Synthesis of (−)-Deoxypukalide, the Enantiomer of a Degradation Product of the Furanocembranolide Pukalide

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A convergent stereoselective synthesis of (−)-deoxypukalide is described. This substance has not yet been found in Nature but is obtained through deoxygenation of pukalide, the first naturally occurring furanocembrane to be structurally elucidated. The route features a new intraannular furan synthesis that entails treatment of a 4-oxopropargylic β-keto ester with silica gel. The product of this novel reaction, a 3-carboxy 2,5-bridged furan, is formed in 96% yield. The synthetic strategy was strongly directed by molecular mechanics calculations, which provided valuable insight into stereodefining steps including double bond stereochemistry and butenolide configuration.

Furanocembranolides are marine natural products isolated from various soft coral species in tropical and temperate waters throughout the world.[1] These compounds have received relatively little attention, in part, because of their limited availability. Studies to date indicate that certain members of the family exhibit potent neurotoxicity, antiinflammatory, and antifeedant activity.[2]

The furanocembranolides may be divided into two classes: those in which the substituent at the C4 position is a CH_3 and those with a more highly oxidized CHO or CO_2Me C4 substituent. Rubifolide[3] is a representative of the former class, whereas the latter more populated class includes pukalide,[4] acerosolide,[5] and lophotoxin.[6]

The few recorded syntheses of furanocembranolides have employed two differing solutions to the challenging problem of constructing the strained furanocyclic structure that typifies these substances. In the first a 2,3,5-trisubstituted furan ring is constructed, the appropriate appendages at C2 and C5 are elaborated, and the macrocycle is closed. This strategy suffers from two problems: (1) the relatively sensitive furan moiety is introduced early in the sequence, which limits the range of conditions that can be employed for subsequent steps, and (2) the bond forming step in the cyclization must be sufficiently energetic to overcome the unfavorable enthalpic and entropic factors attending formation of the strained ring. Paquette and Astles utilized this approach in their synthesis of acerosolide (eq 1).[7]

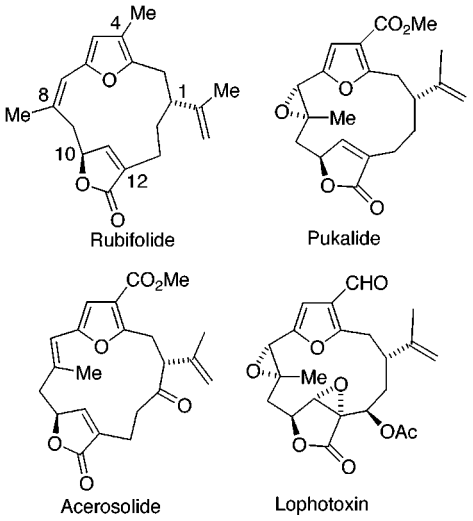
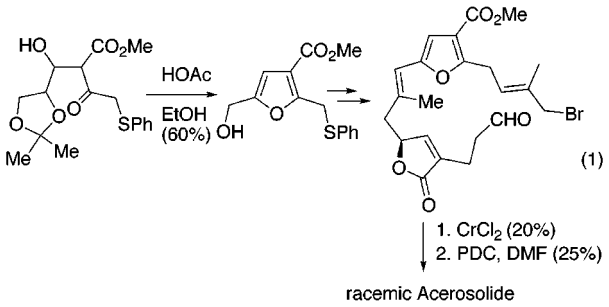


Figure 1. Representative furanocembranolides.



An alternative solution to bridged furan formation entails macrocyclization of an intermediate in which the furan ring is absent but elements of its eventual formation are present. Following cyclization, these elements are modified to enable intraannular furan formation to be effected. This approach offers two advantages: (1) the

(1) Marshall, J. A. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 1.
(2) (a) Wright, A. E.; Burres, N. S.; Schulte, G. K. *Tetrahedron Lett.* **1989**, 3491. (b) Abramson, S. N.; Trischman, J. A.; Tapiolas, F. M.; Harold, E. E.; Fenical, W.; Taylor, P. *J. Med. Chem.* **1991**, *34*, 1798. (c) Groebe, D. R.; Dumm, J. M.; Abramson, S. N. *J. Bio. Chem.* **1994**, *269*, 8885. (d) Hyde, E. G.; Boyer, A.; Tang, P.; Xu, Y.; Abramson, S. N. *J. Med. Chem.* **1995**, *38*, 2231. (e) Hyde, E. G.; Thornhill, S. M.; Boyer, A.; Abramson, S. N. *J. Med. Chem.* **1995**, *38*, 4704. (f) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741. (g) Fenical, W. *J. Nat. Prod.* **1987**, *50*, 1001.
(3) Williams, D.; Anderson, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332.
(4) Missakian, M. G.; Burreson, B. J.; Scheuer, P. J. *Tetrahedron* **1975**, *31*, 2513.
(5) Chan, W. R.; Tinto, W. F.; Laydoo, R. S.; Manchand, P. S.; Reynolds, W. F.; McLean, S. *J. Org. Chem.* **1991**, *56*, 1773.
(6) Fenical, W.; Okuda, R. K.; Bandurraga, M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512.
(7) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165.

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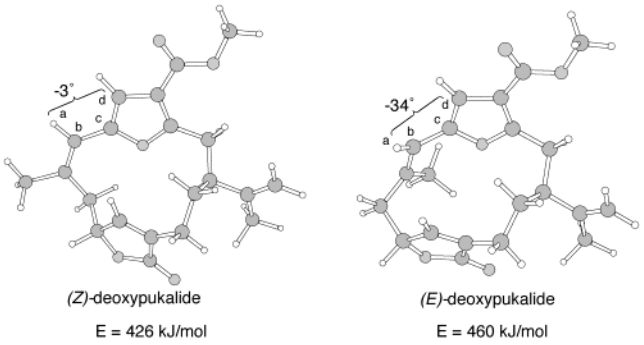
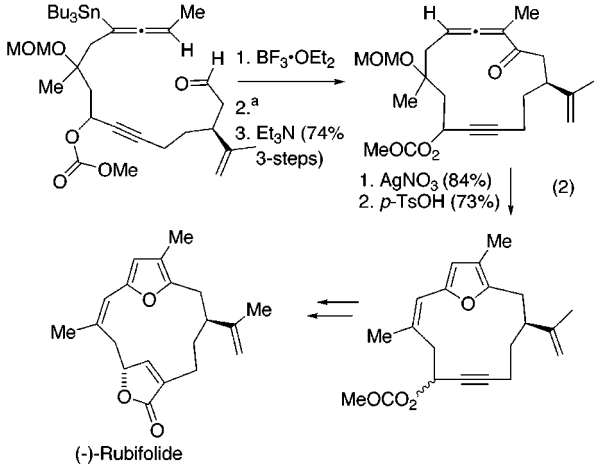


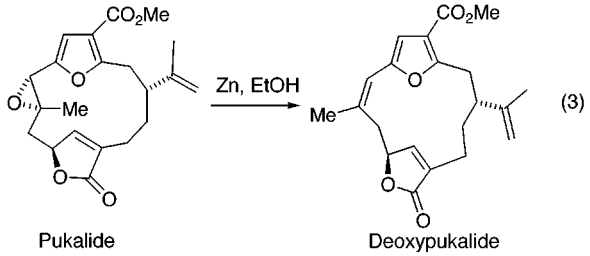
Figure 2. Calculated energy differences (Macromodel 5.5) between (*E*)- and (*Z*)-deoxypukalide (the enantiomer is depicted). Note the significant twist angle a/b/c/d of the vinylfuran moiety in the (*E*) isomer.

enthalpic energy cost of macrocyclization is considerably diminished, and (2) the resonance energy associated with furan formation partially or fully offsets the resultant increase in strain-energy. Our previous synthesis of rubifolide embodied this "furan-last" strategy.[8]



[a] Dess-Martin periodinane oxidation

The target of the present studies is deoxypukalide. This furanocembranolide, not yet found in Nature, can be prepared from pukalide through treatment with Zn and EtOH (eq 3).[9] The double bond stereochemistry was



established by Tius using NOE analysis. That the product of this deoxygenation possesses a (*Z*)-double bond is not surprising given the probable stepwise nature of the deoxygenation reaction and the high strain-energy of the (*E*) isomer (Figure 2).

In our projected synthesis of deoxypukalide we envisioned a "furan-last" strategy similar to that employed

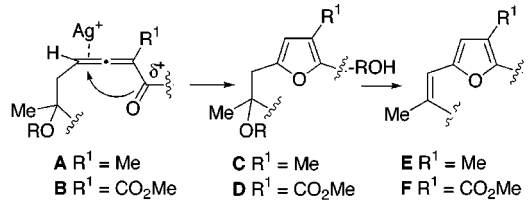


Figure 3. Possible strategies for the synthesis of 2,3,5-trisubstituted furans related to furanocembranolides.

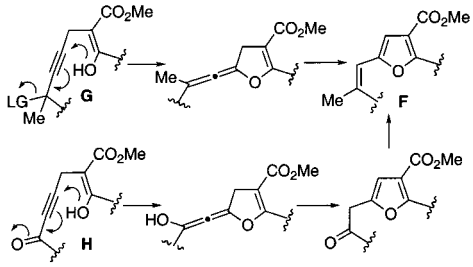


Figure 4. Alternative strategy for the synthesis of 3-carboxy-2,5-disubstituted furans.

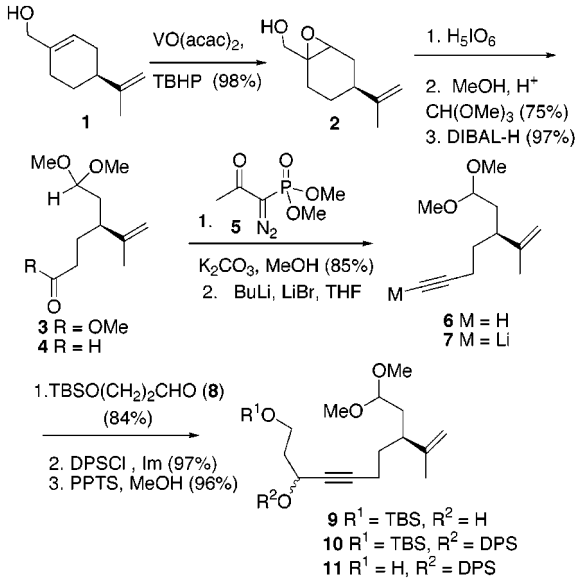
for rubifolide (Figure 3). However, we harbored grave misgivings about the probable success of the furan-forming allenone cyclization step in which the C3 methyl substituent in **C** derived from **A** would be replaced by a CO_2Me group in **D** derived from **B**. Subsequent elimination of the OR substituent in furans **C** or **D** affords the vinylfuran products. Two problems were envisioned in the ester application: (1) unlike **A**, the precursor allenone ester **B** would be highly susceptible to nucleophilic 1,4-addition, and (2) the developing positive charge at the C=O position in **B** would be destabilized by the electron-withdrawing CO_2Me substituent. For these reasons we sought alternative methodology more amenable to the preparation of 3-carboxy-2,5-disubstituted furans.

A simple solution to this problem was arrived at by "rearranging" the allenone keto ester structure to an α-propargylic *β*-keto ester **G** or **H** (Figure 4). The presence of a leaving group at the 4-position of the propargylic substituent, as in **G**, should favor the S_N2' heterocyclization as illustrated. In fact, Wipf and co-workers have effected such a conversion.[10] To further facilitate the cyclization process, we introduced a carbonyl substituent as in **H** for our "leaving group", thereby profiting from the favorable energetics of 1,4-additions and considerably expanding the range of conditions that might be employed for the cyclization. Subsequent enolization toward the furan ring should be favored by conjugation and the (*Z*) double bond geometry would be favored in consideration of the strain noted in Figure 2. The feasibility of this approach was demonstrated with simple acyclic *β*-keto ester ynones,[11] but it remained to be tested in an intramolecular context.

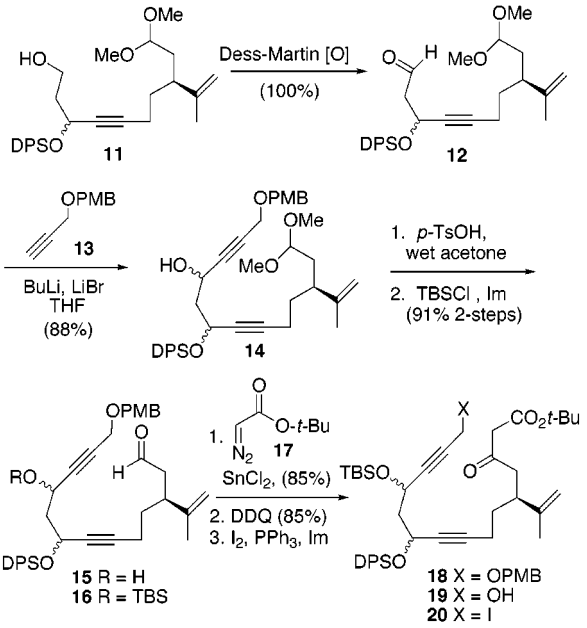
Our projected synthesis of deoxypukalide parallels our previous route to rubifolide in which (*S*)-(−)-perillyl alcohol **1** served as the starting material.[8] Through this choice we would arrive at the enantiomer of deoxypukalide derived from natural material.[4] However, there was no compelling reason to favor the "natural" isomer,

(8) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313.
(9) Tius, M. Department of Chemistry, University of Hawaii. Unpublished results.
(10) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132.
(11) Marshall, J. A.; Zou, D. *Tetrahedron Lett.* **2000**, *41*, 1347.

Scheme 1



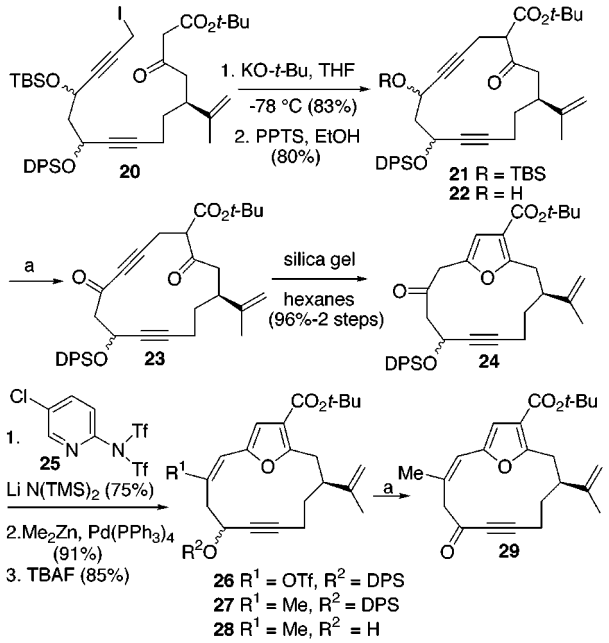
Scheme 2



so the choice was made on a purely economic basis.[12] The starting sequence, depicted in Scheme 1, is an improved version of our previous route to the alkynyl acetal **6** in which the Ohira methodology[13] for alkynylation (**4** → **6**) replaces the previous Corey−Fuchs methodology.[14] Addition of the lithioalkyne **7** to aldehyde **8** followed by protecting group adjustments afforded alcohol **11** in high overall yield.

The derived aldehyde **12** was converted to alcohol **14** through addition of the lithio derivative of propargylic ether **13** (Scheme 2). Although alcohol **14** and the derived intermediates **15**−**20** are most likely mixtures of four diastereoisomers, the ^{1}H NMR spectra of these compounds were remarkably free of extraneous peaks, suggesting that interactions between the various stereo-

Scheme 3



a) Dess-Martin periodinane oxidation

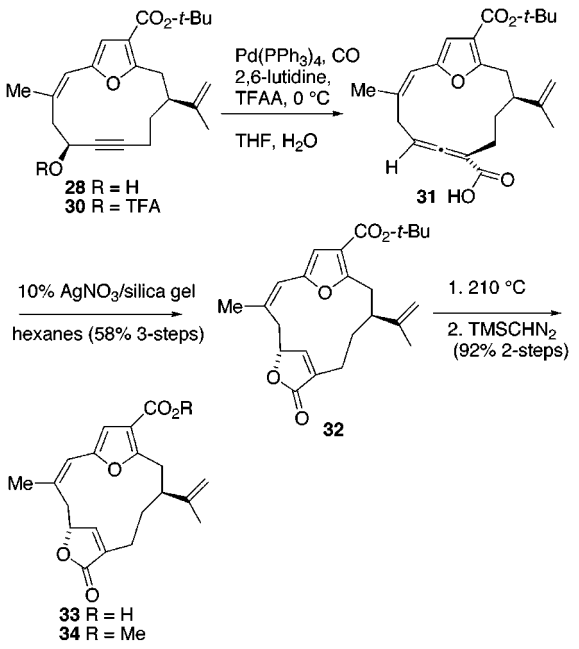
centers are relatively modest. Acetal hydrolysis and subsequent protection of the secondary alcohol **15** led to aldehyde **16**. The *β*-keto ester **18** was efficiently prepared in one step through $SnCl_2$-promoted homologation with *tert*-butyl diazoacetate (**17**).[15] We initially conducted this step with ethyl diazoacetate, which yielded the ethyl *β*-keto ester. However, this derivative was less robust than the *tert*-butyl analogue and a number of the subsequent steps proceeded in lower yield. We also had misgivings about the ultimate conversion of the ethyl ester to its methyl analogue, although this was not a major consideration. Methyl diazoacetate, if it were commercially available, would presumably suffer the same drawbacks encountered with the ethyl ester. As will be seen, the *tert*-butyl ester proved highly satisfactory.

Ensuing selective cleavage of the PMB ether **18** with DDQ at pH 7 and subsequent iodide formation yielded the macrocyclization precursor, *β*-keto ester **20**. The cyclization was effected (Scheme 3) in 83% yield upon treatment of **20** with 0.9 equiv of KO-*t*-Bu in THF at −78 °C at moderately high dilution (0.005 M). The TBS ether in the resulting cyclic ynone **21** was slowly, but selectively, cleaved to alcohol **22** by treatment with PPTS in EtOH at room temperature over a period of 10 days. Increasing the temperature of this reaction led to considerable byproduct formation at the expense of **22**.

Exposure of the Dess−Martin oxidation[16] product, ynone **23**, to silica gel in hexanes gave the carboxy furan **24** in 96% yield for the two steps! As already stated, molecular mechanics calculations[17] clearly showed that a cis double bond at the 7,8-position, as in **26**, would be highly favored over the corresponding trans isomer (see Figure 2). Treatment of ketone **24** with the Comins pyridyl triflimide reagent **25**[18] yielded a 1:1 mixture of diastereomeric enol triflates **26**, which afforded a com-

(12) Current prices for (*R*)- and (*S*)-perillyl alcohol from the 2000−2001 Aldrich catalogue are $33.60/g and $1.59/g.
(13) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(15) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.
(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. We prepared the Dess−Martin periodinane reagent used in this study from a modified procedure that utilizes oxone: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

Scheme 4



parable mixture of methylated products **27** in high yield through Pd-catalyzed coupling with Me_2Zn. Cleavage of the propargylic DPS ether **27** with TBAF and Dess–Martin periodinane oxidation of the propargylic alcohol **28** afforded ketone **29** as a single stereoisomer. The stereochemistry of the double bond was confirmed by NOE studies.

Installation of the embedded butenolide moiety was effected along the lines previously employed in our rubifolide synthesis.[8] Thus reduction of ketone **29** with K-Selectride gave rise to propargylic alcohol *cis*-**28**, as a single diastereomer (Scheme 4). The basis for this selectivity can be seen in the calculated structure, shown in Figure 5, in which the C8 substituent adopts a nearly perfect Felkin-Anh orientation[19] with respect to the C10 carbonyl.

Conversion of alcohol **28** to the trifluoroacetate **30** and in situ Pd-catalyzed carbohydroxylation yielded the allenoic acid **31**, which without purification was stirred with 10% $AgNO_3$ on silica gel in hexanes to afford the butenolide **32** in 58% yield for the three steps. At this point our choice of a *tert*-butyl ester proved remarkably prescient. Pyrolysis in a sealed glass tube at 210 °C for 20 min followed by treatment of the acid pyrolysate **33** with $TMSCHN_2$ afforded crystalline deoxypukalide **34** in 92% yield. The relative stereochemistry of this intermediate was confirmed through single-crystal X-ray structure analysis. Unfortunately, we have been unable to secure spectral data for the authentic material as the

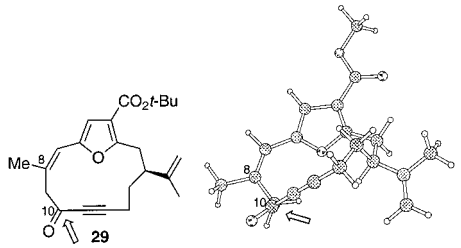


Figure 5. Conformational basis for the stereoselective reduction of ynone **29**. The methyl ester was employed for the calculations.

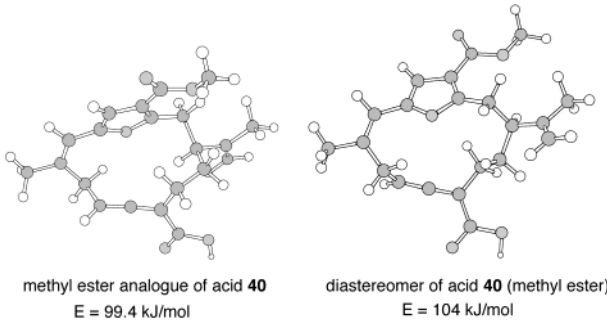


Figure 6. Calculated energies (Macromodel 5.5) of diastereomeric allenic acids.

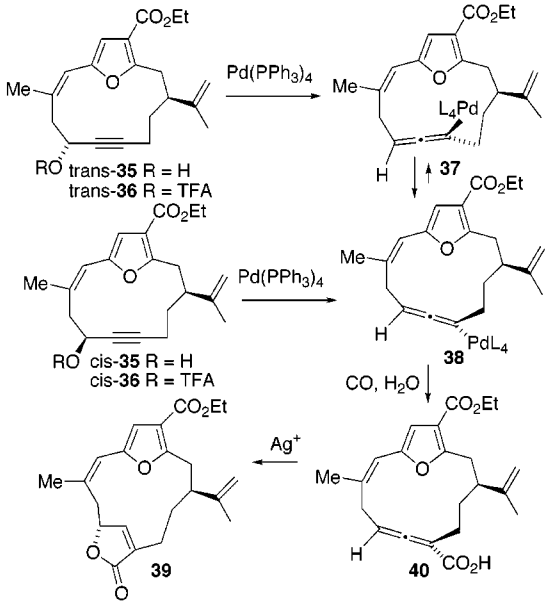


Figure 7. Equilibration of the intermediate allenylpalladium stereoisomers derived from trifluoroacetates **36**.

degradation studies were never published and the original spectra have been either discarded or misplaced.[9]

A slight variation on the route to butenolide starting from the 1:1 mixture of diastereomeric propargylic alcohols **35** was also pursued (Figure 7). These alcohols were synthesized by a route parallel to that described for the *tert*-butyl ester **28** starting from the β-keto ethyl ester analogue of **18**, mentioned previously.[20] The lower yield in several of the steps in the ethyl ester route precipitated our switch to the more efficent *tert*-butyl route. The impetus for the study came from molecular mechanics

(17) The program Macromodel 5.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo option in CSRCH (Conformer Search) employing the MM2 force field in conjunction with the Truncated Newton Conjugate Gradient (TNCG) minimization protocal through multiple step interations (typically 1000 or more) until the minimum energy conformer was found multiple times. For a description of the program, see: (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(18) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, 6299.

(19) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1971**, 379. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(20) The synthesis of this is described in: Van Devender, E. A. Ph.D. Dissertation, University of Virginia, 2002.

calculations,[17] which showed that allenic acid **40** was favored by more than 1 kcal/mol over the diastereomer (Figure 6). We assumed that the allenylpalladium precursor **38** to this acid would be similarly favored over **37**. Acid **40** is the precursor of butenolide **39**. Our previous studies indicated that conversion of enantioenriched propargylic mesylates to allenic esters through Pd-catalyzed carbomethoxylation proceeds with varying amounts of racemization.[21] The percent racemization increased with the mol % of catalyst in keeping with the known behavior of chiral allenylpalladium intermediates.[22] We also noted that allenic esters could be racemized by treatment with Ph_3P, the ligands employed in the carbonylation chemistry. Thus the allenic acid itself is formed in an isomerizing environment. Accordingly, we felt there was a good chance that allene equilibration could be induced and the result would favor the requisite butenolide precursor. In fact when the three-step acylation, carbonylation, and allenic acid cyclization sequence was performed on the 1:1 mixture of alcohols **35** (*trans*-**35** and *cis*-**35** in Figure 7) with a full equivalent of Pd catalyst, butenolide **39** was obtained as the sole product. Furthermore, when the pure alcohol *cis*-**35** was subjected to the three-step sequence with a full equivalent of catalyst, butenolide **39** was again exclusively formed. These results strongly suggest that equilibration of the transient allenylpalladium intermediates **37** and **38** leads to a predominance of **38**, as surmised from our calculations. However, the yields of these reactions were in the 20−30% range. Thus it is possible that small amounts of a minor isomer could have escaped detection. It is also possible that a minor isomer, if present, could have undergone decomposition during the course of the equilibration. Despite repeated efforts, we were unable to separate the mixture of cis and trans alcohols **35** to secure a sample of pure trans isomer for a more rigorous test of the equilibration hypothesis. Given the low efficiency of the equilibration sequence, we did not pursue the matter further.

The foregoing synthesis of (−)-deoxypukalide is notable for its efficiency and high degree of stereocontrol, despite the use of nonselective reactions that led to intermediates consisting of up to eight diastereomers. The ultimate success of the route can be attributed to favorable conformational and steric factors that facilitated highly controlled introduction of the key C10 stereocenter and the C7 double bond.

Acknowledgment. We thank Dr. Michal Sabat for his heroic efforts in solving the difficult X-ray structure of our synthetic ent-deoxypukalide. This research was supported by Grant R01-GM29475 from the National Institute for General Medical Sciences and a grant from the National Science Foundation (CHE-9901319). We gratefully acknowledge the NIH for 20 continuous years of support for our research on cembrane and cembranolide synthesis. The synthesis reported in this article marks the termination of this project. We also acknowledge the kind cooperation of Marcus Tius for permission to cite his unpublished findings on the structure of deoxypukalide.

Supporting Information Available: Complete experimental details for the preparation of all intermediates in the sequence leading to ent-deoxypukalide, selected ^1H NMR spectra, and an ORTEP diagram and structure parameters for synthetic ent-deoxypukalide **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

(22) Racemization of allenyl/propargyl palladium intermediates has been studied previously. See ref 21 and (a) Elsevier, C. J.; Mooiweer, H. H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1984**, 5571. (b) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 3042. (c) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716.