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An Enantioselective Synthesis of Cryptocarya Diacetate

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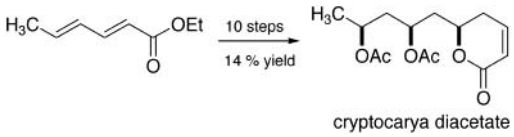
ABSTRACT



The enantioselective synthesis of cryptocarya diacetate has been achieved in 10 steps from ethyl sorbate. The route relies upon an enantio- and regioselective Sharpless dihydroxylation and a palladium-catalyzed reduction to form a δ-hydroxy-1-enoate, which was subsequently converted into a benzylidene-protected 3,5-dihydroxy carboxylic ester. This ester was converted into cryptocarya diacetate in 14% overall yield via an allylation and methathesis ring closure reaction sequence.

The leaves and bark of the South African plant *Cryptocarya latifolia* have been long sought after for their legendary magical and medicinal properties.[1] These properties range from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[1] In a search to find the molecular origins of these effects, Horn found a series of related 6-substituted 5,6-dihydropyran-2-ones in biologically active hexane and acetone extracts.[2] The simplest structures isolated from these mixtures were cryptocarya diacetate (**1**) and cryptocarya triacetate (**2**) (Figure 1).[3] The use of activity-guided fractionation led to the discovery of more complex 1,3-polyol/5,6-dihydropyran-2-one natural products[4,5] with significant antifungal activity, such as passifloricin A (**3**).[5]

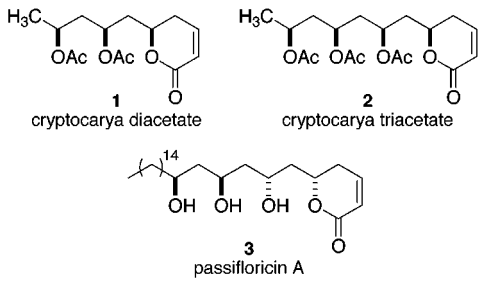


Figure 1.

While the absolute stereochemistry of passifloricin A is unknown, Horn has determined the absolute and relative stereochemistry of the cryptocarya acetates by a combination of the Mosher ester analysis and the Rychnovsky ^{13}C NMR/acetonide analysis.[6] Finally, Nakata confirmed their results by an enantioselective total synthesis of **1** via a 16-step route from the (*S*)-*tert*-butyl 3-hydroxybutyrate.[7,8]

Recently, we have been interested in the development of practical and concise enantioselective approaches to biologically important 1,3-polyol-substituted 5,6-dihydropyran-2-one containing natural products.[9,10] In particular, we have been exploring the use of asymmetric catalysis toward the

(1) Sam, T. W.; Yeu, C. S.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199.

(2) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427.

(3) To the best of our knowledge, lactones **1** and **2** have not been named; thus for simplicity reasons we will refer to **1** as cryptocarya diacetate and **2** as cryptocarya triacetate.

(4) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoecki-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265−269.

(5) Echeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881−885.

(6) Collett, L. A.; Cavies-Coleman, M. T.; Rivett, D. E. A.; Drewes, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935−938.

(7) Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855−8858.

(8) The Aldrich Chemical Co. provides (*S*)-*tert*-butyl 3-hydroxybutyrate at the cost of $41/mL.

(9) (a) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161−5171. (b) Harris, J. M.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 2983−86.

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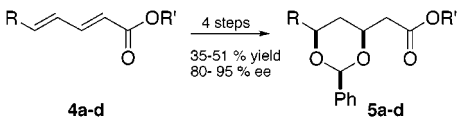
total synthesis of these important targets, which we hoped could be prepared efficiently from benzylidine-protected *syn*-3,5-dihydroxy carboxylic esters **5** (Scheme 1).[11] Accordingly,

Scheme 1

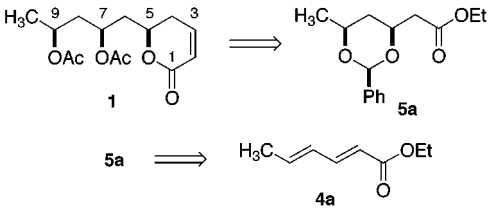


a: R = Me, R' = Et; **b**: R = Pr, R' = Me; **c**: R = Ph , R' = Et; **d**: R = $(CH_2)_2$OTBS, R' = Et

we have developed a concise and enantioselective four-step protocol for the synthesis of protected 1,3-*syn*-diols such as **5** from achiral 1,3-dieneoates such as **4**, where the asymmetry was installed by the Sharpless asymmetric dihydroxylation reaction.[12] Thus, cryptocarya diacetate seemed an ideal target to test the viability of this methodology for natural product synthesis.

We envisioned that the C-5 through C-10 carbons of cryptocarya diacetate could be derived from a commercially available dienoate, ethyl sorbate. The C-7 and C-9 carbonol stereocenters could be established by converting **4a** to **5a** (Scheme 2). In addition, we planned for the introduction of

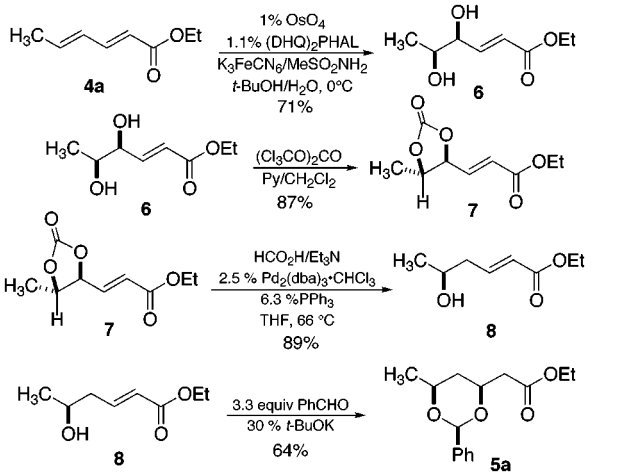
Scheme 2



the C-5 stereocenter of cryptocarya diacetate by a diastereoselective ketone reduction.[13] Herein, we describe our successful implementation of this strategy toward the synthesis of the all-*syn*-1,3-triol-containing cryptocarya diacetate **1**, the simplest member of this family of natural products (Figure 1).[14]

Following our previously reported protocol the commercially available ethyl sorbate[15] **4a** was converted into the protected diol **5a** in four steps and a 35% overall yield (Scheme 2).[11] The Sharpless dihydroxylation of ethyl sorbate **4a** gave diol **6** in a good yield (71%).[16,17] Either enantiomer of diol **6** can be obtained with enantiomeric excesses on the order of 80% from the $(DHQ)_2$PHAL ligand system and >90% from the $(DHQD)_2$PHAL ligand.

Scheme 3



To differentiate the diol functionality, **6** was converted into a cyclic carbonate **7**. The cyclic carbonate **7** was prepared by treating a pyridine/CH_2Cl_2 solution of diol **6** with triphosgene, providing **7** in an 87% yield. At this stage the two hydroxyl groups were readily differentiated by taking advantage of the fact that allylic carbonates are good leaving groups for the formation of π-allyl palladium complexes.[18] Treatment of **7** with a catalytic amount of palladium/triphenylphosphine (2.5% $Pd_2(dba)_3$·$CHCl_3$/6.3% PPh_3)[19] and a mild hydride source (Et_3N/HCO_2H) afforded an excellent yield (89%) of the desired δ-hydroxy ester **8** with no loss of enantiomeric excess.[16] Exposing the δ-hydroxy enoate **8** to 3−4 equiv of benzaldehyde and a catalytic amount of KO*t*-Bu led to a 64% yield of the benzylidene-protected 3,5-dihydroxy carboxylic ester **5a**.[20] Thus, the ester **5a** was conveniently prepared as a single diastereomer (>95%) and in 35% overall yield.

(10) For some recent approaches to related 6-substituted 5,6-dihydropyran-2-one containing natural products, see: (a) Gosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003−1006. (b) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (c) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19−20. (d) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685−88. (e) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512−14.

(11) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049−1052.

(12) For other approaches to *syn*-3,5-dihydroxy carboxylic esters, see: (a) Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyam, K. Miyashita, M. *Chem. Lett.* **1998**, 109−110. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajpakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726. (c) Solladié, G.; Wilb, N.; Bauder, C.; Bonini, C.; Viggiani, L.; Chiummiento, L. *J. Org. Chem.* **1999**, *64*, 5447−52.

(13) Leighton has demonstrated that this can be accomplished by the addition of allyl-(−)-diisopinocamphenylborane to similarly protected aldehydes, but we hoped to find a less expensive alternative. Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894.

(14) The *syn*-1,3-diol structural unit is a common motif in many natural products, with a wide range of biological activities. (a) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753−1765. (b) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc*. **1997**, *119*, 2058−2059. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−40.

(15) The Aldrich Chemical Co. sells ethyl sorbate for $0.30/g.

(16) All levels of enantioinduction were determined by HPLC analysis (8% IPA/hexane, Chiralcel OD) and/or Mosher ester analysis. (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

(17) All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and HRMS.

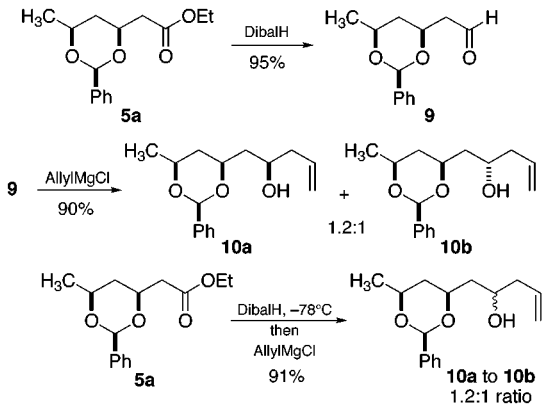
(18) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res*. **1987**, *20*, 140. (b) Hughes, G.; Lautens, M.; Wen, C. *Org. Lett.* **2000**, *2*, 107−110.

(19) This lower than normal (2:1 phosphine to palladium) ratio gave higher yields and faster reaction times.

(20) Evans, D. A. Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446−2453.

Having established a general procedure for the enantioselective synthesis of either enantiomer of benzylidine acetal **5a**, we turned our attention to the diastereoselective construction of the 5,6-dihydropyran-2-one of cryptocarya diacetate via an allylation, acylation and metathesis sequence. At the outset, we envisioned introducing the final C-5 stereocenter by either a diastereoselective allylation of aldehyde **9** or a diastereoselective reduction of ketone **11** (Schemes 4 and 5).

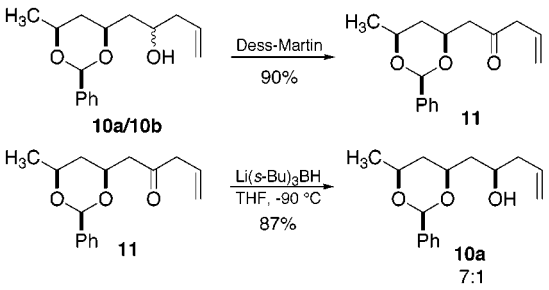
Scheme 4



The aldehyde **9** was easily prepared by exposure of a THF solution of ester **5a** with 1.1 equiv of DIBALH at −78 °C, in a near quantitative yield (>95%). The addition of allylMgCl to **9** gave a 1.2:1 ratio of the desired and undesired homoallylic alcohols *syn*-**10a** and *anti*-**10b** (90%). A much simpler and higher yielding procedure for the production of **10a** and **10b** involved the in situ addition of the allyl Grignard reagent directly to the aldehyde/DIBALH admixture followed by warming to room temperature (91% yield). Unfortunately all of our efforts to improve upon this modest selectivity in the allylation reaction were unsuccessful. These efforts included the addition of various chelating Lewis acids (Al, Ti, Zn) in combination with an allylanion, in an attempt to take advantage of the β-alkoxy group.

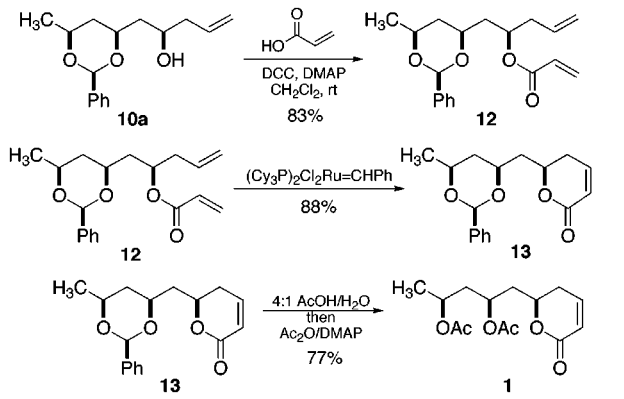
To improve the stereoselectivity for the desired *syn*-isomer **10a**, we decided to investigate the use of an oxidation/reduction sequence on the mixture of isomers of **10a**/**10b** (Scheme 5). Treatment of a diastereomeric mixture of **10a** and **10b** with 1.1 equiv of Dess−Martin reagents gave a clean conversion to the β,γ-unsaturated ketone **11**, without any double bond isomerization (90%). In contrast to aldehyde **9**, the use of various chelating metals in concert with borohydride reagents on ketone **11** gave good selectivities. Our initial investigation with $NaBH_4$ at −78 °C gave us encouraging results (81%, 3:1 **10a**:**10b** ratio). Turning to the more hindered reducing agent L-selectride at −78 °C increased the selectivity for **10a** to 4:1. Further lowering the temperature led to our optimum procedure. Thus, treating a THF solution of **11** with L-selectride at −90 °C provided **10a** in a 7:1 ratio (87% yield).

Scheme 5



Having established the three stereocenters of cryptocarya diacetate in **10a** we looked for conditions for the ensuing conversion into acrylate **12** (Scheme 6). While **10a** was readily converted into **12** upon exposure to acryloyl chloride and pyridine, it unfortunately was formed in only modest yield (51%).[21] Similarly the use of other bases (e.g., Et_3N, DMAP) and/or acid chlorides (crotonyl chloride) gave unsatisfactory yields. This problem was easily solved by resorting to DCC coupling conditions (4 equiv of acrylic acid/DCC in CH_2Cl_2), providing a significantly improved yield of ester **12** (83%).

Scheme 6



To address the formation of the desired 5,6-dihydropyran-2-one ring we turned to the use of a ring closing methathesis reaction (Scheme 6).[22,23] This was easily implemented by exposure of a refluxing CH_2Cl_2 solution of the diene **12** to the Grubbs catalyst (2.5 mol %), resulting in a clean cyclization to dihydropyran-2-one **13** in an 88% yield.

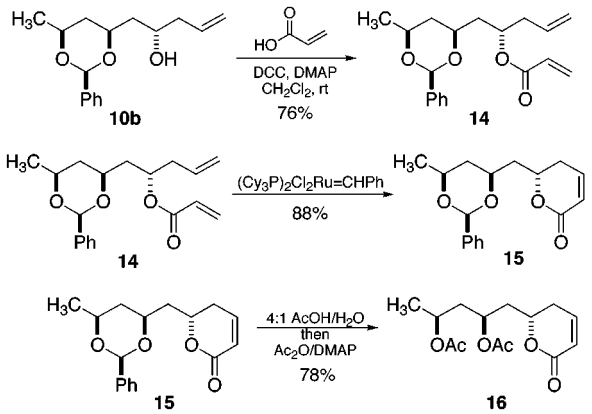
All that remained to complete the synthesis was to selectively remove the benzylidene group in the presence of the pyran-2-one unsaturation and to acetylate the resulting diol (Scheme 6). After some experimentation, we found that this was most easily accomplished by heating **13** in 80%

(21) Others have noted low yields for similar acylations with acryloyl chloride, see ref 10e.

(22) For a excellent review on ring closing metathesis reactions, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(23) For other uses of ring closing metathesis reactions for the formation of pyranones, see: ref 10a,b,e and Cossy, J.; Pradaux, F.; Bouzbouz, S. *Org. Lett.* **2001**, *3*, 2233−2235.

Scheme 7



aqueous acetic acid for 3 h at 60 °C. The crude diol product was directly acylated by solvent removal and addition of acetic anhydride and pyridine (77%). This two-step, one-pot protocol provided excellent yields of cryptocarya diacetate, which had spectral data identical to that of the isolated material (R_f, ^{1}H and ^{13}C NMR spectra).[2,7]

As a final proof of stereochemistry the diastereomeric alcohol **10b** was converted into the C-5 epimer of cryptocarya diacetate **16** (Scheme 7). Acylation of **10b** with DCC and acrylic acid provided the diene **14** (76%), which similarly underwent ring closing methathesis to pyranone **15** (88%). Finally a two-step, one-pot, acid-catalyzed deprotection/acylation reaction sequence provided the isomeric 5-*epi*-cryptocarya diacetate in a 78% yield for the two steps.

In conclusion, a short and enantioselective synthesis of cryptocarya diacetate has been developed that is significantly shorter than the previous approach: 10 steps versus 16 steps.[7] This highly enantio- and diastereocontrolled route illustrates the utility of our recently developed Os/Pd route to benzylidene-protected *syn*-1,3-diols. The synthesis provides cryptocarya diacetate in 10 steps and 14% overall yields (82% average yield) and is amenable for the preparation of either enantiomer in addition to the C-5 distereoisomer **16**. Further studies on the use of these chiral building blocks toward the synthesis of *syn*-1,3-polyol-containing natural products will be reported in due course.

Acknowledgment. We thank the Arnold and Mabel Beckman Foundation for their generous support of our program.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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