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Synthetic Studies Aimed at (−)-Cochleamycin A. Evaluation of Late-Stage Macrocyclization Alternatives

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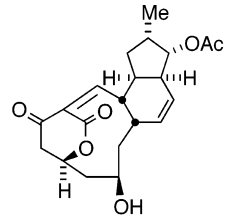
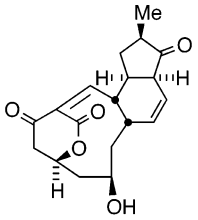
Received June 1, 2004

An efficient route to the fully functionalized ABC ring systems of the unnatural enantiomer of cochleamycin A was developed. L-(−)-Malic and L-(−)-ascorbic acids served well as starting materials for the two building blocks used to construct an (*E*,*Z*,*E*)-1,6,8-nonatriene intermediate. The AB part structure was assembled by way of a stereocontrolled intramolecular Diels−Alder cycloaddition via adoption of an endo transition state. From this vantage point, two general pathways were subsequently explored as to their suitability for elaboration of the CD rings. Initially examined was a protocol involving 10-membered carbocycle construction. When this approach was demonstrated not to be workable, attention was directed to 10-membered macrolactonization as an alternative tactic. Although assembly of the C-ring in this manner was easily achieved, ultimate closure of the six-membered ring to form ring D remains an unsolved problem.

In 1992, Shindo and Kawai reported from the Kirin Brewery Co. the discovery of a small group of novel antibiotics, chief among which was cochleamycin A (**1**).[1] Interest in this substance grew as its appreciable antitumor and antimicrobial properties came to be known.[2] Detailed NMR studies indicated its ring system to consist of a fused 5−6−10−6 tetracyclic core. The assignment of the relative configuration was initially made possible at that time. Only in mid-2003 was the absolute configuration of **1** established as that shown in the illustrated formula.[3] The source of cochleamycin A was a soil sample collected in Aomori, Japan. Almost simultaneously, Abbott scientists succeeded in isolating from strains of *Micromonospora chalcea* several metabolites, the principal component of which was defined as **2** by X-ray analysis and called macquarimicin A.[4] The cytotoxic properties of **2** and its ability to serve as a selective inhibitor of membrane-bound neutral sphingomyelinase have been well documented.[5] Still more recently, announcements have emerged of the isolation and characterization of the closely related cytotoxic agents hexacyclinic acid (**3**)[6] and FR182877 (**4**).[7]



1



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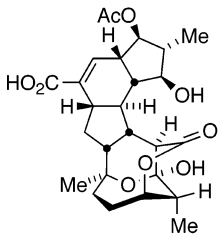

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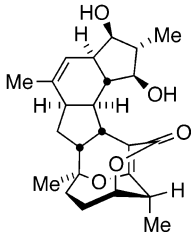

4

Several years ago when the absolute configuration of **1** was still unknown, an enantioselective synthesis of cochleamycin A was initiated in this laboratory.[8] Herein, we detail this early effort together with a comparative evaluation of more advanced end-game macrocyclization strategies targeting (−)-**1**. This enantiomer is antipodal to the natural material. Impressive independent routes to (+)-**1** have recently been reported by Tatsuta and coworkers and by the Roush group.[3] These accomplishments define the three-dimensional structure of the cochleamycins. Finally, attention is called to the elegant completed total syntheses of **2** by Tadano[9] and of **4** in the hands of Evans[10] and Sorensen.[11]

Retrosynthetic Perceptions. Despite the presence of bridgehead unsaturation in **1**,[12] we envisioned that the

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(2) (a) Shindo, K.; Matsuoka, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 241. (b) Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244. (c) Shindo, K.; Sakakibara, M.; Kawai, H.; Seto, H. *J. Antibiot.* **1996**, *49*, 249.

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(4) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Rasmussen, R. R.; Hensey, D. M.; Humphrey, P. E.; Swanson, S. J.; Barlow, G. J.; Premachandran, U.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 462. (b) Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467.

(5) Tanaka, M.; Nara, F.; Yamasato, Y.; Masuda-Inoue, S.; Doi-Yoshioka, H.; Kumakura, S.; Enokita, R.; Ogita, T. *J. Antibiot.* **1999**, *52*, 670.

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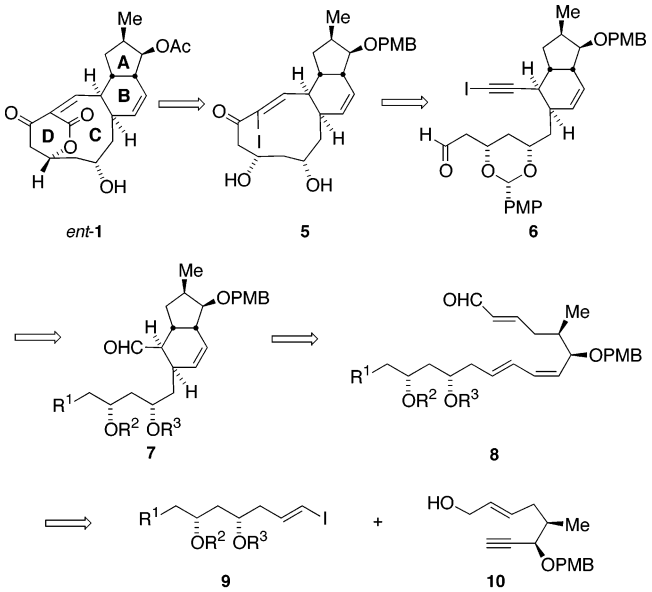
10.1021/jo049084a CCC: $27.50
Published on Web 08/24/2004

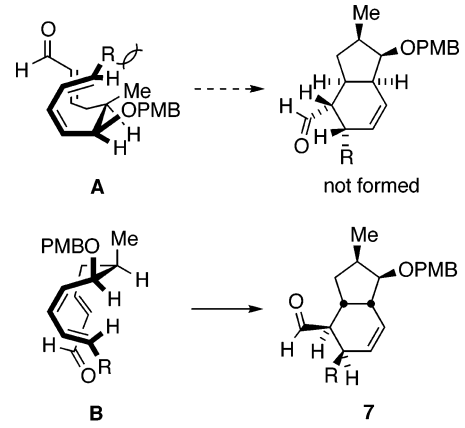
SCHEME 1



tetrahydroindane **7** might serve well as a common advanced intermediate along two reasonably flexible pathways involving different approaches to medium-ring construction. In the first (Scheme 1), the focus of attention was to be directed toward elaboration of the *carbocyclic* 10-membered subunit that was destined to become rings C and D of the target. This goal was expected to be realized by structural modification of both pendant chains as illustrated in **6**.[13,14] Cyclization by either the Nozaki−Hiyama−Kishi protocol[15] or samarium iodide-mediated ring closure would follow.[16] The continuation of this analysis requires a viable route from **6** to an α-iodo enone as typified by **5**,[17] the carbonylation of which in the presence of an appropriate transition metal[18] would generate the complete ABCD framework.

A key consideration in this scenario was the requisite participation of the (*E*,*Z*,*E*)-1,6,8-nonatriene **8** in an intramolecular [4 + 2] cycloaddition via a single low-energy endo-transition-state arrangement.[19] Encouragingly, the two available options (see **A** and **B** in Scheme 2) were seen to differ significantly in the levels of nonbonded steric interaction (particularly $A_{1,3}$ strain) that builds up as C−C bond formation progresses. In **A**, the methyl and OPMB substituents are projected into the region necessarily reserved for proper positioning of the diene unit, thereby disfavoring this arrangement. Since this level of proximity is completely skirted in **B**, the latter transition state was expected to be adopted with exclusive formation of **7**.

SCHEME 2



To implement this plan, **8** was to be generated by the Sonagashira coupling[20] of **9** to **10**, followed by semihydrogenation of the alkyne link to secure the *Z* double bond geometry. The latent functionality in **8** was to be exploited as well by macrolactonization of hydroxy acid **12** (Scheme 3). For the macrocyclization pathway, reductive cyclization of bromo lactone **11** with intramolecular displacement involving a Weinreb amide side chain[11] or aldehyde capture would establish the final C−C bond connection. Although the unnatural enantiomer was targeted, the strategy outlined herein is, of course, also viable for the dextrorotatory form with only minor modification.

Initiation of the Venture. Construction of Building Blocks Related to 10 and 23 and Their Cou-

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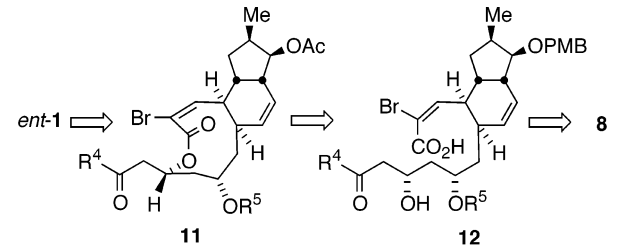
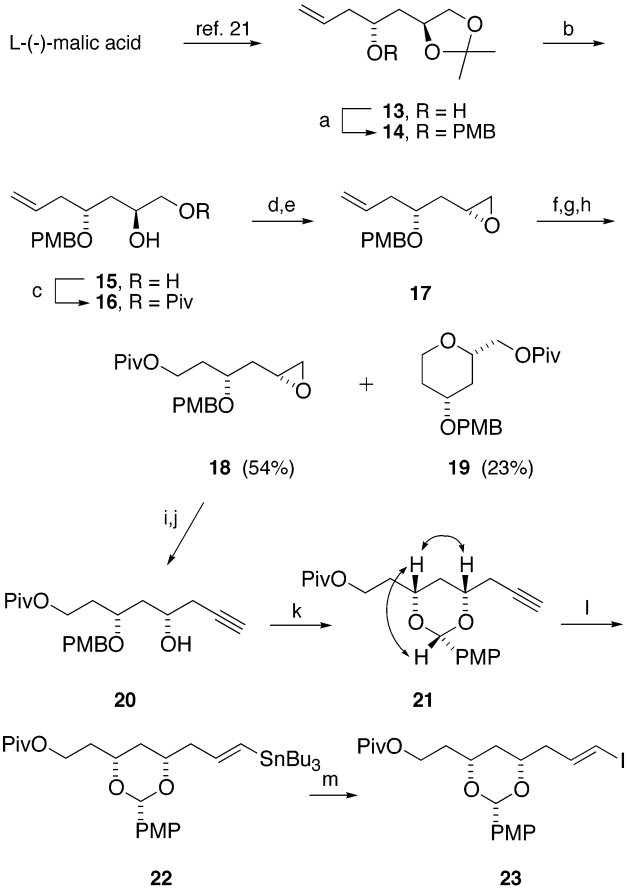
SCHEME 3



SCHEME 4[a]



[a] Reagents and conditions: (a) PMBBr, NaH, DMF (100%); (b) HOAc, H_2O, THF (1:1:1), 50−60 °C (92%); (c) PivCl, pyr, CH_2Cl_2 (91%); (d) CH_3SO_2Cl, DMAP, pyr, CH_2Cl_2 (97%); (e) K_2CO_3, MeOH (89%); (f) O_3, EtOAc, −78 °C, then Ph_3P; (g) $NaBH_4$, MeOH, 0 °C; (h) PivCl, pyr, CH_2Cl_2 (77% for three steps); (i) HC≡CSiMe$_3$, *n*-BuLi, BF_3·OEt_2, THF, −78 °C; (j) (*n*-Bu)$_4$NF, THF, 0 °C (95% for two steps); (k) DDQ, 4 Å molecular sieves, CH_2Cl_2 (85%); (l) (*n*-Bu)$_3$SnH, AIBN, C_6H_6, Δ (99%); (m) I_2, CH_2Cl_2, 0 °C (96%).

pling. The synthesis commenced by transforming L-(−)-malic acid into hydroxy acetal **13** by way of a predescribed four-step sequence [21] (Scheme 4). Masking of the hydroxyl functionality as the *p*-methoxybenzyl ether[22] followed by acidic hydrolysis of the acetonide subunit provided diol **15** in highly efficient fashion (92%). Selective conversion[23] of primary alcohol **15** to the pivalate **16** made possible generation of the terminal epoxide ring resident in **17**.[24] Ozonolytic cleavage of the double bond in **17** could, under properly controlled conditions, be accomplished without excessive intramolecular cyclization. For convenience, the aldehydes so formed were sequentially reduced with sodium borohydride and esterified with pivaloyl chloride. At this point, the product composition could be readily defined as 54% **18** and 23% **19** after chromatographic separation.

Highly regioselective nucleophilic opening of the oxirane ring in purified **18** with lithium trimethylsilylacetylide and subsequent fluoride ion-induced desilylation[25] provided carbinol **20**, whose DDQ-promoted cyclization[26] gave rise to benzylidene acetal **21**. At this juncture, configurational analysis was readily accomplished by NOESY techniques as indicated. Treatment of **21** with tri-*n*-butyltin hydride in refluxing benzene[27] resulted in formation of the (*E*)-vinylstannane **22**, thereby making possible the generation of vinyl iodide **23**[28] in enantiopure form.

Construction of the second cross-coupling partner commenced with butenolide **24**, which was prepared from L-(−)-ascorbic acid via an established six-step sequence.[29] Conjugate addition of lithium dimethylcuprate to **24** furnished the trans 1,4-adduct **25**[30] (Scheme 5). Reduction of **25** to the lactol followed by Wittig chain extension[31] generated alcohol **26**, which was transformed into **27** through deployment of trichloroacetimidate technology.[32] The acquisition of this ester set the stage for reduction and acetylation in advance of desilylation and oxidation with iodoxybenzoic acid (IBX).[33] The aldehyde so formed was then homologated according to the Corey−Fuchs protocol[13] to provide alkyne **10**.

The all-important Sonagashira coupling of **10** to **23** was successfully accomplished with $Pd(PPh_3)_2Cl_2$ and CuI in

(21) (a) Carman, R. M.; Karoli, T. *Aust. J. Chem*. **1998**, *51*, 995. (b) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933. (c) Steel, P. G.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 371. (d) Rodriguez, E. B.; Scally, G. D.; Stick, R. V. *Aust. J. Chem*. **1990**, *43*, 1391. (e) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749.

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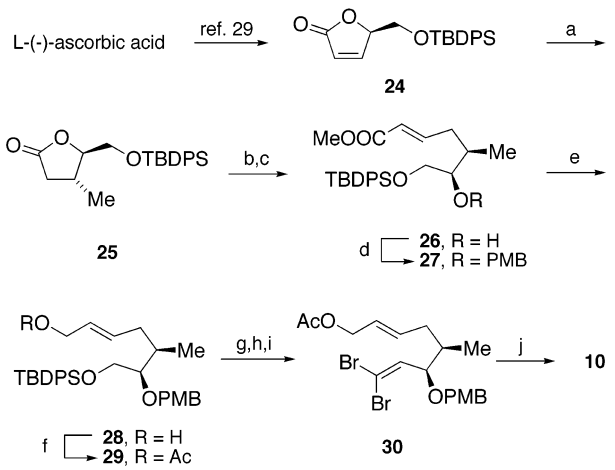
SCHEME 5[a]



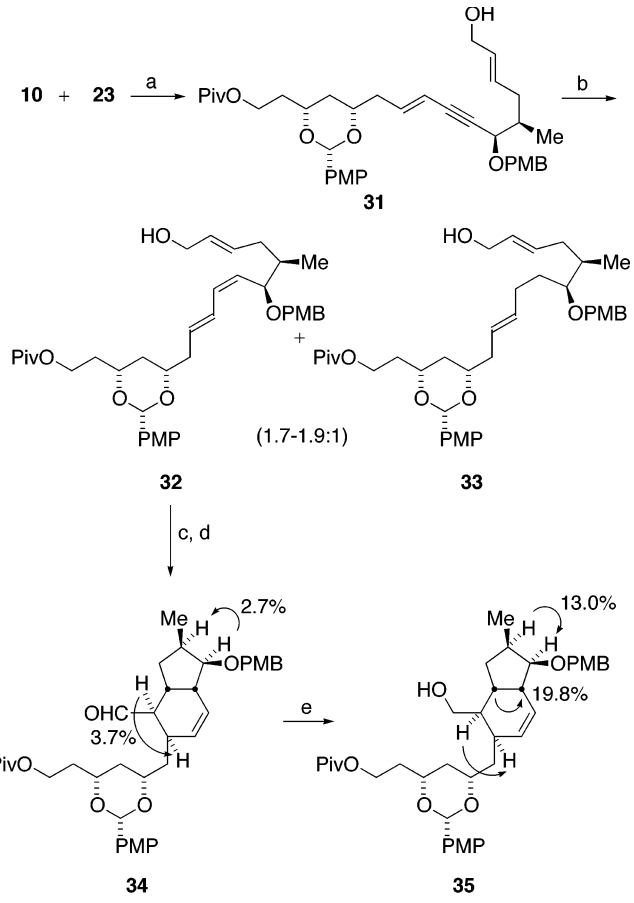
[a] Reagents and conditions: (a) $(CH_3)_2CuLi$, Et_2O, THF, −30 °C (89%); (b) (*i*-Bu)$_2$AlH, CH_2Cl_2, −78 °C; (c) $Ph_3P{=}CHCO_2Me$, C_6H_6, Δ (100% for two steps); (d) PMBOC(=NH)CCl_3, CSA, CH_2Cl_2; (e) (*i*-Bu)$_2$AlH, CH_2Cl_2, −78 °C (60% for two steps); (f) Ac_2O, DMAP, pyr, CH_2Cl_2 (97%); (g) (*n*-Bu)$_4$NF, THF, 0 °C (100%); (h) IBX, THF/DMSO (9:1) (90%); (i) CBr_4, Ph_3P, CH_2Cl_2, −78 °C (98%); (j) *n*-BuLi, THF, −78 °C (90%).

the presence of triethylamine as solvent[20] (Scheme 6). The semihydrogenation of **31** over Lindlar's catalyst proved to be rather problematical, in that the coproduction of overreduced product **33** invariably occurred.[34] Since carbinols **32** and **33** coeluted during chromatography, the mixture was subjected directly to sequential IBX oxidation, heating to 195 °C in toluene, and borohydride reduction. The Diels−Alder product **34** formed uniquely from **32** was now amenable to purification, and its stereochemical features were deduced by NOE measurements on both aldehyde **34** and carbinol **35** (see the illustrations).

Pursuit of 10-Membered Carbocycle Formation. To construct the CD ring system of cochleamycin A, attention was first directed to the generation of aldehyde **6** (Scheme 7). This task was readily accomplished by application of the Corey−Fuchs chain extension to **34**[13] and ensuing treatment with iodine and morpholine.[14] Standard oxidation with pyridinium chlorochromate completed the four-step sequence. It was hoped that **6** would be responsive to one or another modification of the Nozaki−Hiyama−Kishi reaction.[15] Accordingly, this iodo aldehyde was treated with $CrCl_2$ and $NiCl_2$ in THF or DMF under various conditions including ultrasonication, but to no avail. Additionally, numerous attempts to bring about cyclization through the agency of samarium iodide[16] failed to generate **37**.

In light of these reverses, this approach was abandoned in favor of an alternative involving ring-closing metathesis. Toward this end, we turned to the structural modification of **35** such that allylic alcohol **39** and its conjugated keto analogue **40** would be made available.

SCHEME 6[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N (82%); (b) H_2, Lindlar's catalyst, EtOAc/pyr/1-octene (10:1:1); (c) IBX, THF/DMSO (9:1); (d) 20% BHT, toluene, sealed tube, 150−160 °C, 24 h (32% for three steps); (e) $NaBH_4$, MeOH, 0 °C (82%).

In the end, both of these substrates produced complex mixtures when exposed to several ruthenium catalyst systems including **41**.[35] A contributing factor to the foregoing results may well be the presence of a 1,3-dioxane ring in the longer of the two side chains and its associated conformational restrictions. The same structural considerations are not present in the contingency plan outlined in Scheme 3, and we therefore proceeded next in this direction.

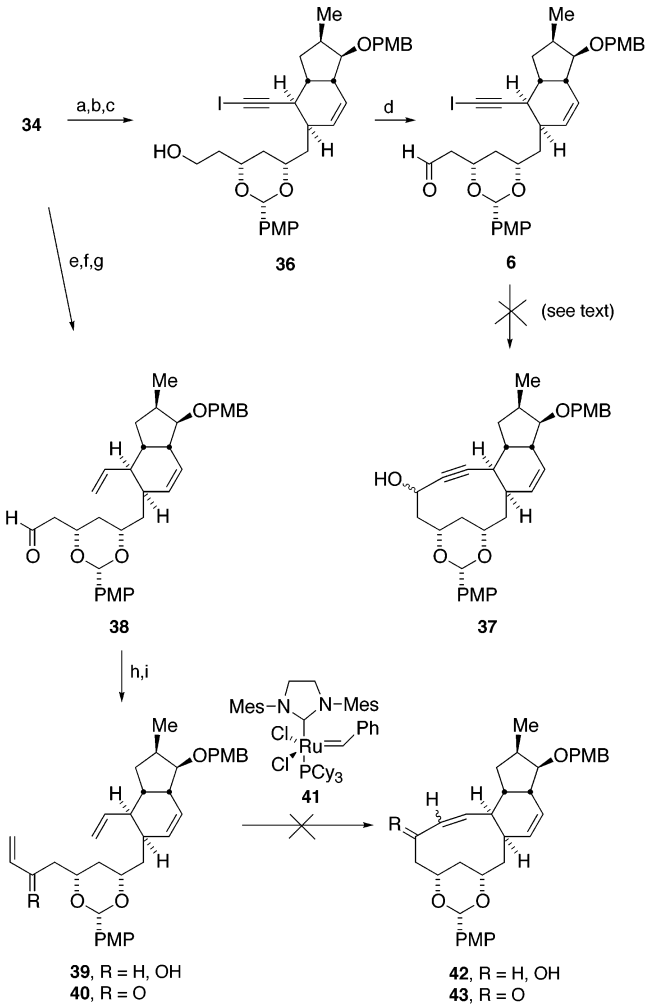
Investigation of the Macrolactonization Alternative. The exploration of this alternative pathway required utilization of a different subset of protecting groups. Therefore, MEM ether **44** was prepared in a manner paralleling that employed earlier for **17**. Nucleophilic opening of the oxirane ring in **44** could then be realized regioselectively with lithium trimethylsilylacetylide to furnish **45** after desilylation and masking of the hydroxyl group with *tert*-butyldimethylsilyl chloride (Scheme 8). Equally uneventful was the ensuing chemoselective ozonolysis that cleaved the terminal olefinic π-bond of **45**, sodium chlorite oxidation of the resulting aldehyde to the carboxylic acid level,[36] and generation of

(33) (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (c) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(34) (a) Nicolaou, K. C.; Ladduwahetty, T.; Taffer, I. M.; Zipkin, R. E. *Synthesis* **1986**, 344. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

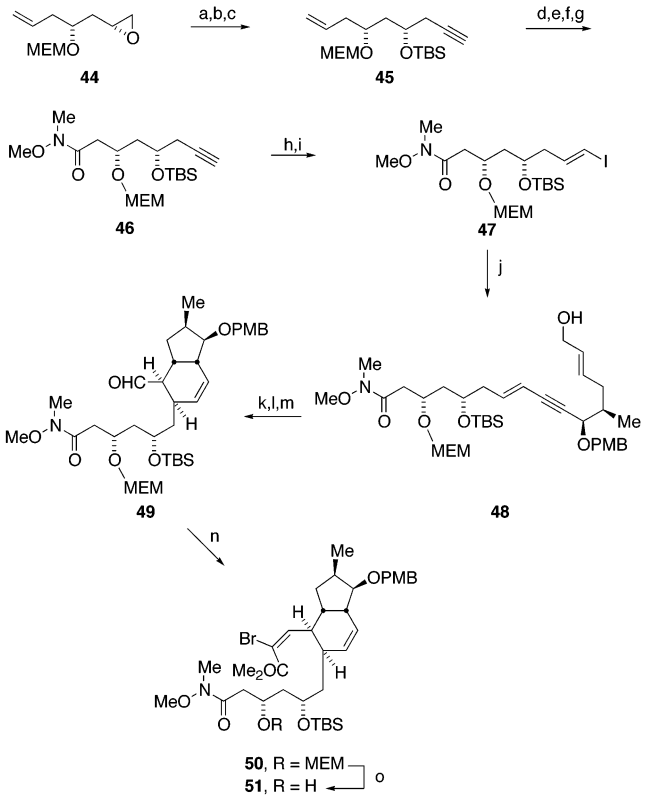
(35) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Nevalainen, M.; Koskinen, A. M. P. *J. Org. Chem.* **2002**, *67*, 1554. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

SCHEME 7[a]



[a] Reagents and conditions: (a) CBr_4, Ph_3P, pyr, CH_2Cl_2, 0 °C (98%); (b) *n*-BuLi, THF, −78 °C (86%); (c) I_2, morpholine, C_6H_6, 50−60 °C (90%); (d) PCC, NaOAc, 4 Å molecular sieves, CH_2Cl_2 (78%); (e) $Ph_3PCH_3^+Br^-$, *n*-BuLi, THF, −78 °C (76%); (f) *n*-BuLi, THF, −78 °C (80%); (g) PCC, NaOAc, 4 Å molecular sieves, CH_2Cl_2, 0 °C (76%); (h) CH_2=CHMgBr, THF, −78 to 0 °C (96%); (i) PCC, NaOAc, 4 Å molecular sieves, CH_2Cl_2, 0 °C (82%).

SCHEME 8[a]



[a] Reagents and conditions: (a) HC≡CTMS, *n*-BuLi, BF_3·OEt_2, THF, −78 °C (90%); (b) TBAF, THF, 0 °C (94%); (c) TBSU, imidazole, DMAP, CH_2Cl_2 (quant); (d) O_3, Ref 23, CH_2Cl_2/MeOH (1:1); Ph_3P (81%); (e) $NaClO_2$, NaH_2PO_4, CH_3CH=$C(CH_3)_2$, *t*-BuOH, H_2O; (f) CH_2N_2, Et_2O (91% for two steps); (g) MeNH(OMe)·HCl, *i*-PrMgCl, THF, −15 °C (77%); (h) *n*-Bu_3SnH, AIBN, C_6H_6, reflux; (i) I_2, CH_2Cl_2, 0 °C (60% for two steps); (j) **10**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N (82%); (k) Zn dust, $Cu(OAc)_2$·H_2O, $AgNO_3$, MeOH/H_2O (1:1), 65 °C (70%); (l) IBX, THF/DMSO (9:1) (97%); (m) BHT, toluene, sealed tube, 170 °C (91%); (n) $(CF_3CH_2O)_2P(O)$-$CHBrCO_2Me$, NaHMDS, THF, 5−10 °C (81%); (o) **52**, CH_2Cl_2, −78 °C (81%).

Weinreb amide **46** from the methyl ester.[37] The viability of the hydrostannylation approach to vinyl iodide **47** was easily demonstrated, as was the now familiar protocol for the Sonagashira coupling of **47** to **10**.

Prior to unmasking of the carboxaldehyde group, partial reduction of the triple bond to the (*Z*)-alkene was necessary. When hydrogenation over Lindlar's catalyst generated a mixture of compounds, reductive decomplexation of the dicobalt hexacarbonyl-ligated acetylene[38] was examined but proved unrewarding. A broader search of metal-promoted reductions was then undertaken. Of these, the action of zinc dust previously activated with copper(II) acetate and silver nitrate[39] in aqueous methanol proved notably effective in transforming the conjugated enyne into the targeted trienol (70% yield). Following the IBX oxidation of this intermediate, heating in toluene containing BHT to 170 °C under sealed tube conditions promoted efficient intramolecular Diels−Alder cycloaddition as before and formation of **49**. To set the proper geometry in α-bromo ester **50**, reliance was placed on the utilization of methyl bis(2,2,2-trifluoroethoxy)-bromophosphonoacetate.[40] In line with previous precedent, **50** was formed as the major isomeric product (81% isolated in a 7:1 epimeric ratio).

The chemical reactivity of advanced intermediate **50** was soon determined to be rather unfavorable. Selective deprotection of the MEM group in the presence of the TBS functionality could be achieved. However, no reaction was observed following treatment with trimethylaluminum or diethylaluminum chloride in CH_2Cl_2 at 0 °C to rt. In contrast, cerium trichloride in refluxing CH_3CN[41]

(36) Hase, T.; Wáhálá, K. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A.; Editor-in-Chief; Wiley: Chichester, U.K., 1995; p 4533.

(37) (a) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (c) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

(38) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609.

(39) (a) Boland, W.; Schroer, N.; Sieler, C. *Helv. Chim. Acta* **1987**, *70*, 1025. (b) Avignon-Tropis, M.; Pougny, J. R. *Tetrahedron Lett.* **1989**, *30*, 4951.

(40) (a) Tago, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 1975. (b) Tago, K.; Kogen, H. *Tetrahedron* **2000**, *56*, 8825.

or trimethylchlorosilane and sodium iodide in CH_2Cl_2 at −20 °C[42] acted on both protecting groups and returned only the diol. Ultimately, clean chemoselectivity was realized with 2-chloro-1,3,2-dithioborolane (**52**) as prepared from boron trichloride and ethanedithiol.[43] This reagent, dissolved in CH_2Cl_2 and cooled to −78 °C, afforded the desired alcohol **51** in 81% yield.[44]

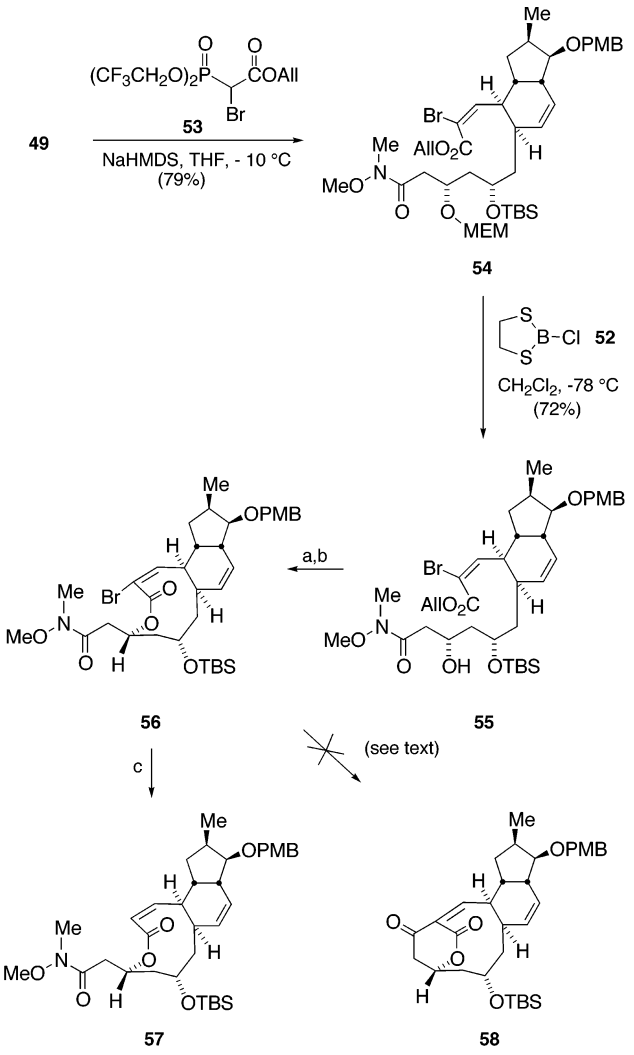
Under the assumption that **51** would be amenable to ester hydrolysis, attempts were made to bring about conversion to the acid under mild saponification conditions or by S_N2 dealkylation.[45] Extensive decomposition was seen under both sets of conditions. When the use of potassium trimethylsilanolate[46] gave comparable results, the decision was made to transform the methyl ester into an allyl ester via conventional exchange conditions (K_2CO_3, allyl alcohol, H_2O). However, this routing was unwieldy and only modestly efficient (46−78% yield of **54**).

To overcome these complications, aldehyde **49** was condensed directly with phosphonate ester **53**.[47] Usefully, **54** was formed in 79% yield. Subsequent recourse to the chloroborolane reagent **52** proved as before to be an appropriate means for effecting specific cleavage of the MEM group (Scheme 9). With **55** in hand, this substance was found to be amenable to deesterification in the presence of palladium acetate, triphenylphosphine, and dimedone in THF solution.[48] At this juncture, the hydroxy carboxylic acid was subjected to the Yamaguchi conditions for macrolactonization.[49] This approach to in situ activation afforded **56** cleanly.

The next hurdle involved the transformation of **56** into keto lactone **58** via a reductive carbon−carbon-bond-forming process.[11,50] To this end, **56** was treated with *tert*-butyllithium in THF at −78 °C. Disappointingly, inefficient conversion to **57** was observed. Through careful exposure of **56** to $(n\text{-Bu})_3SnSiMe_3$ and benzyltriethylammonium chloride in DMF,[51] the loss of bromine could be achieved almost quantitatively. Reaction with samarium iodide in THF containing either HMPA or $Fe(acac)_3$ elicited an entirely parallel result in 93% yield.[52]

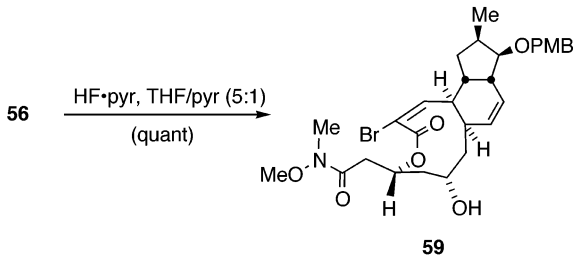
These observations suggested that anion formation was occurring, but that ring closure was inoperative as a consequence of either the low reactivity of the Weinreb amide functionality or the buildup of conformational

SCHEME 9[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$, Ph_3P, dimedone, THF; (b) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; DMAP, toluene, Δ (73% for two steps); (c) $(n\text{-Bu})_3SnTMS$, $BnEt_3NCl$, DMF (97%) or SmI_2, HMPA, THF (93%).

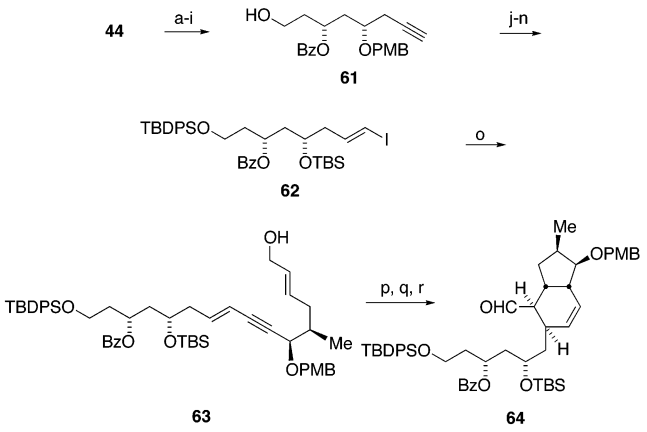
inflexibility during the projected ring closure. In a move designed to reduce hindrance, **56** was successfully desilylated to produce **59**. However, no means was found for



successfully reattaching a smaller protecting group (Me, PMB). Selective reduction of the Weinreb amide to the aldehyde level in the presence of a lactone ring[53] gave equally disappointing results. When this reaction was performed on a small scale (2 mg of **56**), **60** was obtained in acceptable yield. On a larger scale, an unidentified product (not resulting from reduction of the lactone) was

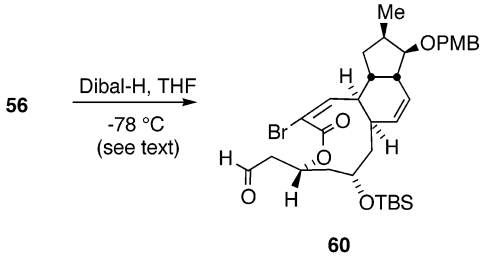
(41) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149.
(42) Rigby, J. H.; Wilson, J. Z. *Tetrahedron Lett.* **1984**, *25*, 1429.
(43) (a) Williams, D. R.; Sakdarat, S. *Tetrahedron Lett.* **1983**, *24*, 3965. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.
(44) Although an 81% yield was realized on one occasion, a lesser efficiency (30−80%) was frequently encountered.
(45) (a) McMurry, J. *Org. React.* **1976**, *24*, 187. (b) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.
(46) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733.
(47) Reagent **53** was prepared from allyl bis(2,2,2-trifluoroethyl)-phosphonoacetate[48a] by Kogen's protocol.[40]
(48) (a) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (b) Casy, G.; Sutherland, A. G.; Taylor, R. J. K.; Urben, P. G. *Synthesis* **1989**, 767. (c) Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019. (d) Arnould, J. C.; Landier, F.; Pasquet, M. J. *Tetrahedron Lett.* **1992**, *33*, 7133. (e) Guibé, F. *Tetrahedron* **1998**, *54*, 2967.
(49) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hoffmann, R. W.; Ditrich, K. *Liebigs Ann. Chem.* **1990**, 23. (c) Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1992**, *161*, 107.
(50) (a) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115. (b) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059. (c) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, *5*, 1115.

SCHEME 10[a]



[a] Reagents and conditions: (a) $HC{\equiv}CSiMe_3$, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C (90%); (b) $(n\text{-}Bu)_4NF$, THF, 0 °C (94%); (c) TBSU, imidazole, DMAP, CH_2Cl_2 (100%); (d) CBr_4, *i*-PrOH, reflux (94%); (e) BzCl, DMAP, Et_3N, CH_2Cl_2 (95%); (f) HF·pyr, THF/pyr (5:1) (96%); (g) $PMBOC(=NH)CCl_3$, CSA, CH_2Cl_2; (h) O_3, Ref 23, −78 °C, $MeOH/CH_2Cl_2$ (1:1), Ph_3P; (i) $NaBH_4$, MeOH (62% for three steps); (j) TBSU, NH_4NO_3, DMF (100%); (k) DDQ, CH_2Cl_2/H_2O (18:1) (91%); (l) TBSU, DMAP, imidazole, CH_2Cl_2 (96%); (m) $(n\text{-}Bu)_3SnH$, AIBN, C_6H_6, reflux; (n) I_2, CH_2Cl_2 (94% for two steps); (o) **10**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N (87%); (p) Zn dust, $AgNO_3$, $Cu(OAc)_2{\cdot}H_2O$, THF/H_2O (1:1), reflux (87%); (q) IBX, THF/DMSO (9:1) (93%); (r) BHT, toluene, sealed tube, 150−160 °C (64%).

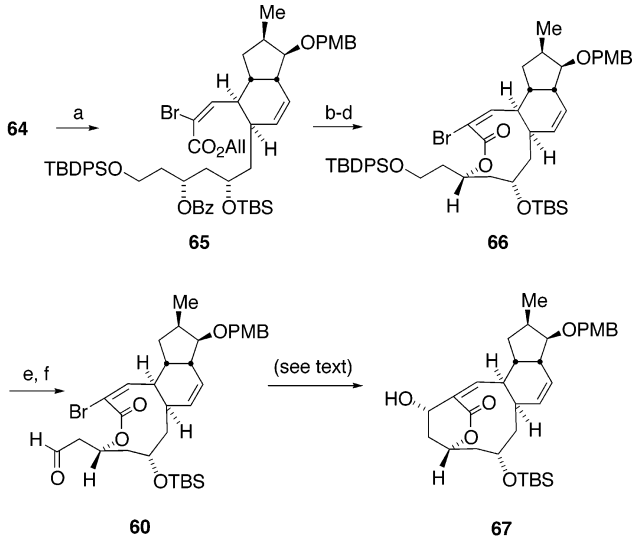
generated efficiently. These issues were avoided by preparing **60** instead from a protected alcohol precursor.



As reflected in Scheme 10, a different subset of protecting groups was introduced for the new intermediates. Although compatibility issues did surface, they were dealt with properly.[54] The more notable steps involved in this series of transformations include (d) the chemoselective unmasking of an MEM ether with carbon tetrabromide in refluxing isopropyl alcohol (94%)[55] and (j) the use of mild reagents (NH_4NO_3, DMF) to install a TBDPS group[56] to avoid the possibility of benzoyl group migration under the basic conditions.

At this point, the conversion of **64** to **65** and then crafting into lactone **66** (Scheme 11) went well. Controlled removal of the primary TBDPS group in the presence of the secondary TBS group was subsequently achieved by

SCHEME 11[a]



[a] Reagents and conditions: (a) $(CF_3CH_2O)_2P(O)CHBrCO_2AlI$, NaHMDS, THF, −78 to −15 °C (64%); (b) $Pd(OAc)_2$, PPh_3, dimedone, THF (88%); (c) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −78 °C; (d) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, DMAP, toluene, reflux (54% for two steps); (e) $(n\text{-}Bu)_4NF{-}HOAc$ (1:1), DMF−THF (1:1) (83%); (f) PCC, NaOAc, 4 Å MS, CH_2Cl_2 (73%).

treatment with a 1:1 mixture of TBAF and acetic acid in 1:1 DMF/THF.[57] Ensuing PCC oxidation delivered aldehyde **60** in preparation for six-membered ring closure. The yields realized were rather variable (67−98%), chiefly because of the instability of **60** to chromatography on silica gel. However, pure product was acquired when Florisil was used instead. Our first attempts to bring about the **60** → **67** conversion by the Nozaki−Hiyama−Kishi reaction made use of relatively high ratios of $NiCl_2$ to $CrCl_2$ (from 1:2[58] to 1:5[59]) as well as high dilution conditions. In all instances, decomposition of the starting material was uniformly observed. An increase in reaction temperature to 40 °C as well as the use of a large excess (100 equiv) of $CrCl_2$[11c] did not rectify matters. When the number of equivalents of $NiCl_2$ was decreased, quantities of **60** ranging from 22% to 36% were recovered, but no **67** was seen. This inability to achieve cyclizatioin of the bromo aldehyde was likewise observed in the presence of Rieke zinc.[60]

These unsatisfactory results have been traced to two contributing factors. The first is the critical instability of **60**. Its *β*-acyloxy part structure is seemingly conducive to *β*-elimination at 30−40 °C such that survival for long periods of time at modestly elevated temperatures is not seen under a variety of conditions. In addition, molecular mechanics calculations[61] (Monte Carlo simulation in MacroModel version 5.0) give evidence that the more

(51) Mori, M.; Kaneta, N.; Isono, N.; Shibasaki, M. *Tetrahedron Lett.* **1991**, *32*, 6139.
(52) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.
(53) (a) Sheppeck, J. E., II; Liu, W.; Chamberlin, A. R. *J. Org. Chem.* **1997**, *62*, 387. (b) Sorensen et al. mentioned a similar transformation briefly in ref 11c. They kindly provided us with the detailed experimental procedure.
(54) For a detailed discussion of the relevant issues, see: Chang, J. Ph.D. Dissertation, The Ohio State University, 2004; Chapter 4.
(55) Lee, A. S.-Y.; Hu, Y.-I.; Chu, S.-F. *Tetrahedron* **2001**, *57*, 2121.
(56) Hardinger, S. A.; Wijaya, N. *Tetrahedron Lett.* **1993**, *34*, 3821.
(57) Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306.
(58) (a) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647. (b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.
(59) Goldring, W. P. D.; Pattenden, G. *Org. Biomol. Chem.* **2004**, 466.
(60) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.
(61) These calculations were performed by David G. Hilmey. Note that the PMB group was replaced by OPh and OTBS by OCH_3 to simplify the approximations.

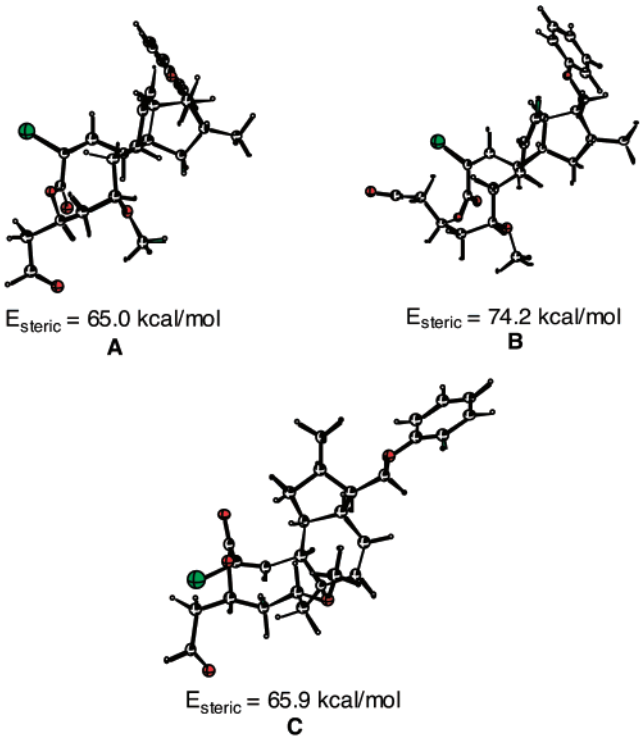


FIGURE 1. Conformational analysis of **60**.

populated, lower energy conformations of **60** are not particularly conducive to ring closure, the kinetics of which should therefore be slowed (Figure 1). The computational analysis indicates the global minimum-energy conformer to be **A**. In this structure, the vinyl bromide and carboxaldehyde functionalities are too distal to become covalently bonded. The proximity factor is no longer an issue with conformer **B**, but this structural arrangement is 9 kcal/mol less stable than **A**. Conformer **C** is higher in energy than **A** by only 1 kcal/mol. However, in this example the lactone bridge is improperly oriented toward the β-face and would therefore lead to an unwanted diastereomer. Consequently, the conformational inflexibility of the macrolactone ring in **60** disallows proximity of the two reaction sites and renders ring closure slow and inefficient.

In summary, a strategy has been developed for the synthesis of stereochemically well defined seco ring D intermediates related to cochleamycin A. The sequence of steps leading to lactones **57**, **59**, and **60** involves adaptation of the Sonagashira coupling reaction and an intramolecular Diels−Alder cycloaddition, alongside stereocontrolled chain extensions. However, the reaction centers positioned external to the macrocycle appear not to be able to approach each other because of unanticipated conformational constraints. These findings teach that topological changes in macrocyclic lactones are not necessarily low-energy processes and merit up-front consideration when being contemplated in retrosynthetic planning.

Acknowledgment. This work was supported in part by the Yamanouchi USA Foundation.

Supporting Information Available: Experimental details and $^{1}H/^{13}C$ NMR spectral data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO049084A