JOC*Article*

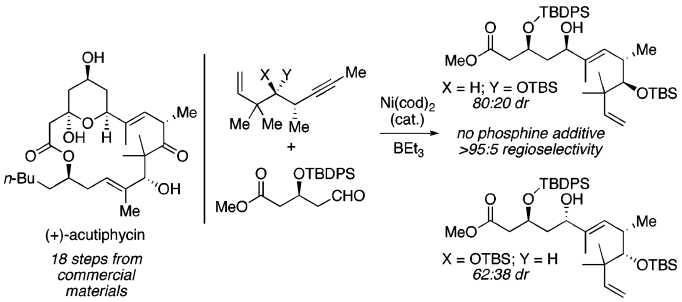
Total Synthesis of (+)-Acutiphycin†

Ryan M. Moslin and Timothy F. Jamison*

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

tfj@mit.edu

Received August 30, 2007



Synthetic studies toward the total synthesis of (+)-acutiphycin (**1**) resulted in the discovery of additive-free, highly regioselective nickel-catalyzed reductive coupling reactions of aldehydes and 1,6-enynes and the construction of an advanced intermediate in studies directed toward the synthesis of **1**. Ultimately, although not employing the nickel-catalyzed reaction, a highly convergent total synthesis of (+)-acutiphycin featuring an intermolecular SmI_2-mediated Reformatsky coupling reaction and macrolactonization initiated by a retro-ene reaction of an alkoxyalkyne was achieved. The resulting synthesis was 18 steps in the longest linear sequence from either methyl acetoacetate or isobutyraldehyde.

Introduction

The complex macrolide (+)-acutiphycin (**1**) was isolated in 1984 by Moore and co-workers and possesses potent in vivo antineoplastic activity against murine Lewis lung carcinoma, as well as significant cytotoxicity against KB and NIH/3T3 cell lines.[1] Since the natural source of acutiphycin (the blue-green alga *Oscillatoria acutissima*) no longer produces this metabolite, detailed investigations of its mechanism of action and therapeutic potential have been very limited, and further studies must be fueled by chemical synthesis. Smith et al. reported the first total synthesis of **1** in 1995,[2] and a series of studies directed toward the total synthesis of **1** have also been described by Kiyooka et al.[3] The strategies employed in both the Smith et al. synthesis and the Kiyooka et al. approach are linear in nature, whereas we recently reported the first convergent total synthesis of (+)-acutiphycin.[4] Herein, we describe our initial strategy for the total synthesis of (+)-acutiphycin and the discoveries that resulted from this approach. A detailed description of the successful route to (+)-acutiphycin is also provided.

The nickel-catalyzed reductive coupling of alkynes and aldehydes[5] has been shown to be a versatile tool in the synthesis of natural products.[6] Although regioselectivity is optimal for aromatic alkynes[7] (Scheme 1, eq 1) and 1,3-enynes (Scheme 1, eq 2),[8] good levels of regiocontrol have also been ob-

* Corresponding author. Fax: (617) 324-0253.

† This work is dedicated to Prof. Edward Piers on the occasion of his 70th birthday.

(1) Barchi, J. J., Jr.; Moore, R. E.; Patterson, F. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193−8197.

(2) (a) Smith, A. B., III; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013−12014. (b) Smith, A. B., III; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc*. **1997**, *119*, 10935−10946.

(3) (a) Hena, M. A.; Kim, C.-S.; Horiike, M.; Kiyooka, S.-i. *Tetrahedron Lett.* **1999**, *40*, 1161−1164. (b) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511−5523.

(4) Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106−15107.

(5) For a review of nickel-catalyzed coupling processes, see: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908. (b) Moslin, R. M.; Miller-Moslin, K. M.; Jamison, T. F. *Chem. Comm.* **2007**, 4441−4449.

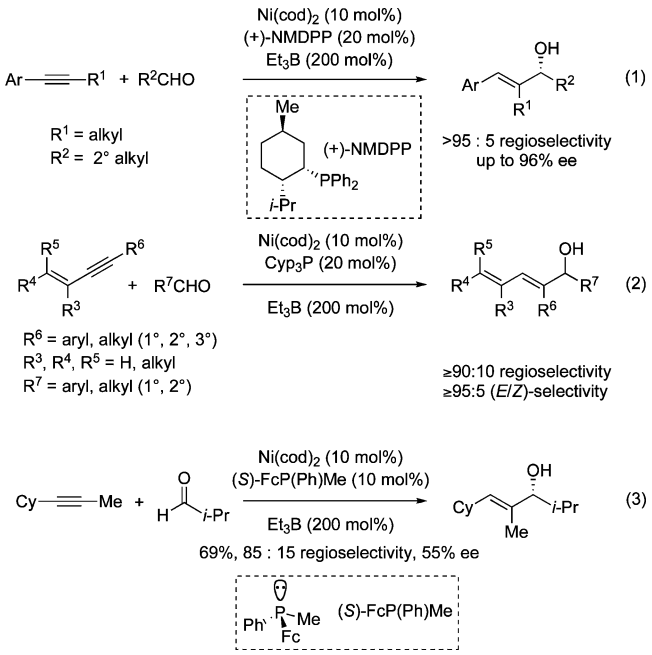
(6) For representative examples of nickel-catalyzed reductive coupling reactions of aldehydes and alkynes in total synthesis: (a) Synthesis of (+)-allopumiliotoxin 339A: Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098−6099. (b) Synthesis of (−)-terpestacin: Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514−11515. (c) Synthesis of (+)-amphidinolide T1: Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998−999.

(7) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443.

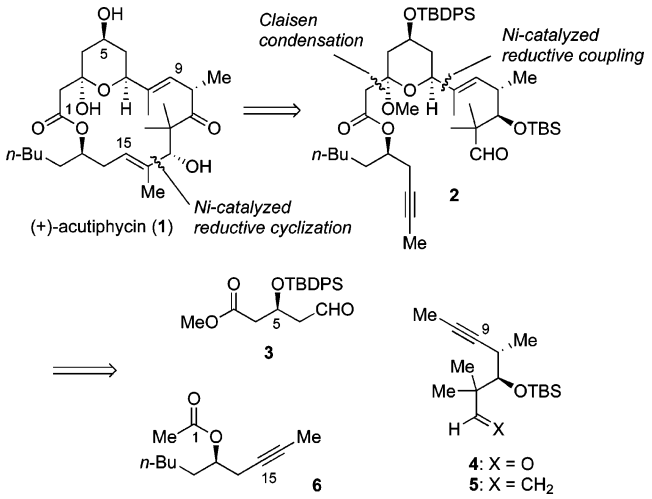
(8) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc*. **2004**, *126*, 15342−15343.

10.1021/jo701821h CCC: $37.00
Published on Web 11/07/2007

SCHEME 1. Nickel-Catalyzed Reductive Coupling Reactions of Alkynes



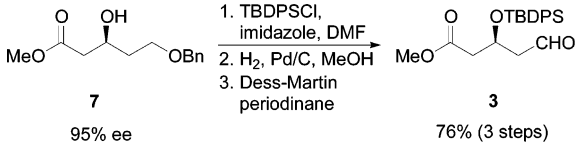
SCHEME 2. Retrosynthetic Analysis of (+)-Acutiphycin



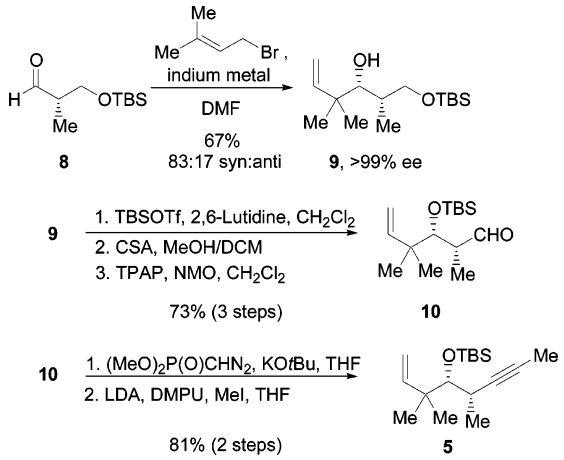
served for alkynes containing two distinct alkyl substituents (Scheme 1, eq 3).[9] All of these transformations give exclusive syn additionto the alkyne, resulting in the formation of (E)-trisubstituted allylic alcohols, and allows for the possibility of catalyst and/or reagent control. In our initial approach to (+)-acutiphycin, we intended to form both of the (E)-trisubstituted olefins and to establish the configurations at C7 and C13 using these catalytic processes (Scheme 2). In addition, due to the challenges associated with macrolactonization en route to **1**,[2b] we initially investigated an alternative C−C bond-forming strategy to close the macrocycle: nickel-catalyzed reductive macrocyclization. Although we considered both reductive coupling reactions to be challenging, the C14−C15 bond was targeted for the ring closing step since the range of oxidation states present along the C1−C7 backbone would make it difficult to reveal the C7 aldehyde. In contrast, the remaining C−C bond would be formed via Claisen condensation with acetate **6**.

(9) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156−166.

SCHEME 3. Synthesis of Aldehyde Fragment 3



SCHEME 4. Synthesis of Enyne 5 via Indium-Mediated Addition of Prenyl Bromide



Results and Discussion

The synthesis of the C2−C7 fragment began with enantiomerically enriched **7**,[10] a well-known intermediate available by alkylation of methyl acetoacetate and subsequent asymmetric reduction (Scheme 3).[11,12] Protection of **7** as the silyl ether followed by reductive debenzylation and oxidation provided **3**. Although hydroxyl groups have been shown to direct addition to aldehydes via chelation,[13] we chose a nonchelating protective group, *tert*-butyldiphenylsilyl (TBDPS), since chelation control via hydroxyl groups has not, to date, been demonstrated in nickel-catalyzed reductive coupling reactions of alkynes and aldehydes.[14]

As shown in Scheme 4, enyne **5** (X = CH_2) was selected rather than **4** (X = O) to avoid competitive reductive cyclization during the fragment coupling with **3**, as well as other competing reactions in the Claisen condensation with **6**. After the reductive coupling step, oxidative cleavage of the terminal olefin reveals the necessary aldehyde functional group. Additionally, although C11 is in the ketone oxidation state in the natural product, the potential for epimerization[2,3] at C10 and other complications suggested that the prudent choice would be to mask C11 as a protected hydroxyl group. The synthesis of **5** began with indium-mediated addition of prenyl bromide to **8**, a commonly used derivative of the Roche ester,[15] to give **9** (Scheme 4).[16,17]

(10) Available in two steps from methyl acetoacetate: Eggen, M.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem.* **2000**, *65*, 7792−7799.

(11) (a) Lee, B. H.; Biswas, A.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 106−109. (b) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157−2164.

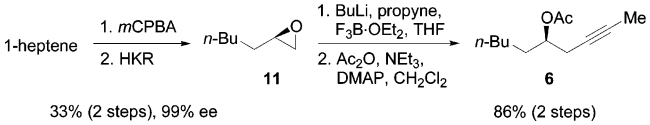
(12) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994; p 56.

(13) For a review of chelation-controlled additions to aldehydes, see: Reetz, M. T. *Angew. Chem., Int. Ed.* **1984**, *23*, 556−569.

(14) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937−2940.

(15) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348−6359.

SCHEME 5. Synthesis of Alkyne 6 via HKR



SCHEME 6. Nickel-Catalyzed Reductive Coupling Reactions of 1,6-Enyne 5

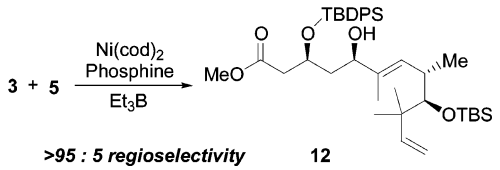


TABLE 1. Discovery of an Olefin-Directing Effect in 1,6-Enynes[a]

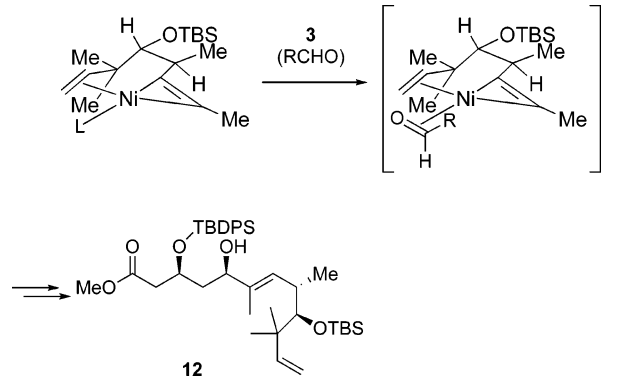
entry	phosphine	yield (%)	dr[b]
1	(+)-NMDPP	39	80:20
2	(−)-NMDPP	45	77:23
3	P(*o*-anisyl)$_3$	52	80:20
4	None	84	80:20

[a] In all cases, the reaction was run neat in 350 mol % Et_3B using 10 mol % $Ni(cod)_2$ and (if employed) 10 mol % phosphine. [b] Determined by ^1H NMR.

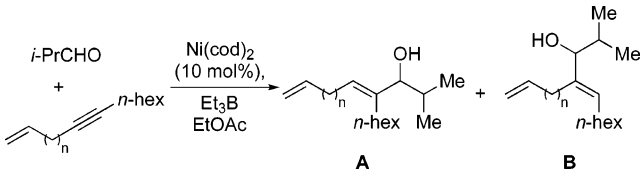
Protection of the secondary alcohol followed by selective deprotection of the primary alcohol and the Ley oxidation[18] provided **10** in good yield over 3 steps. Treatment of **10** with the Seyferth−Gilbert reagent[19] provided a terminal alkyne that was then methylated to yield **5**. The third necessary fragment was available from racemic heptene oxide by way of Jacobsen's hydrolytic kinetic resolution (Scheme 5).[20] Addition of a lithium anion derived from propyne to **11** and subsequent conversion to the acetate ester provided **6**.

Studies of Nickel-Catalyzed Reductive Fragment Coupling Operations. On the basis of data obtained in early model studies,[21] we reasoned that (+)-neomenthyldiphenylphosphine ((+)-NMDPP) would be an excellent candidate ligand for stereoselective reductive coupling of **3** and **5** (Scheme 6 and Table 1, entry 1). Although the regioselectivity was much greater than expected,[22] the yield in these reactions was disappointingly low. Moreover, the diastereoselectivity was largely invariant with respect to the ligand, as demonstrated by the fact that both the other enantiomers of NMDPP and an achiral ligand provided the same sense and essentially the same degree of diastereoselectivity (Table 1, entries 2 and 3). The latter result was most unexpected and prompted us to test the reaction in the absence of a phosphine ligand. Not only was this reaction effective, but a significant increase in yield was observed, and the high degree of regio- and diastereocontrol was maintained (Table 1, entry 4). The success of this coupling stands in stark contrast to all of our previous experience with this chemistry, in which we had never observed any coupling product in the absence of a phosphine ligand.

SCHEME 7. Possible Binding Mode of 1,6-Enyne 5



SCHEME 8. Directing Effects of Tethered Alkenes

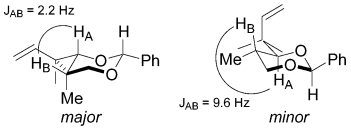


Knochel et al. had previously reported the favorable interaction of a distal alkene in nickel-catalyzed cross-coupling reactions of alkyl halides with dialkylzinc reagents.[23] On the basis of our own results and this precedent, we proposed that the terminal olefin was coordinating to the nickel center, forcing the aldehyde to bind adjacent to carbon *a* (Scheme 7).[24] This hypothesis was studied in more detail, and we have since determined that the high regioselectivity in phosphine-free nickel-catalyzed reductive coupling reactions is general for and specific to 1,6-enynes, while other enynes failed to react (Scheme 8 and Table 2).[25]

Unfortunately, the major diastereomer observed in the coupling of **3** and **5** was of the opposite configuration to that found in **1**. As the use of a phosphine additive was detrimental to reaction yield and the possibility of achieving efficient reagent control was limited, we were left to consider the impact of the stereocenters of **3** and **5**. As C11 is a ketone in (+)-acutiphycin, we had the luxury of using *epi*-C(11)-**5** (**13**). To probe the

(16) Arakis, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831−1833.

(17) Relative stereochemistry was assigned by comparison of coupling constants of the benzylidine derivatives of the major and minor diastereomers.



(18) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.

(19) (a) Seyferth, D.; Hilbert, P.; Marmor, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 4811−4812. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997−4998.

(20) (a) Tokunaga, M.; Larrow, J. F.; Kakuchi, F.; Jacobsen, E. N. *Science (Washington, DC, U.S.)* **1997**, *277*, 936−938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(21) The model study featured 1-cyclohexyl-propyne and (±)-3-(*t*-butyldimethyl-silanyloxy)-3-phenyl-propionaldehyde and gave 77% yield, with 69:31 regioselectivity and 71:29 dr using (+)-NMDPP.

(22) The highest selectivity observed with an alkyne featuring a 2° and a 1° terminus is 85:15 (Scheme 1; eq 3), and frequently lower selectivity is observed. See ref 9.

(23) (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723−2725. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544−3553.

(24) The orientation of the aldehyde and mode of diastereoinduction has not been fully elucidated.

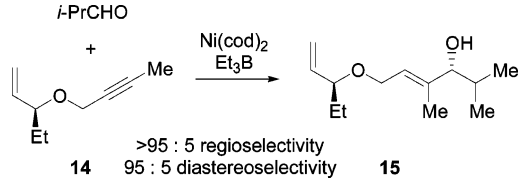
(25) It was also determined that regioselectivity was reversed by the addition of $PCyp_3$. For complete details, see: (a) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342−15343. (b) Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 7598−7610.

TABLE 2. Directing Effects of Tethered Alkenes[a]

entry	enyne	*N*	yield (%)	regioselectivity (**A**/**B**)[b]
1	1,3-	0	<5	n.d.
2	1,4-	1	<5	n.d.
3	1,5-	2	<5	n.d.
4	1,6-	3	53	>95:5
5	1,7-	4	<5	n.d.

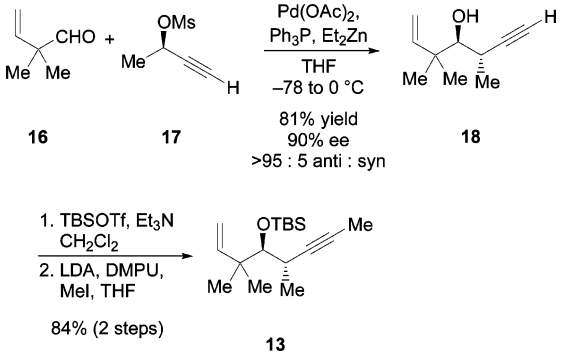
[a] Standard procedure: alkyne (0.50 mmol) was added to a 0 °C solution of $Ni(cod)_2$ (0.05 mmol), *i*PrCHO (1.00 mmol), and Et_3B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir for 15 h at room temperature. [b] Determined by ^1H NMR and/or GC.

SCHEME 9. Diastereselective Reductive Coupling Reaction of 1,6-Enyne 14



14 15

SCHEME 10. Synthesis of 1,6-Enyne 13 via Marshall Coupling

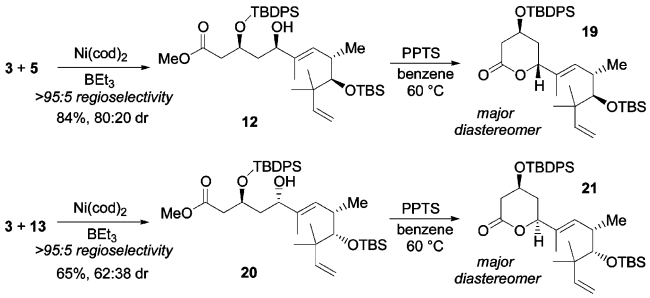


16 17 18 13

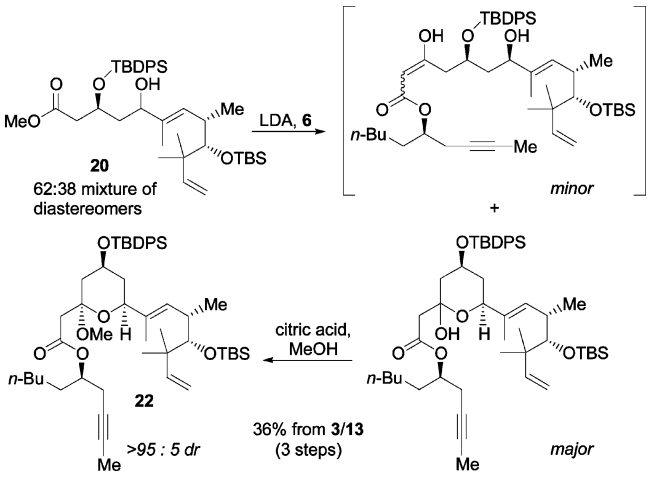
hypothesis that chiral centers on the tether of a 1,6-enyne might influence the diastereoselectivity in nickel-catalyzed reductive coupling reactions of aldehydes and 1,6-enynes, we first synthesized model substrate **14** and investigated it in a reductive coupling with isobutyraldehyde (Scheme 9).[26]

Since **15** was isolated as a single regioisomer and 95:5 diastereoselectivity was observed, the reductive coupling study of **14** clearly demonstrated the impact of chiral centers on the tether of a 1,6-enyne on the stereochemical outcome of coupling reactions. With this result in hand, we prepared **13**, in which the C11 stereocenter on the tether of our 1,6-enyne fragment had been inverted, using Marshall coupling[27] of aldehyde **16**[28] and propargylic mesylate **17**[29] (Scheme 10). Despite the steric bulk of aldehyde **16**, this Marshall coupling proceeded with excellent yield and enantioselectivity to afford the desired anti product **18** as the only observable diastereomer. Protection and methylation then provided **13** in six linear steps from tiglic acid.

SCHEME 11. Phosphine-Free Nickel-Catalyzed Reductive Coupling Reactions



SCHEME 12. Claisen Condensation to Macrocyclic Precursor 22



Gratifyingly, **13** coupled with **3** in a manner analogous to **5**, in this way providing the desired (*S*)-allylic alcohol as the major product (Scheme 11). The diastereomeric alcohols were then converted to their corresponding lactones with PPTS to enable their chromatographic separation and characterization.[30] The strong dependence of diastereoselectivity on the configuration of the remote C11 stereocenter provides further evidence of olefin coordination to the metal center. It is also noteworthy that this coordination appears to be favorable despite the considerable steric bulk along the tether of the 1,6-enyne.

Consequences of the 1,6-Enyne Approach to (+)-Acutiphycin. Allylic alcohol **20** was carried on to the Claisen condensation as a mixture of diastereomers (Scheme 12). Fortuitously, the undesired (minor) diastereomer failed to form the hemiketal and was easily separated from the desired (major) isomer by passing the crude material through a pad of silica. After methanolysis, **22** was obtained as a single diastereomer in 36% overall yield from **3** and **13**. This route thus afforded the entire carbon skeleton of (+)-acutiphycin in three consecutive steps. Unfortunately, conversion of the terminal olefin of **22** to the necessary aldehyde proved to be extremely challenging, as reaction at the C8−C9 olefin was observed exclusively under ozonolysis or epoxidation conditions. Although dihydroxylation was selective for the desired terminal olefin, conversion was very low (<10%) and failed to provide sufficient material to study subsequent steps.

Although the initial retrosynthetic plan for (+)-acutiphycin did not lead to the completion of the total synthesis, it revealed

(26) For synthesis of **14** and the mechanistic implications of this study, see: (a) Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 455−458. (b) Ref 23b.

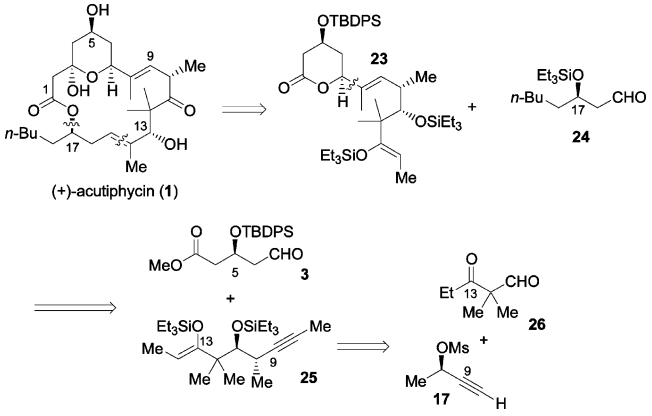
(27) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201−5204.

(28) Compound **15** is available in 3 steps from tiglic acid via deconjugative methylanation. Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron* **1998**, *54*, 4357−4366. See Supporting Information.

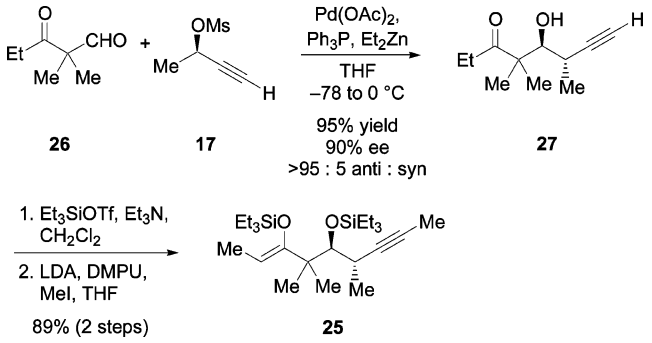
(29) Both enantiomers of 3-butyn-2-ol are commercially available and may also be prepared according to: Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825−7831.

(30) NOE analysis was used to confirm stereochemical assignments. See Supporting Information for details.

SCHEME 13. Revised Retrosynthetic Analysis of (+)-Acutiphycin



SCHEME 14. Synthesis of Silyl-enol Ether 25 via Marshall Coupling



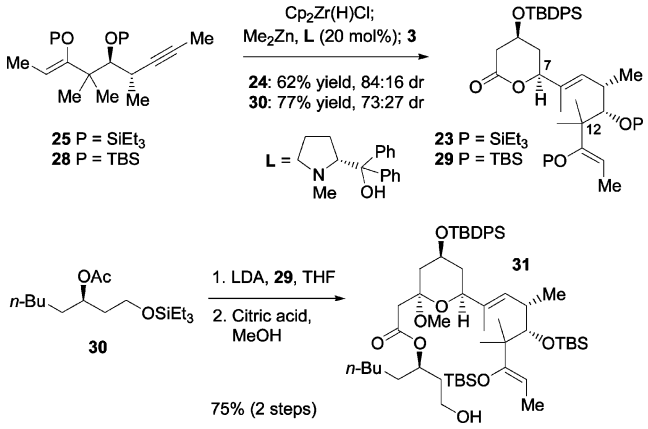
the general utility of 1,6-enynes as substrates for highly regioselective nickel-catalyzed reductive coupling reactions with aldehydes. Additionally, the phosphine-free nickel-catalyzed reductive coupling of **3** and **13** had successfully provided a challenging stereocenter and the (E)-trisubstituted olefin, while also serving as an effective fragment coupling.

Total Synthesis of (+)-Acutiphycin. The initial approach to (+)-acutiphycin allowed for efficient access to three complex fragments. In the revised approach, we sought to retain this convergence as much as possible. However, as the C13−C14 bond had proven to be a significant obstacle in our synthetic efforts, we decided to consider the C14−C15 olefin as an alternate disconnection (Scheme 13). The C7−C8 disconnection was retained, and both the C14−C15 bond and the ester linkage were considered candidates for ring closing. The C15−C22 and C3−C7 fragments were largely unchanged from our initial route; however, our 1,6-enyne now required a ketone functional group and two additional carbons. A silyl-enol ether (**25**) was targeted for its potential use in a Mukaiyama aldol strategy.

Once again, the Marshall coupling served as an excellent means to access homopropargylic alcohol **27** (Scheme 14). Although we were unaware of any precedent for performing the Marshall coupling in the presence of a ketone, this approach seemed viable since organozinc species react significantly more slowly with ketones than with aldehydes.[31] Indeed, the β-keto-aldehyde **26**[32] proved a viable substrate for these conditions, providing **27** as the anti diastereomer in excellent yield and

(31) For a review detailing the difficulties associated with asymmetric additions to ketones and the difficulties associated with this as compared to aldehydes, see: Betancort, J. M.; Garcia, C.; Walsh, P. J. *Synlett* **2004**, 749−760.

SCHEME 15. Consecutive Fragment Coupling Reactions of 25, 3, and 30



enantioselectivity.[33] Protection and methylation afforded **25** in 5 linear steps from isobutyraldehyde.

Ideally, the enol ether would act similarly to the terminal olefin of **13** in directing regioselectivity and diastereoselectivity of nickel-catalyzed reductive coupling reactions with **3**. Unfortunately, it was discovered that trisubstituted enol ethers were not suitable directors in phosphine-free nickel-catalyzed reductive coupling reactions.[34] However, both **25** and **28**[35] could be joined with **3** via the hydrozirconation−transmetallation chemistry of Wipf et al. (Scheme 15).[36] This sequence provided the (E)-trisubstituted allylic alcohols in excellent regioselectivity as easily separable mixtures of diastereomers, with the desired (*S*)-allylic alcohols (**23** and **29**) being favored.[37] A Claisen condensation with **30**[38] and subsequent methanolysis provided **31**. Oxidation of the primary alcohol to the aldehyde was successful; however, the resultant β-acetoxy aldehyde was prone to elimination, liberating a carboxylic acid. This sensitivity, coupled with the stability of the silyl-enol ether, prevented the use of a Mukaiyama aldol reaction to close the macrocycle.

Unanticipated Macrodiolide Formation. The SmI_2-promoted Reformatsky reaction was considered to be a milder way to access the necessary enolate equivalent.[39] Electrophilic bromination of **31** and subsequent oxidation of the primary alcohol afforded **32** (Scheme 16). Slow addition of **32** to a dilute solution of SmI_2 in THF at −78 °C resulted in the formation of a new product originally thought to be the desired macrocycle. However, exposure to Martin sulfurane[40] resulted in the forma-

(32) Available in 2 steps from isobutyraldehyde: Shiojii, K.; Kawaoka, H.; Miura, A.; Okuma, K. *Synth. Commun.* **2001**, *31*, 3569−3575.

(33) Determined by X-ray crystallography. See Supporting Information.

(34) Compound **24** as well as TMS, TBS, and acetate-enol ether were all tested with and without a phosphine additive, and in no case was the coupling product observed.

(35) Early work focused on TBS protecting groups, and although no problems were encountered with this protecting group, the triethylsilyl (TES) protecting group was chosen for later strategies to avoid anticipated difficulties in deprotection at the C11 site.

(36) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197−5200. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454−6455.

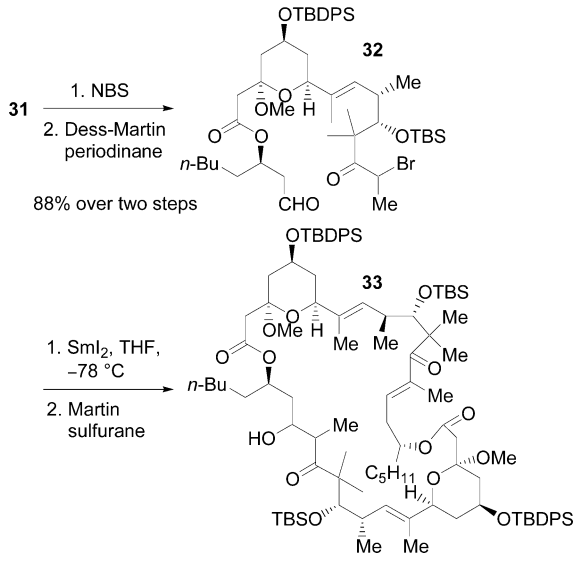
(37) Determined by NOE analysis. See Supporting Information.

(38) Synthesized in a manner analogous to **6**. See Supporting Information for details.

(39) For a discussion of SmI_2-mediated Reformatsky reactions including their remarkable preference to react intramolecularly even in the case of medium-ring lactones, see: (a) Tabuchi, T.; Kawamura, K.; Inanaga, J. *Tetrahedron Lett.* **1986**, *27*, 3889−3890. (b) Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371−6374.

(40) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003−5010.

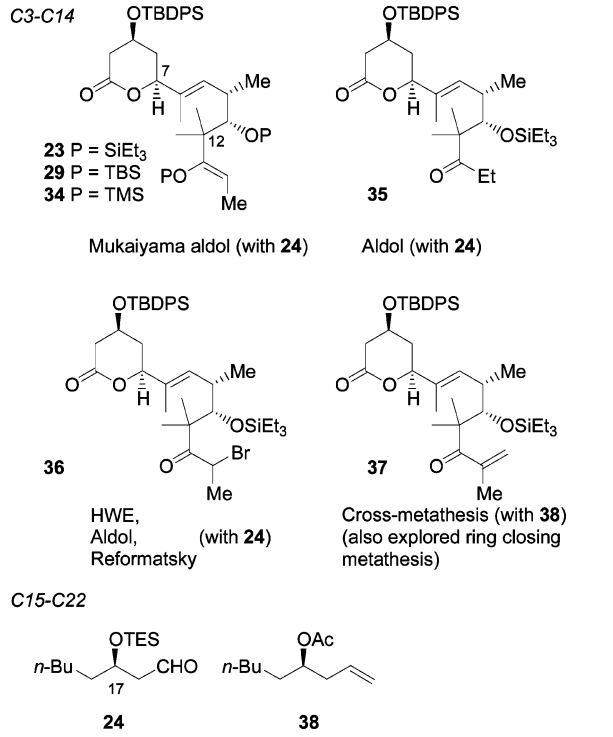
SCHEME 16. Unexpected Formation of the Macrodiolide



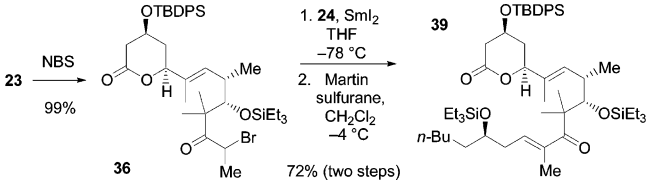
tion of a product that contained both the characteristic signals of an enone and of a β-hydroxy ketone in ^{1}H NMR. A HRMS determined that the exact mass of this compound was 1711.0651, which corresponds to the sum of the exact masses of a monomeric macrocyclic enone (846.5286) and a monomeric macrocyclic β-hydroxy ketone (864.5392).[41] Neither the mass of the monomeric enone nor the β-hydroxy ketone was observed in the mass spectrum. Consequently, it was concluded that the SmI_2 Reformatsky reaction had produced the macrodiolide (32-membered ring) and that the product obtained after the monodehydration was **33**.[42] This intermolecular coupling macrocylization sequence was very unexpected since the preference for intramolecular addition in SmI_2-mediated Reformatsky reactions is well-documented.[39,43]

Macrolactonization Based Strategy. Our focus then shifted to the formation of the C14−C15 olefin via an intermolecular strategy, with the intention of using macrolactonization to close the ring. Some of these strategies are briefly summarized by their respective fragments as shown in Scheme 17. The main obstacle in all these approaches was poor reactivity at the C14 center, due presumably to the steric bulk at C12. Originally, it was anticipated that the pK_a difference between an ester and a ketone would be sufficient to obtain selective enolate formation at C14. However, when the aldol reaction was explored with **35** and **36**, the C4 protons proved to be more easily abstracted than those at C14, resulting either in the elimination of the TBDPSO group or C−C bond formation between C4 and **24**. Therefore, strategies such as the Mukaiyama aldol, cross-metathesis, and Zn-mediated Reformatsky reactions, which include a built-in bias toward reactivity at C14, were considered. However, these systems simply proved to be unreactive and failed to provide any of the desired C−C bond. The Horner−Wadsworth−Emmons (HWE) strategy was not fully tested because of our inability to form the necessary β-keto-phosphonate from **36**, probably also due to the steric bulk at C12.

SCHEME 17. Summary of Fragment Coupling Attempts at C14−C15



SCHEME 18. SmI_2-Mediated Fragment Coupling Reaction



An unusual application of the Reformatsky reaction, however, provided an efficient and novel solution to this problem (Scheme 18). Electrophilic bromination of **23** provided the requisite α-bromoketone (**36**) in quantitative yield. While activated zinc had failed to generate the desired enolate,[44] SmI_2 did so, affording a β-hydroxy ketone derived from **36** and **24**[45] in excellent yield (90%, 1.0 mmol scale) as a mixture of diastereomers. Dehydration with the Martin sulfurane provided **39** in an overall yield of 72% over 2 steps.

While SmI_2 has been commonly employed in intramolecular Reformatsky reactions, its use in intermolecular cases has been extremely limited due to the numerous side reactions that can occur.[46] We propose that the α-quaternary center of **37**, which had proved to be the downfall of the previous methods, prevents oxidative dimerization of the samarium enolate and other competing SmI_2-mediated pathways. When coupled with subsequent dehydration, this 2-step sequence is complementary to the HWE strategies, and it may find use in other sterically hindered systems. Further studies to investigate the generality of this approach are currently underway.

Hydrofluoric acid selectively removed both Et_3Si groups in the presence of the TBDPS group, affording the β-hydroxyl

(41) M + Na^+ was recorded using HRMS; hence, the actual value was 1734.0549. However, for ease of discussion, the M^+ weights are described.

(42) Compound **33** was not characterized further, and its assignment is tentative.

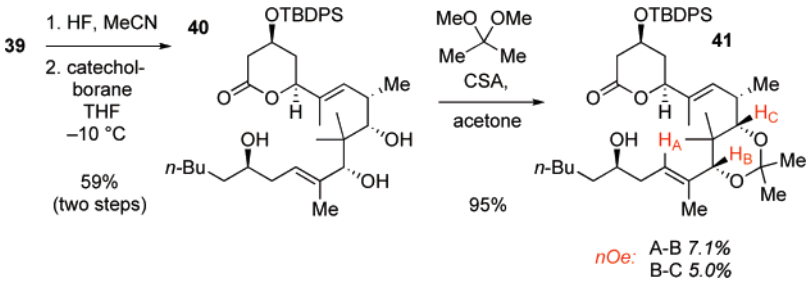
(43) For a review of intramolecular SmI_2-mediated reactions, see: Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371−3403.

(44) In this case, Zn/Ag−graphite was employed: Fürsnter, A. *Synthesis* **1989**, 571−590.

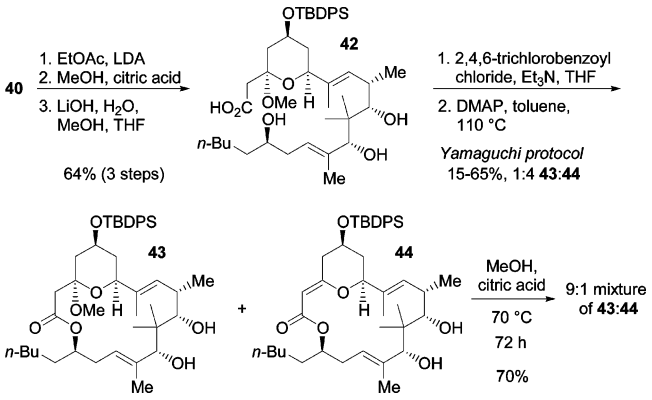
(45) Available in 5 steps from 1-heptene in a manner similar to that described in Scheme 5. See Supporting Information.

(46) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745−777.

SCHEME 19. Syn-Selective Reduction and Determination of Stereochemistry



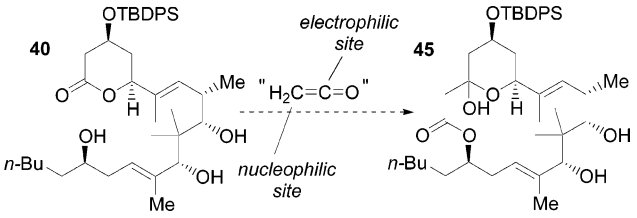
SCHEME 20. Yamaguchi et al. Macrolactonization



group necessary for directed reduction (Scheme 19). Although syn-selective directed reductions of β-hydroxy ketones are well-known, we were surprised to find that there were no prior examples with an all-carbon quaternary center between the directing alcohol and the carbonyl undergoing reduction, as is the case here.[47] Indeed, one of the most common syn-selective techniques (Et_2BOMe and $NaBH_4$)[48] was completely unsuccessful in this system; however, the technique developed by Evans and Hoveyda utilizing catecholborane provided an efficient solution to this problem.[49] The syn stereochemistry of diol **40** and the C14−C15 olefin geometry were determined by NOE analysis of the acetonide derivative **41**, and the configuration at C13 was further supported by the ^{13}C spectra of **41**.[50]

Our early attempts at macrolactonization focused on a strategy similar to that of Smith et al. (Scheme 20).[2] Although the Yamaguchi protocol[51] was successful in the formation of the macrolactone, the mixed anhydride intermediate was very moisture sensitive, and consequently, the yield was variable and often very low. Moreover, elimination of methanol resulted in the formation of **44** as the major product, which could be partially converted to **43** by refluxing in methanol with citric acid. However, the rate of conversion was slow, and despite extended reaction times, the reaction did not proceed to completion. Moreover, **43** was not separable from **44** by chromatography.[52]

SCHEME 21. Hypothetical Ketene Based Macrolactonization



Conversion of **40** to **45** is formally the addition of ketene to the lactone as a nucleophile and also reaction with the 2° alcohol as an electrophile (Scheme 21). An alkoxyethyne seemed ideally suited for this purpose. Deprotonation of the alkyne terminus would provide an efficient nucleophile, and alkoxyalkynes are known to undergo thermal decomposition to ketenes,[53] which are potent electrophiles.[54] The lithium anion of ethoxyethyne (**46**) smoothly added to the carboxyl at C3 to give tetraol **47** (Scheme 22). Slow addition of **47** to refluxing xylenes and Bu_3N effected a thermal retro-ene reaction to form ethylene and ketene **48** that then underwent a highly group-selective coupling with the least hindered (yet most remote) of the four hydroxyl groups to give the desired macrocycle (**45**) in excellent yield (90%).

This macrolactonization method was first reported by Funk et al. as a mechanistic probe[55] but has not been employed previously in the context of total synthesis.[56] As alkynyl ethers lack acidic α-hydrogens, they avoid the problem of competing enolate formation that plagues many macrolactonization techniques.[57] Because of these features, as well as the fact that macrolactonization is one of the most commonly utilized strategies in complex molecule synthesis, this retro-ene macrocyclization certainly warrants further consideration in the field of natural product synthesis.

In contrast to **44**, methanolysis of **45** proceeded efficiently in 10 h to give **43** in >99% yield (Scheme 23). Selective silylation of the allylic alcohol, Dess−Martin oxidation,[58] and exposure to HF afforded **49**. Crystallization from diethyl ether/pentanes allowed for an X-ray crystal structure determination

(47) Three syn-selective reductions of α,α′-difluoro-*b*-hydroxyketones using iBu$_2$AlH/ZnCl$_2$/TMEDA appear to be the closest and only precedents: Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* **1987**, *28*, 6481−6484.

(48) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

(49) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190−5192.

(50) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100.

(51) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(52) Elimination of methanol to give the ene-ester was also the major product in Smith et al.'s synthesis. See ref 2.

(53) For a useful discussion of how different alkoxy substituents affect the temperature at which ethylene is lost, see: Moyano, A.; Pericàs, M. A.; Serratosa, F.; Valentí, E. *J. Org. Chem.* **1987**, *52*, 5532−5538.

(54) Vollema, G.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 305−321.

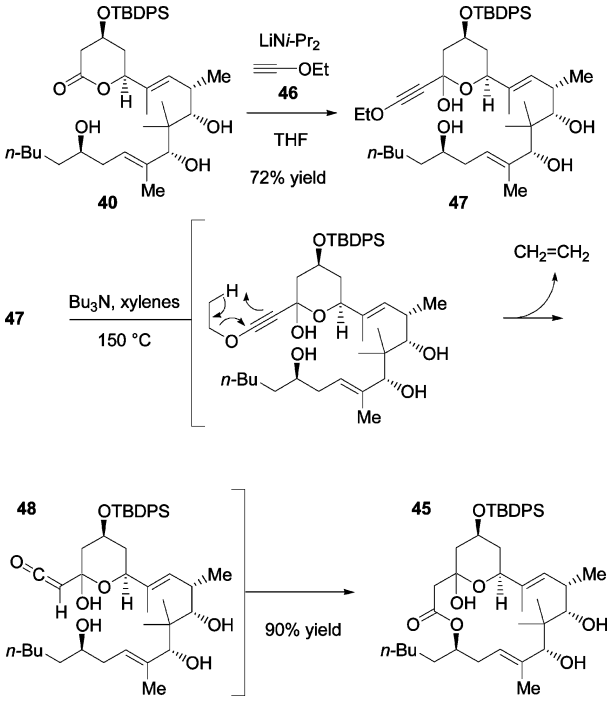
(55) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36−37.

(56) We are aware of only two reports of using this technique to form macrolactones: (a) Magriotis, P. A.; Vourloumis, D.; Scott, M. E.; Tarli, A. *Tetrahedron Lett.* **1993**, *34*, 2071−2074. (b) Liang, L.; Ramaseshan, M.; Magee, D. I. *Tetrahedron* **1993**, *49*, 2159−2168.

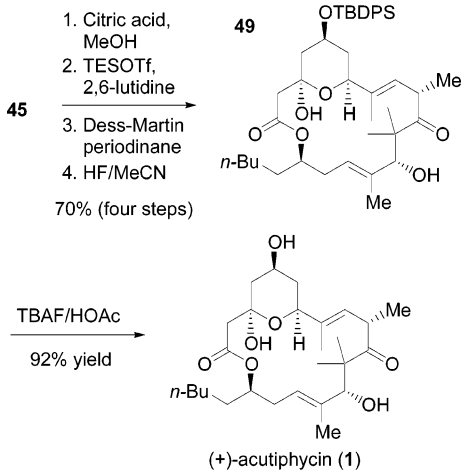
(57) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911−939.

(58) The ketone product of this reaction was previously synthesized by Smith et al. See ref 2.

SCHEME 22. Macrolactonization via in Situ Retro-ene Reaction



SCHEME 23. Completion of Total Synthesis of (+)-Acutiphycin



of **49** (Figure 1). This is the only known crystal structure of an (+)-acutiphycin derivative, and hopefully, the structural information obtained from this compound can be used to further understand the mode of activity of (+)-acutiphycin.[59] Finally, TBDPS was removed by treatment with acetic acid-buffered TBAF,[2] completing the total synthesis of (+)-acutiphycin (**1**).

Conclusion

Nickel-catalyzed reductive coupling reactions of aldehydes and 1,6-enynes show great potential for use in total synthesis due to high regioselectivity, good functional group tolerance, and substrate-controlled diastereoselectivity. Because of difficulties associated with the elaboration of the initial retrosynthetic plan, a new highly convergent synthesis of (+)-acutiphycin (**1**) was developed, with a longest linear sequence of 18 steps from either methyl acetoacetate (4.0%, 84% per step) or isobutyraldehyde (3.1%, 82% per step). Unique features of this work include the first application of an alkynyl ether as a macrolactone precursor in total synthesis and the first use of an intermolecular, SmI_2-mediated Reformatsky reaction as a fragment coupling operation. The modular nature of the route should enable rapid and systematic investigation of the structure−activity relationships of this potent natural product.

(59) On the basis of NMR analysis, Moore et al. postulated a solution phase structure of (+)-acutiphycin, which closely matches the X-ray structure of **49**. See ref 1.

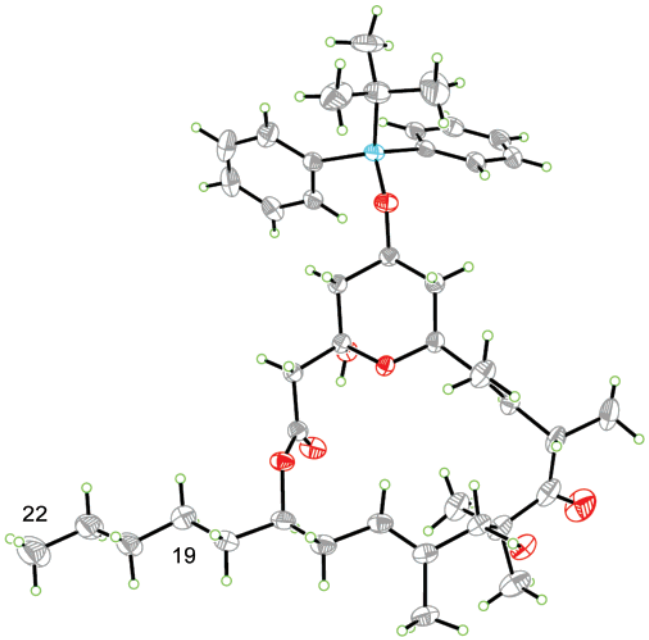


FIGURE 1. X-ray crystal structure of **49**. Diethyl ether and disorder at the terminus of the C19−C22 chain are omitted for clarity.

Experimental Section

Nickel-Catalyzed Reductive Coupling of 3 with 5/13. Representative Procedure for 12 (3 + 5 with No Phosphine Additive). In a glovebox, Ni(cod)$_2$ (5.5 mg, 0.02 mmol, 10 mol %) was added to a predried 25 mL round-bottomed flask, and if phosphine was included, it was added (10 mol %) at this time (in this example, it was not). The flask was then placed under argon on a Schlenk line, and neat Et_3B was added (0.10 mL, 0.69 mmol, 345 mol %). The solution was cooled to 0 °C, and **3** (76.5 mg, 0.2 mmol, 100 mol %) was added followed by the 1,6-enyne (**5**) (57.5 mg, 0.205 mmol, 102 mol %). The reaction was stirred for 1 h at 0 °C and then warmed to room temperature and stirred for 3 additional hours. The reaction was diluted with reagent grade EtOAc, opened to the atmosphere, and stirred for 30 min. Solvent was removed in vacuo, and the crude material was purified via silica gel purified by silica gel chromatography (50:1 hexanes/diethyl ether → 7:2 hexanes/diethyl ether) to give 112 mg (84%) of **12** as a mixture of diastereomers (*c* 80:20 C7 R/S).

A similar procedure (1 mmol scale) was performed for **3** + **13**, giving 435 mg (65%) of **20** as a mixture of diastereomers (*c* 62:38 C7 *S*/*R*).

***δ*-Lactone (19).** Since the diastereomers could not be separated, they were characterized as their *δ*-lactones (Figure 2). The following is a representative procedure: PPTS (1 mg, 0.004 mmol) was added to a solution of **12** (15 mg, 0.022 mmol) in benzene (1.5 mL), the vessel was sealed and heated to 60 °C for 2 h, the solvent was removed in vacuo, and the crude material was purified by silica gel chromatography (10:1 hexanes/diethyl ether) to give 11 mg

(79%) of **19** (more polar) and 2.7 mg (19%) of the other diastereomer (less polar). Spectral data for all four lactone products are provided in the Supporting Information. **19**: $[\alpha]_D$ +1.2 (*c* 1.46, 21 °C, $CHCl_3$); IR 2959 (s), 2931 (s), 2858 (s), 1742 (s), 1472 (m), 1428 (m), 1380 (w), 1236 (m), 1112 (s), 1080 (s), 1028 (s), 911 (w), 834 (m), 702 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.47 (m, 2H), 7.40 (m, 4H), 5.91 (dd, J = 17.6, 10.9 Hz, 1H), 5.51 (NOE 11.7%) (d, J = 9.9 Hz, 1H), 5.16 (NOE 11.7%) (dd, J = 10.6, 3.5 Hz, 1H), 4.97 (dd, J = 17.6, 1.4 Hz, 1H), 4.95 (dd, J = 10.9, 1.4 Hz, 1H), 4.30 (m, 1H), 3.26 (d, J = 2.0 Hz, 1H), 2.64 (m, 1H), 2.60 (dt, J_t = 2.4, J_d = 18.0 Hz, 1H), 2.45 (dd, J = 13.3, 4.5 Hz, 1H), 1.75 (m, 2H), 1.55 (d, J = 1.0 Hz, 3H), 1.09 (s, 9H), 1.01 (s, 3H), 1.00 (s, 3H), 0.95 (s, 9H), 0.91 (d, J = 6.5 Hz, 3H), 0.07 (s, 6H); ^{13}C (125.8 MHz, $CDCl_3$) δ 170.5, 146.5, 136.1, 135.8, 135.8, 133.3, 133.3, 130.3, 130.3, 129.6, 128.1, 128.1, 111.3, 82.6, 81.6, 64.6, 43.4, 39.0, 34.7, 34.4, 27.1, 26.5, 25.7, 23.8, 19.3, 18.9, 15.8, 11.9, −2.6, −3.6; HRMS *m*/*z* (ESI, M + H$^+$) calcd 635.3946, found 635.3968.

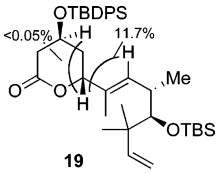


FIGURE 2. NOE evidence for the stereochemistry of δ-lactone **19**.

(+)-δ-Lactone-silyl-enol Ethers (23 and 29, Figure 3). Representative Procedure for Coupling (23). In a darkened fume hood, a solution of $Cp_2Zr(H)Cl$ (694 mg, 2.7 mmol) and **25** (1.10 g, 2.6 mmol) in toluene (20 mL) was heated to 43 °C for 80 min and then cooled to −65 °C. Dimethylzinc (2 M in toluene, 1.31 mL, 2.62 mmol) was slowly added to the cold solution followed by α,α-diphenyl-*N*-methyl-D-prolinol (107 mg, 0.40 mmol). The reaction was allowed to gradually warm up to −30 °C over 90 min, at which point **3** (768 mg, 2.0 mmol) in 5 mL of toluene was added followed by a 3 mL rinse (toluene). The reaction was warmed to −25 °C and stirred for 50 min and then warmed to −15 °C and stirred overnight. The reaction was warmed to room temperature and then heated to 35 °C for 20 min; this was done to ensure complete conversion to the lactone. The reaction was cooled to 0 °C and quenched via the careful addition of saturated aqueous ammonium chloride. The aqueous layer was extracted with diethyl ether, and the combined organics were washed with 0.1 M $NaHSO_4$ and brine, dried over magnesium sulfate, filtered, concentrated, and subject to chromatography: 50:1 hexanes/diethyl ether, 80 mL (removes excess **25** and related) → 9:1 hexanes/diethyl ether, 1 L (**23**) → 6:1 hexanes/diethyl ether (*epi*-C(7)-**23**), to give 810 mg of **23** (52%) and 154 mg of *epi*-C(7)-**23** (10%) as clear oils (data for **23** only). $[\alpha]_D$ +16.0 (*c* 1.85, 22 °C, $CHCl_3$); IR 2957 (s), 2877 (s), 1747 (s), 1664 (w), 1460 (w), 1381 (w), 1317 (w), 1231 (m), 1111 (s), 1008 (s), 738 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.46 (m, 2H), 7.40 (m, 4H), 5.63 (NOE 14.5%) (d, J = 9.5 Hz, 1H), 4.51 (q, J = 6.5 Hz, 1H), 4.31 (NOE 14.5%, 9.4%) (dd, J = 6.5, 3.5 Hz, 1H), 4.12 (NOE 9.4%) (m, 1H), 3.77 (s, 1H), 2.70 (ddd, J = 17.0, 6.0, 1.0 Hz, 1H), 2.62 (m, 1H), 2.49 (dd, J = 17.0, 8.0 Hz, 1H), 1.87 (m, 2H), 1.55 (d, J = 1.0 Hz, 3H), 1.50 (d, J = 6.5 Hz, 3H), 1.07 (s, 9H), 1.03−0.96 (m, 21 H), 0.89 (d, J = 7.0 Hz, 3H), 0.82 (s, 3H), 0.73 (q, J = 8.0 Hz, 6H), 0.64 (q, J = 8.0 Hz, 6 H); ^{13}C (125.8 MHz, $CDCl_3$) δ 171.3, 157.4, 135.9, 133.7, 133.4, 133.0, 130.3, 130.2, 128.9, 128.1, 128.0, 99.1, 82.9, 81.2, 77.2, 65.7, 46.1, 40.1, 37.4, 34.2, 27.0, 25.7, 21.2, 20.6, 19.2, 11.6, 7.5, 7.2, 6.4, 5.9; HRMS *m*/*z* (ESI, M + Na$^+$) calcd 801.4738, found 801.4721.

(+)-Enone (39). SmI_2 (0.1 M THF, 50 mL, 5.0 mmol) was added to a 500 mL teardrop flask that had been thoroughly purged with argon and cooled to −78 °C. A solution of **36** (765 mg, 1.03 mmol) and **24** (282 mg, 1.09 mmol) in THF (52 mL) was added to the reaction vessel over 70 min. Excess SmI_2 was oxidized by bubbling dry air through the solution until the solution turned yellow, the solution was poured into a separation funnel containing aqueous sodium thiosulfate, sodium bicarbonate, and diethyl ether, the layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous sodium thiosulfate (2×), dried over magnesium sulfate, filtered, concentrated, and purified by chromatography: hexanes (flush out iodine) → 10:1 hexanes/ethyl acetate → 6:1 hexanes/ethyl acetate to give the β-hydroxy ketone as a mixture of four diastereomers (852 mg, 90%). To a cold (0 °C) solution of the β-hydroxy ketone (852 mg, 0.924 mmol) in DCM (70 mL) was added Martin sulfurane (4.3 g, 6.39 mmol), and the reaction was stirred at 0 °C for 2 h, sealed, and placed in a freezer (−4 °C) for 50 h. The reaction was quenched with saturated aqueous sodium bicarbonate, and the product was extracted with diethyl ether. The combined organic layers were washed 4 times with 1 M NaOH and once with brine, dried over magnesium sulfate, filtered, concentrated, and purified by chromatography: hexanes → 15:1 hexanes/diethyl ether (400 mL flush) → 13:1 hexanes/ethyl acetate to give 665 mg (80%) **39** as a single detectable isomer. $[\alpha]_D$ +20.5 (*c* 1.28, 21 °C, $CHCl_3$); IR 2957 (s), 2933 (s), 2876 (s); 1746 (m), 1654 (w), 1463 (w), 1379 (w), 1231 (m), 1112 (s), 1008 (m), 739 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.46 (m, 2H), 7.40 (ψt, J = 7.5 Hz, 4H), 6.05 (t, J = 9.5 Hz, 1H), 4.29 (dd, J = 7.0, 3.0 Hz, 1H), 4.18 (s, 1H), 4.11 (m, 1H), 3.78 (q, J = 5.5 Hz, 1H), 2.71 (dd, J = 17.5, 6.0 Hz, 1H), 2.49 (dd, J = 17.5, 8.5 Hz, 1H), 2.38 (q, J = 8.0 Hz, 1H), 2.32 (t, J = 6.0 Hz, 2H), 1.91 (m, 1H), 1.83 (m, 1H), 1.78 (s, 3H), 1.56 (s, 3H), 1.42 (bm, 3H), 1.32−1.24 (bm, 6H), 1.17 (s, 3H), 1.07 (s, 9 H), 1.03 (s, 3H), 1.01−0.93 (bm, 20H), 0.88 (t, J = 7.0 Hz, 3H), 0.66 (q, J = 8.0 Hz, 6H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C (125.8 MHz, $CDCl_3$) δ 211.2, 171.0, 138.0, 135.8, 133.6, 133.4, 132.1, 131.9, 130.8, 130.3, 130.2, 129.7, 128.1, 128.0, 82.3, 80.9, 71.6, 65.7, 54.2, 40.1, 37.3, 37.3, 36.5, 35.3, 32.2, 27.0, 25.5, 25.4, 22.9, 21.1, 20.8, 19.2, 14.8, 14.3, 12.0, 7.4, 7.1, 5.9, 5.2; HRMS *m*/*z* (ESI, M + Na$^+$) calcd 927.5781, found 927.5770.

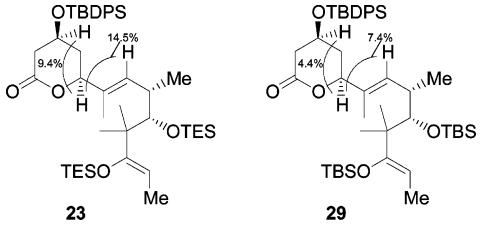


FIGURE 3. NOE evidence for the stereochemistry of δ-lactones **23** and **29**.

(−)-Alkoxyacetylene-tetraol (47). *n*-BuLi (2.5 M in hexanes, 117 μL, 0.29 mmol) was added dropwise to a cold (−10 °C) solution of *i*Pr_2NH (40 μL, 0.29 mmol) in THF (7.2 mL), and the solution was stirred for 15 min and then cooled to −78 °C. Ethoxyethyne (63 wt % in hexanes, 45 μL, 0.29 mmol)[60] was subsequently added, and the solution was stirred for 50 min. After dry (azeotroped with anhydrous toluene) **40** (20 mg, 0.029 mmol) in THF (500 μL) was added dropwise down the side of the reaction vessel, the reaction was stirred for 10 min at −78 °C and then warmed to −42 °C for 45 min. The reaction was quenched with pH 7.2 phosphate buffer and diluted with diethyl ether. The aqueous phase was extracted twice with ethyl acetate, and the combined organic layers were washed with sodium bicarbonate and brine and dried over sodium sulfate. The slurry was filtered, concentrated, and purified by chromatography (3:2 hexanes/ethyl acetate → 4:5 hexanes/ethyl acetate) to give **47** as a clear oil (15.9 mg, 72%).

(60) Although not utilized here, lithiated ethoxyethyne can be generated in situ and added directly to aldehydes and ketones: Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332−2333.

Stereochemistry is unassigned, dr >10:1. $[\alpha]_D$ −16.1 (*c* 0.4, 21 °C, $CHCl_3$); IR 3365 (bm), 2929 (s), 2857 (s), 2226 (s), 1717 (w), 1654 (m), 1471 (m), 1428 (m), 1111 (s), 1008 (s), 703 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.45 (m, 2H), 7.40 (m, 4H), 5.50 (d, J = 10.5 Hz, 1H), 5.46 (t, J = 7.0 Hz, 1H), 4.46 (apparent quint, J = 5.5 Hz, 1H), 4.25 (q, J = 7.0, 2H), 4.16 (d, J = 9.0 Hz, 1H), 3.99 (s, 1H), 3.66 (m, 1H), 3.50 (d, J = 2.0 Hz, 1H), 3.01 (bs, 1H), 2.82 (dd, J = 15.0, 7.5 Hz, 1H), 2.72 (dd, J = 15.0, 6.0 Hz, 1H), 2.65 (m, 1H), 2.48 (d, J = 2.5 Hz, 1H), 2.23 (t, J = 7.0 Hz, 2H), 1.75 (m, 1H), 1.69 (s, 3H), 1.50−1.40 (bm, 8H), 1.35−1.25 (bm, 9H), 1.06 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.72 (s, 3H); ^{13}C (125.8 MHz, $CDCl_3$) δ 185.4, 138.7, 136.2, 136.2, 135.6, 133.5, 133.4, 130.1, 130.1, 127.9, 127.9, 127.0, 125.7, 103.6, 86.9, 84.3, 77.6, 74.0, 71.9, 69.2, 52.2, 45.3, 42.7, 41.3, 37.3, 36.0, 34.1, 32.1, 29.9, 27.1, 25.6, 22.9, 20.6, 19.5, 15.9, 15.2, 14.6, 14.3, 11.9; HRMS *m/z* (ESI, M + Na^+) calcd 771.4627, found 771.4639.

(−)-Macrocycle, Hemi-ketal (45). Dry (azeotroped with anhydrous toluene) **47** (13 mg, 17.4 μmol) in dry xylenes (24 mL) was added dropwise over 5 h to refluxing (150 °C) xylenes (48 mL) and tri-*n*-butylamine (48 μL, 0.20 mmol). The reaction was stirred for an additional 20 min after the slow addition was complete, then poured into a separation funnel containing ice, and diluted with ethyl acetate. The organic layer was washed with 0.1 M $NaHSO_4$ and brine, dried over magnesium sulfate, filtered, concentrated, and purified by silica gel chromatography (20:1 hexanes/ethyl acetate → 4:1 hexanes/ethyl acetate) to give 11.3 mg (90%) of **45** as a single diastereomer. $[\alpha]_D$ −8.1 (*c* 0.19, 21 °C, $CHCl_3$); IR 3452 (bm), 2929 (s), 2858 (s), 1710 (m), 1428 (m), 1378 (m), 1208 (s), 1112 (s), 1058 (s), 998 (s), 702 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.43 (m, 2H), 7.38 (apparent t, J = 7.5 Hz, 4H), 5.42 (d, J = 10.5 Hz, 1H), 5.17 (d, J = 10.0 Hz, 1H) 5.12 (d, J = 2.0 Hz, 1H), 4.92 (m, 1H), 4.29 (apparent sept, J = 5.0 Hz, 1H), 4.12 (dd, J = 12.0, 2.0 Hz, 1H), 3.92 (s, 1H), 3.56 (s, 1H), 2.88 (m, 1H), 2.55 (d, J = 14.0 Hz, 1H), 2.47 (d, J = 14.0 Hz, 1H), 2.37 (m, 1H), 2.04 (d, J = 14.0 Hz, 1H), 1.99 (dd, J = 12.0, 3.5 Hz, 1H), 1.71 (m, 1H), 1.66 (s, 3H), 1.62 (d, J = 1.0 Hz, 3H), 1.55−1.48 (bm, 2H), 1.40−1.32 (bm, 2H), 1.30−1.23 (bm, 8H), 1.06 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.87 (t, J = 7.0 Hz, 3H), 0.64 (s, 3H); ^{13}C (125.8 MHz, $CDCl_3$) δ 172.4, 136.3, 135.9, 134.5, 131.9, 131.4, 129.8, 129.8, 127.8, 127.8, 96.6, 81.2, 79.8, 76.5, 74.4, 66.5, 44.8, 44.2, 43.3, 38.6, 35.8, 34.1, 32.8, 31.8, 27.2, 25.1, 22.7, 22.2, 19.4, 19.4, 18.8, 14.2, 13.0, 11.1; HRMS *m/z* (ESI, M + Na^+) calcd 743.4314, found 743.4334.

(+)-Macrocycle, Methyl-ketal (43). Compound **45** (11.3 mg, 15.7 μmol), citric acid (3.8 mg, 19.8 μmol), and methanol (30 mL) were combined in a sealed tube and then heated to 75 °C overnight. The crude mixture was concentrated and purified by chromatography (20:1 hexanes/ethyl acetate → 4:1 hexanes/ethyl acetate) to give 11.5 mg (100%) of **43**. $[\alpha]_D$ +15.2 (*c* 0.083, 22 °C, $CHCl_3$); IR 3447 (bm), 2926 (s), 2855 (s), 1725 (m), 1462 (m), 1378 (m), 1201 (m), 1113 (s), 1063 (s), 702 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 7.0 Hz, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.63 (t, J = 7.0 Hz, 1H), 5.50 (d, J = 10.5 Hz, 1H), 4.78 (m, 1H), 4.17 (s, 1H), 4.12 (m, 1H), 3.76 (d, J = 11.5 Hz, 1H), 3.41 (d, J = 6.5 Hz, 1H), 2.98 (s, 3H), 2.86 (m, 1H), 2.74 (d, J = 13.5 Hz, 1H), 2.46 (d, J = 13.5 Hz, 1H), 2.44 (m, 1H), 2.20 (m, 1H), 2.01 (dd, J = 7.5, 4.5 Hz, 1H), 1.77 (m, 1H), 1.71 (s, 3H), 1.66 (m, 3H), 1.49 (bm, 2H), 1.37 (q, J = 11.5 Hz, 1H), 1.32−1.20 (bm, 9H), 1.05 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.89 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C (125.8 MHz, $CDCl_3$) δ 169.7, 136.4, 136.4, 135.1, 135.0, 132.1, 130.4, 130.3, 128.5, 128.3, 128.3, 126.4, 100.4, 83.4, 80.4, 77.9, 75.3, 75.1, 67.1, 49.6, 44.5, 44.3, 43.7, 39.1, 35.0, 34.4, 32.4, 31.9, 30.4, 27.6, 25.8, 24.6, 23.2, 21.9, 20.7, 19.8, 14.8, 14.7, 13.5, 13.4; HRMS *m/z* (ESI, M + Na^+) calcd 757.4470, found 757.4464.

(+)-Acutiphycin (1). Compound **49** (3.9 mg, 5.4 μmol) was dissolved in THF (2.1 mL) and treated with 980 μL of TBAF/HOAc solution (TBAF 1 M THF, 2.5 mL; acetic acid 0.15 mL). The reaction was stirred at room temperature for 52 h, diluted with ethyl acetate, washed with sodium bicarbonate (2×) and brine, dried over magnesium sulfate, filtered, concentrated, and purified by silica gel chromatography (3:2 diethyl ether/hexanes) to give **1** as a white solid (2.4 mg, 92%). mp 150−151 °C; $[\alpha]_D$ +151.6 (*c* 0.095, 21 °C, CH_2Cl_2); IR (solution in $CDCl_3$) 3608 (m), 3457 (bw), 2985 (s), 2932 (m), 2902 (s), 1702 (m), 1643 (m), 1562 (m), 1298 (m), 1261 (m), 1216 (s), 1167 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (d, J = 2.4 Hz, 1H), 5.29 (m, 2H), 4.98 (m, 1H), 4.64 (d, J = 3.8 Hz, 1H), 4.33 (dd, J = 12.0, 2.1 Hz, 1H), 4.28 (m, 1H), 4.95 (m, 1H), 2.67 (d, J = 14.6 Hz, 1H), 2.62 (d, J = 14.6 Hz, 1H), 2.42 (ddd, J = 15.1, 10.7, 1.9 Hz, 1H), 2.18 (ddd, J = 11.9, 4.6, 1.3 Hz, 1H), 2.10 (apparent t, J = 13.6 Hz, 1H), 1.89 (dt, J_d = 12.2, J_t = 2.2 Hz, 1H), 1.78 (d, J = 1.3 Hz, 3H), 1.67 (s, 3H), 1.61−1.51 (m, 3H), 1.33−1.24 (m, 9H), 1.12 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.89 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{1}H NMR (500 MHz, 1:1 C_6D_6/$CDCl_3$) δ 5.37 (bs, 1H), 5.21 (d, J = 10.4 Hz, 1H0, 5.16 (d, J = 11.2 Hz, 1H), 4.91 (m, 1H), 4.52 (s, 1H), 4.18 (d, J = 11.9 Hz, 1H), 4.01 (tt, J = 11.1, 4.3 Hz, 1H), 3.87 (m, 1H), 2.42 (d, J = 14.4 Hz, 1H), 2.29 (d, J = 14.4 Hz, 1H), 2.20 (ddd, J = 14.9, 10.7, 1.8 Hz, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.91 (m, 1H), 1.63 (s, 3H), 1.54 (m, 1H), 1.44 (s, 3H), 1.30 (m, 1H), 1.22−1.10 (m, 11H), 1.04 (m, 3H), 1.00 (dt, J_d = 2.2, J_t = 11.5 Hz, 1H), 0.85 (s, 3H), 0.82 (m, 3H); ^{13}C (125.8 MHz, $CDCl_3$) δ 215.7, 172.6, 135.1, 135.0, 131.1, 126.6, 96.8, 79.9, 76.1, 74.4, 64.7, 52.8, 44.8, 43.9, 43.3, 38.2, 35.5, 32.9, 31.8, 25.8, 25.2, 22.7, 19.3, 16.3, 14.2, 13.1, 11.3; ^{13}C (125.8 MHz, DMSO-d_6) δ 214.5, 170.9, 136.2, 134.9, 128.0, 123.6, 96.2, 77.3, 74.1, 73.8, 62.7, 53.1, 45.9, 43.5, 41.3, 38.2, 34.4, 31.7, 31.0, 24.4, 23.3, 22.0, 20.7, 16.7, 13.9, 12.9, 11.9; HRMS *m/z* (ESI, M + Na^+) calcd 503.2979, found 503.2987.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences (GM-063755). We thank Dr. Karen Miller-Moslin for thoughtful discussions on 1,6-enyne reductive coupling reactions. We are grateful to Dr. Li Li for obtaining mass spectrometric data for all compounds and to Dr. Peter Müller for obtaining crystal structures of **27** and **49**.

Supporting Information Available: Experimental procedures and spectral data for **1**, **3**, **5**, **6**, **9**, **10**, **13**, **18**, **19**, **21**−**25**, **27**, **29**, **31**, **36**, **39**−**41**, **45**, **47**, and **49** as well as all unknown (with the exception of the diastereomeric mixture of β-hydroxy ketones resulting from the Reformatsky reaction depicted in Scheme 18) intermediates en route to the successful total synthesis of **1**. X-ray data (CIF) for **27** and **49**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701821H