Enantioselective Syntheses of Cryptocarya Triacetate, Cryptocaryolone, and Cryptocaryolone Diacetate
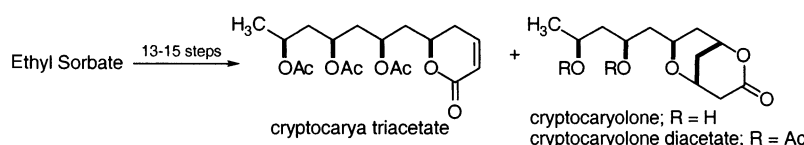
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ABSTRACT

The enantioselective syntheses of three natural products from *Cryptocarya latifolia* have been achieved in 13–15 steps from ethyl sorbate. The route relies upon an enantio- and regioselective Sharpless dihydroxylation and a palladium-catalyzed reduction to establish the absolute stereochemistry. The route also relies upon a highly (*E*)-selective olefin cross-metathesis reaction to form *trans-δ*-hydroxy-1-enoates. The resulting *δ*-hydroxy-1-enoates were subsequently converted into cryptocarya triacetate, cryptocaryolone, and cryptocaryolone diacetate.

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 alleged properties range from the treatment of headaches and morning sickness to the treatment of cancer, pulmonary diseases, and various bacterial and fungal infections.[1] Motivated by these claims, van Staden has tested crude extracts of *C. latifolia* and found significant activity as cyclooxygenase inhibitors (COX-2/COX-1).[2] 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 the biologically active hexane and acetone extracts, including cryptocarya diacetate **1** and cryptocarya triacetate **2**,[3] along with two bicyclic pyranone/polyol structures cryptocaryolone **3** and cryptocaryolone diacetate **4** (Figure 1).[3b] The use of activity-guided fractionation led to the discovery of more complex 1,3-polyol/5,6-dihydropyran-2-one natural products from related trees[4,5] such as passifloricin A and 5,7-bis-*epi*-passifloricin A.[5−7] Due to

the interest in their biological activities, several synthetic approaches to these molecules have been reported by us[8] and others.[9]

Horn has determined the absolute and relative stereochemistry of the cryptocarya acetates **1** and **2** by a combination of Mosher ester analysis and Rychnovsky ^{13}C NMR/acetonide analysis.[3b] Finally, Nakata confirmed their results by an enantioselective total synthesis of both **1** and **2** via 16- and 24-step routes, respectively, from the (*S*)-*tert*-butyl 3-hydroxybutyrate.[10,11] While the absolute and relative stereochemistries for both cryptocaryolone **3** and cryptocary-
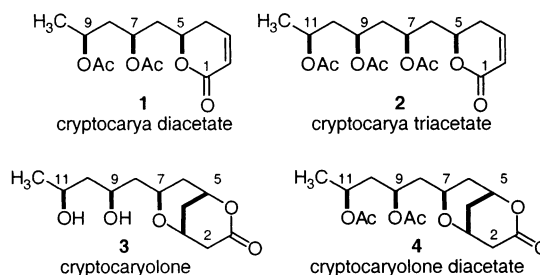

Figure 1.

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

(2) Zschocke, S.; van Staden, J. *J. Ethnopharmacol.* **2000**, *71*, 473.

(3) (a) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427. (b) Collett, L. A.; Cavies-Coleman, M. T.; Rivett, D. E. A.; Drewes, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935.

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

olone diacetate **4** have been assumed on the basis of the structure of crytocarya triacetate, no structural proof has been offered. Only the relative stereochemistry between C-7 and C-9 and the relative stereochemistry of the bicyclic portion of the cryptocaryolones are known.

To determine the exact pharmacological role of the polyol and pyranone portions of these molecules, we have endeavored to prepare this class of natural products as well as both stereoisomeric and homologous analogues. An important element to our synthetic strategy is the use of asymmetric catalysis to establish the initial asymmetry in addition to the use of efficient diastereoselective reactions to install the remaining stereochemistry.[12] Herein, we describe our successful implementation of this strategy toward the syntheses of the all-syn 1,3-polyol containing natural products cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4** (Figure 1).

Scheme 1
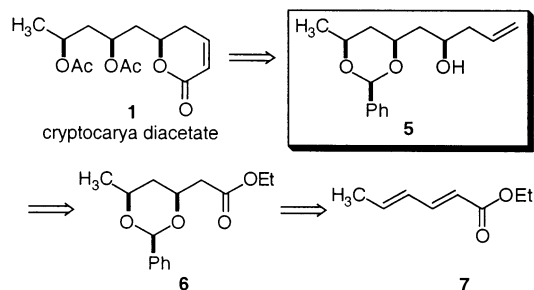
Inspired by the diverse range of structurally related 1,3-polyol-substituted 5,6-dihydropyran-2-ones, we have been interested in the development of practical and concise enantioselective approaches to *syn*-1,3-polyol functionalities.[13] As part of our successful efforts toward the total synthesis of the diol and triol natural products (tarchonan-

thuslactone and cryptocarya diacetate **1**), we found that the benzylidene-protected *syn*-ethyl-3,5-dihydroxyhexanoate **6** was a useful precursor.[8a] Accordingly, **6** was easily prepared from ethyl sorbate **7** in either optically enriched form in four steps and ~36% yield.

Scheme 2
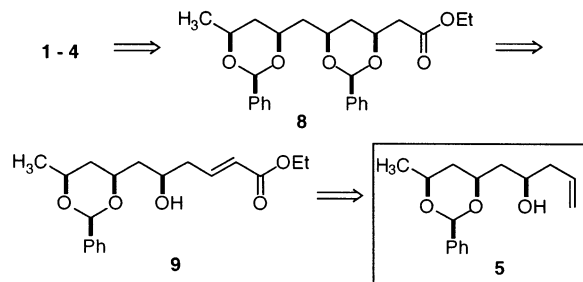
Turning our attention to the stereochemically more complex natural products **2**−**4**, we envisioned a protected all-syn bis-benzylidene-protected tetraol intermediate **8**, which contained all the stereochemical information needed for their synthesis. On the basis of our previous results, we believed that the second dioxane ring in **8** could be prepared by the Evans acetal-forming reaction from **9**, which in turn could be prepared by a cross-metathesis reaction between ethyl acrylate and **5**. Previously we have found **5** to be easily and enantioselectively prepared from ethyl sorbate in seven steps and 25% yield. Thus, the problem was reduced to an efficient synthesis of *trans*-δ-hydroxy-1-enoates **9**.[14,15] Herein, we describe our approach to the synthesis of these key building blocks via an efficient asymmetric and diastereoselective reaction sequence.

Typically, a three-step protection/oxidative cleavage/Wittig reaction sequence was used for the homologation of homoallylic alcohol **5** to **9**.[16] We anticipated that a much simpler procedure would result from a transition metal-mediated cross-metathesis coupling reaction of homoallylic alcohols and acrylates providing *trans*-δ-hydroxy-1-enoates (i.e., **10** plus **11** to yield **12**).[17] Previously, Crowe has shown that the Schrock molybdenum catalyst (Mo(CHCMe$_2$Ph) (NAr) [OCMe(CF$_3$)$_2$]$_2$) cross couples acrylonitrile and protected homoallylic alcohols to give good yields of a ~5:1 cis:trans ratio of double-bond isomers.[18] More recently, Grubbs has

(5) (a) Echeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881. (b) Herz, W.; Ramakrishnan, G. *Phytochemistry* **1978**, *17*, 1327.

(6) (a) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199. (b) Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nicholson, D. E. *Planta Med.* **1982**, *45*, 31.

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

(8) (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3* (17), 2777. (b) Garaas, S.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67* (8), 2682.

(9) (a) Nakata, T.; Hata, N.; Iida, K.; Oishi, T. *Tetrahedron Lett.* **1987**, *28*, 5661. (b) Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809. (c) Mori, Y.; Kageyama, H.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2574. (d) Solladié, G.; Gressot-Kempf *Tetrahedron: Asymmetry* **1996**, *7* (8), 2371. (e) Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855. (f) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512. (g) Gosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003. (h) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (i) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19. (j) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685.

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

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

(12) At the outset of this project, we set the goal for efficiency as three steps/stereocenter of the target molecule.
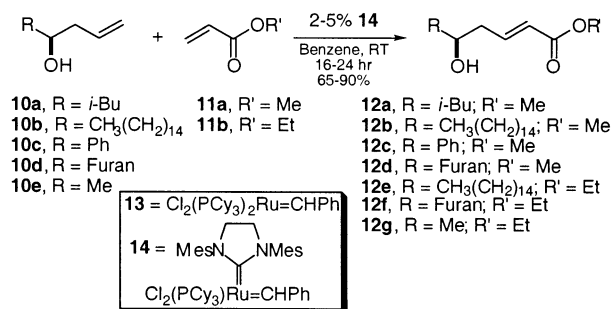
(13) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3* (17), 1049. Also see, ref 8.

(14) We have found that for the successful implementation of the Evans acetal-forming reaction, the δ-hydroxy-1-enoates must be in their trans form to prevent lactonization.

(15) For vinylogous aldol approaches to δ-hydroxy-1-enoates, see: (a) Fleming, I. *Bull. Soc. Chem. Fr.* **1981**, *2*, 7. (b) Barloy-Da Silva, C.; Benkouider, A.; Pale, P. *Tetrahedron Lett.* **2000**, *41*, 3077. (c) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288. For aldol/Wittig approaches, see ref 16 and: (d) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. (e) Solladie, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem.* **2000**, 357.

(16) For examples of the Wittig approach to *trans*-δ-hydroxy-1-enoates from homoallylic alcohols, see: Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menendez, C. J. *Tetrahedron* **1992**, *48* (37), 7899.

Scheme 3

Scheme 3

10a, R = i-Bu
10b, R = CH₃(CH₂)₁₄
10c, R = Ph
10d, R = Furan
10e, R = Me

11a, R' = Me
11b, R' = Et

12a, R = i-Bu; R' = Me
12b, R = CH₃(CH₂)₁₄; R' = Me
12c, R = Ph; R' = Me
12d, R = Furan; R' = Me
12e, R = CH₃(CH₂)₁₄; R' = Et
12f, R = Furan; R' = Et
12g, R = Me; R' = Et

13 = Cl₂(PCy₃)₂Ru=CHPh

14 = MesN⌒NMes / Cl₂(PCy₃)Ru=CHPh

shown that ω-hydroxy-α-olefins smoothly undergo the cross-coupling reaction with various acrylic esters and amides.[19]

Table 1[a].

	10	11	12	mol % of 14	reaction time (h)	yield of 12	E/Z ratio of 12
1	10a	11a	12a	2	16	70%	20:1
2[b]	10b	11a	12b	2	16	65%	20:1
3	10c	11a	12c	2	24	83%	10:1
4	10d	11a	12d	5	16	90%	>25:1
5	10b	11b	12e	5	24	55%	>20:1
6	10d	11b	12f	2	16	63%	>20:1
7	10e	11b	12g	2	24	75%	>20:1

[a] Typical reaction conditions were performed with a 1:2 ratio of 10 to 11 at room temperature and in a 0.2 M benzene solution. [b] This reaction was run in a 0.2 M CH₂Cl₂ solution.

To test the feasibility of a cross-metathesis sequence with homoallylic alcohols, we decided to start with 4-phenyl-butenol **10c**, which can be prepared in a racemic form from benzaldehyde and allyl-Grignard. Our initial reactions using Grubbs' bis-tricyclohexylphosphine catalyst **13** were entirely unsuccessful. For example, when a benzene solution of **10a** and **11a** (0.2 M, 1:5 ratio of **10a** to **11a**) was stirred in the presence of 5% **14** at room temperature for 4 days, no indication of the formation of enoate **12a** was observed. Similarly, no product was detected after heating an identical solution at 80 °C for 3 days. Success was achieved upon switching to the new, more reactive Grubbs' phosphine/carbene ligand catalyst **14**. We found that using carbene **14** for the cross-coupling reaction of **10a** and **11a** provided a good yield of enoate **12a** with excellent double-bond control.[20] Typical reaction conditions involved stirring a room-temperature solution (0.2 M in benzene) of a 1:2 ratio of homoallylic alcohol (**10a−d**) and acrylate (**11a−b**) in the

presence of **14** (2−5%) for 16 h. These conditions consistently gave good yields (55−90%) of enoates **12a−g**.[21] Unfortunately, we found that the Weinreb amide of acrylic acid failed to cross-couple with **10a** under these same conditions.[22]

Having established the viability of cross-coupling homoallylic alcohols **10** and acrylates **11** to form δ-hydroxy enoate **12**, we turned our attention to the synthesis of **2−4** from homoallylic alcohol *syn*-**5**. Previously, we have demonstrated that *syn*-**5** can be prepared from either **12g** (Scheme 4), which

Scheme 4
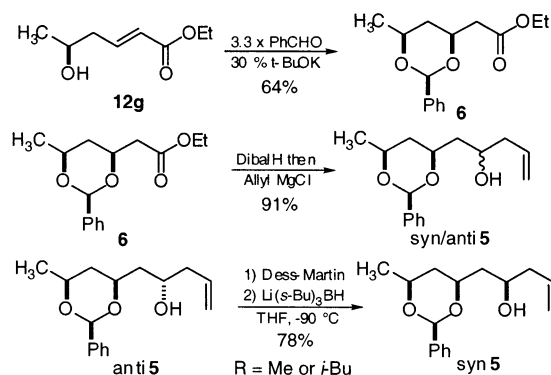
in turn was prepared from **10e** (Scheme 3), or in an asymmetric fashion from ethyl sorbate **7** (Scheme 1).[8]

Applying the optimized cross-coupling conditions to the more complex homoallylic alcohol *syn*-**5** and ethyl acrylate **11b** (Scheme 5) provided near quantitative yields of **9** in a

Scheme 5
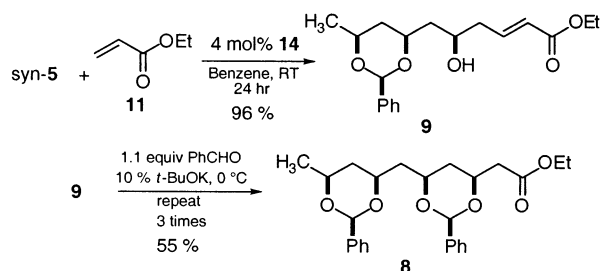
20:1 trans:cis ratio of double-bond isomers (96%). The final stereocenter of cryptocarya triacetate was installed by exposing **9** to the Evans acetal-forming reaction. Reacting the δ-hydroxy enoate **9** with 4 equiv of benzaldehyde and a catalytic amount of KO*t*-Bu led to a 55% yield of the bis-

(17) As this methodology was being completed, Cossy reported similar cross-metathesis acetyl-protected homoallylic alcohols and enoates; see: (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451. (b) Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459. For a related example, see: (c) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341.
(18) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.
(19) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.

(20) All levels of double-bond selectivity were determined by ¹H NMR analysis (at 500 MHz).
(21) All new compounds were identified and characterized by ¹H NMR, ¹³C NMR, FTIR, HRMS, and/or elemental analysis.
(22) This result was somewhat surprising given that Grubbs et al. have shown that ω-hydroxy-α-olefins smoothly undergo the cross-coupling reaction with the Weinreb amide of acrylic acid; see ref 19.

benzylidene-protected tetraol **8** along with 23% recovered starting material.[23]
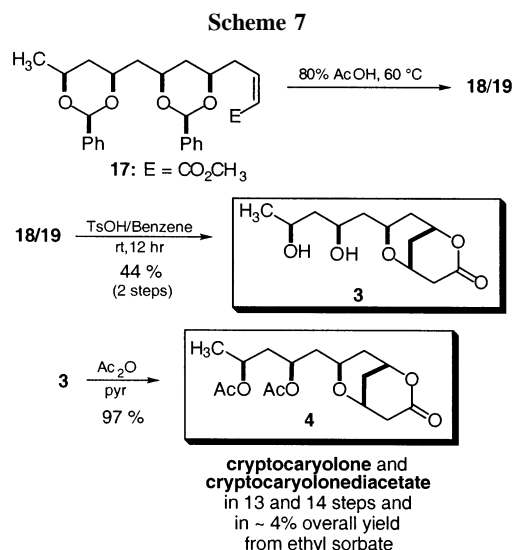
With the establishment of an enantioselective route to the bis-benzylidene acetal **8**, we decided to address the installation of the pyranone functionality of cryptocarya triacetate (Scheme 6).[24] To this end, we planned to convert ester **8**

Scheme 6
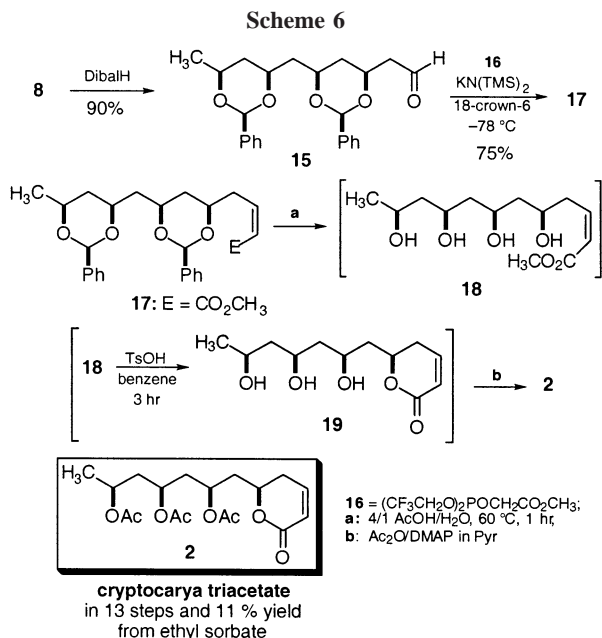
into the *cis*-enoate **17**, which possesses all of the desired carbon atoms and the correct double-bond stereochemistry of **2**. Aldehyde **15** was easily prepared in an excellent yield (90%) by exposure of a THF solution of ester **8** with 1.1 equiv of DibalH at −78 °C. Treatment of **15** with the potassium salt of **16** and 18-crown-6 afforded a 75% yield of **17** with a 4:1 double-bond cis:trans stereoselectivity.[25]

Next, we looked to investigate the potential for a deprotection and lactonization reaction sequence to convert enoate **17** to pyranone **19** and not bicyclic lactone **3** (Schemes 6 and 7). In the course of our tarchonanthuslactone and cryptocarya diacetate **1** syntheses, we found that the benzylidene protecting group could be easily removed by refluxing in 80% aqueous acetic acid. Exposing **17** to these conditions for ∼1 h gave primarily tetraol **18** with a small amount of lactone **19**. In vacuo removal of solvent followed by the addition of benzene and 1% TsOH gave good conversion to triol **19** with minimal amounts of **3** after only 3 h. Because of our concerns with bicycle formation, crude **19** was peracylated with excess Ac₂O/Pyr and catalytic DMAP providing good yields of cryptocarya triacetate.

Not surprisingly, a similar acid-catalyzed deprotection strategy was used to prepare the cyrptocaryolones (Scheme

(23) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

(24) For other approaches to pyranone synthesis, see refs 8b and 9d and: (a) Hayakawa, H.; Miyashita, M. *Tetrahedron Lett.* **2000**, *41*, 707. (b) Tosaki, S.-Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495.

(25) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

Scheme 7

7). In fact, allowing the mixture of **18**/**19** to stir longer in the TsOH/benzene solution (16 instead of 3 h) gave high conversions of the bicyclic natural product **3**. Thus, a 44% yield of cryptocaryolone **3** was isolated after the two-step aqueous acetic acid, TsOH/benzene procedure. As reported by Drewes et al. in their isolation paper,[3] **3** was easily peracylated with excess Ac₂O/Pyr to give excellent yields of cryptocaryolone diacetate **4** (97%).

Comparison of the spectral data of synthetic **3**, **5**, and **6** with the reported spectral data (IR, ¹H NMR, and ¹³C NMR spectra) for cryptocarya triacetate, cryptocaryolone, and cryptocaryolone diacetate showed complete agreement.[3] Thus, for the first time, both the absolute and relative stereochemistries of cryptocaryolone and cryptocaryolone diacetate were established as drawn in Scheme 7.

In conclusion, three short and enantioselective syntheses of three natural products isolated from *C. latifolia* have been presented. The route to cryptocarya triacetate is significantly shorter than the previous approach, requiring only 13 steps instead of 24 steps.[9] The approach also allows for the first time the syntheses of two related natural products, cryptocaryolone and cryptocaryolone diacetate, which occurred with similar efficiency (13 and 14 steps, respectively). This highly enantio- and diastereocontrolled route illustrates the utility of our recently developed use of Grubbs cross-metathesis and Os/Pd route to benzylidene-protected *syn*-1,3-diols. The syntheses provide cryptocarya triacetate in 11% overall yield and cryptocaryolone and cryptocaryolone diacetate both in 4% overall yields.

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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