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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6325–6328

A new synthetic approach for 4(*S*)-hydroxycyclopent-2-enone: a precursor to prostanoid synthesis

Chih-Tsung Chang,[a] Sheila H. Jacobo,[a] William S. Powell,[b] John A. Lawson,[c] Garret A. FitzGerald,[c] Domenico Pratico[c] and Joshua Rokach[a,*]

[a]*Claude Pepper Institute and Department of Chemistry, Florida Institute of Technology, 150 W. University Blvd., Melbourne, FL 32901, USA*
[b]*Meakins-Christie Laboratories, Department of Medicine, McGill University, Montreal, Quebec, Canada H2X 2P2*
[c]*Institute for Translational Medicine and Therapeutics, The University of Pennsylvania, Philadelphia, PA 19104, USA*

Received 2 June 2005; revised 7 July 2005; accepted 8 July 2005
Available online 26 July 2005

Abstract—A new and efficient approach to 4(*S*)-hydroxycyclopent-2-enone is presented. This methodology allows the preparation of 4(*S*)-hydroxycyclopent-2-enone in large scale and with high optical purity.

4(*S*)-Hydroxy and 4(*R*)-hydroxycyclopent-2-enone, synthons **1** and **2**, have been the key building blocks in the syntheses of several natural products.[1–5] For example, 4(*R*)-hydroxycyclopent-2-enone **2** was widely used in the syntheses of prostaglandins through the 3-component coupling route (Scheme 1a).[6–10] Our group had recently used 4(*S*)-hydroxycyclopent-2-enone **1** as starting point in the thermal-Diels–Alder approach to isoprostanes (Scheme 1b).[11] The importance of these synthons is clearly revealed by the numerous syntheses reported in the literature. These syntheses can be categorized into two groups: enzymatic/semisynthetic[12–18] and synthetic.[19–25]

Recently, we have reported a synthesis of 4(*S*)-hydroxycyclopent-2-enone.[26] This synthetic procedure afforded **1** in high quality and enantiomeric purity. A brief outline of the synthesis is shown in Scheme 2. As can be seen, all the steps from the dithio intermediate **9** to the final compound **1** are acid-catalyzed steps. As a result, contamination of **10**, **11** and **1** in steps 1 and 2 (Scheme 2) makes purification, even with good yield reactions, tedious and time consuming. In addition, determination of the stereochemical purity of the –OH group by our procedure relying on making the Mosher ester derivative is time consuming and has to be performed on every batch of the material.

We are reporting here on a straightforward procedure for the synthesis of **1**. This synthetic approach is based on olefin metathesis. Over the few past years, olefin metathesis has emerged as an excellent method for carbon–carbon bond formation. It has been used to prepare several natural products.[27,28] Preparation of compounds with complex ring systems from acyclic synthons was made possible with the development of Grubbs' catalysts.[29–31] One advantage of using Grubbs' catalyst in the synthesis of organic compounds is its good tolerance to thef functional groups.

We have designed the synthesis of **1** in such a way that it is amenable to large scale preparation and at the same time affords an optically pure compound. We have decided to synthesize the dithio intermediate **13** from D-arabinose **12**, as described by us previously.[32] Using this procedure, 200 g of **13** can be prepared in one batch. **13** can also be synthesized following a new two-step procedure from 2-deoxy-D-ribose **14** (Scheme 3).

Scheme 4 shows the detailed synthesis of **1** from dithio intermediate **13**. First, the –OH group in **13** was protected with TBDMSCl affording **15** in 99% yield. Treatment of **15** with periodic acid in THF/ether gave the aldehyde, which was immediately reacted with 5 equiv

Keywords: 4(*S*)-Hydroxycyclopent-2-enone; Olefin metathesis; Synthesis.
* Corresponding author. Tel.: +1 3216 747329; fax: +1 3216 747743; e-mail: jrokach@fit.edu

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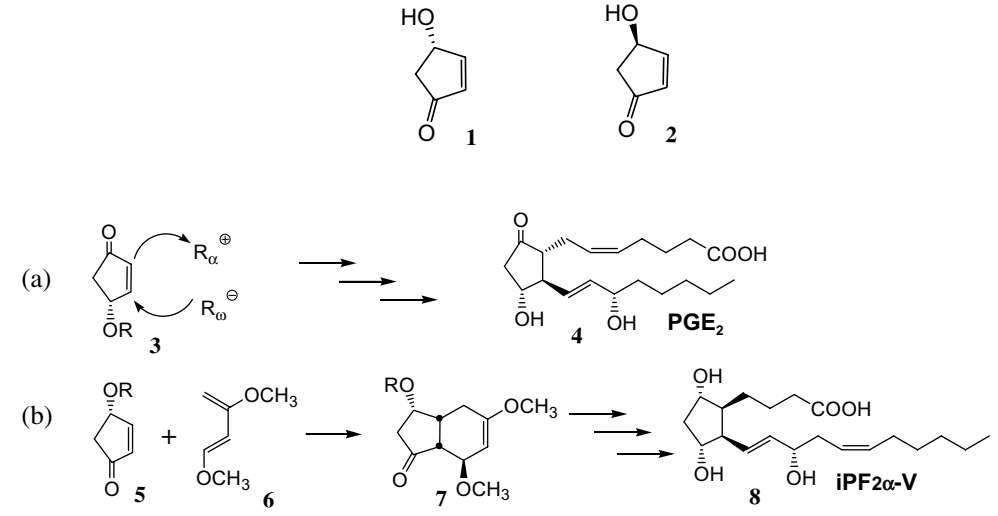
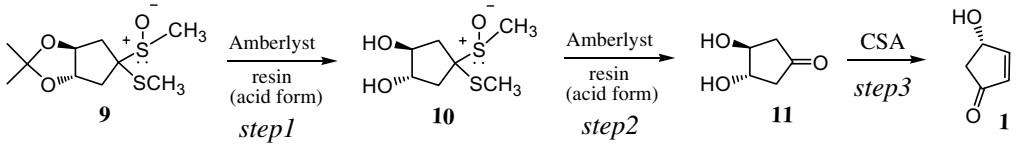
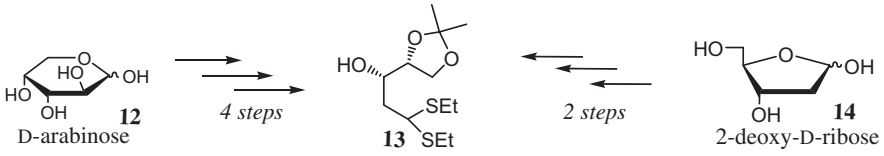
doi:10.1016/j.tetlet.2005.07.035



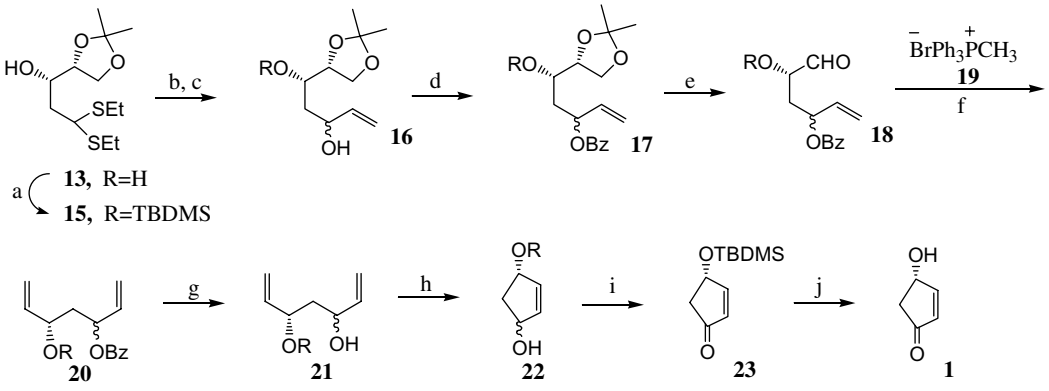
Scheme 1.



Scheme 2.

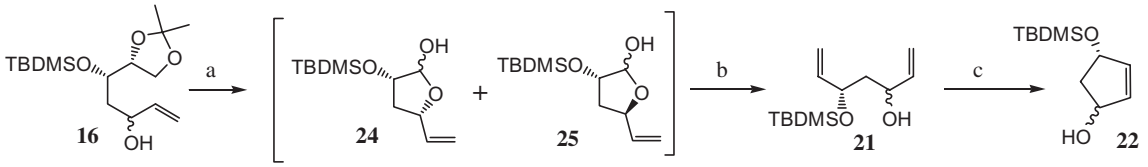


Scheme 3.



Scheme 4. Reagents and conditions: (a) TBDMSCl, Im, DMF, 100 °C, 2 h, 99%; (b) H_5IO_6, THF/Et_2O, 0 °C, 15 min; (c) $CH_2CHMg^+Br^-$ (5 equiv), rt, 1.5–2 min, 74% (two steps); (d) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 12 h, 93%; (e) H_5IO_6, THF/Et_2O, rt, 12 h, 98%; (f) NaHMDS, THF, −30 °C to rt, 1.5 h, 76%; (g) K_2CO_3, MeOH, 10 h, rt, >99%; (h) Grubbs' catalyst (1st Gen), 6 mol % catalyst, CH_2Cl_2, 4 h, rt, 89%; (i) Dess–Martin periodinane, CH_2Cl_2, 2.5 h, rt, 99%; (j) HF·py, pyridine, 30 min, rt, 97%.

of vinyl magnesium bromide at rt, affording **16** in 74% yield (two steps). After protecting **16** with benzoyl group using benzoyl chloride in CH_2Cl_2, the resulting intermediate (**17**) was treated with periodic acid in THF/ether and was stirred overnight to afford aldehyde **18** in 98% yield. **18** was coupled with the phosphorane derived from the commercially available phosphonium salt **19** to give diene **20** in 76% yield. Treatment of **20** with K_2CO_3 afforded hydroxy-diene **21** in quantitative yield. Ring closing metathesis of **21** catalyzed by Grubbs' first



Scheme 5. Reagents and conditions: (a) H_5IO_6, THF/Et_2O, 15 h, rt, 58%; (b) $Br^-Ph_3P^+CH_3$, NaHMDS, THF, −30 °C to rt, 7 h, 20%; (c) Grubbs' catalyst (1st Gen), 6 mol % catalyst, CH_2Cl_2, 4 h, rt, 89%.

generation catalyst [PhCH=$RuCl_2(PCy_3)_2$] afforded **22** in 89% yield. Oxidation of **22** with Dess–Martin periodinane gave **23** in quantitative yield. Finally, hydrolysis of **23** with HF·py gave the desired compound **1** in 97% yield. The NMR[33] and other analytical data are identical to the one reported by us previously.[26]

It is interesting to note that cyclization of **21** using Grubbs' second generation catalyst also afforded **22** in excellent yield. However, we opted to use Grubbs' first generation catalyst since it is more economical.[34–36]

To make sure that the optical purity of hydroxy group in **1** was preserved after a series of steps from D-arabinose or 2-deoxy-D-ribose, a Mosher ester derivative was prepared by acylation of **1** with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in pyridine as described by us previously.[26] By NMR analysis, a high ee of >96% was observed.

We initially performed the synthesis in a slightly simpler way as shown in Scheme 5. The hydroxy group in **16** was not protected with benzoyl group and thus upon treatment with periodic acid resulted to the formation of lactols **24** and **25.** However, the one-carbon Wittig reaction of **24** and **25** with **19** gave a low yield of the desired product **21** (∼20%). We think that the synthesis shown in Scheme 5 is, in spite of the low yield Wittig reaction, a good alternative to the one shown in Scheme 4.

In summary, we have developed an efficient synthesis of 4(*S*)-hydroxycyclopent-2-enone **1** and its derivatives. This approach not only allows us to prepare **1** in large quantities but also with high optical purity.

Acknowledgements

The present study was supported by grants from the National Institutes of Health (DK-44730 (J.R.), HL-69835 (J.R.), HL-70128 (G.A.F.), AG-11542 (D.P.)); the NSF for an AMX-360 NMR instrument (CHE-90-13145); the Canadian Institutes of Health Research (MOP-6254) (W.S.P.); the Heart and Stroke Foundation of Québec (W.S.P.).

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