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A Synthetic Approach toward Nitiol: Construction of Two 1,22-Dihydroxynitianes

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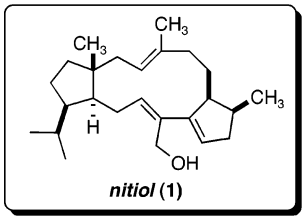
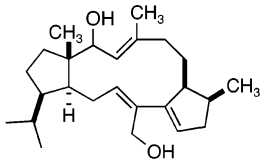


***nitiol* (1)**



1,22-dihydroxynitianes

Synthetic work toward the total synthesis of nitiol has culminated in the construction of two epimeric hydroxylated derivatives, the 1,22-dihydroxynitianes. Key stereodefining steps in the construction of the A-ring fragment (**13**) were the use of a siloxy−epoxide rearrangement reaction, a Pauson−Khand reaction, a Norrish 1 photochemical cleavage reaction, and a highly regio- and stereoselective hydrostannylation reaction of an ynoate. The stereochemistry of the synthetically challenging C-ring fragment (**20**) was established using an Ireland−Claisen reaction and a Grubbs ring-closing metathesis process as key steps. The 12-membered B-ring of the nitiane skeleton was constructed using a copper-promoted Stille cross-coupling and a Kishi−Hiyama−Nozaki carbonyl addition reaction. Unfortunately, the carbonyl addition reaction produced hydroxyl functionality that could not be selectively removed. Consequently, a synthesis of epimeric 1,22-dihydroxynitianes, which are compounds that are structural hybrids of two natural products, nitiol and variculanol, was completed.

Introduction

Gentianella nitida (Gentianaceae), commonly known as "Hercampuri" or "Hircampure", is a biennial medicinal plant from the Andes region of Peru. Aqueous extracts of the whole plants are used in traditional Peruvian folk medicine. Chemical investigations of *G. nitida* by Kawahara and co-workers led to the discovery of the novel sesterterpenoids nitiol (**1**) and nitidasin (Figure 1).[1] The Kawahara group assessed the capability of these terpenoids to modulate the gene expression of interleukin-2 (IL-2) in Jurkat cells, a human T-cell line, using a competitive PCR-based bioassay.[2] After incubation for 6 h, the IL-2 mRNA level in the cells treated with **1** was roughly three times higher than that in the control cell line. Nitisadin had no significant effect. Thus, **1** appears to be an enhancer of IL-2 gene expression. As other known modulators of IL-2 gene transcription are calcineurin inhibitors (cyclic polypeptides or macrolides), **1** or its structural relatives are suggested to be useful tools for the discovery of novel signal transduction pathways guiding the transcription of the IL-2 gene.

The structural complexity of **1** is characterized by a number of features. Two five-membered rings are fused to a central 12-membered macrocycle that contains two trisubstituted alkenes. In addition, the isopropyl group at C18 in the A ring is cis to the C23 methyl group at the ring junction. These structural attributes are also observed in the presumably biosynthetically related compound, variculanol, which was isolated in 1991.[3] The structural complexity of **1**, paired with its potential biological activity, prompted us to initiate a program targeted toward its synthesis.

Analysis of **1** suggested a bifurcative synthetic approach (Scheme 1). Disconnection of the C1−C2 bond produced an uncyclized precursor. In the synthetic direction, a number of possibilities, including a carbonyl addition reaction, a transition-

(1) Nitiol: (a) Kawahara, N.; Nozawa, M.; Kurata, A.; Hakamatsuka, T.; Sekita, S.; Satake, M. *Chem. Pharm. Bull.* **1999**, *47*, 1344. Nitidasin: (b) Kawahara, N.; Nozawa, M.; Flores, D.; Bonilla, P.; Sekita, S.; Satake, M. Kawai, K.-I. *Chem. Pharm. Bull.* **1997**, *45*, 1717.

(2) Hakamatsuka, T.; Tanaka, N. *Bio. Pharm. Bull.* **1997**, *20*, 464.

(3) Singh, S. B.; Reamer, R. A.; Zink, D.; Schmatz, D.; Dombrowski, A.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 5618.

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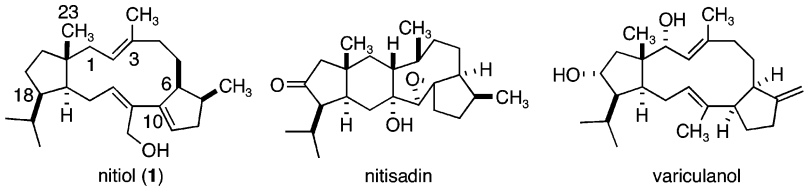
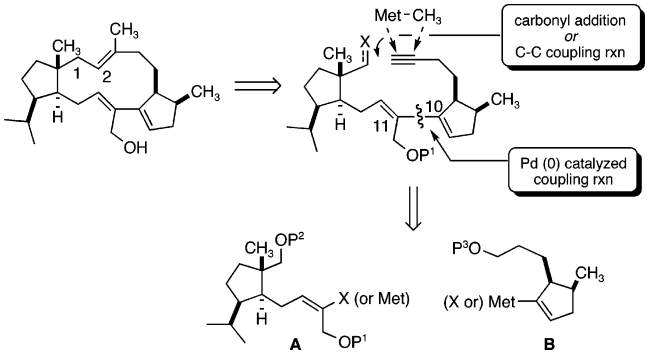


FIGURE 1. Nitiol and structurally related compounds.

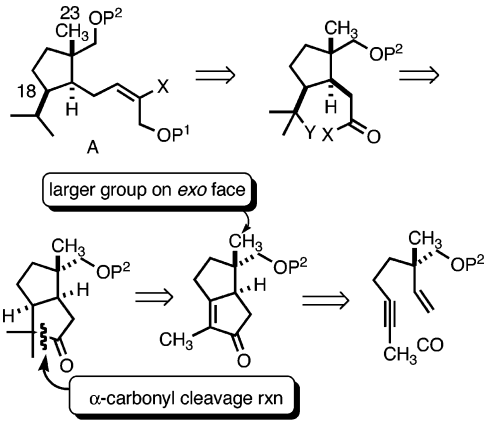
SCHEME 1. Analysis of 1



metal-catalyzed coupling process, or a tandem carbometalation−S_N2 displacement, were envisioned to connect this crucial ring-forming bond. The necessary double bond geometry prior to the ring-closing reaction would be generated by regio- and stereoselective carbometalation of a terminal alkyne. Subsequent disconnection of the C10−C11 bond generates two halves, **A** and **B**. The construction of that bond was conceived to be possible using standard palladium(0)-catalyzed cross-coupling protocols.

Functionalized cyclopentane **A**, the "A-ring" of nitiol, contains a cis stereochemical relationship between the C23 methyl group and isopropyl groups at C18 (nitiol numbering) in addition to what will become the trans ring junction of the A−B ring system. A key issue in any construction of nitiol is the establishment of the configuration of the isopropyl moiety on the cyclopentane A ring.[4] A classic method for setting stereochemistry is to use the bias of a cyclic system, after which the ring is broken open. A *trans*-hydrindane ring system may seem like an appropriate precursor to **A**. However, it is well established that reactions generating *trans*-hydrindanes bearing pendant methyl and isopropyl groups on the five-membering ring almost exclusively result in a trans relationship between the methyl and isopropyl groups.[5] For this reason, the conformational bias of a [3.3.0]bicyclooctane system was a key design element in our synthetic approach to **A**. As envisioned, this conformational bias would control the (relative) stereochemical outcomes of reactions that established the stereogenic centers at C17 and C18 (Scheme 2). A number of methods were

SCHEME 2. Analysis of the A-Ring Fragment



conceived to cleave the designated bond in the bicyclooctane, including a Baeyer−Villiger reaction, a fragmentation proceeding through an oxygen-based radical or a Norrish type 1 process. The required bicyclooctane was thought to be obtainable using a carbonylative cycloisomerization of an appropriate enyne—specifically the Pauson−Khand reaction.[6,7] Of interest to us was the question of diastereoselectivity in the Pauson-Khand process. Earlier elegant studies had examined the stereoselectivity of cyclizations of enynes containing substituents at the allylic or propargylic positions. In general, the reaction path placed the larger substituent on the exo face of the bicycle in the major product.[8] In this proposed application of the Pauson−Khand reaction, would there be enough steric differentation between a methyl group and a protected hydroxymethylene group to achieve reasonable amounts of the desired diastereomer? As this reaction would establish the necessary trans-ring junction for the A−B ring fusion in **1**, this consideration was an important issue at the outset.

(4) For synthetic sequences to produce structures related to that of the nitiol A-ring, see: (a) Kato, N.; Wu, X.; Nishikawa, H.; Nakanishi, K.; Takeshita, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1047. (b) Kato, N.; Wu, X.; Nishikawa, H.; Takeshita, H. *Synlett* **1993**, 293. (c) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765. (d) Mehta, G. *Pure Appl. Chem.* **1990**, *62*, 1263. (e) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1299. (f) Mehta, G.; Krishnamurthy, N. *Tetrahedron Lett.* **1987**, *28*, 5945.

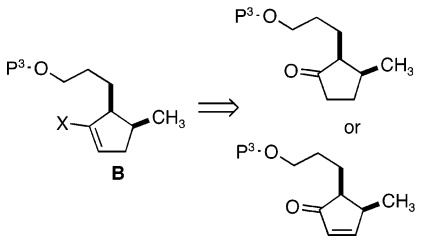
(5) See, for example, in retigeranic acid A-ring construction: (a) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339. (b) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872. (c) Attah-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.

(6) Reviews dealing with the Pauson−Khand reaction: (a) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022. (b) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873. (c) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (d) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (e) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 1037. (f) Schore, N. E. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, p 2. (g) An interesting overview of other synthetic processes under the conditions of the Pauson−Khand reaction: Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795.

(7) Examples of recent synthetic work using the Pauson−Khand reaction as a critical step: (a) Winkler, J. D.; Lee, E. C. Y.; Nevels, L. I. *Org. Lett.* **2005**, *7*, 1489. (b) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053. (c) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 885. (d) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682.

(8) (a) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761. (b) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903. (c) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (d) Magnus, P.; Becker, D. *J. Am. Chem. Soc.* **1987**, *109*, 7495 and references therein.

SCHEME 3. Analysis of the C-Ring Fragment



The "C-ring" fragment **B** (X = halogen, pseudohalogen, or metal), which contains a protected hydroxyl function as a synthetic precursor to an alkyne function, was believed to be most directly derivable from a cis-2,3-disubstituted cyclopentanone or a cis-4,5-disubstituted 2-cyclopentenone (Scheme 3). There were a number of concerns, though. One was the known sensitivity of compounds of these types to epimerization or alkene migration processes. As those destructive pathways are promoted by acidic, basic, or thermal conditions, care would be necessary in the preparation, handling, and further reactions of such a synthetic intermediate.[9] In addition, although synthetic protocols to generate such cis-disubstituted ketones have been reported, these have limitations in terms of generality, and importantly, most are not easily adaptable for the formation of enantioenriched material.[9,10] Therefore, our *enantioselective* synthetic route to **B** would have to incorporate mild conditions to minimize destructive side reactions. It would be also be useful for the synthetic community if this method could be generally adaptable for the construction of structurally related cis-2,3-disubstituted cyclopentanones. This report summarizes our efforts toward that end.

Results and Discussion

Enantioselective Synthesis of the A-Ring Fragment. The preparation of an A-ring fragment in enantioenriched form was patterned on our previously reported synthetic route to a racemic A-ring fragment (Scheme 4).[11] However, the establishment of the quaternary stereogenic center in an enantiocontrolled manner was required. To that end, we opted to use a siloxy−epoxide rearrangement reaction to construct the quaternary center.[12] Allyl alcohol **2**, which is readily available from geraniol,[13] was subjected to standard Sharpless epoxidation conditions to produce epoxy alcohol **3** in 93% yield (94% ee).[14,15] Protection of the alcohol function of **3** as its *tert*-butyldimethylsilyl ether set the stage for the siloxy−epoxide rearrangement reaction. Following the procedures of Yamamoto, the treatment of **4** with methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR), a bulky aluminum-based Lewis acid, in CH_2Cl_2 from −78 −40 °C generated aldehyde **5** in 95% yield (94% ee).[16] As precedented, this rearrangement proceeded with rigorous chirality transfer arising from antiperiplanar migration of the siloxymethylene function to the epoxide moiety. This synthetically valuable transformation is highly recommended. The spectral data for **5** produced in this manner was identical to that of the previously prepared sample of racemic **5**.[11]

With multigram quantities of enantioenriched **5** available, efforts were focused on advancing this material to the fully functionalized A-ring fragment. A standard Wittig olefination reaction was used to convert **5** to enyne **6** (95%). A number of conditions for the Pauson−Khand reaction were screened during our earlier studies. The treatment of enyne **6** with $Co_2(CO)_8$, powdered 4 Å molecular sieves, and NMO resulted in the production of a 6:1 ratio of bicycles **7a** and **7b** in 86% yield.[17] Separation of the diastereomers was readily performed using column chromatography. The relative stereochemistry of each diastereomer was supported through selective NOE experiments.

Treatment of **7a** with lithium tri-*sec*-butylborohydride (L-Selectride) in THF at −78 °C generated, in a site-selective manner, the more substituted enolate which was subsequently quenched with methyl iodide to yield **8** in 92% yield. The [3.3.0] bicyclic framework ensured that the conjugate reduction occurred to produce a cis-ring junction, thus establishing the stereochemical identity for what would become the C18 isopropyl group in the nitiol A-ring. Although a number of options to cleave the bicycle were entertained, the first process we selected turned out to be most effective for our purposes (Scheme 5). In an optimized, gram-scale experiment, ketone **8** was dissolved in dry methanol (to a 0.01 M solution) in a quartz flask and subjected to UV light for roughly 24 h to produce ester **9** in 82% yield (90% based on recovered starting material). This Norrish type 1 fragmentation process is envisioned as proceeding through an excited state that undergoes homolytic cleavage of the more electron-rich α-bond.[18] After intersystem crossing of the resulting biradical, a hydrogen abstraction forms a ketene intermediate that reacts with methanol, the solvent, to produce **9**. The Norrish type 1 fragmentation works exceedingly well in the context of this synthetic route.[19] The isopropyl group of the A-ring is established in high yield without the need for the removal of extra functional groups.

As we had decided to prepare the A-ring fragment as the organometallic component for a potential cross-coupling reac-

(9) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008.

(10) (a) Mander, L. N.; Thomson, R. J. *J. Org. Chem.* **2005**, *70*, 1654. (b) Zanoni, G.; Porta, A.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 4346. (c) Zanoni, G.; Porta, A.; Castronovo, F.; Vidari, G. *J. Org. Chem.* **2003**, *68*, 6005. (d) Crombie, L.; Mistry, K. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1981. (e) Helmchen, G.; Ernst, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4054. (f) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438. (g) Whitesell, J. K.; Minton, M. *J. Am. Chem. Soc.* **1987**, *109*, 6403.

(11) Wilson, M. S.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2041.

(12) For syntheses of compounds that utilize a siloxy−epoxide rearrangement reaction as a key step, see: (a) Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1998**, *120*, 11633. (b) Eom, K. D.; Raman, J. V.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **2003**, *125*, 5415. (c) Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S.; Fujioka, H. *J. Org. Chem.* **1997**, *62*, 4991. (d) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (e) Fenster, M. D. B.; Dake, G. R. *Chem.−Eur J.* **2005**, *11*, 639.

(13) (a) Muto, S.-E.; Nishimuram Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2159. (b) Halcomb, R. L.; Mohr, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 1712. For an earlier synthesis of **2**, see: (c) Abidi, S. L. *J. Org. Chem.* **1986**, *51*, 2687.

(14) (a) The Sharpless epoxidation of **2** has been reported previously: Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033. (b) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (c) Gao, Y.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

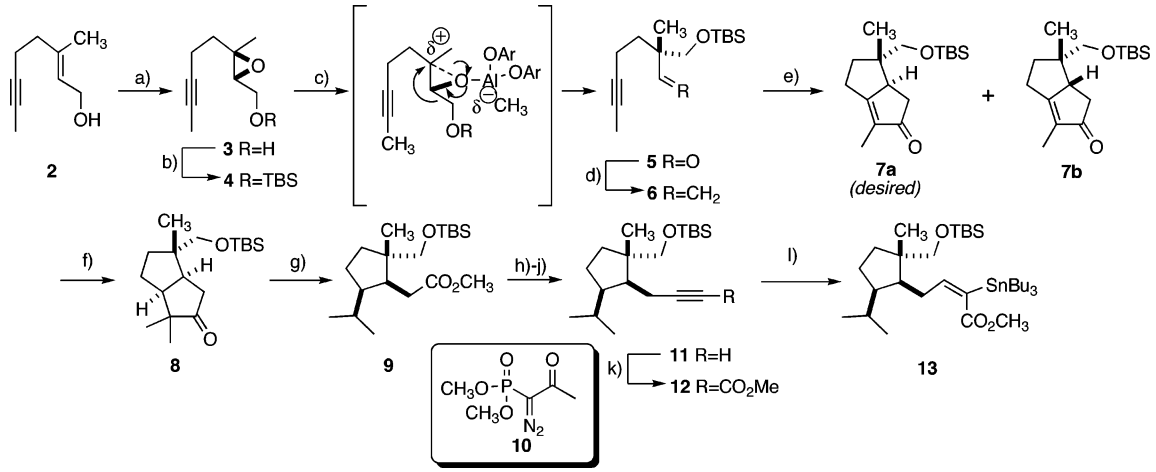
(15) The ee for this reaction was established by converting **3** to its (*R*)-(−)-*O*-acetylmandelic ester. See the Supporting Information for details.

(16) (a) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431. (b) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983.

(17) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Org. Lett.* **1999**, *1*, 1187.

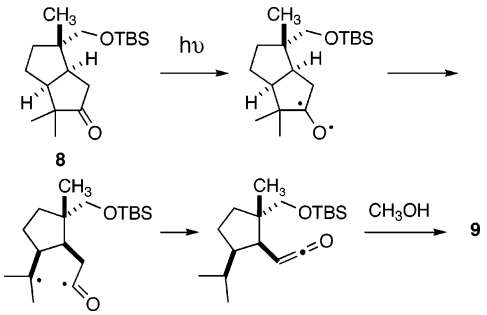
(18) Reviews: (a) Bohne, C. In *CRC Handbook of Photochemistry and Photobiology*; Harspool, W. M., Song, P. S., Eds.; CRC Press: New York, 1995; Chapter 34, pp 416−422. (b) Bohne, C. In *CRC Handbook of Photochemistry and Photobiology*; Harspool, W. M., Song, P. S., Eds.; CRC Press: New York, 1995; Chapter 35, pp 423−436. (c) Horspool, W. M. *Photochemistry* **1994**, *25*, 67.

SCHEME 4. Enantioselective Construction of the A-Ring Fragment[a]



[a] Reaction conditions: (a) Ti(O-*i*-Pr)$_4$, (−)-DIPT, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −20 °C (93%, 94% ee); (b) TBSCl, imidazole, DMF, rt (97%); (c) MABR, CH_2Cl_2, −78 to −40 °C (95%); (d) KHMDS, CH_3PPh_3Br, THF, −78 °C to rt (95%); (e) $Co_2(CO)_8$, 4 Å MS, NMO (9 equiv), CH_2Cl_2 (86%, 6.2:1 of **7a**/**7b**); (f) (i) LiHB(*s*-Bu)$_3$, THF, −78 °C, (ii) CH_3I, −78 °C to rt (92%); (g) *hν* (>190 nm), quartz filter, 0.01 M in CH_3OH, 28 h (90% brsm); (h) DIBAL-H, CH_2Cl_2, −78 °C to rt (91%); (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C (92%); (j) Ohira−Bestmann phosphonate (**10**), K_2CO_3, CH_3OH, 0 °C to rt (94%); (k) LDA, $ClCO_2CH_3$, THF, −78 °C to rt (95%); (l) Bu_3SnH, $Pd(PPh_3)_4$ (3 mol %), THF, rt (96%).

SCHEME 5. Norrish Fragmentation Reaction



tion, the stereocontrolled preparation of an appropriate vinylstannane was a key problem. Further processing of **9** using relatively standard synthetic manipulations (reduction, oxidation, alkyne formation using the Ohira−Bestmann phosphonate **10**,[20] alkyne methoxycarbonylation) provided ynoate **12** in excellent yield. Treatment of **12** with tri-*n*-butyltin hydride in the presence of 3 mol % of tetrakis(triphenylphosphine)palladium(0) generated vinylstannane **13** in 96% yield in a regio- and stereocontrolled manner.[21] Slow addition of the tin hydride over 45 min to the reaction mixture was crucial to produce consistently satisfactory results. This sequence enabled the preparation of multigram quantities of **13**, a suitable A-ring fragment.

Enantioselective Synthesis of the C-Ring Fragment. Allyl alcohol **14**, available by minor modification of the known kinetic resolution of the racemic alcohol using a Sharpless epoxidation,[22] was esterified with 5-(*p*-methoxylbenzyl)oxypentanoic acid[23] using DCC and DMAP (Scheme 6). Conversion of this ester to its (*E*)-ketene silyl acetal using literature conditions ((i) NEt_3, TMSCl, −78 °C; (ii) LDA, −78 °C) followed by heating produced, after aqueous workup, carboxylic acid **16**.[24] The well-accepted chair topology in the transition state of the Ireland−Claisen reaction provided excellent transmission of stereochemical information from the starting material to the desired product. Conversion of the carboxylic acid to its corresponding Weinreb amide proved to be quite difficult, and so specific conditions were developed to circumvent this problem.[25] To that end, the reaction of **16** with methanesulfonyl chloride (1.1 equiv) and triethylamine (3 equiv) followed by *N*,*O*-dimethylhydroxylamine (1.5 equiv) produced the Weinreb amide in 80% yield. Its conversion to enone **17** was smoothly carried out using vinylmagnesium bromide. Ring-closing metathesis using a second-generation Grubbs catalyst **18** in degassed dichloromethane produced functionalized cyclopentanone **19** in 81% yield.[26,27] Interestingly, the remainder of the product mixture

(19) For examples of the use of Norrish 1 chemistry in synthesis, see: (a) Nicolaou, K. C.; Gray, D.; Tae, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675. (b) Muraoka, O.; Okumura, K.; Maeda, T.; Wang, L.; Tanabe, G. *Chem. Pharm. Bull.* **1995**, *43*, 517. (c) Muraoka, O.; Okumura, K.; Maeda, T.; Tanabe, G.; Momose, T. *Tetrahedron: Asymmetry* **1994**, *5*, 317. (d) Hwu, J. R.; Gilbert, B. A.; Lin, L. C.; Liaw, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 161. (e) Morizur, J. P.; Tortajada, J. *Bull. Chim. Soc. Fr.* **1983**, II-175. (f) Kossanyi, J.; Furth, B.; Morizur, J. P. *Tetrahedron Lett.* **1973**, *36*, 3459. (g) Bidan, G.; Kossanyi, J.; Meyer, V.; Morizur, J. P. *Tetrahedron* **1977**, *33*, 2193.

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(22) Wessel, T. A.; Berson, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 495. "Aging" of the reaction components at −20 °C rather than −40 °C for 30 min prior to the addition of oxidant was important to achieve high selectivities. Our attempts to resolve this alcohol using enzyme catalysis gave unsatisfactory results.

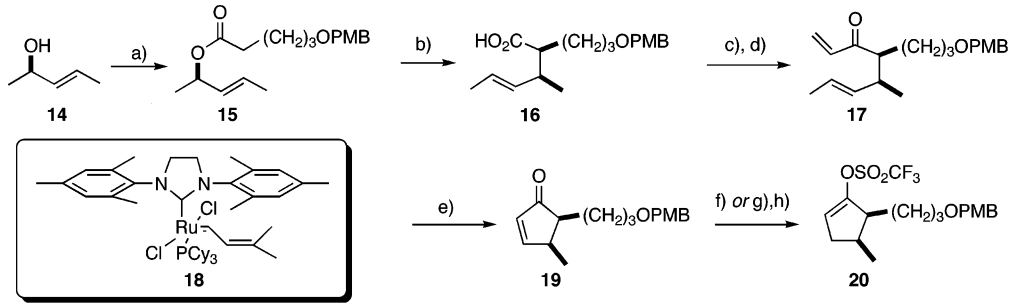
(23) This compound was generated from monoprotection of 1,5-dihydroxypentane (NaH, PMBCl) followed by a Jones oxidation (CrO_3, sulfuric acid, acetone).

(24) (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. (b) Boeckman, R. K.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *43*, 4152. (c) Kurth, M. J.; Burns, D. H.; O'Brien, D. H. *J. Org. Chem.* **1984**, *49*, 731. For a recent review of the Ireland−Claisen rearrangement, see: (d) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905.

(25) Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984.

(26) (a) Chatterjee, A. K.; Morgan, J. P. Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3873. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (c) Wilhelm, T. E.; Belderrain, T. R.; Brown, S. N.; Grubbs, R. H. *Organometallics* **1997**, *16*, 3867. (d) Christ, M. L.; Sabo-Etienne, S.; Chaudret, B. *Organometallics* **1994**, *13*, 3800.

SCHEME 6. Enantioselective Construction of the C-Ring Fragment[a]



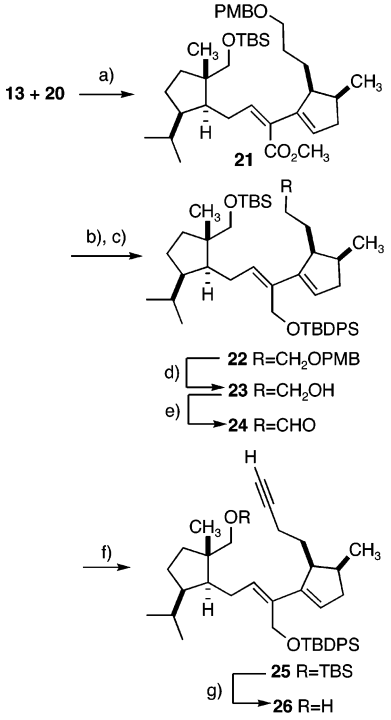
[a] Reaction conditions: (a) 5-(*p*-methoxybenzyl)oxypentanoic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt (85%); (b) (i) TMSCl, NEt_3, THF, −78 °C, (ii) LDA, −78 to +60 °C, (iii) 1 N HCl (91%); (c) (i) MsCl, NEt_3, *N*,*O*-dimethylhydroxylamine, THF, 0 °C (80%); (d) vinylmagnesium bromide, THF, 0 °C to rt (82%); (e) **18** (5 mol %), CH_2Cl_2, 40 °C (reflux) (81%); (f) (i) LiHB(*s*-Bu)$_3$, THF, −78 °C, (ii) $PhNTf_2$ (69%); (g) H_2, Pd/C (88%); (h) LHMDS, $PhNTf_2$, THF, −78 °C to rt (43%).

from the metathesis reaction resulted from dimerization of **17** at the enone function. Reactions using the related benzylidene catalyst from Aldrich resulted in lower yields (∼50−60%) of **19** due to increased cross-metathesis. The diastereomeric ratio of **19** to its trans epimer (synthesized independently, see below) after the metathesis reaction was 12:1, satisfactory for our purposes.

Conversion of **19** to the substituted C-ring fragment could be carried out by one of two methods. Catalytic hydrogenation of **19** could subsequently be followed by kinetic enolization (LHMDS, −78 °C) with subsequent reaction with *N*-phenyltriflimide to produce **20** with minimal epimerization. An alternate route that was also explored was the reaction of enone **19** with L-Selectride followed by quenching with *N*-phenyltriflimide to produce **20** in 69% yield.[28] Of the two protocols, the latter proved to be more convenient. To ensure that minimal epimerization occurred along this synthetic sequence, the trans-disubstituted diastereomer of **20** (in racemic form) was constructed following this protocol in Scheme 6 using the (*Z*)-diastereomer of **15** as the starting material.[29] It could be established that **20** was produced in a 10:1 diastereomeric ratio.

Fragment Coupling. The two fragments **13** and **20** were combined using a Stille reaction modified by the addition of a Cu(I) reagent (Scheme 7).[30] This process proceeded efficiently in 74% yield using 10 mol % of tetrakis(triphenylphosphine)-palladium(0), CuCl (5 equiv), and LiCl (6 equiv) in DMSO at 60 °C. At this point, the ester functionality was reduced to an alcohol and protected at its *tert*-butyldiphenyl silyl ether. The *p*-methoxybenzyl ether proved to be quite resistant to deprotection without affecting the conjugated diene. Both DDQ and CAN cleaved the benzyl ether, but each reagent also appeared to isomerize the alkene within the C-ring to form a tetrasubstituted alkene. After significant experimentation, catecholboron bromide in the presence of 2,6-lutidine was found to cleanly deprotect the PMB ether in excellent yield (91%).[31] Oxidation of the alcohol function in **23** using Dess−Martin periodinane[32] and reaction with the Ohira−Bestmann phosphonate[20] furnished the terminal alkyne **25** in 85% yield (over two steps). At this point, deprotection of the *tert*-butyldimethylsilyl ether within **25** in the presence of the *tert*-butyldiphenyl silyl ether was necessary. The reaction of **25** with 5 mol % of bis(acetonitrile)-palladium chloride with water (5 equiv) in acetone at 75 °C,

SCHEME 7. Fragment Coupling[a]



[a] Reaction conditions: (a) $Pd(PPh_3)_4$ (10 mol %), CuCl (5 equiv), LiCl (6 equiv), DMSO, rt to 60 °C (74%); (b) DIBAL-H, CH_2Cl_2, −78 °C (87%); (c) TBDPSCl, imidazole, DMF, 0 °C to rt (93%); (d) catecholboron bromide (3 equiv), 2,6-lutidine, 0 °C (91%); (e) Dess−Martin periodinane (5 equiv), 2,6-lutidine (87%); (f) phosphonate **10**, K_2CO_3, CH_3OH, 0 °C to rt (96%); (g) $(CH_3CN)_2PdCl_2$ (5 mol %), acetone/H_2O, 75 °C (77%, 90% based on recovered starting material).

(27) For pioneering examples of the use of Claisen and RCM reactions in sequence to produce stereodefined cyclic compounds, see: (a) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158. (b) Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160. (c) Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2000**, *65*, 1222. (d) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716. (e) Francais, A.; Bedel, O.; Picoul, W.; Meddour, A.; Courtieu, J.; Haudrechy, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1141. (f) Fujiwara, K.; Goto, A.; Sato, D.; Kawal, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465.

(28) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.

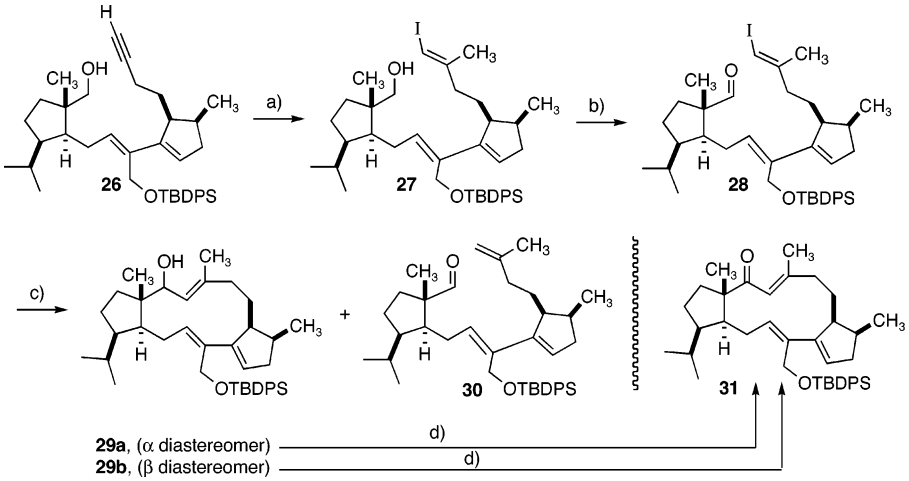
(29) Please refer to the Supporting Information for details.

(30) (a) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600. (b) Piers, E.; Yee, J. G. K.; Gladstone, P. L. *Org. Lett.* **2000**, *2*, 481. (c) Piers, E.; McEachern, E. J.; Romero, M. A.; Gladstone, P. L. *Can. J. Chem.* **1997**, *75*, 694.

(31) Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

(32) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

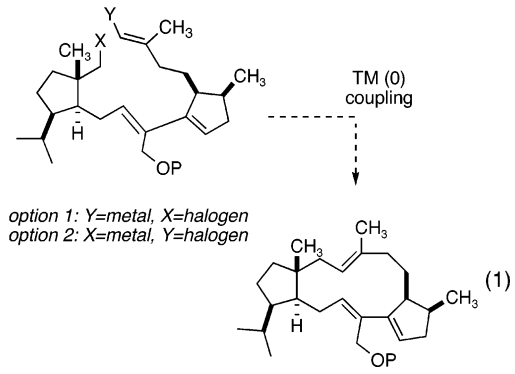
SCHEME 8. Macrocyclization by Carbonyl Addition[a]



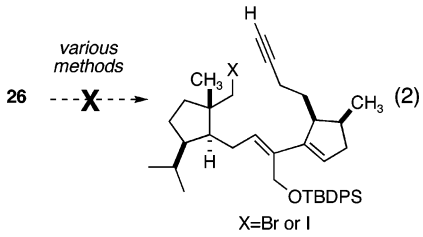
[a] Reaction conditions: (a) (i) $Al(CH_3)_3$, Cp_2ZrCl_2, CH_2Cl_2, −20 °C to rt, (ii) I_2, THF, −30 °C to rt (82%); (b) Dess−Martin periodinane, 2,6-lutidine, CH_2Cl_2 (90%); (c) $NiCl_2$ (1.3 equiv), $CrCl_2$ (9 equiv), 3:1 DMSO−THF (70% of **29**, 1:1 ratio of diastereomers; 21% of **30**); (d) Dess−Martin periodinane, 2,6-lutidine, CH_2Cl_2, (∼80%).

conditions developed by Keay and Wilson, achieved this desired tranformation effectively (77%, 90% based on recovered starting material).[33] With significant quantities of **26** in hand, our attempts to construct the B-ring of **1** began.

Macrocyclization Strategy Using Cross-Coupling. The initial, motivating retrosynthetic thinking regarding the construction of the macrocyclic B-ring centered on the use of a cross-coupling reaction. Two options were generally considered (eq 1). Provided that a vinylmetal species could be selectively generated from an alkyne in the presence of an alkyl halide, a relatively unusual cross-coupling process between an sp^2-hybridized organometallic and a sp^3-hybridized alkyl halide could be used to form the final critical C−C bond (option 1).[34] In the event that this reaction was not feasible, an alternative idea was to take advantage of the known ability of elemental zinc to selectively react with an alkyl halide bond in the presence of an alkenyl halide (option 2).[35] After the appropriate organometallic species was generated using either option, the addition or presence of a group 10 catalyst system might enable an intramolecular Negishi-type cross coupling reaction forming a macrocycle.



Unfortunately, the investigations into such a bond-forming event were completely stymied by our inability to convert alcohol **26** to its corresponding alkyl halide (eq 2). Despite reasonable precedent for this process within the literature and in our research group using structurally related compounds, a number of reaction conditions (e.g., Tf_2O then NaI, solvent or I_2, PPh_3, imidazole, or DEAD, PPh_3, ZnX_2) failed to secure any of the necessary alkyl halide products.[36] Our attempts to convert **26** to its trifluoromethanesulfonate derivative were unsuccessful—the product (not fully characterized) that was obtained in these attempts did not have a signal in its ^{19}F NMR spectrum. This setback forced us to consider alternative methods to close the 12-membered ring of **1**.



Macrocyclization Strategy Using Carbonyl Addition. At this point, there was some concern that the macrocycle could be not formed under any conditions, and consequently, a more deliberate approach was taken. The Kishi−Nozaki−Hiyama (K−N−H) carbonyl addition reaction has excellent precedent for the construction of large rings.[37] Consequently, its application toward the construction of **1** was investigated. The vinylorganometallic species generated by the reaction of the alkyne

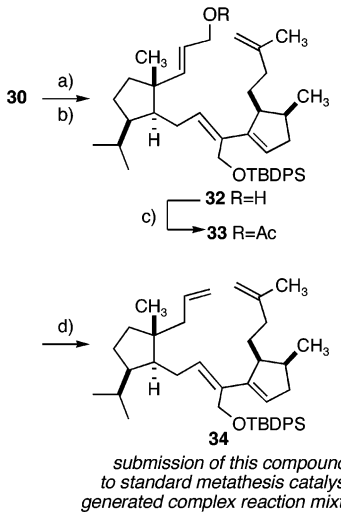
(33) Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918.

(34) At the project's conception, this was an aggressive tactic. More recent work demonstrates that this is conceptually achievable: (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186. (b) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (c) Kirchhoff, K.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (d) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (f) Mentzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718. (g) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (h) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056. (i) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403. (j) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (k) Nakamura, M.; Matsuo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (l) Martin, M.; Fürtsner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955.

(35) Fenster, E. Ph.D. Thesis, University of British Columbia, February 2006.

(36) (a) Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5544. (b) Wright, J.; Drtina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806. (c) Ho, P. T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.

SCHEME 9. Synthesis of Metathesis Precursor[a]

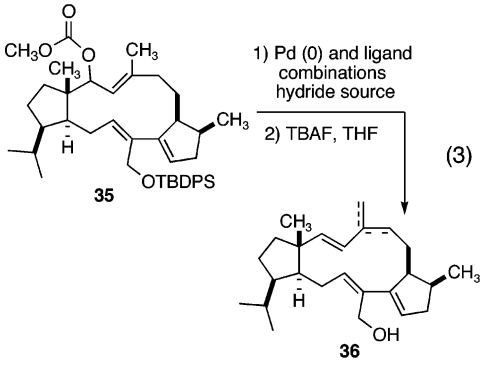


[a] Reaction conditions: (a) $(CH_3O)_2POCH_2CO_2CH_3$, NaH, THF; (b) DIBAL-H, CH_2Cl_2, −78 °C to rt (77%, two steps); (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (86%); (d) $Pd_2(dba)_3$, P(*n*-Bu)$_3$, Et_3NHCO_2H, 1,4-dioxane, 100 °C (94%).

function within **26** with trimethylaluminum in the presence of bis(cyclopentadienyl)zirconium chloride was quenched with iodine using the conditions defined by Negishi to generate alkenyl iodide **27** in 82% yield (Scheme 8).[38] The aldehyde **28** was produced using the Dess−Martin protocol.[32] Gratifyingly, the treatment of **28** to K−N−H macrocyclization conditions as used by the Pattenden laboratory produced a 70% yield of **29** as a 1:1 mixture of diastereomers.[39] A small amount of aldehyde **30**, an uncyclized byproduct, was recovered from the product mixture as well. Alcohols **29a** and **29b** could be separated using column chromatography. The relative configuration of each epimer was established spectroscopically at a later stage (see below). Oxidation of each diastereomeric alcohol gave macrocyclic ketone **31**. As the feasibility of the macrocycle closure had been convincingly demonstrated, we decided to examine a third possibility for ring closure.

Macrocyclization Strategy Using Ring-Closing Metathesis. The byproduct of the K−N−H cyclization, alkene **30**, presented an opportunity to examine a third method for the closure of the macrocycle. A ring-closing metathesis strategy, if effective, would generate the desired ring system of nitiol without generating an extraneous functional group that requires removal. Consequently, this synthetic route appeared to have clear advantages over the K−N−H protocol. To test the metathesis reaction, aldehyde **30** was elaborated to allyl alcohol **32** using conventional conditions (Horner−Wadsworth−Emmons reaction, DIBAL-H reduction) (Scheme 9). The isolated yield for the recovery of **32** was 77% over the two steps. The conversion of alcohol to allylic acetate **33** using standard conditions (Ac_2O, Et_3N, DMAP, CH_2Cl_2, 86%) was followed by a palladium(0)-catalyzed reduction.[40] The reaction of **33** with triethylammonium formate in the presence of 5 mol % of $Pd_2(dba)_3$ and tri-*n*-butylphosphine in dioxane at 100 °C enabled the isolation of a 94% yield of the terminal alkene **34**. Although this sequence produced the requisite ring-closing metathesis precursor, the limited quantities of **34** (from **30**) did not permit an extensive examination of possible metathesis reaction conditions. In most instances, subjecting **34** to a second-generation Grubbs metathesis catalyst resulted in compound decomposition. Possible macrocyclization products were not detected using GC−MS analysis of the reaction mixture. At this point, it was evident that the allyl alcohols **29** from the K−N−H cyclization would have to serve as key synthetic intermediates if our route to nitiol was to be successful.

Attempts to Deoxygenate 29. Our prior experience using Pd(0)-catalyzed reduction to convert **33** to **34** suggested that this protocol was particularly attractive for the C1 deoxygenation of **29**. Although the formation of alkene isomers was a significant point of concern using this method, a limited number of options at this point forced us to accept this possible outcome. To that end, **29** was converted to its corresponding allylic carbonate **35** using the method of Wuts and co-workers (*N*-carboxymethylbenzotriazole, Et_3N, DMAP, 80%).[41] Quite surprisingly, the submission of **35** to specific sets of conditions as reported in the literature resulted in no reaction.[42] Although somewhat forcing conditions such as $Pd(PPh_3)_4$ (5 mol %) and *n*-BuZnCl in THF at 70 °C resulted in reaction,[43] the examination of the product mixture, after TBAF treatment to remove the silyl protecting group, suggested that a diene mixture of type **36** was produced (eq 3).[44]



Concurrently with the experimental studies outlined in eq 3, a simpler model system **37** was being used to survey potential reduction conditions (Figure 2). The results of these studies were particularly disappointing. Most of the tested conditions did not

(37) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (c) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (d) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343. (e) For an excellent review, see: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

(38) (a) Okukado, E.; Negishi, E.-I. *Tetrahedron Lett.* **1978**, *19*, 2357. (b) Van Horn, D. E.; Negishi, E.-I. *J. Am. Chem. Soc.* **1978**, *100*, 2252. (c) Negishi, E.-I.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis*, **1979**, 501. (d) Negishi, E.-I.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (e) Rand, C. L.; Van Horn, E.-I.; Moore, M. W.; Negishi, E.-I. *J. Org. Chem.* **1981**, *46*, 4093. (f) Negishi, E.-I.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

(39) Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2002**, 1736.

(40) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623.

(41) Wuts, P. G. M.; Ashford, S. W.; Andherson, A. M.; Atkins, J. R. *Org. Lett.* **2003**, *5*, 1483.

(42) (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1. (b) Tsuji, J. *Pure Appl. Chem.* **1989**, *61*, 1673. (c) Tsuji, J. *Tetrahedron* **1985**, *41*, 4361. (d) Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, *48*, 3545. (e) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4380. (f) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H.; Takagaki, H.; Yamazaki, K. *Chem. Lett.* **1986**, 1177.

(43) Matsushita, H.; Negishi, E.-I. *J. Org. Chem.* **1982**, *47*, 4161.

(44) (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *20*, 2301.

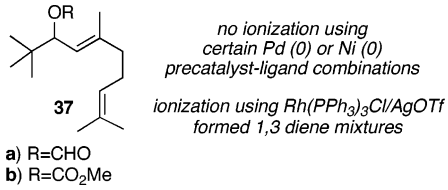
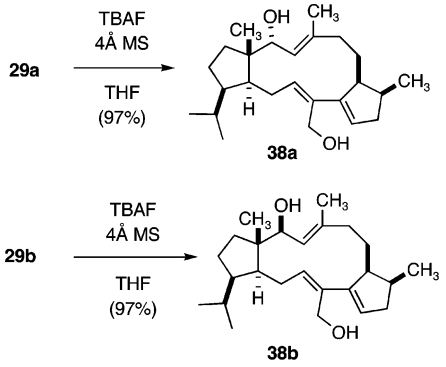


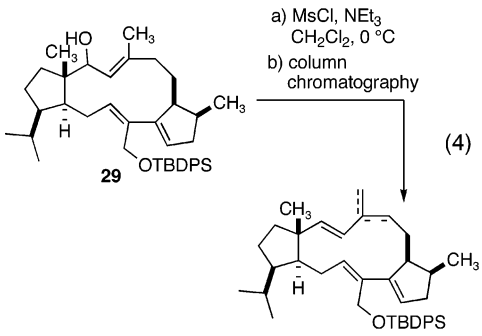
FIGURE 2. Model system for deoxygenation studies.

SCHEME 10. Deprotection to 1,22-Dihydroxynitianes



ionize the allylic leaving group. The exception was the use of a cationic rhodium(I) catalyst system that ultimately generated mixtures of 1,3-dienes, similar to the results in eq 3.[45]

The allylic carbonate within **35** was problematic. A better leaving group than carbonate was considered to be a potential solution to this problem. Unfortunately, the reaction of alcohol **29** to standard mesylation conditions only produced eliminated products (eq 4).



At this point, synthetic material was at a mininum. Consequently, the separated allylic alcohols **29a** and **29b** were deprotected using TBAF in the presence of 4 Å molecular sieves to generate 1-hydroxynitiol derivatives (Scheme 10). These compounds, the 1,22-dihydroxynitianes, were fully characterized spectroscopically. Selective NOE NMR experiments were used on each diastereomer **38a** and **38b** to support the assigned relative stereochemical assignment.

Although the end result was certainly frustrating to some extent, the synthetic 1,22-dihydroxynitianes (1-hydroxynitiol) can be viewed as a structural hybrid of nitiol and variculanol. As variculanol, a structural relative of nitiol, is oxidized at its C-1 position, it is encouraging to speculate that one of these two unnatural products may be isolated from Nature in the future. Although the total synthesis of nitiol was not achieved, a number of our initial synthetic objectives, specifically the control of the relative stereochemistry within the A and C rings of the natural product, was accomplished.

Conclusions

The synthesis of derivatives of nitiol containing a hydroxyl function at the 1-position was completed in our laboratory. Important synthetic operations within the sequence forming the A-ring of nitiol included a siloxy−epoxide rearrangement reaction, a diastereoselective Pauson−Khand reaction, and a Norrish type 1 photofragmentation. The construction of the C-ring fragment used the well-established Ireland−Claisen reaction to establish stereochemistry and a ring-closing metathesis reaction to generate the necessary substituted cyclopentenone. This reaction sequence would likely be generally applicable to the synthesis of a number of enantiomerically enriched 4,5-cis-disubstituted 2-cyclopentenones. Formation of the macrocycle required a copper(I)-promoted Stille cross-coupling and a Kishi−Nozaki−Hiyama carbonyl addition reaction. Unfortunately, the latter reaction produced a synthetic intermediate that, in our hands, could not be elaborated to the desired natural product. The derivatives produced, however, are structural hybrids of known related natural products.

Experimental Section

Some representative experimental procedures for key transformations are supplied here. For a general experimental protocol and complete experimental procedures and characterization data, please refer to the Supporting Information.

Aldehyde 5. To a solution of 4-bromo-3,6-di-*tert*-butylphenol (32.4 g, 114 mmol) in DCM (200 mL) was added trimethylaluminum (28.4 mL, 2 M in hexanes, 56.8 mmol). After 1 h of stirring at rt, the solution was cooled to −78 °C and a solution of **4** (7.62 mg, 28.4 mmol) in DCM (60 mL) was added dropwise. The resulting solution was stirred at −78 °C for 1 h then at −40 °C for 1 h before being poured into 1 N HCl. The aqueous layer was separated and extracted with DCM (4 × 100 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography [15:1 petroleum ether/ether)] to yield 7.33 g (95%) of **5** as a colorless oil. IR (neat): 2931, 1729, 1472, 1362, 1256, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 3.61 (d, J = 10.1 Hz, 2H), 3.57 (d, J = 10.1 Hz, 2H), 2.12−2.03 (m, 2H), 1.87−1.80 (m, 1H), 1.68−1.61 (m, 1H), 1.70 (t, J = 2.4 Hz, 3H), 1.00 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 79.1, 67.2, 51.4, 32.4, 26.1, 18.5, 16.2, 14.2, 3.8, −5.3. LRMS (CI+ (isobutane)): $(M + 1)^+ = 269$. $[\alpha]^{26.3}_D = -2.63$ (c = 1.540, $CHCl_3$).

Ester 9. A 500 mL quartz round-bottom flask was charged with a solution of **8** (1.29 g, 4.15 mmol) in anhydrous methanol (400 mL). The methanol solution was degassed (Ar sparge) for 45 min. The degassed solution was subjected to $h\nu$ (≥190 nm) for 28.5 h. The solvent was removed by rotary evaporation and the residue was purified using flash chromatography [20:1 (hexanes/ethyl acetate)] to yield 1.16 g of **9** (82%) and 122 mg of **8** (9.5%). IR (neat): 2954, 2858, 1742, 1471, 1436, 1386, 1368, 1256 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.36 (d, J = 9.5 Hz, 1H), 3.21 (d, J = 9.5 Hz, 1H), 2.42 (ddd, J = 3.4 Hz, 6.4 Hz, 10.1 Hz, 1H), 2.25 (dd, J = 3.4 Hz, 16.2 Hz, 1H), 2.11 (dd, J = 10.4

(45) Examples of conditions that were attempted. With formate **37a**: Pd(PPh3)4; Pd2(dba)3, PPh3; Pd2(dba)3, PCy3; Pd2(dba)3, PBu3; Pd2(dba)3, PBu3 and PPh3; Pd2(dba)3, dppp; Pd2(dba)3, dppb; Pd2(dba)3, Xantphos; Rh(PPh3)3Cl, AgOTf; Ni(COD)2, PPh3; Ni(COD)2, PCy3; Ni(PPh3)2Cl2, 2 equiv of MeLi; Ni(PPh3)2Cl2, 2 equiv of MeLi, PCy3. With carbonate **37b**: Pd2(dba)3, PCy3, NaBH4; Pd2(dba)3, PCy3, Et3SiH.; Pd2(dba)3, PCy3, PHMS.; Rh(PPh3)3Cl, AgOTf, Et3SiH.; Rh(PPh3)3Cl, AgOTf, PHMS.; Rh(PPh3)3Cl, AgOTf, NaBH4.

Hz, 16.2 Hz, 1H), 1.73−1.64 (m, 2H), 1.51−1.14 (m, 4H), 0.89 (s, 9H), 0.88 (s, 3H), 0.86 (d, J = 1.5 Hz, 3H), 0.85 (d, J = 1.5 Hz, 3H), 0.01 (d, J = 1.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 71.0, 51.5, 50.2, 47.6, 41.4, 33.4, 30.8, 29.5, 27.8, 25.9, 22.1, 21.7, 21.1, 18.2, −5.5. HRMS (CI+ (NH_3^+/isobutane)): calcd for $C_{19}H_{38}O_3Si$ $(M + 1)^+$ 343.26685, found 343.26615. $[\alpha]^{20.2}_D$ = +5.31 (c = 0.231, $CHCl_3$).

Diene 21. A flame-dried 50 mL Schlenk flask was charged with lithium chloride (660 mg, 15.6 mmol), copper(I) chloride (1.29 g, 13.0 mmol), and tetrakis(triphenylphosphine)palladium (300 mg, 0.26 mmol) in a glovebox. The mixture of solids was degassed four times. A solution of **20** (1.04 g, 2.55 mmol) in degassed DMSO (11 mL) was added dropwise. Then, a solution of **13** (1.87 g, 2.85 mmol) in degassed DMSO (11 mL) was added. The resulting mixture was degassed using the freeze−pump−thaw method. The mixture was stirred in a foil-wrapped flask for 1 h at rt before being heated to 60 °C for 37 h. The reaction was cooled to rt, diluted with Et_2O (300 mL), and washed with a mixture of brine (400 mL) and 5% NH_4OH (80 mL) resulting in a bright blue aqueous layer. The aqueous layer was separated and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with water (3 × 75 mL) and brine (3 × 75 mL), dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified using flash chromatography [10:1 (petroleum ether/ether)] to yield 1.18 g (74%) of **21**. IR (neat): 2953, 2924, 2857, 1730, 1614, 1514, 1466, 1433, 1383, 1362, 1302, 1249, 1200, 1175 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.79 (dd, J = 6.4 Hz, 11.0 Hz, 1H), 5.57 (s, 1H), 4.37 (s, 2H), 3.78 (s, 3H), 3.75 (d, J = 2.1 Hz, 3H), 3.35 (t, J = 6.7 Hz, 2H), 3.34 (d, J = 9.5 Hz, 1H), 3.11 (d, J = 9.5 Hz, 1H), 2.75−2.66 (m, 1H), 2.48−2.39 (m, 1H), 2.39−2.31 (m, 1H), 2.27−2.20 (m, 1H), 2.20−2.10 (m, 1H), 2.06−1.95 (m, 1H), 1.95−1.88 (m, 1H), 1.74−1.56 (m, 3H), 1.56−1.43 (m, 3H), 1.39−1.16 (m, 4H), 1.03 (dd, J = 2.4 Hz, 7.0 Hz, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.83 (dt, J = 1.8 Hz, 6.1 Hz, 6H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 159.0, 144.4, 137.6, 130.9, 130.4, 129.1, 127.8, 113.7, 72.4, 71.2, 70.7, 55.2, 51.4, 50.8, 47.8, 46.6, 44.6, 39.7, 37.2, 34.0, 29.2, 27.8, 25.9, 25.7, 24.5, 22.3, 22.1, 22.0, 18.3, 15.3, −4.0. Anal. Calcd for $C_{38}H_{62}O_5Si$: C, 72.79; H, 9.97. Found: C, 72.59; H, 10.08. $[\alpha]^{27.1}_D$ = +1.09 (c = 1.024, CH_2Cl_2).

Cyclization of 28 to 29 and 30. A flame-dried 25 mL round-bottom flask was charged with chromium(II) chloride (63 mg, 0.513 mmol) and nickel chloride (13 mg, 0.103 mmol) in the glovebox. A 3:1 mixture of degassed DMSO/THF (7 mL) was added, and the suspension was stirred in the dark for 10 min. A solution of **28** (41 mg, 0.056 mmol) in 3:1 DMSO/THF (12 mL) was added dropwise. The reaction mixture was stirred in the dark for 42 h. The reaction was quenched with basic NH_4Cl (pH = 8 buffer) and extracted with Et_2O (4 × 25 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified using flash chromatography [gradient: (1) (30:1 petroleum ether/ether), (2) (8:1 petroleum ether/ether), (3) (5:1 petroleum ether/ether)] to yield 7.2 mg (21%) of **30**, 11.7 mg (35%) of **29a** and 12.1 mg (35%) of **29b** (70% total).

29a. IR (neat): 3446, 3071, 1049, 2954, 2929, 2857, 1464, 1428, 1377, 1363, 1112, 1071, 1027 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 6.55 Hz, 4H), 7.45−7.28 (m, 6H), 5.67 (dd, J = 1.9 Hz, 7.7 Hz, 1H), 5.50 (s, diast), 5.45 (s, 1H), 5.37 (d, J = 8.5 Hz, 1H), 5.28 (d, J = 8.5 Hz, diast), 4.27 (q, J = 11.2 Hz, 2H), 4.07 (d, J = 8.1 Hz, 1H), 2.69 (t, J = 6.9 Hz, 1H), 2.50−2.33 (m, 1H), 2.33−2.17 (m, 2H), 2.16−1.72 (m, 6H), 1.62 (s, 3H), 1.54−1.12 (m, 2H), 1.42 (s, 1H), 1.07 (d, J = 6.9 Hz, 3H), 1.01 (s, 9H), 0.85 (dd, J = 6.2 Hz, 10.4 Hz, 6H), 0.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 140.7, 136.2, 135.8, 133.8, 131.5, 129.5, 127.5, 125.7, 122.9, 75.4, 60.7, 55.1, 51.5, 51.3, 41.2, 39.8, 39.3, 38.8, 37.5, 30.3, 28.2, 27.9, 26.8, 26.4, 24.4, 23.3, 22.3, 22.1, 19.3, 19.0, 14.9. LRMS (EI): $(M)^+$ = 610. $[\alpha]^{21.7}_D$ = −30.54 (c = 0.497, CH_2Cl_2).

29b. IR (neat): 3420, 3071, 2954, 2927, 2856, 1718, 1636, 1465, 1430, 1387, 1262, 1112, 1072, 1007, 822, 740, 702, 610, 518 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 6.2 Hz, 4H), 7.45−7.28 (m, 6H), 5.50 (s, diast), 5.44 (s, 1H), 5.39−5.27 (m, 2H), 4.28 (dd, J = 11.2 Hz, 30.4 Hz, 2H), 4.06 Hz, d, J = 9.6 Hz, 1H), 2.45−2.12 (m, 3H), 2.12−1.89 (m, 3H), 1.85 (s, 3H), 1.75−1.36 (m, 9H), 1.42 (s, 1H), 1.33−1.16 (m, 3H), 1.05 (dd, J = 6.2 Hz, 35.1 Hz, 3H), 1.02 (s, 9H), 0.84 (dd, J = 6.2 Hz, 18.5 Hz, 6H), 0.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 138.6, 136.4, 135.8, 133.9, 133.8, 130.8, 129.5, 127.5, 126.9, 122.9, 60.5, 53.4, 50.5, 46.9, 46.6, 41.1, 39.0, 37.9, 36.6, 30.3, 29.7, 28.1, 28.9, 26.9, 26.2, 24.4, 22.4, 22.1, 20.7, 19.3, 16.9, 14.6. LRMS (EI): $(M)^+$ = 610. $[\alpha]^{22.1}_D$ = +43.05 (c = 0.428, CH_2Cl_2).

30. IR (neat): 3071, 3046, 2957, 2931, 2867, 1728, 1648, 1471, 1459, 1428, 1388, 1374, 1365, 1112, 1069, 886, 823, 742, 702, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.67 (d, J = 7.3 Hz, 4H), 7.46−7.31 (m, 6H), 5.67 (s, 1H), 5.56 (s, diast.), 5.47 (t, J = 6.6 Hz, 1H), 4.62 (s, 1H), 4.60 (s, 1H), 4.35 (dt, J = 11.2 Hz, 16.2 Hz, 2H), 2.77−2.65 (m, 1H), 2.51−2.25 (m, 2H), 2.14−1.82 (m, 7H), 1.76−1.13 (m, 3H), 1.66 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.03 (s, 9H), 0.95 (t, J = 11.2 Hz, 3H), 0.78 (d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4, 147.3, 146.6, 135.7, 134.0, 133.7, 131.0, 129.6, 127.6, 125.7, 109.2, 77.2, 65.8, 60.3, 58.1, 51.7, 46.1, 44.5, 40.0, 37.6, 30.0, 29.2, 27.3, 26.8, 26.5, 22.8, 22.7, 22.0, 21.7, 19.3, 17.9, 15.4. Anal. Calcd for $C_{41}H_{58}O_2Si$: C, 74.19; H, 10.43. Found: C, 74.24; H, 10.58. $[\alpha]^{22.0}_D$ = +9.67 (c = 1.18, CH_2Cl_2).

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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