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Total Synthesis of Pyranicin

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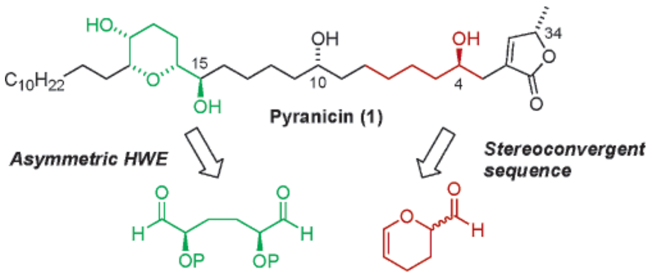
ABSTRACT



A stereocontrolled convergent synthesis of the annonaceous acetogenin pyranicin (1) is presented. Asymmetric Horner–Wadsworth–Emmons (HWE) reactions were used to access key intermediates. The tetrahydropyran derivative 2 was obtained via an asymmetric desymmetrization of the *meso*-dialdehyde 6, and the butenolide fragment was constructed using a stereoconvergent reaction sequence involving a parallel kinetic HWE resolution followed by a Pd-catalyzed allylic substitution. The C10/C15 1,6-diol motif was installed using Carreira's asymmetric acetylide addition methodology.

In recent years, the annonaceous acetogenin group of natural products has been the focus of extensive synthetic efforts[1] as a result of the interesting biological properties exhibited by these compounds.[2] Pyranicin (**1**) was first isolated from the stem bark of *Goniothalamus giganteus* by McLaughlin et al.[3] Structurally, it belongs to the nonclassical subgroup of annonaceous acetogenins together with other tetrahydropyran (THP) acetogenins such as mucocin, pyragonicin, and jimenicin. Interesting structural features include a unique absolute and relative configuration of the THP stereocenters. A previous synthesis of **1** has been reported by Takahasi et al.[1c] We herein report a convergent total synthesis of **1** employing asymmetric Horner−Wadsworth−Emmons (HWE) reactions[4] as well as a stereoconvergent reaction sequence[5] to install key stereocenters.

Retrosynthetically, we planned to access the substituted THP intermediate **2** via an asymmetric HWE desymmetrization of dialdehyde **6** (Scheme 1), through a strategy related to our previously reported synthesis of the THP subunit of mucocin.[6] We planned to control the C4 stereocenter via a parallel kinetic resolution of racemic acrolein dimer.[5b] In conjunction with a Pd(0)-catalyzed stereoconvergent allylic substitution, both enantiomers of *rac*-**7** would overall give the exact same intermediate **5**, with simultaneous incorporation of a protective group suitable for last-step global deprotection. The butenolide would be constructed via condensation with a lactaldehyde derivative as described previously.[7] The C10 and C15 stereocenters would be installed using Carreira's stereoselective addition of TMS-acetylene to aldehydes.[8]

Our synthesis began with the desymmetrization of *meso*-dialdehyde **6a** (readily available in five steps from cyclo-

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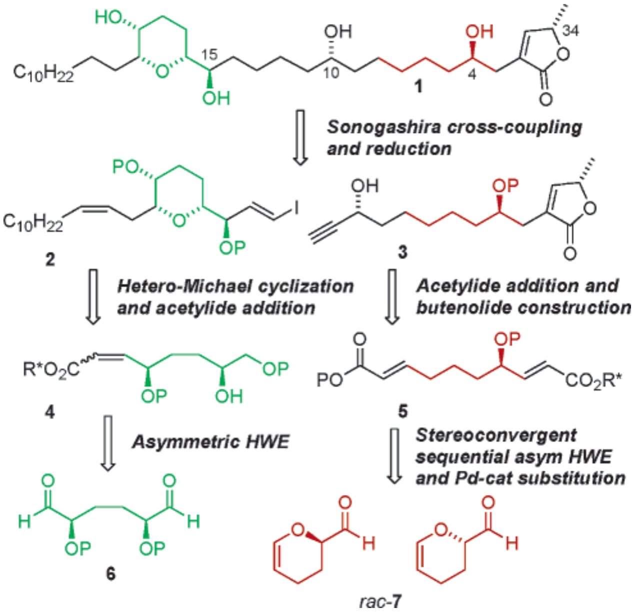
(1) For recent examples, see: (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702−14703. (b) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751−4754. (c) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353−1356.
(2) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540 and references therein.
(3) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833−5844.
(4) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579−594.
(5) (a) Pedersen, T. M.; Hansen, E. L.; Kane, J.; Rein, T.; Helquist, P.; Norrby, P.-O.; Tanner, D. *J. Am. Chem. Soc.* **2001**, *123*, 9738−9743. (b) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535−538.
(6) Vares, L.; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226−7237.
(7) Marshall, J. A.; Jiang, H. *J. Nat. Prod.* **1999**, *62*, 1123−1127.
(8) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606 and references therein. NME = *N*-methylephedrine.

10.1021/ol0479242 CCC: $30.25

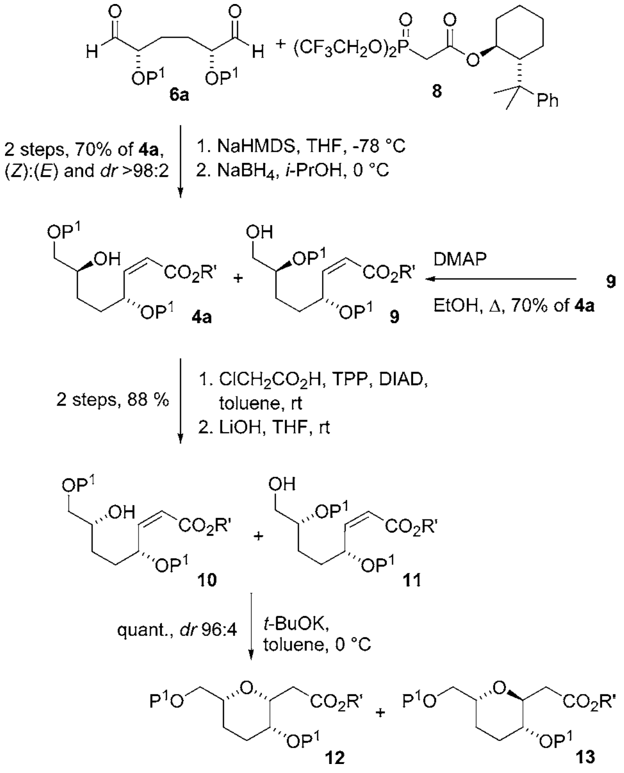
Scheme 1. Retrosynthetic Analysis



P = protective group; R* = chiral auxiliary.

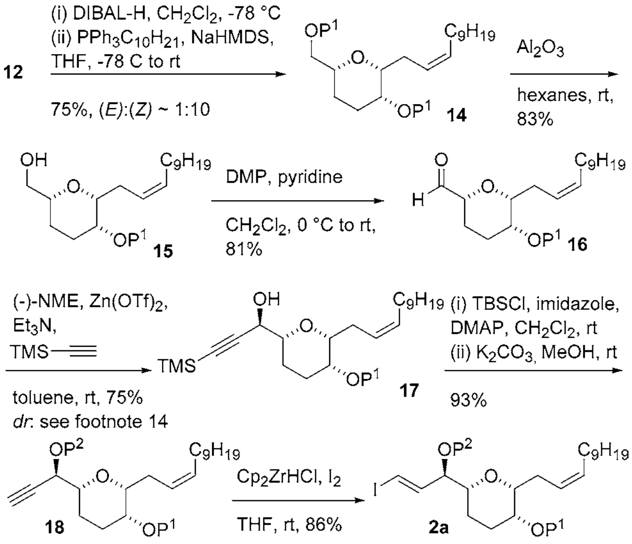
hexadiene[6]) through an asymmetric HWE olefination (Scheme 2).[9] Reduction with $NaBH_4$ in tandem with partial protective group migration of the TBDPS group to the primary position gave the secondary alcohol **4a** together with minor amounts of regioisomer **9**.[10] A Mitsunobu reaction followed by basic hydrolysis of the chloroacetate then gave the inverted product **10** together with minor amounts of regioisomer **11**. In the subsequent hetero-Michael cyclization, the desired *cis-cis*-THP **12** was formed with 96:4 stereoselectivity. On the basis of work by Martín and co-workers,[11] we expected the (*Z*)-olefin to give the *trans-trans*-THP **13** as the kinetically favored product. However, we were pleased to find that although **13** was formed initially, it rapidly equilibrated under the reaction conditions to give the desired **12**. Using toluene as a solvent, we could also achieve tandem protective group migration and cyclization, resulting in an essentially quantitative yield of **12** from a mixture of **10** and **11**. The full relative configurations of the THP rings in **12** and **13** were unambiguously determined by ^1H NOESY correlations. This stereoselective approach to **12** is complementary to our previous work[6] in that a different relative configuration of the THP stereocenters is obtained.

Scheme 2. Synthesis of the THP Fragment



P^1 = TBDPS; R′ = nor-8-phenylmentyl.

Scheme 3. Synthesis of the THP Fragment (Continued)



P^1 = TBDPS; P^2 = TBS.

The aliphatic side chain was added via a one-pot DIBAL reduction/Wittig olefination to give **14** (Scheme 3). Selective deprotection, by treatment with activated alumina,[12] followed by Dess−Martin oxidation of the resulting primary alcohol **15**, gave the corresponding aldehyde **16**. The zinc-mediated asymmetric addition of acetylides to aldehydes as published by Carreira et al. has previously been exploited in the stereocontrolled synthesis of chiral tetrahydrofuran deriva-

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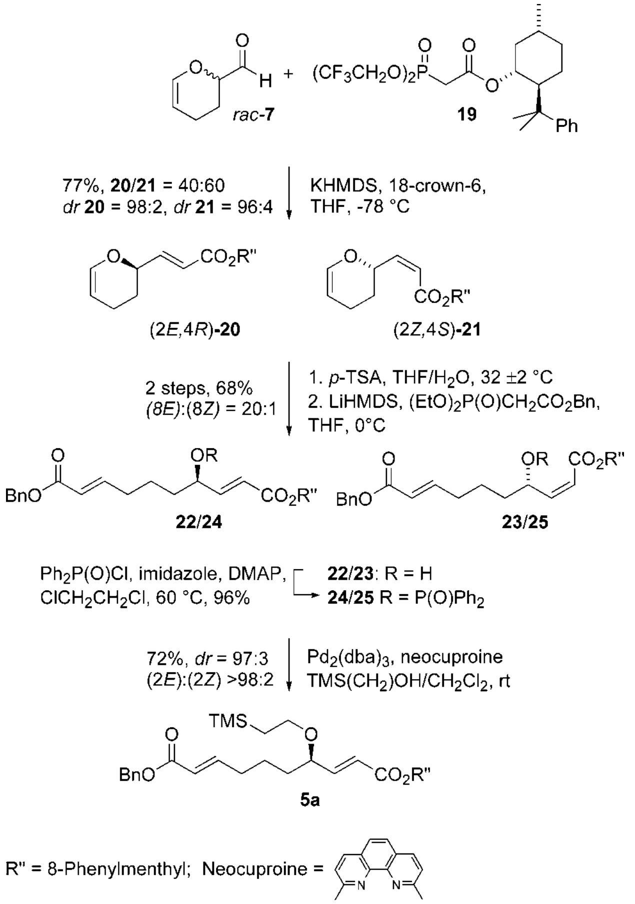
[9] For use of nor-8-phenylmenthol containing phosphonates, see: Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805−826.

[10] Initially, a 9:1 mixture of **4a** and **9** was obtained, from which pure **4a** was isolated in 70% yield. The remaining mixture could be reequilibrated (DMAP, EtOH, Δ, 70%) to increase the overall yield of **4a**.

[11] (a) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570−4583.

[12] Feixas, J.; Capdevila, A.; Guerrero, A. *Tetrahedron* **1994**, *50*, 8539−8550.

Scheme 4. Synthesis of the Butenolide Fragment



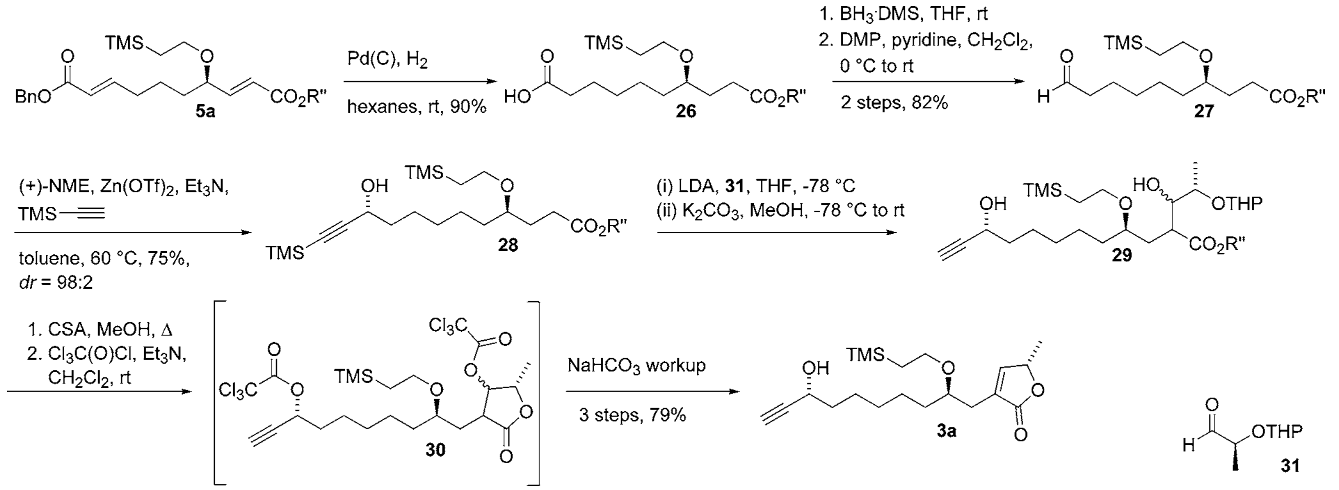
tives.[13] However, good levels of stereocontrol have not previously been achieved in direct formation of syn products from 2-formyl-THP derivatives analogous to **16**. We were delighted to find that employment of the Carreira methodology in a stereoselective addition of TMS-acetylene to **16** gave the propargylic alcohol **17** in good yield and diastereoselectivity.[14] Subsequently, a one-pot procedure served to first protect the propargylic hydroxyl group and then to deprotect the TMS group to afford **18**. Hydrozirconation of the acetylene using Schwartz reagent followed by addition of elemental iodine then gave the desired vinyl iodide **2a**.

Our synthesis of the butenolide subunit began with a parallel kinetic resolution of racemic acrolein dimer using phosponate **19**, which afforded the desired mixture of (2*E*,4*R*)-**20** and (2*Z*,4*S*)-**21** as product with high stereoselectivity (Scheme 4). A subsequent acid-catalyzed addition of water to the vinyl ethers gave the corresponding hemiacetals, the open chain forms of which could then be trapped in an HWE reaction to give **22** and **23**. Careful optimization of the HWE conditions was required due to the predisposition of the (2*Z*,4*S*)-alkene **23** to lactonize under basic conditions. Activation of the secondary alcohols through formation of phosphinate esters **24**/**25** then provided substrates suitable for the stereoconvergent Pd(0)-catalyzed allylic substitution. In this step, the (2*Z*)-olefin undergoes a $\pi-\sigma-\pi$ rearrangement resulting in a net inversion of both the alkene geometry and the configuration at C4, while the (2*E*)-olefin reacts with overall retention at both stereogenic units. The conditions previously developed for an analogous case[5a] gave unsatisfactory results due to slow reaction and extensive β-elimination. We were, however, pleased to find that use of neocuproine as a ligand in combination with a 1:1 mixture of CH_2Cl_2/nucleophile[15] as a solvent almost completely suppressed the undesired elimination ($\leq$10%) and also increased the reaction rate significantly. It should be emphasized that separation of **20**/**21**, **22**/**23**, and **24**/**25**, respectively, was not necessary since **24** and **25** are both transformed to **5a**.

In this context, it could be noted that although TMS-$(CH_2)_2-$ is well established as a protective group for carboxylic acids, it has been used only sparingly as a protective group for alcohols.[16]

Hydrogenation/hydrogenolysis of **5a** using Pd/C in hexanes followed by reduction with BH_3·DMS and Dess−Martin

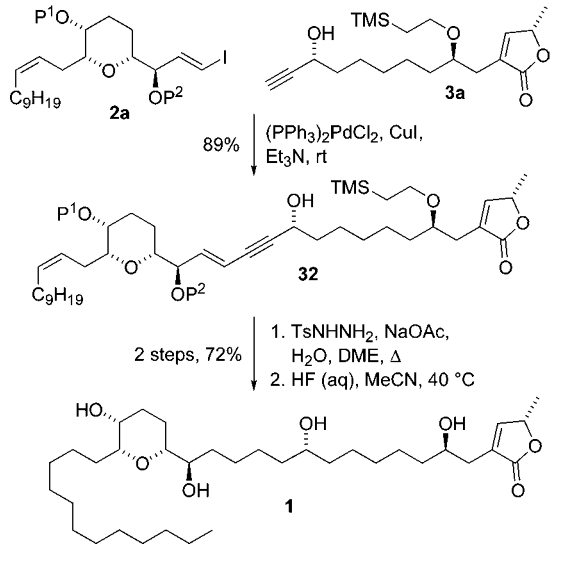
Scheme 5. Synthesis of the Butenolide Fragment (Continued)



oxidation gave the corresponding aldehyde **27** in good yield (Scheme 5). We intended to again utilize the Carreira addition of TMS-acetylene to install the C10-stereocenter. As indicated by literature precedence,[17] this proved to be difficult, and standard conditions gave only trace amounts of product. However, use of excess acetylide at 60 °C in a sealed vessel afforded the desired propargylic alcohol **28** in good yield and with excellent diastereoselectivity.[18] Construction of the butenolide proceeded as expected, beginning with a one-pot aldol addition of aldehyde **31**[19] followed by removal of the TMS group with K_2CO_3/MeOH to give **29**. Subsequent lactonization under acidic conditions gave the desired lactone as a diastereomeric mixture. Activation and in situ elimination of the C33-hydroxy group was accomplished via formation of the bis-trichloroacetate **30**, which spontaneously gave the desired butenolide under the reaction conditions. Finally, the propargylic alcohol could be released upon mild hydrolytic workup without compromising the integrity of the butenolide stereocenter to afford **3a**.

The complete pyranicin framework was assembled through a Sonogashira coupling[20] of **2a** and **3a**, giving ene-yne **32**. Finally, a selective diimide reduction followed by global deprotection using HF in MeCN afforded pyranicin (**1**) in good yield (Scheme 6). Spectroscopic properties of our synthetic material were in all respects identical to those reported by Takahashi.[1c,21] In addition, we used Figadère's method[22] to confirm that, within limits of detection, no epimerization of the C34 stereocenter had occurred.

Scheme 6. Endgame



P¹ = TBDPS; P² = TBS.

In summary, we have developed a stereoselective and convergent total synthesis of pyranicin (**1**). The longest linear sequence comprises 19 isolated intermediates starting from cyclohexadiene (14 from **6a**), with an overall yield of 6.3% (11.0% from **6a**). Key features of the synthesis are (i) extension and application of our strategies based on asymmetric HWE reactions and (ii) use of Carreira's zinc-mediated asymmetric acetylide addition to install key stereocenters. Further studies directed toward the synthesis of related acetogenins as well as evaluation of biological properties will be reported in due course.

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

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(13) (a) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Eur. J.* **2004**, *10*, 672−680.

(14) Since intermediates **14**−**18**, **2a**, and **32** were carried through the synthesis as ~1:10 (*E*):(*Z*) mixtures, an exact quantification of the selectivity of the TMS-acetylide addition has not been performed. However, ^{1}H NMR analysis indicates ≥95:5 diastereoselectivity. The relative configuration was assigned by analogy with the literature.[8]

(15) TMS$(CH_2)_2$OH could be recovered through bulb-to-bulb distillation of the crude product in 80% yield.

(16) Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445−448.

(17) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197−3199.

(18) Diastereomeric ratio of **28** was determined by ^{1}H and ^{19}F NMR analysis of the corresponding (+)- and (−)-MTPA derivatives. The relative configuration was assigned by analogy with literature.[8]

(19) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767−5790.

(20) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771−1779.

(21) Takahashi et al.[1c] confirmed McLaughlin's original assignment[3] of the relative and absolute configuration of pyranicin. There is, however, a strong discrepancy in the optical rotation reported for the natural product and that of synthetic material: natural material, $[\alpha]_D^{23}$ −9.7 (c 0.01, $CHCl_3$); synthetic material (Takahashi), $[\alpha]_D^{23}$ +19.5 (c 0.55, $CHCl_3$); our synthetic material, $[\alpha]_D^{23}$ +21.1 ($c = 0.24$, $CHCl_3$).

(22) Latypov, S.; Franck, X.; Jullian, J.-C.; Hocquemiller, R.; Figadère, B. *Chem. Eur. J.* **2002**, *8*, 5662−5666.