ORGANIC LETTERS

1999
Vol. 1, No. 12
1905−1907

Efficient Palladium(II)-Mediated Construction of Functionalized Plakortone Cores

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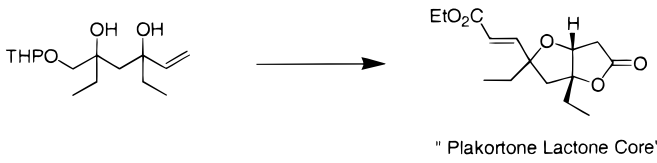
Received September 16, 1999

ABSTRACT



Appropriate enediols experience a one-pot palladium(II)-mediated hydroxycyclization–carbonylation–lactonization sequence to provide side-chain-functionalized 2,6-dioxabicyclo[3.3.0]octan-3-ones, the core structures of the plakortones, a novel class of activators of cardiac SR-Ca^{2+}-pumping ATPase, from the sponge *Plakortis halichondrioides*.

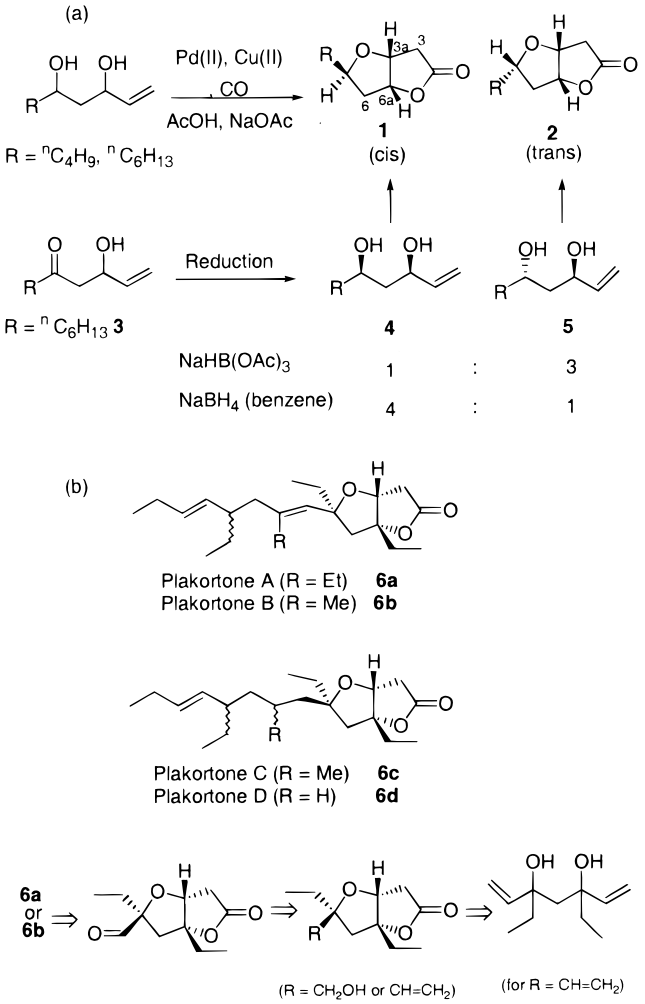
Recently we reported efficient syntheses of the bicyclic lactones **1** and **2** in both racemic and enantiomeric forms and confirmed their presence in the lactone-rich Hagen's glands of certain species of parasitic wasps.[1] Our approach to **1** and **2** utilized a palladium (II)-catalyzed hydroxycyclization−carbonylation−lactonization sequence in a "one-pot" conversion of appropriate enediols (Scheme 1a). Previous stereochemical assignments for **1** and **2**[1,2] have now been confirmed by directed syntheses of either the *cis* or *trans* lactones from enediols of appropriate relative stereochemistry. Kinetic aldol product **3**, on reduction with $NaBH_4$ in benzene, afforded predominantly *syn*-1,3 diol **4** whereas use of $NaBH(OAc)_3$ in benzene or $HOAc-CH_3CN$ (−40 °C)[3] provided mainly *anti*-diol **5** on the basis of ^{13}C chemical shifts[4] of the acetonide CH_3 groups (DEPT spectra). (Acetonide of **4** showed CH_3 shifts at δ 19.7 and 30.1 and of **5** at 25.3 and 24.6 ppm.) Diol regeneration and Pd(II) cyclization cleanly afforded the lactones **1** and **2** (R = $^nC_6H_{13}$) from *syn*- and *anti*-diols respectively, in agreement with earlier conclusions[1,2] (Scheme 1a). The cyclizations now described proceeded in good yields (≈ 80%, see Supporting Information), and when diastereomeric mixtures of enediols were employed, this was reflected in the ratio of isomeric lactones.

Because this bicyclic lactone system occurs in other natural systems,[5] we now describe further developments of this sequence[6] and in particular apply it for acquisition of systems capable of side-chain elongation to the plakortones **6a**−**d** (Scheme 1b), recently isolated from the sponge *Plakortis halichondrioides*.[7] The plakortones are micromolar activators of Ca^{2+} pumping in cardiac muscle sarcoplasmic reticulum (SR) and are relevant to correction of relaxation abnormalities.

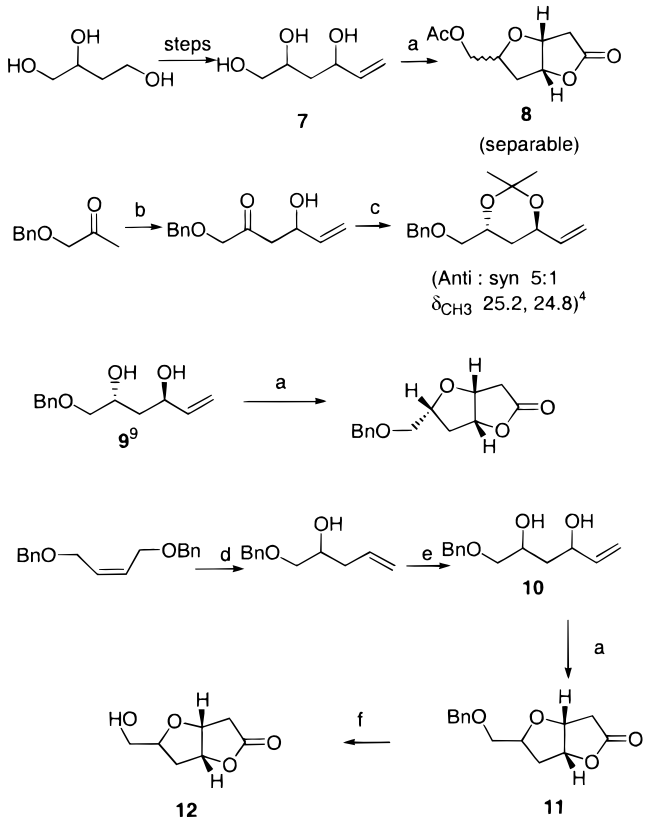
(1) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; König, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479.
(2) Paddon-Jones, G. C. Ph.D. Thesis, The University of Queensland, November, 1998.
(3) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.
(4) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*, **1990**, *31*, 945.
(5) See, for example: Fang, X. P.; Anderson, J. E.; Chang, C. J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1655, Fang, X. P.; Anderson, J. E.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1991**, *54*, 1034.
(6) For a palladium(II)-based route to (−)goniofufurone,[2] see: Gracza, T.; Jäger, V. *Synlett* **1992**, 191.
(7) Patil, A. D.; Freyer, A. J.; Bean, M. F.; Carte, B. K.; Westley, J. W.; Johnson, R. K. *Tetrahedron* **1996**, *52*, 377.

10.1021/ol991055c CCC: $18.00
Published on Web 11/18/1999

Scheme 1



Scheme 2



a. Pd(II), Cu(II), CO, AcOH, NaOAc. b. (i) LDA, (ii) Acrolein. c. (i) NaBH(OAc)$_3$ (C_6H_6), (ii) PPTS,dimethoxypropane. d. (i) O_3, CH_2Cl_2 (ii) $\nearrow^{MgBr}$, H_3O^+. e. (i) O_3, CH_2Cl_2 (ii) $\nearrow^{MgBr}$, H_3O^+.f. H_2/Pd, MeOH.

Our approach to the plakortone system[7] was based on proximate (side chain) double bond disconnection for either plakortone A or B, **6a** or **6b**. Consequently, efficient access to the plakortones was dependent on the ability of the Pd(II)-mediated process to deliver tertiary centers in the presence of the additional functionality necessary for chain extension (Scheme 1b). Introduction of the hydroxymethyl group at C-5 would require the cyclization to proceed with a 1,2,4-triol arrangement, and use of unprotected triol **7** yielded acetate **8** as the isolated product. For provision of a suitably protected lactone derivative, benzyl-protected triol systems **9** and **10** were obtained as shown below (Scheme 2). These were successfully cyclized under the normal conditions to **11** and finally deprotected to yield desired hydroxy lactone **12**.[8]

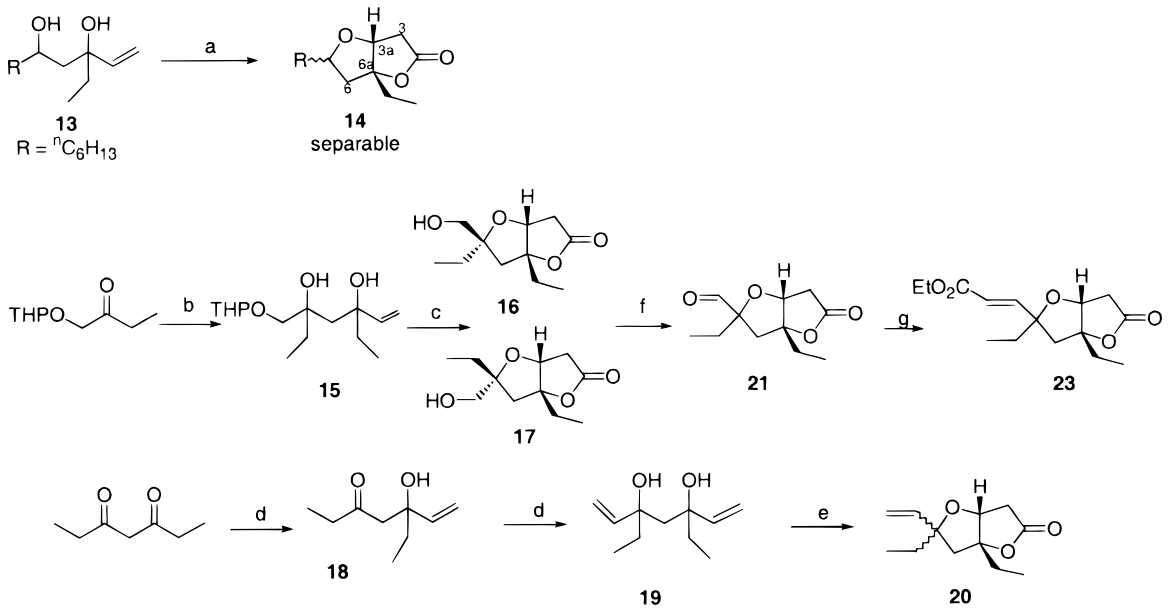
With respect to ethyl group introduction, *tert*-allylic alcohol **13** (as a diastereomeric mixture) was transformed to lactone mixture **14** which was separated (HPLC), and the relative stereochemistry was assigned by NMR methods. The absence of a signal for H6a was notable, with a prominent ion for (M − C_6H_{13}) in the GC-MS, and spectral comparisons indicated that the introduction of the ethyl group at C-6a had minimal impact on ring geometries[2] (Scheme 3).

Formation of the actual plakortone core with ethyl attachment at both C-6a and C-5 can be envisaged by cyclization of the protected triol **15**, and this delivered the readily separated lactones **16** and **17**. Their ^{1}H NMR spectra were remarkably similar, and this is reflected in the calculated geometries and observed and calculated coupling constants.[2] NOE-based relative stereochemistry, and comparisons with the data for plakortone D, indicate that *cis*-isomer **16** probably corresponds to the plakortone structure.[7]

An alternative cyclization precursor, **19**, was accessible in principle by double addition of vinylmagnesium bromide to heptane-3,5-dione (Scheme 3), and ozonolysis of **20** would then provide the aldehyde for planned Wittig extension. Despite the potential for side reactions, the simplicity of this process was attractive, and a two-step procedure via **18** was developed for the provision of diol **19** which was immediately cyclized. Flash chromatography provided an isomer of **20**, and this procedure is being optimized.

(8) Hydroxylactone **12** was efficiently oxidized by Dess−Martin periodinane to the corresponding aldehyde (δ_{CHO} 9.6, d, 1.4 Hz), but Swern conditions, as employed in the acquisition of **21** (Scheme 3), are a better practical approach for these systems.

Scheme 3



With respect to chain extension, aldehyde **21** (δ_{CHO} 9.76, br s *m*/*z* 183, $M^+ - CHO$) was treated with a slight excess of stabilized ylide **22** and afforded enoate **23** as an E−Z (12:1) mixture, suggesting that this general approach would be applicable to side-chain attachment necessary for acquisition of the plakortones.[9] A full report of this work will appear at a later date.

(9) Recently the synthesis of a lactone analogous to **16** but with an ^{n}butyl side chain in place of the hydroxymethyl group was reported. Bittner, C.; Burgo, A.; Murphy, P. J.; Sung, C. H.; Thornhill, A. J. *Tetrahedron Lett.* **1999**, *40*, 3455.

Acknowledgment. The authors are grateful to the Australian Research Council for financial support.

Supporting Information Available: Illustrative procedure for Pd(II)-mediated hydroxycyclization−carbonylation−lactonization. Characterization data including ^{1}H and ^{13}C NMR data for compounds **8**, **11**, **12**, **14**, **16**, **17**, **20**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991055C