: (a) 1.0 equiv of Mg, THF, 23 °C, 2 h, then added to 0.05 equiv of Li_2CuCl_4, THF, −35 °C, 35 min, then 0.7 equiv of **34**, −35 °C, 10 min, 97%, *Z*/*E* > 49:1; (b) 1.2 equiv of KH, THF, 0−23 °C, 22 h, then added to 2.0 equiv of lithium trimethylsilylacetylide (prepared from trimethylsilylacetylene and *n*-BuLi, THF, −78 °C, 10 min), THF−hexane, −78 °C, 10 min, then 1.1 equiv of $BF_3{\cdot}Et_2O$; (c) 0.07 equiv of $VO(acac)_2$, 2.2 equiv of TBHP, CH_2Cl_2–decane, 23 °C, 16 h, 71%, d.r. 19:1; (d) 3.2 equiv of TMEDA, 2.0 equiv of TBSCl, DMF, 23 °C, 13 h; (e) 1.1 equiv of K_2CO_3, MeOH, 23 °C, 6 h; (f) 1 atm of H_2, 0.02 equiv of Lindlar catalyst, 2.1 equiv of quinoline, hexane, 23 °C, 15 min, 86% (3 steps).

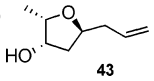
Table 2. Opening of Epoxide with Alkynylmetal Reagents



32 R = TBS
40 R = H

41a R = TBS, R' = $CO_2{}^t$Bu
41b R = TBS, R' = TMS
41c R = H, R' = $CO_2{}^t$Bu

42a R = TBS, R' = $CO_2{}^t$Bu
42b R = TBS, R' = TMS
42c R = H, R' = $CO_2{}^t$Bu

entry	R	R′	conditions	result
1	TBS	$CO_2{}^t$Bu	1.0 equiv of $BF_3{\cdot}Et_2O$	85%, **41a**/**42a** 1.7:1
2	TBS	$CO_2{}^t$Bu	1.0 equiv of Et_2AlCl	mixtures of epichlorhydrin
3	TBS	$CO_2{}^t$Bu	1.0 equiv of $AlMe_3$, then 1.0 equiv of $BF_3{\cdot}Et_2O$	no conversion
4	TBS	TMS	1.0 equiv of $AlMe_3$, then 1.0 equiv of $BF_3{\cdot}Et_2O$	62%, **41b**/**42b** 1:1.3
5	H	$CO_2{}^t$Bu	i. $Ti(O^iPr)_4$ ii. $BF_3{\cdot}Et_2O$	39%, **41c**/**42c** 0:1
6	H	$CO_2{}^t$Bu	1.0 equiv of $BF_3{\cdot}Et_2O$	74%, **41c**/**42c** 0:1
7	H	$CO_2{}^t$Bu	i. aluminum tris(2,6-diphenylphenoxide) ii. $BF_3{\cdot}Et_2O$	37%, **41c**/**42c** 1.3:1
8	H	$CO_2{}^t$Bu	$Sc(OTf)_3$	50%  **43**
9	H	$CO_2{}^t$Bu	$SnCl_4$, Et_3N	no reaction
10	H	$CO_2{}^t$Bu	$Mg(OTf)_2$	no reaction

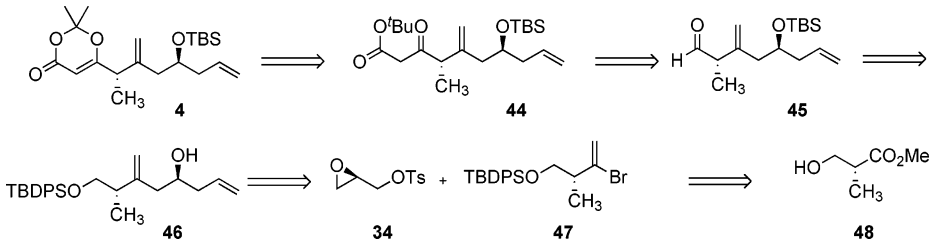
to give alcohol **35** in 97% yield. We found that simply using a slight excess of Grignard reagent did afford complete conversion in less than 5 min on a 20 g scale. Treating alcohol **35** with KH for 7−22 h gave the corresponding epoxide, which was not isolated, but rather was treated with the lithium salt of trimethylsilylacetylene in the presence of $BF_3{\cdot}Et_2O$, to afford alkyne **36**. Crude **36** was directly treated with catalytic $VO(acac)_2$ and excess TBHP[36] to afford epoxide **37** in an excellent 80% yield over the two steps. Pleasingly, ^1H NMR spectroscopy analysis indicated a 19:1 diastereomeric ratio. O-Silylation (TBSCl, TMEDA), followed with C-desilylation (K_2CO_3 in methanol) and Lindlar reduction of the alkyne gave the desired epoxide **32** in 86% overall yield for the three steps.

Unfortunately, regioselectivity for the epoxide opening using $BF_3{\cdot}Et_2O$ turned out to be very low (1.7:1 in favor of the desired isomer), giving the two separable isomers **41a** and **42a** in 85% combined yield (Table 2, entry 1). The two products were unambiguously identified by the splitting pattern of the hydrogen α to the alkyne, i.e., dq for **41a** and dt for **42a**. The use of Et_2AlCl instead of $BF_3{\cdot}Et_2O$ gave only a mixture of epichlorhydrins (entry 2). We also tested the alane prepared from *tert*-butylpropiolate (*n*-BuLi, $AlMe_3$) in this reaction, but it was unreactive (entry 3). The use of the alane derived from the trimethylsilylacetylide also resulted in low selectivities, favoring the undesired isomer **42b** (entry 4).

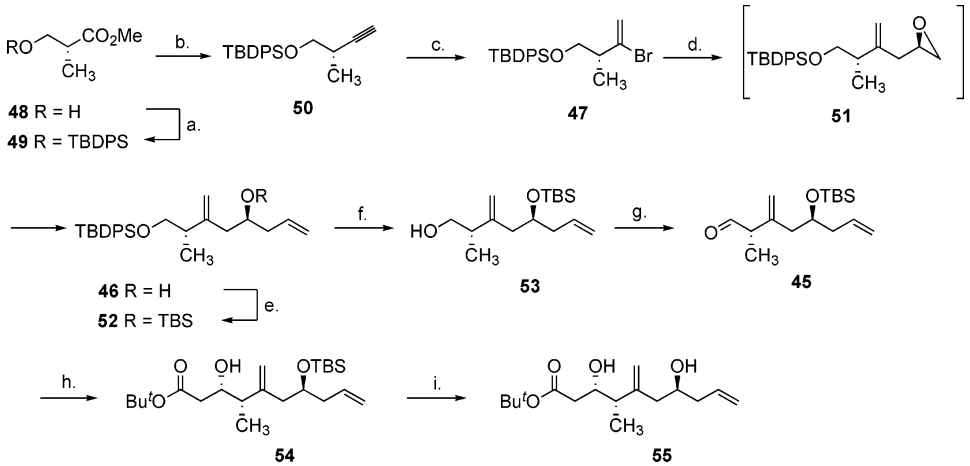
We sought to increase the steric bulk on the alkoxy side of the epoxide by preparing a TIPS analogue of epoxide **32**. However, this alcohol was unreactive toward TIPSCl, even under forcing conditions, whereas TIPSOTf caused decomposition of the epoxide and TIPSH under rhodium catalysis gave no reaction. A trityl analogue of **32** could be prepared (1.5 equiv TrCl, 2.0 equiv DBU, CH_2Cl_2, 22 °C, 21 h), but the ratio of products under the conditions of entry 1 was still only 2:1, favoring the desired product (not shown). We then decided to test the unprotected alcohol (**40**) in the presence of bidentate Lewis acids, in the hope that a five-membered chelate should favor alkylation at the desired position. To the best of our knowledge there is no precedent for this reaction with β-(1,2-disubstituted)-epoxy alcohols. Strong Lewis acids are required to activate the oxirane toward attack by carbon nucleophiles, and $BF_3{\cdot}OEt_2$ has been used extensively,[37] with Et_2AlCl being

(36) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

Scheme 10. Retrosynthetic Analysis for the Preparation of Dioxenone **4**



Scheme 11. Synthesis of the Alkene Coupling Partner[a]



[a] Reagents and conditions: (a) 1.0 equiv of TBDPSCl, 1.3 equiv of imidazole, CH_2Cl_2, 23 °C, 0.5 h; (b) 1.15 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 60 min, then 1.35 equiv of MeOH, −78 °C to 24 °C, then added to 2.5 equiv of $CH_3(CO)CHN_2P(O)(OMe)_2$, 2.5 equiv of NaOMe, THF, −78 °C to 0 °C, 20 min, 83% (2 steps); (c) 2.0 equiv of 9-Br-9-BBN, CH_2Cl_2–hexane, 0 °C, 6 h, then 14 equiv of AcOH, 0 °C, 1 h, 96%; (d) 2.0 equiv of *t*-BuLi, ether, −78 °C, 1 h, then 1.3 equiv of ThCu(CN)Li, THF, −78 °C to −45 °C, −45 °C, 1 h, then 2.0 equiv of **34**, THF, −45 to 0 °C, 0 °C, 5 h, then 2.0 equiv of vinyllithium, 2.0 equiv of $BF_3{\cdot}Et_2O$, THF, −78 °C, 20 min, 71%; (e) 1.8 equiv of TBSOTf, 4.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min; (f) 1.2 equiv of $TBAF{\cdot}3H_2O$, 1.2 equiv of AcOH, DMF, 23 °C, 13 h, 77% (2 steps); (g) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 4.6 equiv of Et_3N, CH_2Cl_2, −78 °C to −20 °C, 20 min; (h) 4.0 equiv of *t*-BuOAc, 4.0 equiv of LDA, THF−hexanes, −78 °C, 1 h, then **45**, THF, −78 °C, 10 min, 78% (2 steps); (i) 1.5 equiv of TBAF, THF, 24 °C, 4 h, 89%.

the other metal complex of choice. The use of *catalytic* $AlMe_3$ in conjunction with alkynyllithium reagents and β- or γ-epoxy ethers results in an equilibrium between the aluminum ate-complex and the chelate complex with the epoxide, to give good yields of product.[38] Crucially, however, this has only been demonstrated with monosubstituted epoxides. First treating **40** with $Ti(O^iPr)_4$, and adding it to the lithiated propiolate and $BF_3{\cdot}OEt_2$, resulted in the exclusive formation of the undesired isomer **42c** in 39% yield (entry 5). The use of the same conditions, but in the absence of $Ti(O^iPr)_4$, gave only the undesired isomer in 74% yield (entry 6). Precomplexation with a very bulky Lewis acid[39] gave the desired isomer **41c** in low selectivity and low yield (entry 7). Use of $Sc(OTf)_3$ gave a product whose structure was tentatively assigned as the tetrahydrofuran derivative **43** (entry 8). We also tested a variety of Lewis acids with alcohol **40** and trimethylacetylide but were not able to find conditions that afforded the desired product. Although the $BF_3{\cdot}Et_2O$-catalyzed reaction with *tert*-butylpropiolate (Table 2, entry 1) represented an improvement (85% yield, 1.7:1 ratio of separable isomers) over the results obtained with the aldol route (Table 1, entry 6), the remaining difficulties associated with this route made it a dicey bet for a rapid access to the long-awaited dioxenone **4**. We therefore decided to settle for a safer, less ambitious but nonetheless concise route, which we expected would afford a straightforward access to **4**.

Our third approach is depicted in Scheme 10, with commercially available (*R*)-glycidyl tosylate (**34**) and (*R*)-hydroxyisobutyric acid methyl ester (Roche ester, **48**) envisioned as starting material. We planned to prepare vinyl bromide **47** from alcohol **48**. We envisioned that epoxide **34** would serve as a linchpin to connect metalated **47** and vinyllithium, thus exploiting the difference of reactivity between the two electrophilic sites of **34**. Alcohol **46** thus obtained would then be converted in five steps to dioxenone **4**, via **45** and **44**.

The Roche ester (**48**) was protected with TBDPSCl in quantitative yield (Scheme 11). Initially, the crude product **49** was reduced to the corresponding aldehyde with DIBAL-H, which was converted to alkyne **50** using the Seyferth−Ohira−Bestmann reagent.[40] Bestmann's conditions, using K_2CO_3 in methanol at 0 °C to effect deacetylation of the reagent, induced significant elimination and **50** was isolated in a modest 40% yield. We found that the homogeneous conditions optimized by Nicolaou et al. (1 equiv NaOMe/phosphonate, THF, −78 °C to r.t)[41] were very efficient, allowing isolation of alkyne **50** in a very reproducible 76% yield over the three steps $\{[\alpha]^{26}_D$ −5.3, *c* 4.1, $CHCl_3\}$. Only on an 80 mmol scale, did we observe a drop in the yield (59%), and this was largely due to the

(37) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. (b) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *106*, 3693.
(38) Ooi, T.; Kagoshima, N.; Ichikawa, H.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 3328.
(39) (a) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131. (b) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.
(40) (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(41) Nicolaou, K. C.; Li, Y.; Fylaktadikou, K. C.; Mitchell, H. J.; Wei, H.-X.; Weyershausen, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849.

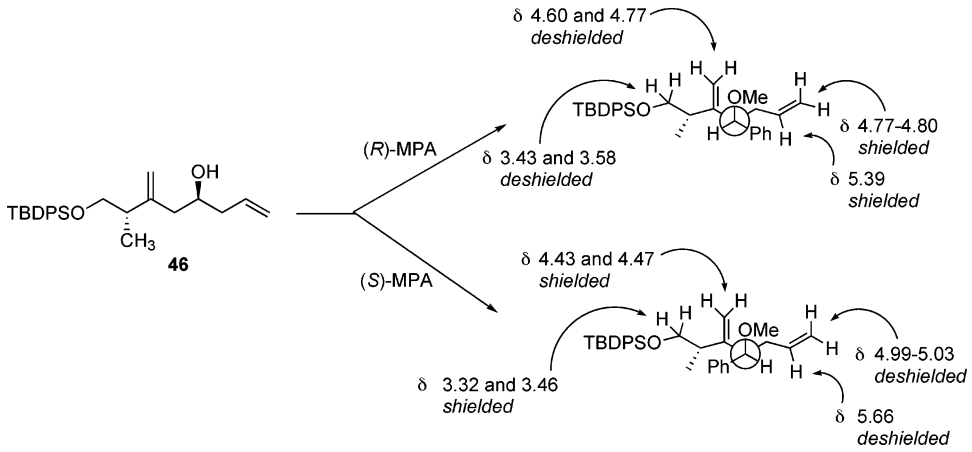
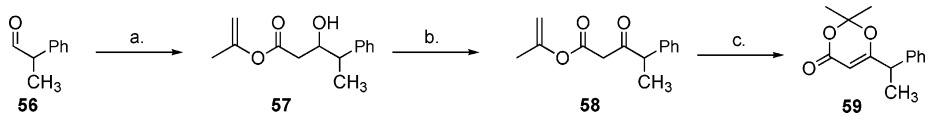


Figure 2. 500 MHz ^{1}H NMR spectroscopy analysis of the esters derived from **46** and (*R*)- and (*S*)-methoxyphenyl acetic acid (MPA) confirmed the absolute stereochemistry of alcohol **46**.

Scheme 12. Model Studies for Dioxenone Formation[a]



[a] Reagents and conditions: (a) 3 equiv of isopropenyl acetate, 3 equiv of LDA, −78 °C, 5 min; (b) 4 equiv of PCC, 1 equiv of NaOAC, 4 Å MS, CH_2Cl_2, 18 h, 24% (2 steps); (c) toluene−acetone (100 equiv) 2:1 v/v, 90 °C, 40 min, 77%.

formation of a larger amount of alcohol in the DIBAL-H reduction step. We surmised that aluminum salts should not prevent the alkynylation reaction and that it should be possible to prepare **50** without isolating the intermediate aldehyde. After stirring **49** with 1.15 equiv of DIBAL-H in CH_2Cl_2 at −78 °C for 1 h, 1.35 equiv of MeOH was added, and the mixture was warmed to r.t., and then added to 2.5 equiv of Seyferth−Ohira−Bestmann reagent which had been premixed with 2.5 equiv of NaOMe in THF at −78 °C. After warming to 0 °C over 20 min and standard workup, alkyne **50** was isolated in an improved 83% yield from **48** (Scheme 11). The drawback of this procedure is the excess of Seyferth−Ohira−Bestmann reagent needed, as 2.2 equiv gave a 62% yield and 1.5 equiv afforded **50** in ca. 40% yield. Alkyne **50** could then be converted into **47** in excellent yields, using 9-Br-9-BBN, followed by an acetic acid quench. The standard hydrogen peroxide−sodium hydroxide workup led to lower yields of product and was omitted. Although this meant that the crude product was contaminated with large amounts of material of very low solubility, it did not prove to be detrimental to the purification of **47** by flash silica gel chromatography. The coupling of **47** with (*R*)-glycidyl tosylate **34** required extensive optimization. We initially focused on forming the Grignard reagent and found that it could only form at the reflux temperature of THF, with 1,2-dibromoethane-mediated activation of the magnesium, and this reaction was always accompanied with the formation of unacceptable amounts of debrominated alkene. We were able to effect clean bromine−lithium exchange, providing that this reaction was carried out in ether, using a fresh solution of *t*-BuLi. Formation of Lipshutz' mixed cyanocuprate[42] afforded epoxide **51**, which upon treatment with vinyllithium in the presence of $BF_3{\cdot}Et_2O$ afforded alcohol **46** in good yields. The two operations could be done in one flask, without isolation of **51**, with no detrimental effect on the yield. The stereochemistry of **46** was confirmed by preparing the corresponding (*R*) and (*S*)-*O*-methyl mandelate esters derivatives.[16] 500 MHz ^{1}H NMR spectroscopy analysis showed a single diastereomer for each compound, and analysis of the chemical shifts unambiguously confirmed the *S* configuration of the alcohol (Figure 2).

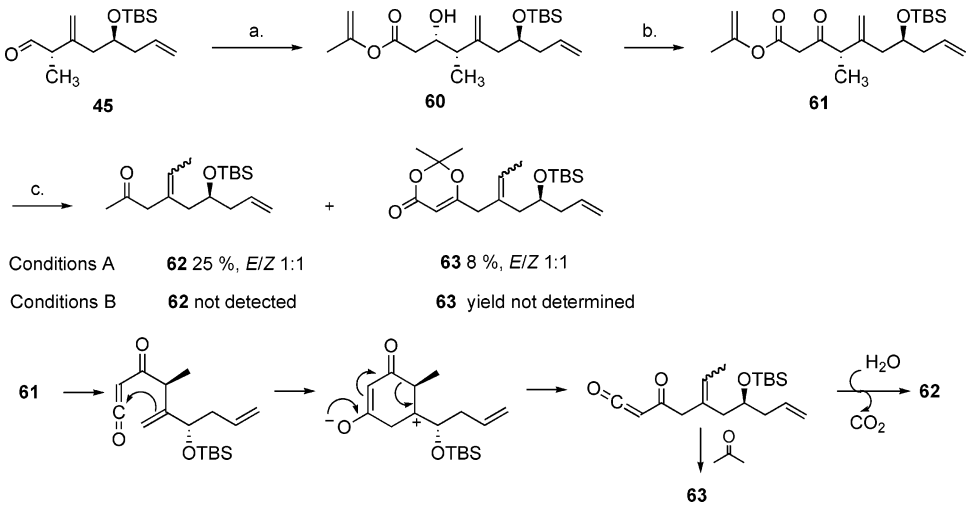
TBS protection of **46** afforded compound **52** which was used in the next step without purification. Selective hydrolysis of the primary silyl ether using TBAF in the presence of acetic acid in DMF,[43] gave alcohol **53** (Scheme 11). Moffat−Swern oxidation, followed by addition of the lithium enolate of *tert*-butyl acetate, gave ester **54** in 78% yield, and as a 2.8:1 mixture of diastereoisomers (the presumably major Felkin−Anh product is shown). As the formation of the dioxenone proved problematic and the study of the alkene−alkyne coupling progressed (vide infra), the desilylated substrate **55** became attractive and could be obtained from **54** in 89% yield using TBAF in THF. We were unable to find conditions that would allow us to prepare **55** without resorting to intermediate TBS protection of the secondary alcohol.

Conditions for the formation of the dioxenone were initially examined on a model system. Precedents for this reaction stem from studies by Eastman chemists, Clemens, Witzeman, and Hyatt, who studied the formation and mechanism thereof of acylketene from β-ketoesters and dioxenones.[9] In particular, they established that formation of acylketene was most favorable with *tert*-butyl acetoacetate compared with methyl, ethyl, isopropyl, and isobutyl[9a] and also that isopropenyl acetoacetate forms 2,2,6-trimethyl-1,3-dioxen-4-one upon heating with excess acetone.[9b] We prepared isopropenyl ester **57** from commercially available methylpropionaldehyde (**56**) and submitted it to Clemens' and Witzeman's conditions (Scheme 12).[9b] Upon heating with 100 equiv of acetone in toluene in a stoppered flask, **58** afforded

(42) (a) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437. (b) *Organocopper Reagents: A practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994.

(43) Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306.

Scheme 13. Attempted Dioxenone Formation[a]



[a] Reagents and conditions: (a) 5 equiv of isopropenyl acetate, 5 equiv of LDA, −78 °C, 5 min, 45%; (b) 4 equiv of PCC, 1 equiv of NaOAC, 4 Å MS, CH_2Cl_2, 4 h, 50%. (c) Conditions A: toluene−acetone (100 equiv) 2:1 v/v, 90 °C, 90 min. Conditions B: acetone, 56 °C, 3.5 h.

dioxenone **59** in 77% yield, although the purity of the product was modest as judged by ^{1}H NMR spectroscopy.

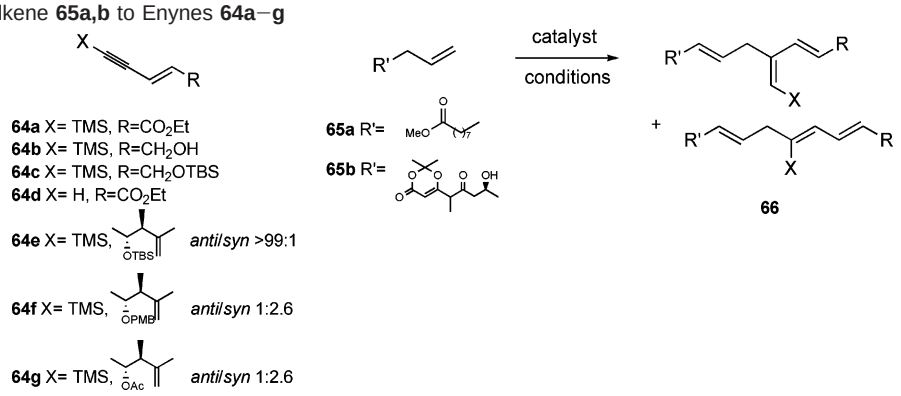
We then prepared the isopropenyl ester (**61**) derived from aldehyde **45** (Scheme 13), but when heated in the presence of acetone, none of the desired dioxenone was formed. Instead, two products were isolated (conditions A), methyl ketone **62** and dioxenone **63**, presumably via the mechanism depicted in Scheme 13. In neat acetone (conditions B), the reaction still proceeded, although at a lower rate, and only the dioxenone **63** was observed by TLC. This was unanticipated as Williams used a similar β-ketoester, going through a similar acylketene to accomplish the macrocyclization.[5d] In the complete amphidinolide P system, the acylketene got smoothly trapped by the alcohol 12 carbons away to form the 15-membered ring (starting from the methyl ester, 90 min, toluene, reflux). With alkenes **54** and **55** in hand, we could certainly envisage completing the synthesis, and we did not do any further studies on dioxenone synthesis.

Studies of the Ruthenium-Catalyzed Enyne−Alkene Coupling. As mentioned in the Introduction, enynes had never been tested as substrates for the alkene−alkyne coupling, and we therefore carried out some model studies. Enynes **64a**−**g** and alkenes **65a** and **65b** were prepared[31] (we were not able to identify conditions to convert ketone **65b** into the desired olefin) and coupled under various conditions using [$CpRu(CH_3CN)_3$]-PF_6 (**67**) or CpRu(COD)Cl (**68**), and the results are compiled in Table 3.

We first studied the reaction with methyl 10-undecenoate (**65a**) in the presence of 10 mol % of catalyst **67**. With TMS-alkynes **64a**−**c** fast conversions (<10 min) and low turnovers were observed (Table 3, entries 1−5), although as expected, only the branched product was detected by ^{1}H NMR spectroscopic analysis. Removing the TMS group resulted in increased turnover (entry 6 vs entry 1) although the linear product was now the major product. Switching to DMF and increasing the temperature improved the yield further and favored the branched product (entries 7−9). The yield could be increased up to 56% by heating the reaction mixture at 70 °C in DMF (preheated oil bath), and an improved branched-to-linear ratio of 2.7:1 was observed. The CpRu(COD)Cl (**68**) catalyst fared poorly in this reaction (entry 10). Next we studied racemic alkynes **64e**−**g**. The result obtained with **64c** (entry 5) was nicely reproduced with the desired, more functionalized analogue **64e** since the coupling reaction with olefin **65a** in a 1:1 ratio in acetone at room temperature in the presence of **67** (10 mol %) yielded the desired compound **66ea** in 46% yield (brsm 65%) as well as several unidentified byproducts (entry 11). Treatment of **66ea** in acetone in the presence of 20 mol % **67** led to a 95% recovery, which pointed to the stability of the product. With the use of dioxenone **65b**, the reaction was carried out in acetone at r.t., and again rapid conversion and low yield of product was observed (entry 12). Poor reactivity of alkene **65b** might be inferred from the facts that the alkyne was fully consumed and that alkene recovery was excellent. Unlike what has been occasionally observed,[6c] adding another portion of catalyst resulted in no further conversion. Using 1 equiv of catalyst **67** gave worse conversion (entry 13) which might indicate the formation of catalytically inactive aggregates, or self-catalyzed decomposition, although poor mass recovery points to a possible different reaction manifold. Curiously, when DMF was used, no reaction was observed (entry 14). The reaction of **64g** also proceeded poorly (entry 16), while the addition of a bidentate acid to the medium was detrimental to the conversion (entry 17). Again DMF was not a suitable solvent, affording no product (entry 17).

At this point in time we had alkenes **54** and **55** in hand, and the alkene−enyne coupling was then tested with those substrates, as shown in Table 4. Alkene **54** was unstable in the presence of the catalyst **67** in acetone (entry 1), and no reaction occurred in DMF (entry 2), except under forcing conditions (100 °C), where the silyl ether was hydrolyzed, demonstrating the Lewis acid character of the ruthenium(II) species. Surmising that steric hindrance might preclude coordination of both coupling partners to the ruthenium center, we removed the TMS group and tested the reaction with alkyne **25**, to no avail (entry 4). Pushing the idea further, we carried out the reaction with diol **55** and alkyne **25** and were pleased to isolate the product **70** in 28% yield (entry 5). Using an excess of alkene was essential in order to obtain good conversion. Importantly, no linear isomer was detected by 500 MHz ^{1}H NMR spectroscopy,

Table 3. Addition of Alkene **65a,b** to Enynes **64a−g**



entry[a]	alkyne	alkene	catalyst (mol %)	solvent	temp °C	product % (brsm)[b]	branched-to-linear ratio
1	**64a**	**65a**	**67** (10)	acetone	24	**66aa** 31 (70)	1:0
2	**64a**	**65a**	**67** (10)	DMF	24	**66aa** 5 (73)	n.d.
3	**64a**	**65a**	**67** (10)	DMF	55	**66aa** 5 (65)	n.d.
4	**64b**	**65a**	**67** (10)	acetone	24	no reaction	
5	**64c**	**65a**	**67** (10)	acetone	24	**66ca** 45 (75)	1:0
6	**64d**	**65a**	**67** (10)	acetone	24	**66da** 26 (75)	1:2
7	**64d**	**65a**	**67** (10)	DMF	24	**66da** 36 (78)	1.8:1
8	**64d**	**65a**	**67** (10)	DMF	55	**66da** 50 (76)	1.8:1
9	**64d**	**65a**	**67** (10)	DMF	70	**66da** 56 (68)	2.7:1
10	**64d**	**65a**	**68** (5)	MeOH	65	**66da** 13 (53)	2.3:1
11	**64e**	**65a**	**67** (10)	acetone	24	**66ea** 46 (65)	1:0
12	**64f**	**65b**	**67** (10)	acetone	24	**66fb** 27 (100)	n.d.
13	**64f**	**65b**	**67** (100)	acetone	24	**66fb** 10 (25)	n.d.
14	**64f**	**65b**	**67** (10)	DMF	60	**66fb** no reaction	
15	**64g**	**65b**	**67** (10)	acetone	24	**66gb** 10 (40)	n.d.
16[c]	**64g**	**65b**	**67** (10)	acetone	24	**66gb** traces	
17	**64g**	**65b**	**67** (10)	DMF	65	**66gb** no reaction	

[a] All reactions were run at 0.1M for 1−4 h using a 1:1 ratio of alkene to alkyne. [b] brsm indicates the yield based on recovered alkene. [c] 1 equiv of malonic acid was added.

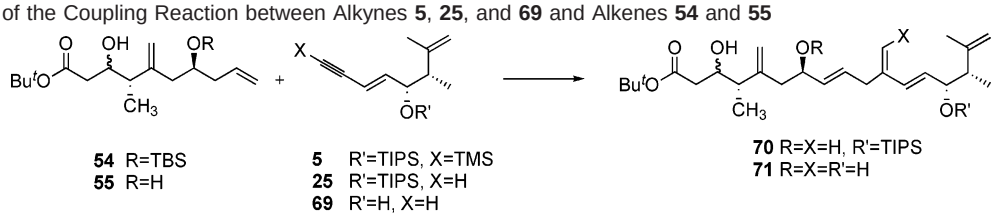
and unreacted alkene recovery was good. To try and obtain full conversion, we tested the CpRu(COD)Cl (**68**) catalyst.[6c,d] At the reflux of methanol in the presence of ammonium ion and using a 3-fold excess of alkene, full conversion was obtained and product **70** was obtained in 57% yield (entry 6). Again, no linear isomer was detected by 500 MHz ^{1}H NMR spectroscopy, and unreacted alkene recovery was good.

Since the reaction was almost quantitative in alkene **55**, and significant decomposition of the alkyne occurs, the reaction was attempted at lower catalyst loading and lower alkyne concentration (entries 7 and 8). Only a marginal improvement was observed with 5 mol % of **68** using a 4.5:1 ratio of **55**/**25**, whereas using 2 mol % resulted in incomplete conversion, although the yield based on recovered starting material was 66%. The quality of the solvent was crucial in this process, since the use of methanol purified using a column solvent purification apparatus,[44] which was most likely contaminated with basic alumina, led to no conversion. We returned to catalyst **67** (10 mol %) using a 4.5:1 ratio of **55**/**25** at 0.06 M, and found that the reaction proceeded slowly but cleanly in dry acetone at r.t. to give **70** in 72% yield (entry 9). However, on scale-up, a lot of decomposition was observed (entry 10). This difference of catalyst activity might be due to a difference in water concentration between the small scale and large scale reactions, and we hypothesized that water might be a ligand for the active catalytic species. Similar results as those of entry 9 were obtained on a small scale when acetone from a wash bottle was used, in which case, at 0.06M, the molar ratio of water to ruthenium was at least 15. More work will need to be done to understand the effect of water in the alkene−alkyne coupling using catalyst **67**. To this day, it remains unclear what the structure of the active catalyst is. With the use of the optimized conditions (entry 9), the addition of 10 mol % of TBAC totally shut down the reaction (entry 11, TBAC and **67** were mixed under argon, acetone was added, followed with **55** and **25**, which were both recovered quantitatively after several hours). With the use of the conditions of entry 7, but the replacement of **68** with 10 mol % of **67** and 10 mol % of TBAC, only traces of **70** were observed (entry 12). These results would seem to indicate that the active catalyst is different in acetone and methanol (notwithstanding the role of the solvent as a ligand), with the chloride remaining bound to the ruthenium when methanol is used as solvent. Adding chloride to **67** in acetone shut down the reaction (entry 11), and conversely, it could be that no active chloride-bound ruthenium catalyst was formed when **67** and TBAC were mixed in methanol (entry 12). Alkene−alkyne couplings do proceed with catalyst **68** in methanol in the absence of NH_4PF_6 (where presumably the active catalyst is a Cp−ruthenium chloride species), and in fact NH_4PF_6 provides only modest improvements.[6d] We did not however run this experiment (entry 6 conditions) without NH_4PF_6.

In view of the subsequent macrocyclization step, it was interesting to find out whether the reaction could be carried out

(44) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P. J.; Petrs, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Educ.* **2001,** *78*, 64. (c) http://www.glasscontour.com/.

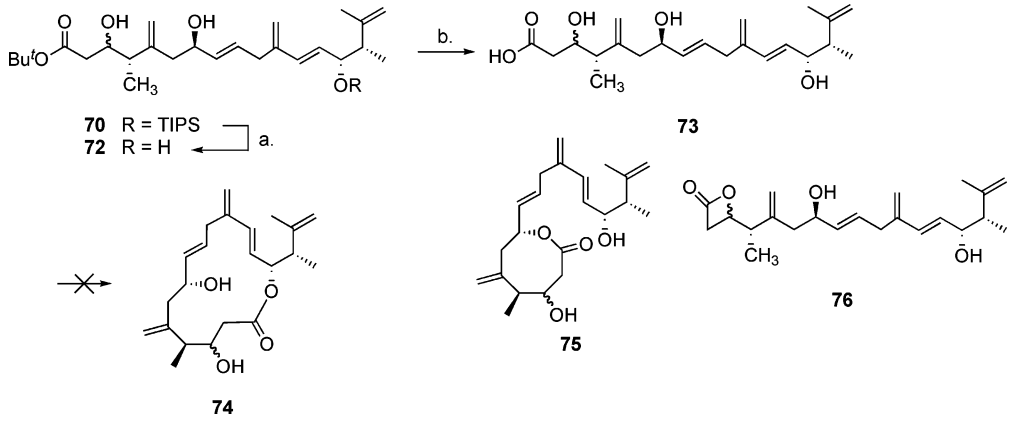
Table 4. Studies of the Coupling Reaction between Alkynes **5**, **25**, and **69** and Alkenes **54** and **55**



entry	alkene	alkyne	alkene/alkyne ratio	catalyst (mol %)	solvent (alkyne concn)	temp °C	reaction time	product % (recovered alkene, recovered alkyne)[a]
1	**54**	**5**	1:1	**67** (10)	acetone (0.15)	24	2 h	complex mixture
2	**54**	**5**	1:1	**67** (10)	DMF (0.15)	24 to 100	2 h	− (60,[b] 100)
3	**54**	**5**	2:1	**67** (10)	DMF−acetone 3:1 (0.20)	24	16 h	− (100, 100)
4	**54**	**25**	1.1:1	**67** (10)	acetone (0.25)	24	1.5 h	− (57, n.d.)
5	**55**	**25**	2:1	**67** (10)	acetone (0.15)	24	2 h	28 (80, 45)
6	**55**	**25**	2.7:1	**68** (10)[c]	methanol (0.10)	67	20 min	57[d] (80, *e*)
7	**55**	**25**	4.5:1	**68** (5)[c]	methanol (0.06)	67	75 min	61[d] (86, *e*)
8	**55**	**25**	4.5:1	**68** (2)[c]	methanol (0.06)	67	2 h	43[d] (77, 35)
9[f]	**55**	**25**	4.5:1	**67** (10)	acetone (0.06)	24	15 h	72 (95, *e*)
10[g]	**55**	**25**	4.5:1	**67** (10)	acetone (0.06)	24	13 h	50 (42, *e*)
11	**55**	**25**	4.5:1	**67** (10)[h]	acetone (0.06)	24	3 h	− (100, 100)
12	**55**	**25**	4.5:1	**67** (10)[i]	methanol (0.10)	67	3 h	traces (n.d., n.d.)
13	**55**	**69**	1.3:1	**68** (5)[c]	methanol (0.10)	67	48 h	17[d] (96, *e*)
14	**55**	**69**	5.5:1	**68** (5)[c]	methanol (0.06)	67	16 h	20[d] (84, *e*)
15	**55**	**69**	3:1	**68** (10)[c]	methanol (0.05)	67	3 h	30[d] (70, *e*)
16	**55**	**69**	2.5:1	**67** (5)[c]	acetone (0.05)	24	3 h	traces (n.d., n.d.)

[a] In all the cases where the product was isolated, the branched-to-linear ratio was found to be >49:1 as judged by 500 MHz ^{1}H NMR analysis. [b] Desilylation was observed. [c] 2 equiv/Ru of NH_4PF_6 was added. [d] Yield adjusted for the amount of alkyne consumed in the [2 + 2 + 2] reaction with the COD ligand. [e] Full alkyne conversion was observed. [f] 0.04 mmol scale. [g] 1 mmol scale. [h] 10 mol % tetra-*n*-butylammonium chloride was added. [i] 10 mol % tetra-*n*-butylammonium chloride and 10 mol % NH_4PF_6 were added.

Scheme 14. Preparation of Seco-Acid **73** and Attempted Macrolactonization[a]



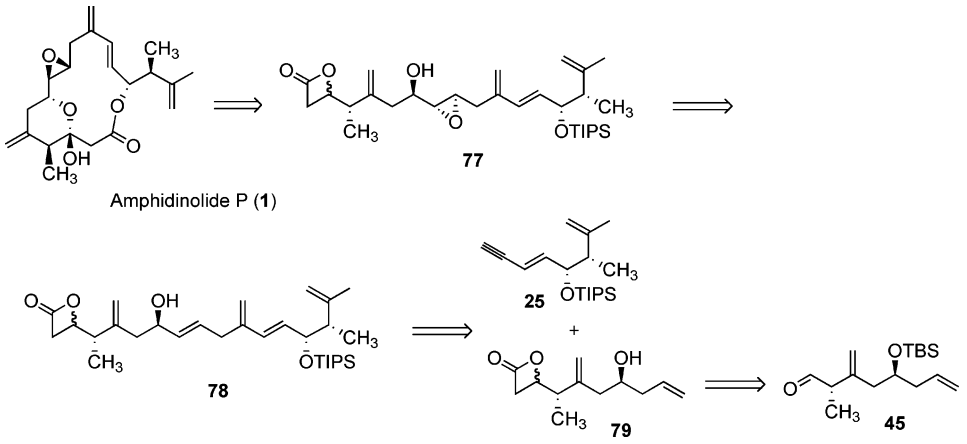
[a] Reagents and conditions: (a) 4.0 equiv of TBAF, THF, 24 °C, 2 h, 94%; (b) 7.5 equiv of TMSOTf, 11.5 equiv of 2,6-lutidine, 0 °C, 3 h, 24 °C, 30 min, quant.

with desilylated **69**, which was obtained from **25** (3 equiv of TBAF, THF, r.t., 15 min, 50% unoptimized). It turned out **69** afforded very low rates compared to **25**, presumably because **69** is a better ligand than **25** and is not displaced easily by the alkene (entries 13−16). None of it was recovered, and only low yields of **71** were observed.

Completion of the Synthesis. With the full backbone of amphidinolide P in hand (**70**), we could now focus on the final steps of the synthesis. Without the dioxenone functionality, and with the *C*-3 and *C*-7 alcohols both deprotected, macrocyclization through acylketene formation seemed precluded. Even if we could selectively oxidize the *C*-3 alcohol, we thought that formation of a stable hemi-acetal might considerably slow or even shut down the formation of the acylketene. We thus decided to test more standard macrocyclization techniques, through acyl activation of the corresponding acid. Compound **70** was therefore treated with excess TBAF to afford alcohol **72** in excellent yield (Scheme 14), and **72** was subjected to a variety of conditions to convert it to the acid, all leading to extensive decomposition. In spectacular contrast, we found that TMSOTf was an excellent Lewis acid for this transformation,[45] and after an aqueous HCl workup, acid **73** was obtained in quantitative yield and did not require additional purification. Reversing the order of steps also gave acid **73** in good yield, but purification was then required. We found that acid **73** was a very unstable compound, which decomposed in a few days upon standing, even at −20 °C. It was nonetheless submitted to a variety of macrocyclization conditions. The macrolactonization methods reported by the groups of Yamaguchi,[46] Trost,[47] Mukaiyama,[48] Keck,[49] and Mitsunobu[50] all gave complex

(45) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540.

Scheme 15. Novel End-Game for the Synthesis of **1**, Using a β-Lactone Precursor



mixtures. With the use of Mukaiyama's or Keck's systems, some residue could be isolated that displayed IR stretching frequencies of 1720 and 1830 cm^{-1}, indicative of a mixture of medium-sized lactone and β-lactone, respectively. When the Corey−Nicolaou methodology[51] was employed, eight-membered ring **75** was isolated in 20−30% yields. Intrigued by the possibility that β-lactone **76** was an intermediate in the formation of **75**, and rather than trying to optimize the reaction with this unstable seco-acid, we wondered whether we could not use the β-lactone functionality[52] as an activated acyl system, stable enough to undergo several synthetic steps, albeit reactive enough to undergo transesterification to some larger, more stable ring systems. This novel strategy for macrolactonization would not require a redesign of our synthetic route since, in theory, aldehyde **45** could undergo a [2 + 2] cycloaddition reaction to form a β-lactone (Scheme 15), which would provide an interesting substrate for our alkene−alkyne coupling reaction. A potentially big advantage of intermediate **78** over **70** was the presence of only one free hydroxyl, which could reduce chemoselectivity problems in the end-game. Indeed, studies of the hydroxyl-directed epoxidation of ester **70** led to complex mixtures, partly due to lack of chemoselectivity. In this respect, the β-lactone would act as a "productive protecting group".

We investigated conditions to form β-lactone **79** from aldehyde **45**. The Lewis acid-catalyzed cycloaddition of ketene and an aldehyde has been known for some time.[53] However, the generation of ketene requires burdensome equipment. Alternatively, a stable ketene equivalent such as trimethylsilyketene (**80**)[54] or dichloroketene could be used, where the stabilizing substituents could be removed in the product; another alternative is to generate ketene in situ, by dehydrohalogenation of acetyl halides with an amine base.[55] We initially focused on the latter, inspired by the work of Nelson et al.,[56] who generated ketene from Hünig's base and acetyl chloride and used $Al(SbF_6)_3$ (generated in situ from $AgSbF_6$ and $AlCl_3$) as a Lewis acid to promote the cycloaddition. Although we had some degree of success with this protocol, in our hands it was a very capricious reaction that led to unreproducible results, and none of the alternative Lewis acids tested gave satisfactory results (replacing $AlCl_3$ with $GaCl_3$, $InCl_3$, $Al(OTf)_3$, or Me_2AlCl). AcBr offered no improvement, and various sulfonamide/trimethylaluminum systems[57] offered only modest amounts of β-lactone. The $LiClO_4$ methodology reported by Lecea et al.[58] was also inneffective. We briefly studied the tandem aldol−lactonization reaction,[59] using ketene triethylsilylthioacetal and **45** in the presence of $ZnCl_2$, but again only low yields of β-lactone were obtained. We next turned our attention to the use of trimethylsilylketene (**80**).[54] This compound can be prepared very conveniently by silylation of ethyl ethynyl ether to give ethyl trimethylsilyl-ethynyl ether, which upon heating to 120 °C, undergoes a 1,5-hydrogen shift to give off ethylene and **80** (bp 81−82 °C) in 70% yield. Ketene **80** was stored in the freezer and no decomposition was observed after 6 weeks. The cycloaddition of **80** and **45** did not proceed when catalyzed by $MgBr_2 \cdot Et_2O$,[60] whereas $BF_3 \cdot Et_2O$ gave the lactone (**81**) in 49% yield. Me_2AlCl however afforded **81** as an inconsequential 1.6:1 mixture of diastereomers in a very reproducible 90% yield, using just 1.1 equiv of **80** (Scheme 16).[61] This was consistent with literature results that show that Al(III) is predominantly the metal catalyst of choice for [2 + 2] reactions between aldehydes and ketenes.[56,57,61,62] Next, we looked for conditions that would cleave both the O−Si bond and the C−Si bond in one pot. TBAF gave the fully desilylated product **79** ($\upsilon_{C=O}$ 1827 cm^{-1})

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(54) (a) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607. (b) Shchukovskaya, L. L.; Pal'chik, R. I.; Lazarev, A. N. *Dokl. Akad. Nauk. SSSR* **1965**, *164*, 357.
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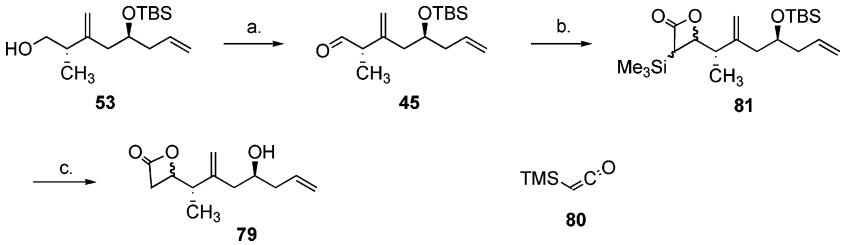
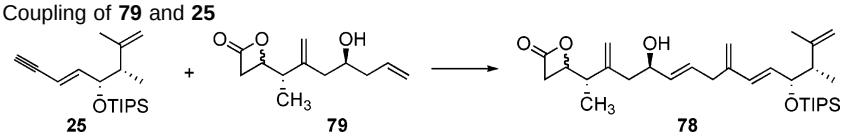
Scheme 16. Synthesis of β-Lactone **79**[a]



[a] Reagents and conditions: (a) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 4.6 equiv of Et_3N, CH_2Cl_2, −78 °C to 0 °C; (b) 1.0 equiv of Me_2AlCl, 1.1 equiv of **80**, CH_2Cl_2, −78 °C, 0.5 h; (c) 1.5 equiv of $KF{\cdot}2H_2O$, CH_3CN, 25 °C, 1 h, then 40% HF(aq), 0 °C, 0.5 h, 69% (3 steps), d.r. 1.6:1.

Table 5. Alkene−Alkyne Coupling of **79** and **25**



entry	conditions	scale (mmol **25**)	yield **78** (%)	recovered **79** (%)
1[a]	10 mol % **67**, acetone, 0.05 M, r.t., 13 h, **25**/**79** 1:3.5	0.14	75	87
2[a]	10 mol % **67**, acetone, 0.05 M, r.t., 10 h, **25**/**79** 1:3.5	0.20	69	86
3[a]	10 mol % **67**, acetone, 0.05 M, r.t., 12 h, **25**/**79** 1:3.3	0.44	68	87
4[a]	10 mol % **67**, acetone, 0.05 M, r.t., 12 h, **25**/**79** 1:3.5	0.80	56	91
5[a]	10 mol % **67**, acetone, 0.05 M, r.t., 10 h, **25**/**79** 1:2.8	0.36	64	90
6[b]	10 mol % **67**, acetone, 0.05 M, r.t., 22 h, **25**/**79** 1:3.4	0.04	72	75

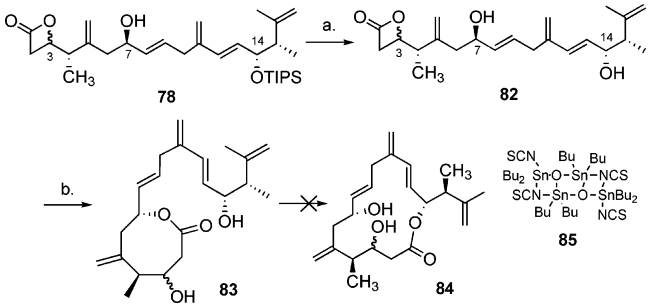
[a] Acetone was distilled from $CaCl_2$. [b] Acetone was taken from a wash bottle.

in only 26% yield, and aqueous HF did not cleave the C−Si bond. It is known that $KF{\cdot}2H_2O$ desilylates β-lactones,[60] so **81** was first treated with $KF{\cdot}2H_2O$ until TLC analysis indicated complete conversion, whereupon the mixture was cooled to 0 °C, and aqueous HF was added. With the use of this procedure, **79** was very reliably obtained in 69% yield over the three steps. As an added bonus, the two diasteromers were separable, and although this epimeric center would eventually be destroyed, working with a single diastereomer simplified the studies of the remaining steps.

Despite slight concerns about the compatibility of the somewhat Lewis acidic (see for example Table 4, entry 2) catalyst **67** and the β-lactone functionality, coupling between alkene **79** and alkyne **25** proceeded well (Table 5, entry 1). However, a steady decrease of the yield was observed as the scale of the reaction was increased (entry 1 vs 2 vs3 vs 4). This was accompanied with a higher recovery of the excess alkene **79**, indicating a greater propensity for the alkyne **25** to decompose. The use of 3.5 equiv of alkene seemed optimal, since a slight decrease in yield was observed when only 2.8 equiv were used (68% vs 64%, entry 3 vs entry 5). It is worth noting that a similar result was observed when acetone from a wash bottle (entry 6) was used instead of distilled acetone (entry 1).

We then submitted **78** to TBAF and obtained **82** in 71% yield (Scheme 17). When we heated oxetanone **82** at the reflux of hexane in the presence of 10 mol % of Otera's catalyst[63] (**85**) at 0.001 M for 20 min, we only isolated eight-membered lactone **83** in quantitative yield. Lowering the catalyst loading to 1 mol % gave **83** in 88% yield after 45 min. We did not observe any conversion to the 15-membered macrolide after 3 h using 10 mol % catalyst, which would suggest, somewhat counterintuitively, that **83** is in fact more stable than the corresponding 15-membered ring (**84**). This somewhat unanticipated result suggested, at the cost of one extra step, an excellent strategy to differentiate between the three secondary alcohols. While the two alcohols at *C*-3 and *C*-14 were protected as a β-lactone and a TIPS ether (**78**, Scheme 17), respectively, the alcohol at *C*-7 would be used to direct the epoxidation. Leaving the TIPS group on, and after isomerization from the four- to the eight-membered lactone, we could anticipate oxidizing the newly unmasked alcohol at *C*-3. Removing the TIPS would then reveal the *C*-14 allylic alcohol. We expected that with this substrate, the 8- to 15-membered ring isomerization would be favored, driven by concomitant hemi-acetal formation and giving the natural product amphidinolide P (**1**). We briefly investigated the substrate-directed epoxidation of alkene **78**. It is well established in the literature that *E*-1,2-disubstituted olefins are poor substrates for hydroxyl-directed epoxidation with allylic alcohols, since they sustain minimal A-1,2 *and* A-1,3 interactions in the transition state, usually giving the syn product with

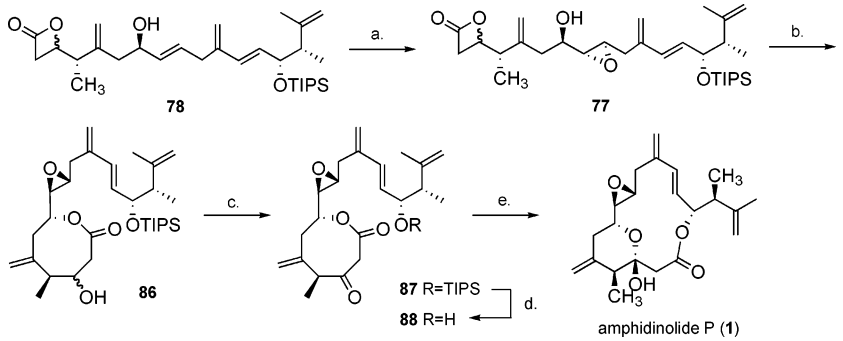
Scheme 17. Attempted Formation of the Amphidinolide 15-Membered Ring System[a]



[a] Reagents and conditions: (a) 4.0 equiv of TBAF, THF, 0 °C, 5 h, 71%; (b) 0.1 equiv of **85**, hexane, 0.001 M, reflux, 20 min, quant.

(63) (a) Otera, J.; Ioka, S.; Nozaki, H. *J. Org. Chem.* **1989**, *54*, 4013. (b) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307. (c) Orita, A.; Sakamoto, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899.

Scheme 18. Final Steps[a]



[a] Reagents and conditions: (a) 1.0 equiv of $Ti(O^iPr)_4$, 1.2 equiv of (−)-DET, 2.0 equiv of TBHP, 4 Å MS, CH_2Cl_2, −20 °C, 2 h, 83%; (b) 0.05 equiv of **85**, hexane, 0.002 M, reflux, 1 h, 93%; (c) 3.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 23 °C, 1 h, 82%; (d) 5.0 equiv of TBAF, THF, 0−23 °C, 23 °C, 1 h, 95%; (e) 0.20 equiv of **85**, hexane, 0.001 M, reflux, 8 h, 84%.

very poor selectivities.[64] Only the $VO(acac)_2$/TBHP system is known to be anti-selective for this particular class of allylic alcohols. We tested this system with *syn*-**78** in various solvents (dichloromethane, hexane, toluene, benzene, chlorobenzene), and although mass recovery was good, close to 1:1 ratios were obtained in all cases. The major product in the toluene, hexane, CH_2Cl_2 experiment was assigned the anti configuration based on literature precedent (the coupling constants are not diagnostic in these systems), and later, on the result of the reagent-controlled epoxidation (vide infra). A reversal of selectivity was observed in chlorobenzene and benzene (which gave the highest selectivity, 1:2). We then resorted to the Katsuki−Sharpless tartrate/$Ti(O^iPr)_4$ system.[65] On the basis of multiple literature precedents,[66] the use of (−)-tartrate was expected to be a matched case. Indeed the reaction with *anti*-**78** gave 3,4-*anti*-**77** in 87% yield, and a single diastereomer using (−)-diethyl tartrate (diisopropyl tartrate gave a similar result but was inseparable from the product). Reaction with the mixture of diastereomers *anti*-**78** and *syn*-**78** gave a partially separable mixture of 3,4-*syn*-**77** and 3,4-*anti*-**77** in 83% yield (Scheme 18). As anticipated, when we submitted **77** to catalyst **85**, eight-membered lactone **86** ($\upsilon_{C=O}$ 1732 cm^{-1}) was obtained in 93% yield using 5 mol % catalyst at 0.002 M in hexane. The *C*-3 alcohol could then be oxidized using Dess−Martin periodinane to give ketone **87** in 83% yield ($\upsilon_{C=O}$ 1756 and 1715 cm^{-1}). Desilylation using excess TBAF in THF at r.t. gave alcohol **88** in near quantitative yield. This was a very clean reaction, and no double-bond isomerization or epimerization were observed. No enol was detected in $CDCl_3$, as judged from the ^1H NMR spectroscopy spectrum. Finally, when **88** was submitted to 20 mol % **85** for 8 h at 0.001 M in hexane at reflux, amphidinolide P (**1**) was isolated in an excellent 84% yield.

Data for synthetic **1** was identical to the data reported for the natural product, except for the optical rotation: $[\alpha]^{23}_D$ −27.4 (*c* 0.17, MeOH), lit.[7] $[\alpha]^{20}_D$ +31 (*c* 0.098, MeOH). Four optical rotation measurements in absolute methanol at slightly different concentrations gave consistent values. Concentrations of 0.09, 0.17, 0.19, 0.23 gave $[\alpha]^{23}_D$ values of −27.2, −27.4, −31.7, and −28.3, respectively. No change of optical rotation was observed after 5 h of storage in methanol, and the ^1H NMR spectra of **1** in C_6D_6 and CD_3OD were also unchanged. Williams et al. reported a synthesis of **1** which relied on two Sharpless asymmetric epoxidations to introduce the chirality, both of them using the (+)-diethyl tartrate ligand, and which should give synthetic **1** of opposite absolute configuration to the one reported herein.[5d] Yet they also reported a negative optical rotation, $[\alpha]^{23}_D$ −30 (*c* 0.09, MeOH). Unfortunately, Professor Williams was not able to provide us with a sample of synthetic **1**, and no direct comparative measurement could be done.

Conclusion

The synthesis of amphidinolide P demonstrated that β-lactones could be used as a handle for the construction of medium-sized rings and as an alternative macrolactonization strategy. The use of a β-lactone in this work also allowed for the differentiation of three secondary alcohols, thereby minimizing the use of protecting groups in the end-game and increasing the efficiency of the synthesis. This work also highlighted the chemo- and regioselectivity of the ruthenium-catalyzed addition of alkene to alkynes. In the course of these studies, we showed that this reaction was compatible with silyl ethers, esters, β-lactones, allylic alcohols, and disubstituted alkenes and that enynes gave perfect regioselectivity for the branched product to give 2-allylated-1,3-dienes. As a result, a novel highly convergent synthetic strategy emerged for the synthesis of amphidinolide P. Indeed the required alkene was prepared in nine steps and 30% yield, and the alkyne also in nine steps and 26% yield, both from readily available and inexpensive chiral building blocks.

Experimental Section

(*E*)-(5*S*,6*S*)-6,7-Dimethyl-5-triisopropylsilanyloxy-1-trimethylsilanyl-octa-3 ,7-dien-1-yne (5). To a solution of **15** (1.73 g, 4.36 mmol) and triphenylphosphine (3.46 g, 13.19 mmol) in dry toluene (20 mL) was added diisopropyl azodicarboxylate (2.67 g, 13.20 mmol), and the flask was lowered into a preheated oil bath (80 °C). After stirring at this temperature for 20 min, the volatiles were removed in vacuo and the residue was purified by flash silica gel column chromatography (petroleum ether) to give alkyne **5** (1.37 g, 3.61 mmol, 83%) as a colorless oil and an 8:1 inseparable *E*/*Z* mixture (Found: C, 69.59; H, 11.14. $C_{22}H_{42}OSi_2$ requires C, 69.77; H, 11.18%); $[\alpha]^{23}_D$ +1.7 (*c* 3.41, $CHCl_3$); R_f 0.40 (petroleum ether); ν_{max}/cm^{-1} 2945, 2868, 2361, 2134, 1464, 1250, 1059, 958, 883, 843, 760, 679, 654; *E* isomer: δ_H (500 MHz, $CDCl_3$) 0.18 (9 H, s), 0.97 (3 H, d, *J* 7.0), 1.07 (21 H, s), 1.76 (3 H, s), 2.40 (1 H, br. quin., *J* 6.0), 4.46 (1 H, td, *J* 5.0, 2.0), 4.75 (1

(64) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(65) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.
(66) For an excellent example demonstrating the exquisite selectivity of the Katsuki−Sharpless reagent, see: Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3016.

H, s), 4.85 (1 H, s), 5.70 (1 H, dd, *J* 16.0, 2.0), 6.09 (1 H, dd, *J* 16.0, 5.0); δ_C (125 MHz, $CDCl_3$) 0.0, 12.3, 12.5, 18.1, 22.2, 47.1, 74.1, 94.1, 103.8, 110.0, 111.9, 144.5, 146.0; *Z* isomer: δ_H (500 MHz, $CDCl_3$) 0.17 (9 H, s), 0.97 (3 H, d, *J* 7.0), 1.06 (21 H, s), 1.80 (3 H, s), 2.40 (1 H, masked), 4.46 (1 H, masked), 4.75 (1 H, s), 4.85 (1 H, s), 5.49 (1 H, d, *J* 11.5), 5.89 (1 H, dd, *J* 11.5, 9.0).

(4*S*,7*S*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-7-methyl-6-methylene-oct-1-en-4 -ol (46). To a solution of thiophene (0.76 g, 9.03 mmol) in THF (8 mL) at −30 °C was added *n*-BuLi (2.58 M, 3.50 mL, 9.03 mmol) dropwise. The mixture was stirred for 30 min, whereupon it was cannulated into a slurry of CuCN (99.99%, 809 mg, 9.03 mmol) in THF (8 mL) at −78 °C. The cooling bath was removed, and upon reaching r.t., a clear brown solution was obtained. This solution was kept at ca. −20 °C until the vinyllithium reagent was ready (vide infra).

To a solution of vinyl bromide **47** (2.79 g, 6.91 mmol) in ether (28 mL) was added *t*-BuLi (1.44 M, 10 mL, 14.4 mmol) at −78 °C over 10 min. After another 45 min, the freshly prepared solution of 2-thienyllithiumcyanocuprate was cannulated into it. The pale brown heterogeneous mixture was warmed to −45 °C (chlorobenzene/dry ice bath) and stirred at this temperature for 1 h. A solution of (*R*)-glycidyl tosylate (**34**) (3.1 g, 13.58 mmol) in THF (11 mL) was then cannulated into the mixture, and the resulting slurry was warmed to 0 °C over 10 min. After an additional 5 h at 0 °C, the mixture was recooled to −78 °C and a vinyllithium solution (13.93 mmol, prepared from *n*-BuLi and tetravinyltin at −78 °C, 45 min then warming to 24 °C) in THF (14 mL) was added, followed after 5 min, with $BF_3{\cdot}Et_2O$ (1.97 g, 13.93 mmol). The resulting mixture was stirred for 20 min, then quenched with a 9:1 solution of saturated aqueous NH_4Cl solution/NH_4OH and diluted with ether. After 20 min of vigorous stirring followed by filtration through Celite, the organic phase was washed with brine. The combined aqueous phase was back-extracted twice with ether. After drying the combined organic phase over $MgSO_4$, the volatiles were removed in vacuo to give a residue that was purified by silica gel flash chromatography (petroleum ether−ethyl acetate, 19:1 to 9:1) to afford the alcohol **46** (2.01 g, 4.92 mmol, 71%) as a colorless oil (Found: C, 76.43; H, 9.02. $C_{26}H_{36}O_2Si$ requires C, 76.42; H, 8.88%); $[\alpha]^{22}_D$ −13.1 (*c* 3.22, $CHCl_3$); R_f 0.30 (petroleum ether−ethyl acetate, 9:1); ν_{max}/cm^{-1} 3448, 2960, 2931, 2858, 1472, 1428, 1121, 1080, 823, 740, 702, 614; δ_H (400 MHz, $CDCl_3$) 1.05 (9 H, s), 1.07 (3 H, d, *J* 7.0), 2.04 (1 H, dd, *J* 14.0, 9.5), 2.19−2.23 (3 H, m), 2.35 (1 H, broad sex, *J* 7.0), 3.49 (1 H, dd, *J* 10.0, 7.0), 3.62 (1 H, dd, *J* 10.0, 6.0), 3.71 (1 H, dddd, *J* 9.5, 6.0, 6.0, 4.5), 4.93 (1 H, s), 4.94 (1 H, s), 5.09−5.14 (2 H, m), 5.83 (1 H, ddt, *J* 17.0, 10.5, 7.0), 7.35−7.43 (6 H, m), 7.64−7.68 (4 H, m); δ_C (100 MHz, $CDCl_3$) 16.7, 19.2, 26.8, 41.4, 43.6, 68.2, 68.5, 112.7, 117.5, 127.6, 129.6, 133.6, 133.7, 134.9, 135.6, 135.6, 148.8.

(8*E*,12*E*)-(4*S*,7*R*,14*R*,15*S*)-3,7-Dihydroxy-4,15,16-trimethyl-5,11-dimethyle ne-14-triisopropylsilanyloxy-heptadeca-8,12,16-trienoic acid *tert*-butyl ester (70). Conditions of Table 4, entry 7: A dry flask was charged with alkene **55** (2.8:1 d.r., 83 mg, 0.292 mmol) and alkyne **25** (20 mg, 0.065 mmol) and flushed with argon. Methanol (1.1 mL) was added, followed with CpRu(COD)Cl (1.0 mg, 0.003 mmol) and NH_4PF_6 (1.0 mg, 0.006 mmol), and the mixture was heated to reflux over 10 min. After 75 min, the mixture was allowed to cool and concentrated in vacuo. Purification by flash silica gel column chromatography (petroleum ether−ethyl acetate, 4:1 to 7:3) afforded some recovered alkene **55** (72 mg, 0.252 mmol) and the ester **70** (24 mg, 0.040 mmol, 61%) as a yellow oil and an inseparable 2.8:1 mixture of *C*-3 epimers (Found: C, 71.01; H, 10.77. $C_{35}H_{62}O_5Si$ requires C, 71.14; H, 10.57%); $[\alpha]^{22}_D$ −6.0 (*c* 4.06, $CHCl_3$); R_f 0.39 (petroleum ether−ethyl acetate, 7:3); ν_{max}/cm^{-1} 3427, 2966, 2942, 2867, 1729, 1462, 1368, 1255, 1154, 1059, 970, 884; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.97 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.10 (3 H, d, *J* 7.0), 1.45 (1.46) (9 H, s), 1.75 (3 H, s), 2.21 (1 H, dd, *J* 14.5, 9.0), 2.18−2.40 (3 H, m), 2.36 (1 H, dd, *J* 16.0, 9.0), 2.42 (2.49) (1 H, dd, *J* 16.0, 3.5 (2.5)), 2.90 (2 H, d, *J* 6.5), 3.97 (1 H, ddd, *J* 9.0, 5.5, 3.5), 4.21−4.30 (1 H, m), 4.36 (1 H, broad t, *J* 5.5), 4.70 (1 H, s), 4.78 (1 H, s), 4.93 (1 H, s), 4.98 (1 H, s), 4.99 (1 H, s), 5.04 (5.02) (1 H, s), 5.53−5.58 (1 H, m), 5.62 (1 H, dd, *J* 16.0, 7.0), 5.73−5.79 (1 H, m), 6.16 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$, minor diastereomer in brackets) 12.5, 13.3, 14.9 (15.6), 18.1 (18.1), 21.8, 28.1(29.7), 35.0, 39.9 (39.5), 44.0 (43.9), 44.2 (45.3), 47.8, 70.3 (71.2), 70.4 (70.9), 75.5, 81.2, 111.5, 113.8 (114.1), 115.7, 129.2 (128.8), 130.5, 131.9, 133.8 (133.9), 143.9, 146.9, 148.2 (148.3), 172.5.

Conditions of Table 4, entry 9: To a solution of alkyne **25** (13 mg, 0.042 mmol) and alkene **55** (2.8:1 d.r., 54 mg, 0.190 mmol) in dry acetone (0.7 mL) at 0 °C was added $[CpRu(CH_3CN)_3]PF_6$ (1.8 mg, 0.004 mmol). The mixture was warmed to r.t. and stirred for 15 h, whereupon it was concentrated in vacuo. The residue was purified by silica gel flash chromatography (petroleum ether−ethyl acetate, 30%) to afford some recovered alkene **55** (43 mg, 0.151 mmol) and the ester **70** (18 mg, 0.030 mmol, 72%) as a yellow oil and an inseparable 2.8:1 mixture of *C*-3 epimers.

4-((1*S*,4*S*)-4-Hydroxy-1-methyl-2-methylene-hept-6-enyl)-oxetan-2-one (79). To a solution of DMSO (1.68 g, 21.56 mmol) in CH_2Cl_2 (75 mL) at −78 °C was added oxalyl chloride (1.36 g, 10.77 mmol), and the mixture was stirred for 20 min, whereupon a solution of alcohol **53** (1.54 g, 5.41 mmol) was added dropwise. After another 20 min at −78 °C, triethylamine (3.26 g, 32.29 mmol) was added and the cooling bath was removed. Upon reaching 0 °C, the mixture was partitioned between ether and saturated aqueous NH_4Cl. The organic phase was washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude aldehyde (**45**), which was obtained as a yellow oil (1.55 g), was immediately redissolved in CH_2Cl_2 (50 mL) and cooled to −78 °C. Me_2AlCl (1.0 M in hexanes, 5.4 mL, 5.4 mmol) was added over 5 min. The bright yellow mixture was stirred for 3 min, whereupon neat trimethylsilylketene (0.65 g, 5.72 mmol) was added dropwise. After another 30 min, 0.5 M aqueous $NaHSO_4$ (20 mL) and ether (100 mL) were added and the mixture was allowed to warm to r.t. with vigorous stirring. Additional 0.5 M aqueous $NaHSO_4$ (150 mL) and ether (100 mL) were added, and the two clear phases were separated. The organic phase was washed with brine (100 mL), and the combined organic phase was back-extracted with ether (2 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The yellow residue (**81**, 2.15 g) was taken up in acetonitrile (60 mL) and $KF{\cdot}2H_2O$ (0.76 g, 8.06 mmol) was added. The mixture was vigorously stirred for 1 h, whereupon it was cooled to 0 °C. Aqueous 49% HF (13 mL, 364 mmol) was added dropwise, and the mixture was stirred at 0 °C for 30 min. After dilution with ether (100 mL), solid $NaHCO_3$ (30 g) was added portionwise over 5 min. After stirring for another 5 min, the mixture was filtered through a sintered funnel packed with $MgSO_4$. The solids were well rinsed with ether and the combined filtrate was concentrated in vacuo. The residue was purified by silica gel flash chromatography (petroleum ether−ethyl acetate, 7:3 to 3:2) to afford the lactone **79** (0.78 g, 3.71 mmol, 69%) as a yellow oil and a 1.6:1 mixture of separable diastereomers (Found: M^+, 210.1254. $C_{12}H_{18}O_3$ requires M 210.1256, 0.7 ppm, EIMS);

One *C*-3 Epimer: $[\alpha]^{26}_D$ +20.8 (*c* 1.73, $CHCl_3$); R_f 0.19 (petroleum ether−ethyl acetate, 7:3); ν_{max}/cm^{-1} 3417, 2924, 1827, 1642, 1412, 1278, 1127, 914, 867; δ_H (400 MHz, $CDCl_3$) 1.22 (3 H, d, *J* 7.0), 2.14−2.35 (4 H, m), 2.50 (1 H, br. quin, *J* 7.0), 3.15 (1 H, dd, *J* 16.5, 4.5), 3.45 (1 H, dd, *J* 16.5, 6.5), 3.77−3.83 (1 H, m), 4.45 (1 H, ddd, *J* 8.5, 6.5, 4.5), 4.94 (1 H, s), 5.04 (1 H, s), 5.16 (1 H, d, *J* 18.0), 5.17 (1 H, d, *J* 11.0), 5.33 (1 H, dddd, *J* 18.0, 11.0, 7.5, 7.0); δ_C (100 MHz, $CDCl_3$) 16.1, 41.6, 41.8, 43.1, 43.7, 68.9, 73.8, 113.9, 118.6, 134.2, 146.5, 168.1.

Other *C*-3 Epimer: $[\alpha]^{26}_D$ −14.4 (*c* 1.4, $CHCl_3$); R_f 0.13 (petroleum ether−ethyl acetate, 7:3); ν_{max}/cm^{-1} 3417, 2933, 1827, 1642, 1412, 1278, 1127, 913, 869; δ_H (500 MHz, $CDCl_3$) 1.10 (3 H, d, *J* 7.0), 2.16−2.26 (3 H, m), 2.29−2.34 (2 H, m), 2.52−2.58 (1 H, m), 3.13 (1 H, dd, *J* 16.5, 4.5), 3.48 (1 H, dd, *J* 16.5, 6.0), 3.78−3.83 (1 H, m), 4.46 (1 H, ddd, *J* 8.0, 6.0, 4.5), 5.05 (1 H, s), 5.06 (1 H, s), 5.12−5.17 (2 H, m), 5.80−5.89 (1 H, m); δ_C (125 MHz, $CDCl_3$) 14.7, 41.4, 41.6, 43.0, 43.1, 68.6, 73.4, 114.0, 118.2, 134.4, 146.3, 167.8.

4-((5*E*,9*E*)-(1*S*,4*R*,11*R*,12*S*)-4-Hydroxy-1,12,13-trimethyl-2,8-dimethylene-11-triisopropylsilanyloxy-tetradeca-5,9,13-trienyl)-oxetan-2-one (78). To a solution of alkyne **25** (42 mg, 0.137 mmol) and alkene **79** (1.6:1 d.r., 100 mg, 0.475 mmol) in dry acetone (2.5 mL) at 0 °C was added $[CpRu(CH_3CN)_3]PF_6$ (6.0 mg, 0.0138 mmol). The mixture was warmed to r.t. and stirred for 13 h, whereupon it was concentrated in vacuo. The residue was purified by silica gel flash chromatography (petroleum ether−ethyl acetate, 20 to 40%) to afford some recovered **79** (62 mg, 0.295 mmol, 87%) and the lactone **78** (52 mg, 0.100 mmol, 75%) as a yellow oil and a 1.6:1 mixture of *C*-3 epimers (Found: $[M + Na]^+$, 539.3517. $C_{31}H_{52}O_4Si$ requires M + Na 539.3533, 2.9 ppm, ESIMS); $[\alpha]^{26}_D$ −0.2 (*c* 0.85, $CHCl_3$); R_f 0.40 (petroleum ether−ethyl acetate, 7:3); ν_{max}/cm^{-1} 3441, 2943, 2866, 1831, 1645, 1462, 1374, 1125, 1059, 970, 882; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.97 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.20 (1.09) (3 H, d, *J* 7.0), 1.75 (3 H, s), 2.18−2.33 (2 H, m), 2.38 (1 H, br quin., *J* 7.0), 2.90 (2 H, d, *J* 6.5), 3.12 (3.13) (1 H, dd, *J* 16.5, 4.5), 3.42 (3.45) (1 H, dd, *J* 16.5, 5.5), 4.20−4.25 (1 H, m), 4.35−4.38 (1 H, m), 4.43 (4.46) (1 H, ddd, *J* 7.0, 5.5, 4.5), 4.69 (1 H, s), 4.78 (1 H, s), 4.91 (2 H, s), 4.98 (5.03) (1 H, s), 5.02 (5.06) (1 H, s), 5.53 (5.55) (1 H, dd, *J* 15.0, 7.0), 5.61 (5.62) (1 H, dd, *J* 16.0, 6.5), 5.76 (5.76) (1 H, dt, *J* 15.0, 7.0), 6.16 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$, minor diastereomer in brackets) 12.4, 13.2 (13.3), 16.0, 18.1, 21.8, 35.0, 41.6 (41.2), 43.4 (42.9), 43.8 (43.6), 47.7, 71.1 (70.6), 73.8 (73.3), 75.3 (75.4), 111.4, 113.9 (114.1), 115.7, 129.6 (129.3), 130.5 (130.4), 131.8 (131.9), 133.7 (133.6), 143.7 (143.8), 146.0 (145.7), 146.9, 168.1 (167.8).

(5*S*,8*R*)-8-[(2*S*,3*R*)-3-((*E*)-(5*R*,6*S*)-6,7-Dimethyl-2-methylene-5-triisopropyl silanyloxy-octa-3,7-dienyl)-oxiranyl]-4-hydroxy-5-methyl-6-methylene-oxocan -2-one (86). Lactone **77** (1:1 mixture of *C*-3 epimers, 128 mg, 0.240 mmol) and distannoxane **85** (14 mg, 0.011 mmol) were placed in a dry flask, and dry hexane (120 mL) was added. The mixture was stirred at reflux for 1 h, cooled and concentrated in vacuo. The residue was purified by silica gel flash chromatography (petroleum ether−ethyl acetate, 17:3) to afford the lactone **86** (119 mg, 0.223 mmol, 93%) as a pale yellow oil and an inseparable 1:1 mixture of *C*-3 epimers (Found: M^+, 532.3567. $C_{31}H_{52}O_5Si$ requires M 532.3584, 3.2 ppm, EIMS); $[\alpha]^{25}_D$ +26.0 (*c* 1.93, $CHCl_3$); R_f 0.21 (petroleum ether−ethyl acetate, 7:3); ν_{max}/cm^{-1} 3448, 2943, 2886, 1732, 1644, 1462, 1373, 1251, 1162, 1127, 1102, 1059, 1014, 992, 987, 884; EIMS *m*/*z* 532 (M^+, 3), 463 $[(M - C_5H_9]^+$, 100);

One *C*-3 Epimer: δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.18 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.10 (1 H, dq, *J* 9.5, 7.0), 2.37−2.54 (4 H, m), 2.52 (1 H, dd, *J* 11.5, 7.0), 2.55 (1 H, dd, *J* 13.5, 3.0), 2.71 (1 H, dd, *J* 11.5, 5.0), 2.89 (1 H, dd, *J* 5.5, 2.5), 3.11 (1 H, td, *J* 5.5, 2.0), 3.66 (1 H, m), 4.25 (1 H, ddd, *J* 11.0, 5.5, 2.0), 4.40 (1 H, br. t, *J* 6.0), 4.68 (1 H, br. s), 4.78 (1 H, br. s), 5.03 (1 H, br. s), 5.06 (1 H, br. s), 5.07 (1 H, br. s), 5.12 (1 H, br. s), 5.60 (1 H, dd, *J* 16.0, 6.5), 6.20 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$) 12.4, 13.0, 18.1, 21.9, 34.17, 37.9, 41.2, 42.7, 45.0, 47.6, 56.4, 58.4, 73.3, 75.1, 81.1, 111.5, 116.7, 118.9, 130.64, 131.8, 140.8, 144.9, 146.8, 171.7.

Other *C*-3 Epimer: δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.23 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.01 (1 H, dq, *J* 9.5, 7.0), 2.37−2.54 (4 H, m), 2.49 (1 H, dd, *J* 12.5, 5.0), 2.61 (1 H, dd, *J* 14.0, 1.5), 2.91 (1 H, dd, *J* 5.0, 2.0), 2.97 (1 H, dd, *J* 12.5, 4.0), 3.14 (1 H, ddd, *J* 6.0, 5.0, 2.0), 4.10 (1 H, m), 4.40 (1 H, br. t, *J* 6.0), 4.59 (1 H, ddd, *J* 11.0, 5.0, 2.5), 4.68 (1 H, br. s), 4.78 (1 H, br. s), 5.07 (2 H, br. s), 5.12 (1 H, br. s), 5.21 (1 H, br. s), 5.60 (1 H, dd, *J* 16.0, 6.5), 6.20 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$) 12.4, 13.0, 18.1, 21.9, 34.21, 37.9, 41.2, 42.8, 43.7, 47.6, 55.8, 58.5, 73.3, 75.1, 79.3, 111.5, 116.1, 118.9, 130.68, 131.8, 140.8, 144.9, 147.4, 172.2.

Amphidinolide P (1). Lactone **88** (14.0 mg, 0.037 mmol) and distannoxane **85** (9 mg, 0.007 mmol) were placed in a dry flask, and dry hexane (37 mL) was added. The mixture was stirred at reflux for 8 h, cooled, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (petroleum ether−ether, 17:3) to afford amphidinolide P (**1**) (11.7 mg, 0.031 mmol, 84%) as a colorless oil; $[\alpha]^{23}_D$ −27.4 (*c* 0.17, MeOH); R_f 0.35 (petroleum ether−ethyl acetate, 17:3); ν_{max}/cm^{-1} 3482, 3084, 2971, 2942, 1712, 1650, 1433, 1376, 1361, 1291, 1243, 1189, 1111, 988, 967, 896; δ_H (500 MHz, C_6D_6) 0.91 (3 H, d, *J* 7.0), 0.92 (3 H, d, *J* 7.0), 1.67 (3 H, br. s), 1.93−1.96 (1 H, m), 2.10 (1 H, dd, *J* 12.7, 11.5), 2.17 (1 H, br. dd, *J* 13.5, 9.5), 2.27 (1 H, d, *J* 12.0), 2.36 (1 H, d, *J* 12.0), 2.43 (1 H, dq, *J* 9.5, 7.0), 2.48 (1 H, dt, *J* 9.5, 1.5), 2.52 (1 H, dd, *J* 12.7, 2.7), 2.62 (1 H, dd, *J* 8.5, 1.5), 2.68 (1 H, br. d, *J* 13.5), 3.47 (1 H, ddd, *J* 11.5, 8.5, 2.7), 4.27 (1 H, d, *J* 2.0), 4.77 (1 H, m), 4.81 (1 H, br. s), 4.81−4.82 (1 H, m), 4.87−4.89 (1 H, m), 4.89−4.90 (1 H, m), 4.94 (1 H, m), 5.29 (1 H, br. t, *J* 8.5), 5.60 (1 H, dd, *J* 16.2, 7.5), 6.20 (1 H, d, *J* 16.2); δ_C (125 MHz, C_6D_6) 11.8, 16.1, 19.5, 36.3, 39.4, 45.0 (−2), 45.2, 58.2, 62.7, 73.5, 78.5, 99.2, 110.0, 112.3, 118.2, 129.1, 133.6, 142.2, 143.7, 146.5, 172.4.

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Supporting Information Available: Experimental procedures and characterization data for compounds **6**−**11**, **14**−**28**, **32**, **35**−**42**, **44**−**47**, **49**, **50**, **52**−**55**, **64**−**66**, **70**, **77**−**79**, **82**, **83**, **86**−**88** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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