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An Enantioselective Synthesis of Benzylidene-Protected *syn*-3,5-Dihydroxy Carboxylate Esters via Osmium, Palladium, and Base Catalysis

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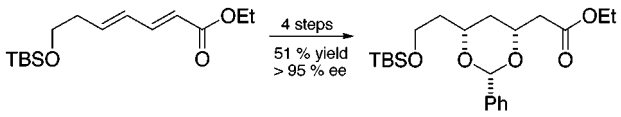
ABSTRACT

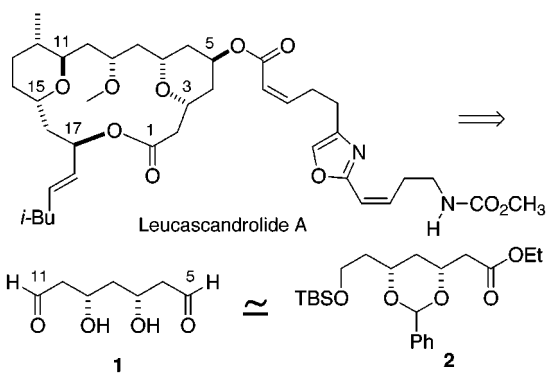


The enantioselective syntheses of several protected *syn*-3,5-dihydroxy carboxylic esters have been achieved from the corresponding achiral 1,3-dieneoates. The route relies upon an enantio- and regioselective Sharpless dihydroxylation and a palladium-catalyzed reduction to form *δ*-hydroxy-1-enoates. The resulting *δ*-hydroxy-1-enoates are subsequently converted into benzylidene-protected 3,5-dihydroxy carboxylic esters in one step. The benzylidene-protected 3,5-dihydroxy carboxylic esters are produced in good overall yields (25% to 51%) and high enantiomeric excesses (80% to >95%).

In the course of a project aimed at a total synthesis of the potent antifungal and cytotoxic macrolide leucascandrolide A,[1,2] we were interested in a concise route to protected *syn*-3,5,7-trihydroxyheptenoic acid ester **2**, a potential differentiated synthon of diol **1** (Scheme 1). We envisioned that a suitably protected and desymmetrized variant of **1** could become the C-5 through C-11 fragment of leucascandrolide A. In addition, we planned for the introduction of the C-5, C-11, and C-12 stereocenters of leucascandrolide A by two sequential diastereoselective anion additions: allyl at C-5 and then crotyl at C-11.[3] Thus, we decided to devise an efficient and enantioselective route to **2** which would derive the asymmetry via a catalytic enantioselective asymmetric reaction.[4]

Naturally, synthons of **1** would be of general use for the synthesis of many 1,3-polyol containing natural products.[5]

Scheme 1



(1) Ambrosio et al. have shown leucacandrolide to have significant activity against *Candida albicans* and in vitro IC_{50} values of 0.05 and 0.25 μg/mL against KB and P388 cell lines, respectively, see: Ambrosio, M. D.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51−59.

(2) Leucascandrolide A has recently been synthesized by the Leighton group, see: (a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. For another approach, see: (b) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597−599.

(3) Leighton has demonstrated that this can be accomplished with allyl-(−)-diisopinocamphenylborane and (*E*)-crotyl-(−)-diisopinocamphenylborane.

(4) For a nine-step Sharpless asymmetric epoxidation route to a derivative of **2**, see: (a) Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyam, K. Miyashita, M. *Chem. Lett.* **1998**, 109−110. For a nine-step resolution approach, see: (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajpakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*(29), 8671−8726.

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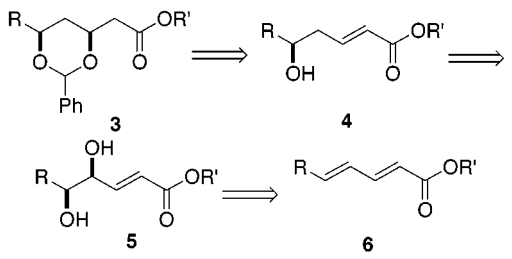
The *syn*-1,3-diol structural unit is a common motif in many natural products with a wide range of biological activities.[6] Due to the wide distribution of the *syn*-1,3-polyol motif in natural products, many synthetic methodologies have been employed to synthesize this core structure. These range from the use of stoichiometric chiral reagents such as enolates[7] and allyl anions[8] to the more elegant use of catalytic reagents.[9] Perhaps the most successful application of enantioselective catalysis is Rychnovsky's[5,6] use of the Noyori hydrogenation.[10] More recently, Leighton has developed two carbonylation approaches to 1,3-*syn*-diols of type **1**.[11]

Recently, we developed several effective routes to various carbohydrate-based natural products using the Sharpless dihydroxylation and aminohydroxylation to establish the absolute stereochemistry.[12] Continuing our investigations on the utility of these transformations, we decided to investigate its merit toward the synthesis of the *syn*-1,3-diol structural motif. We envisioned establishing 3,5-dihydroxy carboxylic esters from δ-hydroxy-1-enoates **4**, which Evans has shown can be converted into a benzylidene-protected 3,5-dihydroxy carboxylic ester **3** in a single step (Scheme 2).[13]

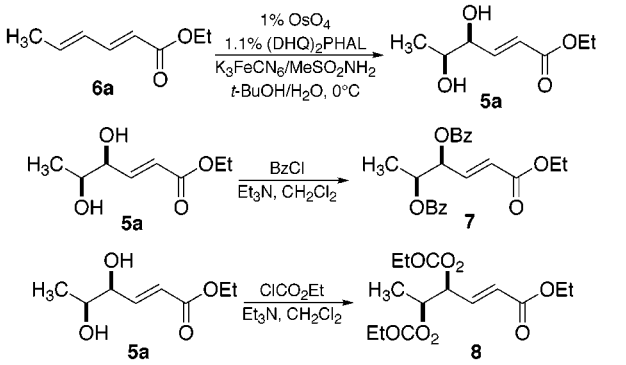
Scheme 2



Thus, the problem was reduced to an efficient asymmetric synthesis of δ-hydroxy-1-enoates.[14] We hoped these δ-hydroxy-1-enoates could be prepared by the selective reduction of a 3,4-dihydroxy-1-enoate, which in turn could be prepared via an asymmetric dihydroxylation of a dienoate such as **6**.[15] Miyashita has developed a similar reduction strategy to prepare δ-hydroxy-1-enoates from γ,δ-epoxy acrylates.[4a] Herein, we describe our approach to the synthesis of these key building blocks via an efficient asymmetric and diastereoselective reaction sequence.

To test the feasibility of this sequence, we decided to start with commercially available ethyl sorbate (**6a**). Following Sharpless's protocol for the dihydroxylation of **6a**, diol **5a** was provided in good yields and enantiomeric excesses (Scheme 3).[16,17] Either enantiomer of diol **5a** was obtained

Scheme 3



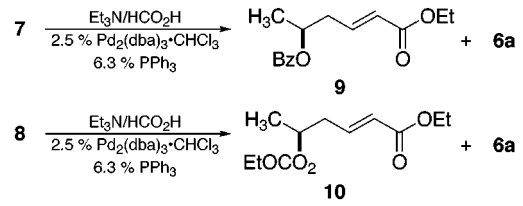
with enantiomeric excesses on the order of 80% from the $(DHQ)_2PHAL$ ligand system and > 90% from the $(DHQD)_2$-PHAL ligand.

Diol **5a** was conveniently converted into bis-benzoate **7** or bis-ethyl carbonate **8** by treatment with benzoyl chloride or ethyl chloroformate (57 and 81% yields, respectively). At this stage the two functional groups were readily differentiated by taking advantage of the fact that allyl benzoates and carbonates are good leaving groups for the formation of π-allyl palladium complexes.[18]

Thus, treatment of **7** with a catalytic amount of a palladium(0) source and triphenylphosphine (2.5% $Pd_2(dba)_3 \cdot CHCl_3$/6.3% PPh_3) and a mild hydride source (3 equiv, Et_3N/HCO_2H) gave the reduced product **9** in low yield (43%)

(5) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040.
(6) (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.
(7) (a) Evans, D. A. *Aldrichimica Acta*. **1982**, *2*, 23. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
(8) For good reviews see: (a) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*(1), 123−30. (b)Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293.
(9) (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837−8838. (b) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815. (c) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788−789. (d) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581−8584. (e) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.
(10) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102.
(11) (a) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118−11119. (b) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3205−3208. (c) Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997**, *119*, 12416−12417.
(12) (a) Harris, J. M.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 2983−2986. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17−36. (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863−866. (d) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982−2983. (e) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401−404.
(13) See: ref 4b and Evans, D. A. Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446−2453.
(14) For vinylogous aldol approaches to δ-hydroxy-1-enoates, see: (a) Fleming, I. *Bull. Soc. Chem. Fr.* **1981**, *2*, 7−13. (b) Barloy-Da Silva, C.; Benkouider, A.; Pale, P. *Tetrahedron Lett.* **2000**, *41*, 3077−3081. (c) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288−302. For aldol/Wittig approaches, see: ref 4 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**, 357−364.
(15) Previously Sharpless had shown that the AD mix reagent dihydroxylates simple dienoates **6a** and **6c** with good enantio- and diastereocontrol, see: (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570−7571. (b) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−76.
(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, HRMS, and/or elemental analysis.
(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.

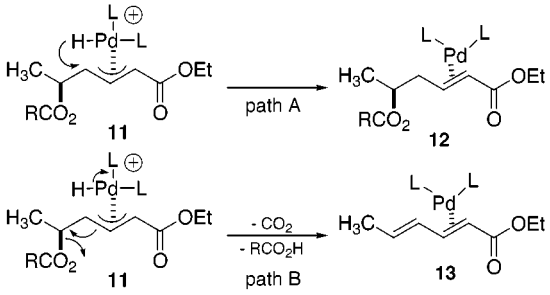
Scheme 4



(Scheme 4). More rigorous examination of the reaction mixture led to the identification of less than 10% of ethyl sorbate **6a**. Unfortunately, varying the substrate to the bis-ethyl carbonate **8** did not change the yield of reduced product **10** (47%) or the relative amount of ethyl sorbate (4:1). To determine if the ethyl sorbate was being formed from an elimination reaction, both palladium reaction products were reexposed to the reaction conditions without palladium present. Both enoates **9** and **10** were completely stable to refluxing THF solutions of Et_3N and Et_3N/HCO_2H. No ethyl sorbate was detected even as the reaction was concentrated by solvent distillation, indicating that ethyl sorbate was a direct product from the palladium reaction conditions.[19]

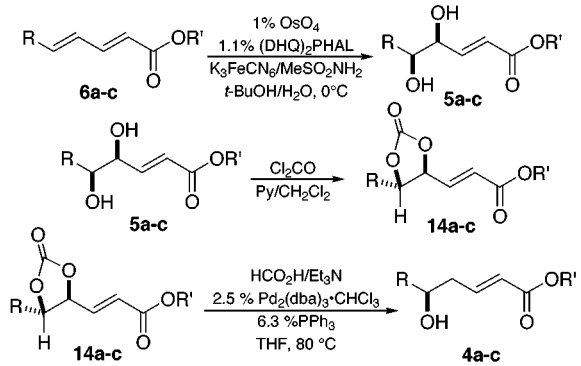
The formation of ethyl sorbate must have occurred via an alternative reaction pathway available to the π-allyl palladium intermediate **11**. Presumably **11**, in addition to the normal hydrogen migration to the γ-carbon, can undergo a loss of a proton and concomitant β-elimination of the C-5 ethyl carbonate or benzoate to give palladium-bound ethyl sorbate **13** (path B, Scheme 5).[20] To minimize the β-elimination side

Scheme 5



reaction, we decided to make the C-5 substituent a poorer leaving group (i.e., negatively charged). This was easily accomplished by activating the allylic alcohol functionality as a cyclic carbonate. The cyclic carbonate **14a** was prepared by treating a pyridine/CH_2Cl_2 solution of diol **5a** with triphosgene, providing **14a** in excellent yield (87%). Treatment of **14a** with a catalytic amount of palladium/triphenylphosphine (2.5% $Pd_2(dba)_3$•$CHCl_3$ or $(allylPdCl)_2$/6.3% PPh_3) and a mild hydride source (Et_3N/HCO_2H) provided the desired δ-hydroxy ester **4a** in good yield (70%), with no loss of enantiomeric excess (Scheme 6). Varying the

Scheme 6

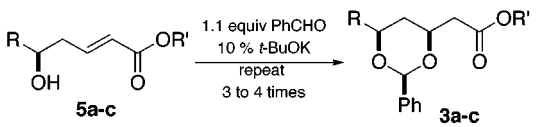


a, R = Me, R' = Et; **b**, R = Pr, R' = Me; **c**, R = Ph, R' = Et

substitution on the dienoate from methyl to propyl, **6b**, or phenyl, **6c**, had no detrimental effects on the yields of this reaction sequence and inevitably improved the enantiomeric excess of the asymmetric dihydroxylation. Both diols **5b** and **5c** were formed from **6b** and **6c** in 80% and 79% yields and greater than 95% enantiomeric excesses. Similarly, **5b** and **5c** were converted into cyclic carbonates **14b** (94%) and **14c** (91%) and then reduced upon exposure to the palladium procedure to form the homoallylic alcohols **4b** and **4c** (80% and 72% yields, respectively). The methyl-, propyl-, and phenyl-substituted dienoates **6a**−**c** were converted into the corresponding δ-hydroxy enoates in good overall yields (47−67%) in three steps and with no loss of enantiomeric excess (80−95% ee).

Having established a general procedure for the enantioselective synthesis of homoallylic alcohols **4**, we turned our attention to the base-catalyzed acetal/conjugated addition reaction. Exposing the three δ-hydroxy enoates **4a**−**c** to the Evans procedure (1.1 equiv of benzaldehyde and 0.1 equiv of KO*t*-Bu, 0 °C, repeat 3−4 times every 15 min)[13] led to good yields of the benzylidene-protected 3,5-dihydroxy carboxylic esters **3a**−**c** (Scheme 7). Three stereochemically

Scheme 7



a, R = Me, R' = Et; **b**, R = Pr, R' = Me; **c**, R = Ph, R' = Et

enriched esters **3a**, **3b**, and **3c** were formed as a single diastereomer (>95%) and in good yields (60%, 60%, 50%, respectively).

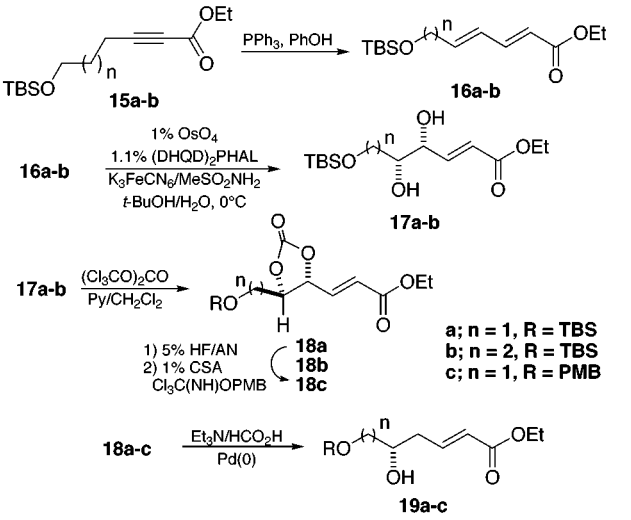
With the success of the model system, we decided to test the compatibility of the reaction sequence with the oxygen-

(19) Furthermore, the ratios of **9**/**6a** and **10**/**6a** for both reactions were equivalent at both low and high conversion.

(20) These results do not preclude the mechanistic possibility for the formation of ethyl sorbate via a β,γ-unsaturated regioisomer of **9** and **10** and subsequent base- and/or palladium-catalyzed elimination.

ated dienoates **16a** and **16b**. These dieneoates were readily prepared by a PPh_3/PhOH-catalyzed deconjugation of ynoates **15a** and **15b** (80% and 95% yields, respectively).[21] Both ynoates **15a** and **15b** were readily prepared from 5-hexyn-1-ol and 4-pentyn-1-ol in two steps, in 93% and 97% overall yields, respectively (TBSCl, Et_3N, 0 °C; *n*-BuLi then $ClCO_2CH_2CH_3$, 0 °C). The exposure of **16a** and **16b** to the dihydroxylation conditions gave diols **17a** and **17b** in 82% and 91% yields and ~90% and >95% ee, respectively (Scheme 8). These diols were subsequently converted into

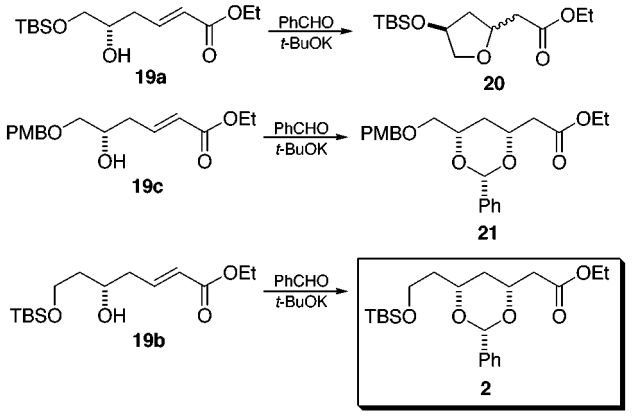
Scheme 8



carbonates **18a** (94%) and **18b** (95%) upon treatment of a CH_2Cl_2/pyridine solution with triphosgene. Similarly, the carbonates **18a** and **18b** were reductively opened to form the homoallylic alcohols **19a** (88%) and **19b** (87%) in good yields. Because of the instability of the primary TBS group in later sequences, the TBS group of **18a** was converted into a PMB group by TBS deprotection (5% HF/AN, 93% yield) and PMB protection (1% CSA, $Cl_3C(NH)OPMB$, 61% yield) forming carbonate **18c** in a 57% overall yield. Similarly, cyclic carbonate **18c** underwent palladium-catalyzed reduction to give the homoallylic alcohol **19c**, but with a slightly lower efficiency (66%).

With access to the oxygenated substrates **19a**−**c**, we were ready to address the formation of the desired synthon **2**. Unfortunately, the vicinal *tert*-butyldimethylsiloxy group in **19a** was incompatible with the basic conditions of the benzylidene acetal formation reaction. Exposure of the hexenoate **19a** to the Evans' procedure resulted in a TBS-group migration/cyclization reaction, yielding the tetrahydrofuran product **20** as a mixture of diastereoisomers (88% yield). However, exposure of the PMB-protected variant **19c** to the same conditions led to a clean conversion into the desired benzylidene acetal **21** in a 61% yield. In contrast, the homologous TBS-protected substrate **19b** did not undergo a similar silyl-group migration and subsequent rearrangement under the same conditions. Treatment of **19b** to the sequential KO*t*-Bu/benzaldehyde procedure[22] yielded the benzylidene-protected *syn*-1,3-diol **2** in good yield (68%) (Scheme 9).

Scheme 9



In conclusion, this highly enantio- and diastereocontrolled route to benzylidene-protected *syn*-1,3-diols illustrates the utility of the asymmetric dihydroxylation/palladium-catalyzed reduction reaction sequence. This methodology provides rapid and enantioselective access to densely functionalized molecules starting from commercially available and inexpensive starting materials, as well as, providing an alternative to vinylogous aldol strategies. Further studies on the use of these chiral building blocks toward the synthesis *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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(21) We found the Rychnovsky phenol variant of the Trost procedure was the best for these substrates. (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659−60. For the original Trost procedure, see: (b) Trost, B.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933−35.

(22) Benzaldehyde (1.1 equiv) with 0.1 equiv of KO*t*-Bu; after 15 min more benzaldehyde (1.1 equiv) and KO*t*-Bu (0.1 equiv).