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Divergence en Route to Nonclassical Annonaceous Acetogenins. Synthesis of Pyranicin and Pyragonicin†

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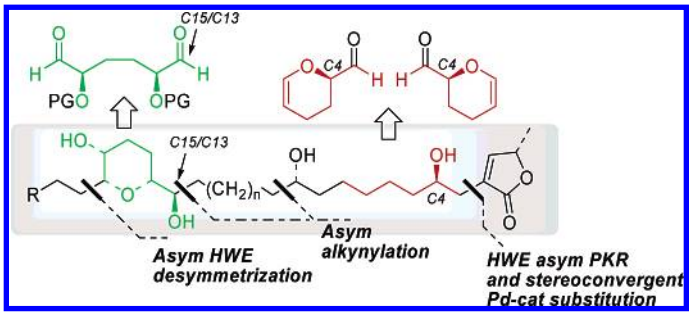

Syntheses of the nonclassical annonaceous acetogenins, pyranicin, and pyragonicin from common late-stage intermediates are presented. The construction of key elements relies on asymmetric HWE reactions, including the desymmetrization of a *meso*-dialdehyde and a parallel kinetic resolution of a racemic aldehyde. A stereoconvergent Pd-catalyzed substitution serves to install the C4 stereocenter in protected form with different orthogonal protective groups. A divergent strategy to form 1,4- and 1,6-diols, employing stereoselective Zn-mediated alkynylations, is used for completion of the core structures. Notably, the stereoselective coupling reaction toward pyragonicin proceeds with highly functionalized fragments. The methodology is further expanded by a divergent synthesis of all stereoisomers of the 2,3,6-trisubstituted tetrahydropyran subunit.

Introduction

Since the discovery of uvaricin in 1982,[1] the annonaceous acetogenins (ACGs) class of natural products has been a center of attention for chemists and biologists alike.[2] This interest stems from the structural diversity and potent biological effects exhibited by these structures, including antimicrobial, pesticidal, and cytotoxic properties. An especially attractive feature is their ability to inhibit multiple drug resistant (MDR) tumor cell lines.[3] The cytotoxic effects exhibited by ACGs are at least in part due to the inhibition of NADH-ubiquinone oxidoreductase (mitochondiral complex I) of the respiratory chain.[4] This inhibition results in a depletion of ATP levels which causes arrest in the cell cycle at the G1 phase, and subsequently apoptosis is induced.[5] The exact details of this mechanism still remains elusive however.[2a]

Structurally, the ACGs are a series of C-35 or C-37 fatty acid derivatives, typically bearing one or more tetrahydrofuran

† This paper is dedicated, with respect and gratitude, to Professor Stephen F. Martin on the occasion of his 60th birthday.

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(1) Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151−3153.

(2) (a) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (c) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. (d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts* **1998**, *11*, 803−827.

(3) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1995**, *115*, 73−79.

(4) The ACGs are among the most potent inhibitors of NADH−ubiquinone oxidoreductase known; see ref 2a.

(5) (a) Yuan, S.-S. F.; Chang, H.-L.; Chen, H.-W.; Yeh, Y.-T.; Kao, Y.-H.; Lin, K.-H.; Wu, Y.-C.; Su, J.-H. *Life Sci.* **2003**, *72*, 2853−2861. (b) Morre, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci. 1995*, *56*, 343−348. (c) Hollingworth, R. M.; Ahammadsahib, K. I.; Gadelhak, G.; McLaughlin, J. L. *Biochem. Soc. Trans.* **1994**, *22*, 230−233.

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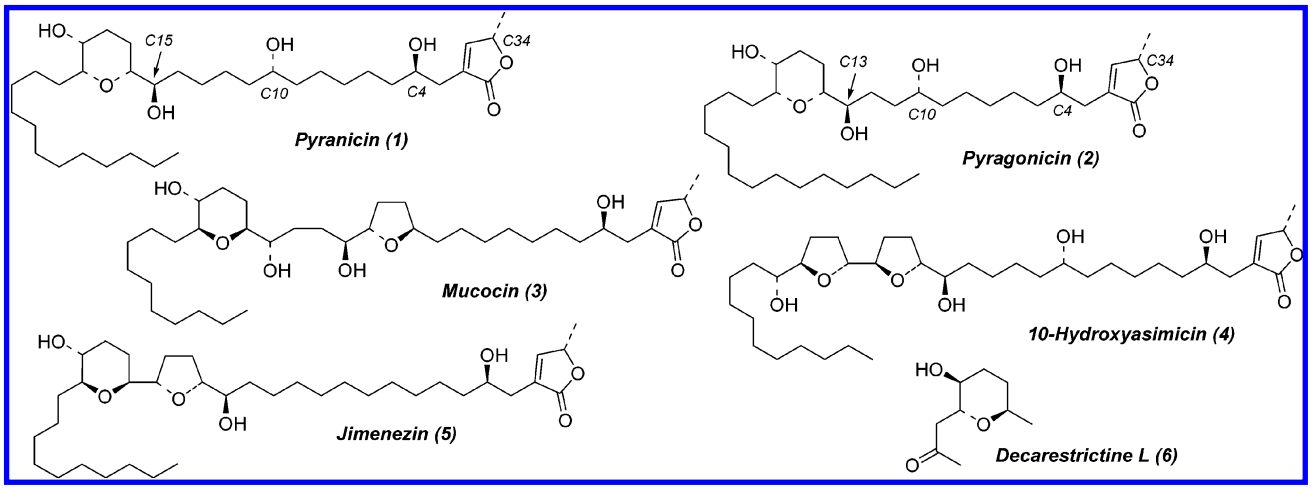

FIGURE 1. Pyranicin, pyragonicin, and some structurally related natural products.

(THF) or tetrahydropyran (THP) rings, often flanked by adjacent hydroxyl groups (Figure 1). The lion's share of the synthetic efforts toward these structures has been directed toward the mono-THF and adjacent bis-THF subclasses.[6] Some of these studies have employed a modular approach to access several natural ACGs[7] or synthetic analogues[8] from common synthetic intermediates or through a common synthetic sequence, including an elegant example of a mix/split fluorous tag strategy by Curran and co-workers in the synthesis of murisolin and isomers thereof.[9]

Pyranicin (**1**) and the related pyragonicin (**2**) are members of the nonclassical subgroup of acetogenins,[10] and both were isolated from the stem bark of *Goniothalamus giganteus* by McLaughlin and co-workers in 1998.[11] When tested against a panel of human carcinoma solid tumor cell lines, pyranicin was shown to exhibit selective inhibitory action against PACA-2 (human pancreatic cancer) cell lines with a potency of about 10 times that of clinically used adriamycin. Pyranicin was also found to be generally about 10 times more potent compared to pyragonicin, which is in good agreement with the observed structure activity relationship (SAR) that optimum potency is achieved in acetogenins bearing ring systems starting at C15.[12] A previous synthesis of pyranicin has been reported by Takahashi and co-workers.[13] We have recently reported convergent strategies for the synthesis of pyranicin[14] and pyragonicin[15] (the latter published back-to-back with a coincident independent synthesis by Takahashi et al.[16]). Herein we report the full details of these syntheses.

Results and Discussion

Synthesis Plan. We envisioned the construction of both **1** and **2** from a common butenolide fragment **12** joined to either of two THP fragments **7** or **8** which, in turn, would be accessed through a common route (Scheme 1). Thus, the key disconnection in our retrosynthetic analysis is the C−C bond joining C15 and C14 in **1** and C13 and C12 in **2**, respectively. For the pyranicin case we envisioned, in the synthetic direction, the asymmetric addition of an acetylenic unit to each of the two fragments **8** and **13**; a subsequent metal-catalyzed cross-coupling would then provide the desired 1,6-diol motif. In the pyragonicin case, the related 1,4-diol would arise from a direct stereoselective coupling of an identical butenolide fragment **12** to an intermediate **8**, differing from the pyranicin intermediate **8** only in the length of the terminal aliphatic chain, thus enabling late-stage divergence to the two targets.

Previously, we have shown that an asymmetric HWE desymmetrization of *meso*-dialdehydes[17] such as **10** can be utilized for the construction of analogues of **8**[18] via a substrate-controlled intramolecular oxa-Michael cyclization.[19] However, to access the desired all-cis stereochemistry in the THP ring of pyranicin/pyragonicin, the meso symmetry of **10** has to be modified via inversion of one stereocenter. This extra step is well compensated for by the divergent nature of such an approach, allowing access to several diastereomers of the 2,3,6-trisubstituted THP subunit from a common precursor. The C4 stereocenter of the butenolide fragment would originate from racemic acrolein dimer (**14**), which is subjected to a parallel kinetic resolution[20]

(6) For recent examples see: (a) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818−10819. (b) Nattrass, G. L.; Diez, E.; McLachlan, M. M.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 580−584. (c) Han, H.; Sinha, M. K.; D'Souza, L. J.; Keinan, E.; Sinha, S. C. *Chem. Eur. J.* **2004**, *10*, 2149−2158. (d) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790−12791.

(7) For examples see: (a) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396−10399. (b) Das, S.; Li, L.-S.; Abraham, S.; Chen, Z.; Sinha, S. C. *J. Org. Chem.* **2005**, *70*, 5922−5931. (c) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771−1779. (d) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1780−1785. (e) Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889−1904. (f) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640−7641.

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(9) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36−37.

(10) The nonclassical subgroup is defined as acetogenins bearing a THP and/or a ring-hydroxylated THF moiety.

(11) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron Lett.* **1998**, *54*, 5833−5844.

(12) For further details on SAR, see refs 2a,b and references therein.

(13) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353−1356.

(14) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199−202.

(15) Takahashi, S.; Ogawa, N.; Koshino, H.; Nakata, T. *Org. Lett.* **2005**, *7*, 2783−2786.

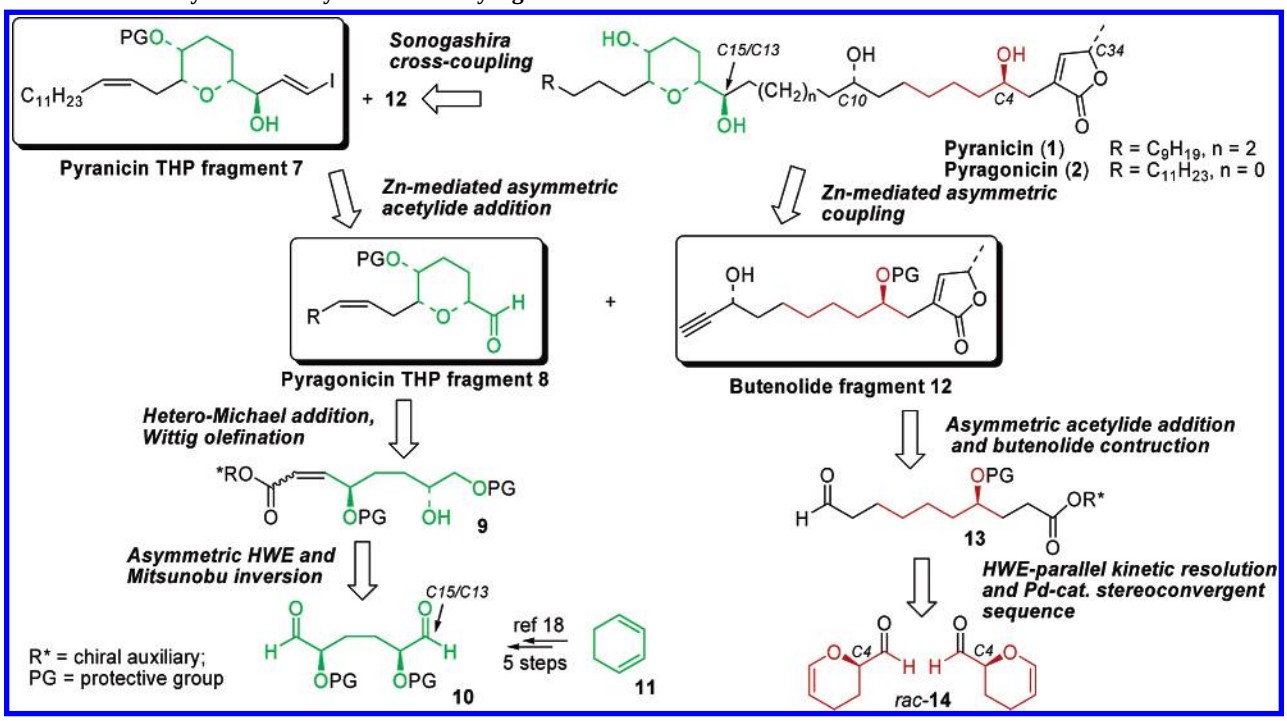
(16) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 2779−2781.

(17) For recent review concerning asymmetric HWE reactions see: Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579−594.

(18) Vares, L.; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226−7237.

(19) (a) Betancort, J. M.; Martin, V. S.; Padron, J. M.; Palazon, J. M.; Ramirez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570−4583. (b) Betancort, J. M.; Martin, V. S.; Padron, J. M.; Palazon, J. M.; Ramirez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570−4583. See also: (c) Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73−82.

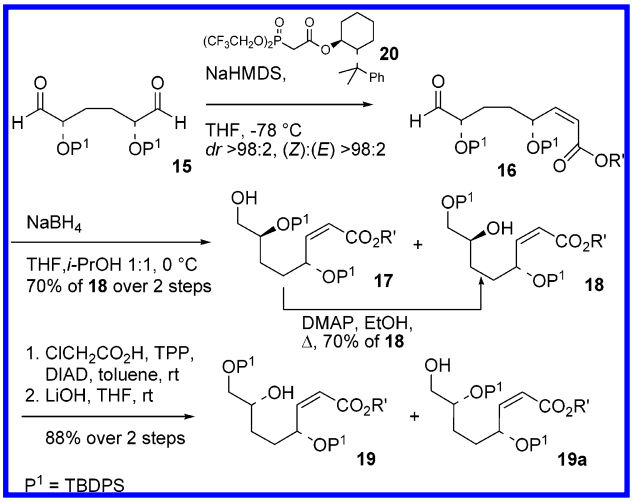
SCHEME 1. Retrosynthesis of Pyranicin and Pyragonicin



followed by a stereoconvergent reaction sequence.[21] In the key Pd-catalyzed transformation, we hoped to expand our previous methodology by introducing a protective group suitable for last-step global deprotection. The butenolide moiety would then be constructed using well-established methodology through a condensation with a lactaldehyde derivative.[22]

Synthesis of the Hetero-Michael Precursors 19 and 22. The first key transformation was an asymmetric HWE desymmetrization of *meso*-dialdehyde **15**, readily available in multigram scale in five steps using Bäckvalls *syn*-1,4-diacetoxylation of cyclohexadiene.[18,23] Crucial for the application of this desymmetrization reaction to the synthesis of **1** and **2** was access to a practical analogue of the antipode[24] of the previously used (−)-(1*R*,2*S*,5*R*)-8-phenylmenthol. Gratifyingly, the commercially available (1*S*,2*R*)-nor-8-phenylmenthol[25] showed a virtually identical behavior to that of 8-phenylmenthol in the desymmetrization of **15**, giving **16** in good yield as a single detected isomer (77%, dr >98:2, (*Z*):(*E*) >98:2) (Scheme 2). Reduction of aldehyde **16** proceeded as expected using $NaBH_4$ in *i*-PrOH/THF at 0 °C, with the desired migration of the

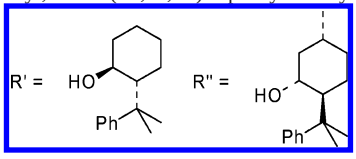
SCHEME 2. Synthesis of (*Z*)-Hetero-Michael Precursor 19[26]



secondary TBDPS group to the less hindered primary position, giving a readily separable 90:10 mixture of secondary/primary alcohols from which the desired secondary alcohol was isolated in good yield (70%). A more convenient procedure, in which crude aldehyde **16** was filtered through a short silica column and subjected to the reduction/migration conditions, enabled the isolation of pure secondary alcohol **18** in 70% yield over two steps. The remaining mixture of secondary/primary alcohol (**17**/**18**) could be reequilibrated in refluxing EtOH with a catalytic amount of DMAP in 70% yield (isolated secondary alcohol **18**) to further increase the overall yield of the sequence.

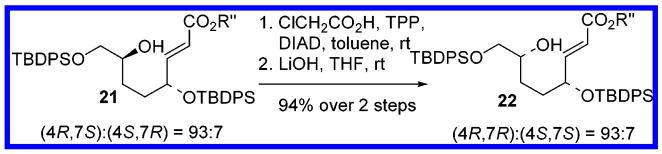
To access the stereochemistry needed to reach **8**, an inversion of the C7 stereocenter of **18** was required. This was accomplished using standard Mitsunobu contitions (TPP, DIAD, chloroacetic acid).[27] The use of toluene as a reaction medium

(20) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535−538.
(21) 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.
(22) Marshall, J. A.; Jiang, H. *J. Nat. Prod.* **1999**, *62*, 1123−1127.
(23) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619−4631.
(24) (+)-(1*S*,2*R*,5*S*)-8-phenylmenthol is now commercially available. For preparation, see: Buschmann, H.; Scharf, H. D. *Synthesis* **1988**, 827−830.
(25) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656−4661. See also: Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805−826.
(26) For clarity, the chiral auxiliaries used are abbreviated: R′ = (1*S*,2*R*)-nor-8-phenylmenthyl; R″ = (1*R*,2*S*,5*R*)-8-phenylmenthyl.

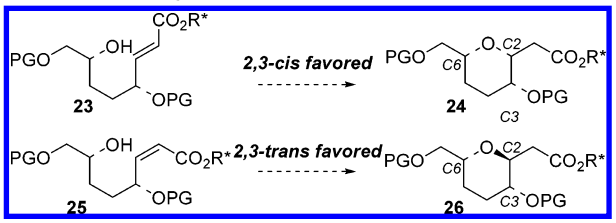


(27) Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317−4320.

SCHEME 3. Synthesis of (*E*)-Hetero-Michael Precursor 22[26]



SCHEME 4. Predicted Kinetic Products of the Hetero-Michael Cyclizations



proved beneficial over THF, resulting in a cleaner and faster reaction, giving the inverted chloroacetate in excellent yield (95%). The selective hydrolysis of the chloroacetate over the nor-8-phenylmenthol ester was then readily accomplished with 0.4 M LiOH in THF/H_2O at ambient temperature in excellent yield (92%). The more sterically demanding nor-8-phenylmenthyl ester is virtually inert to these conditions, and the secondary alcohol was isolated as a 10:1 separable mixture of **19** and **19a**.

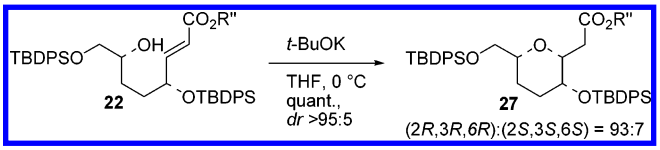
To evaluate which substrate was the most suitable for the hetero-Michael cyclization, we also exploited the (*E*)-selective asymmetric HWE desymmetrization of *meso*-dialdehyde **15**, giving, after reduction, the secondary alcohol **21**,[18] which was readily inverted to give **22** over two steps (Scheme 3). This route however suffers from a lower yield and a somewhat lower enantiotopic selectivity (dr = 93:7) in the desymmetrization step, resulting in the isolation of (4*R*,7*R*)-**22** and (4*S*,7*S*)-**22** as an inseparable 93:7 mixture in 94% over two steps from **21**.

Stereoselective Hetero-Michael Cyclizations. In a detailed study by Martín and co-workers,[19a,b] it was shown that the stereochemical outcome of oxa-Michael cyclizations with substrates similar to **19** and **22** is influenced by the allylic stereocenter and the alkene geometry, resulting in a preference for the (*E*)-alkene substrates to cyclize to 2,3-*cis*-THP derivatives and for the (*Z*)-alkenes to give the corresponding 2,3-*trans*-THP products under kinetically controlled conditions.[28] On the basis of these findings, we expected the (*E*)-olefin **23** to give the desired *2,3-cis*-2,6-*cis*-THP **24** and the (*Z*)-olefin **25** to give the 2,3-*trans*-2,6-*trans*-THP **26** as the initial products (Scheme 4), although we anticipated **24** to be thermodynamically favored.

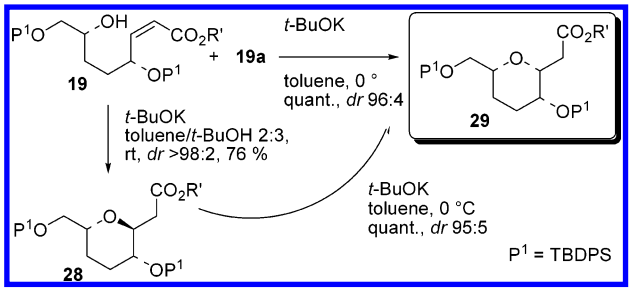
Preliminary results showed that the desired 2,3-*cis*-2,6-*cis*-THP **27** is indeed formed as the major product in the cyclization of (*E*)-alkene **22**, but unfortunately as an inseparable mixture with its diastereomer (2*S*,3*S*,6*S*)-**27** originating from the minor product of the initial (*E*)-selective HWE desymmetrization (Scheme 5).[29]

Pleasingly, the secondary alcohol **19** derived from the (*Z*)-selective HWE desymmetrization and inversion sequence formed, when exposed to our standard cyclization conditions, the desired 2,3-*cis*-2,6-*cis*-THP **29** in quantitative yield with a 96:4 dias-

SCHEME 5. Michael Cyclization of the (*E*)-Substrate 22[26]



SCHEME 6. Michael Cyclization of the (*Z*)-Substrate 19[26]



tereoselectivity (Scheme 6), thus overall being clearly superior to (*E*)-alkene **22** for the purpose of accessing **29**. The use of catalytic rather than stoichiometric amounts of base completely suppressed the formation of byproducts. Running the reaction in THF resulted in no protective group migration, and any primary alcohol **19a** present in the starting material was recovered unaffected by the reaction conditions. Change of solvent to toluene, however, gave the same level of stereoinduction as well as allowed for protective group migration, resulting in a quantitative yield of **29** from the mixture of secondary and primary alcohols **19** and **19a** obtained from the hydrolysis of the chloroacetate.

With this result at hand we became interested in the possibility of stopping the reaction at the presumed transient 2,3-trans-2,6-trans isomer. By running the reaction at low temperature we could occasionally at very low conversion isolate this product as a single diastereomer, but not in a reproducible manner. However, by using a nonnucleophilic protic cosolvent (1:1 *t*-BuOH/toluene), we were successful in promoting the cyclization to give **28** in good yield (76%) in a perfectly stereocontrolled manner. An interesting aspect of this result is that we now, in conjuction with previous results, have controlled access to all eight stereoisomers of these 2,3,6-trisubstituted THP derivatives (Figure 2). Isomers **33**/**32** and **34**/**31** can be directly formed via the cyclization of (*Z*)-alkene **18** or the corresponding (*E*)-alkene as previously described,[18] whereas isomers **35**/**24** and **30**/**26** can be accessed from **18** via a Mitsunobu inversion and control of the reaction conditions in the subsequent cyclization. The relevance of this is further emphasized by the presence of these substructures in, besides pyranicin/pyragoncin, several other natural products such as decarestrictine L (**6**),[30] jimenezin (**5**),[31] and mucocin (**3**)[32] (Figures 1 and 2).

We also investigated the possibility of accessing THP **29** directly from chloroacetate **36** (Scheme 7) by in situ hydrolysis under the cyclization conditions; this was achieved by the use of hydroxide ions generated from an excess of *t*-BuOK (3.0 equiv) and water (2.0 equiv).[33,34] A similar level of stereose-

(28) This trend was efficiently exploited in the hetero-Michael cyclizations of **18** and **21** as described in ref 18.

(29) Upon cleavage of the chiral auxiliary in the subsequent step, the relationship between the products becomes enantiomeric, thus preventing removal of the minor isomer until a further reagent controlled asymmetric transformation is carried out.

(30) Grabley, S.; Hammann, P.; Huetter, K.; Kirsch, R.; Kluge, H.; Thiericke, R.; Mayer, M.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176−1181.

(31) Chavez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419−421.

(32) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-m.; Zhao, G.-x.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409−10410.

(33) Chang, F. C.; Wood, N. F. *Tetrahedron Lett.* **1964**, 2969−2973.

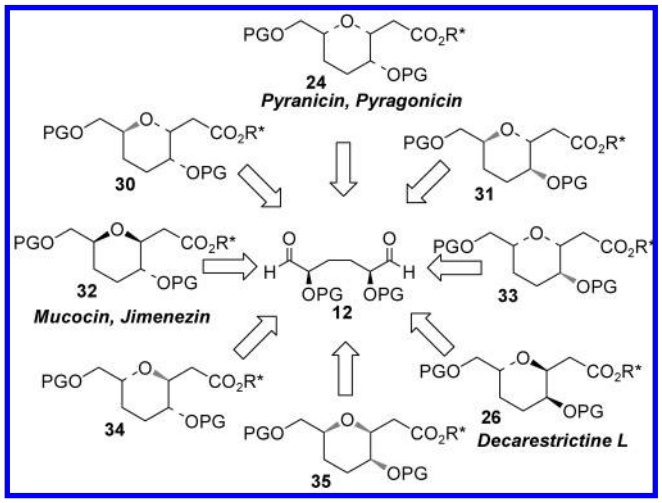
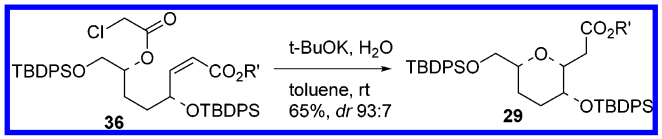


FIGURE 2. THP substructures of natural products accessible from *meso*-dialdehyde **12**.

SCHEME 7. Direct Cyclization of the (*Z*)-Chloroacetate 36[26]



lectivity was observed (dr = 93:7) in preference of the 2,3-cis-2,6-cis product, but given that the yield over two separate reactions was higher, 92% compared to 65% for the one-step procedure, the two-step route was found superior.

Mechanistic Insights into the Hetero-Michael Cyclizations of 19 and 22. The results of the ring closure reactions prompted us to perform a computational investigation of the intramolecular Michael addition. The experimental results indicate that the 2,3-*trans*-2,6-*trans*-THP **28** is the kinetic product from the ring closure of (*Z*)-substrate **19** and that the 2,3-*cis*-2,6-*cis*-THP **29** is the thermodynamic product. The thermodynamic preference was addressed by molecular mechanics calculations, employing the MMFF force field[35] in MacroModel 7.2.[36] MMFF is one of the most accurate force fields available, and yields conformational energies comparable to high-level quantum mechanical calculations,[37] while still being fast enough to allow full conformational searching. The conformational space was explored using a combined Monte Carlo[38]/Lowmode[39] search protocol as implemented in MacroModel. Solvation was included through the GB/SA continuum model[40] in MacroModel, employing the only organic solvent implemented in our version of MacroModel, chloroform. For the kinetic preference, we investigated the conformational space of the anionic reactant, with the distance between the alkoxide and the β-position harmonically constrained to 1.5 Å. This approach, which does not allow actual bond formation, will not give reaction barriers, but only the steric cost of approaching the nucleophile to the Michael acceptor. However, for diastereomeric transition states, the barrier should correlate with the calculated energies.

The computational results are depicted in Scheme **8**. Looking first at the (*Z*)-reactant **37**, we see that the conformational space is restricted by allylic strain. For the $\beta-\gamma$ bond, only one rotamer is energetically accessible, enforcing nucleophilic attack from one side only, leading to the 2,3-trans-2,6-trans product **39**. In the presence of suitably acidic protons (*t*-BuOH), the ring closure product is immediately neutralized to yield **40**. However, in the absence of a proton source, the Michael attack is reversible, but free rotation around the $\alpha-\beta$ bond before the retro-Michael reaction now leads to the (*E*)-reactant **43**. This TS lacks the allylic strain and therefore has a lower barrier than the reverse reaction to the (*Z*)-reactant **37**.

For the (*E*)-reactant, two rotameric forms **43** and **44** are accessible, allowing nucleophilic attack from either face of the Michael acceptor. The more favorable path, as judged from the near-TS constrained conformations, is the one leading to the 2,3-cis-2,6-cis product **47**.

Finally, investigating the possible configurations and conformations of the neutral product, we note that the 3- and 6-THP substituents must always be cis and that one of them therefore must assume an axial position in a chair conformation. The alternative boat or twist-boat conformations consistently have high energies, as expected. Interestingly enough, the preferred conformation always has the 3-TBDPS−O-substituent in an axial position, even in the 2,3-*trans*-2,6-*trans*-THP, which thus assumes a 2,3-diaxial conformation **41**. Obviously, the repulsion between the 2- and 3-substituents in the diequatorial conformation is large enough to compensate for the 1,3-diaxial interactions that each substituent experiences with hydrogen atoms on the THP ring in the diaxial conformation. Given the axial preference of the 3-substituent, we get the expected result that the 2,3-*cis*-2,6-*cis*-THP with two equatorial substituents is ca. 6 kJ/mol more stable than the best conformation of the 2,3-*trans*-2,6-*trans*-THP with only one equatorial substituent. The experimentally observed ratio of ca. 20:1 corresponds to a free energy difference of ca. 8 kJ/mol. A deviation of 2 kJ/mol is a very good result considering the size of the system and the complexity of the conformational space, but not unexpected from MMFF.[37]

Completion of the THP Fragments. With the intermediate **29** at hand, we turned to the completion of the THP fragments. Reduction of ester **29** with DIBAL to the corresponding alcohol in CH_2Cl_2 at −78 °C was sluggish and often led to a mixture of the corresponding aldehyde and alcohol; furthermore, the aldehyde could not be readily separated from the released nor-8-phenylmenthol. This was circumvented by reduction to the aldehyde followed by in situ addition of the appropriate phosphorus ylide in THF at −78 °C and allowing the reaction mixture to warm to room temperature (Scheme 9). Workup

(34) Procedure: To a stirred solution of chloroacetate **36** (31 mg, 0.032 mmol) in 1.5 mL of toluene was added a freshly prepared solution of water (1.17 μL, 0.065 mmol) and *t*-BuOK (9.7 μL, 1.0 M in THF) in 0.7 mL of toluene at 0 °C. The temperature was brought to room temperature over 1 h. The reaction was then quenched by addition of phosphate buffer pH 7 and subjected to the usual workup giving the cyclisized product **29** (18.3 mg, 65%).

(35) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490−519.

(36) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467. For more recent versions, see: www.schrodinger.com.

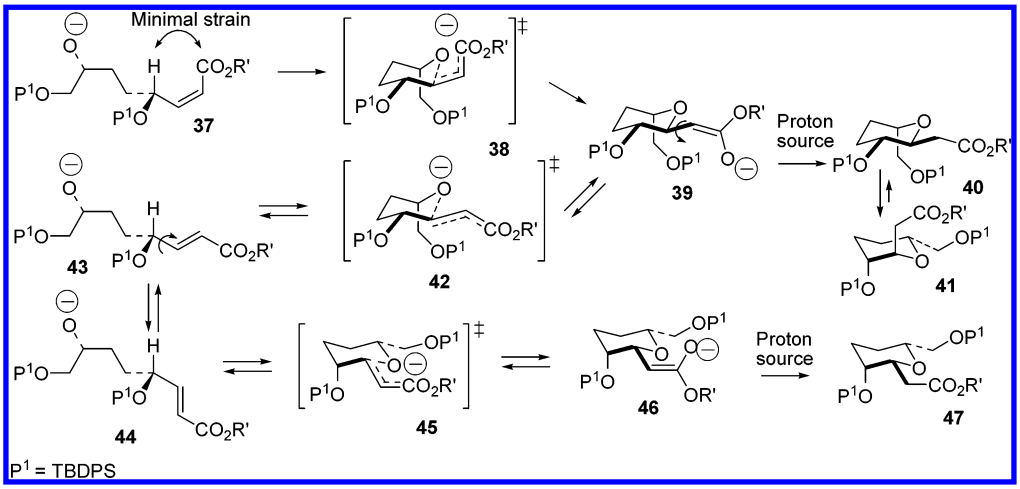
(37) (a) Gundertofte, K.; Liljefors, T.; Norrby, P.-O.; Pettersson, I. *J. Comput. Chem.* **1996**, *17*, 429−449. (b) Liljefors, T.; Gundertofte, K.; Norrby, P.-O.; Pettersson, I. In *Computational Medicinal Chemistry for Drug Discovery*; Bultinck, P., Tollenaere, J. P., De Winter, H., Langenaeker, W., Eds.; Dekker: New York, 2004; pp 1−28.

(38) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379−4386.

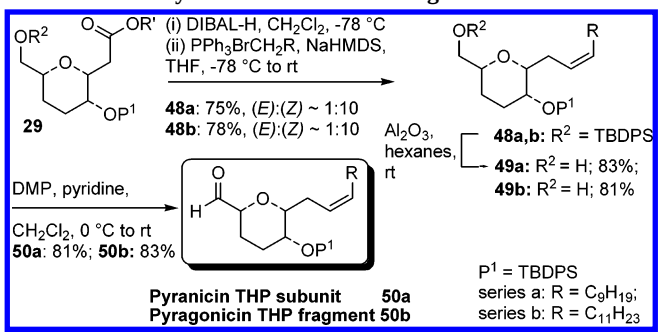
(39) Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 5011−5019.

(40) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6129.

SCHEME 8. Mechanism for the Intramolecular Michael Addition of 19[26]



SCHEME 9. Synthesis of the THP Fragments Continued[26]



problems due to formation of insolubles associated with the Wittig reaction and to some degree the DIBAL reductions was conveniently avoided by direct evaporation of the reaction mixture onto silica, and purification by flash chromatography gave the olefinated products **48a** and **48b** directly from the ester in good yields (**48a**, 75%; **48b**, 78%) and (*Z*):(*E*) selectivities (~10:1 in both cases).

Selective deprotection at the primary position through adsorption onto activated alumina from hexanes[41] proceeded as expected to give the desired primary alcohols **49a** and **49b** in good yields (**49a**, 83%; **49b**, 81%). The subsequent oxidations using Dess−Martin periodinane in CH_2Cl_2 then gave the corresponding aldehydes in good yields (**50a**, 81%; **50b**, 83%). For series b, toward pyragonicin, this provided the completed THP fragment **50b**.

To complete the pyranicin THP fragment, three additional steps were needed, starting with a syn-stereoselective addition of a two-carbon spacer to **50a**. The direct addition of organometallic reagents to analogous 2-formyl-THP derivatives has been studied previously in syntheses of mucocin,[42] muconin,[43] and jimenezin,[44] but with only modest levels of the desired syn-selectivity, requiring an additional two-step oxidation/reduction sequence to achieve good stereocontrol. Since a 1,2-cyclic Cram-chelate controlled addition would afford the desired syn-product (Figure 3), addition of TMS−acetylene magnesium bromide in the presence of a 10-fold excess of $MgBr_2$[45] was attempted on

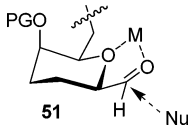


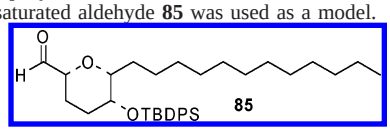
FIGURE 3. Expected outcome of a Cram-chelatecontrolled addition.

a closely related model substrate,[46] only to give a disappointing 57:43 selectivity. It thus appears that substrates such as **50a**, having a 2,3-cis-2,6-cis configuration, do not give a strong bias in chelate-controlled additions or do not readily form chelates.

We therefore turned our attention to the reagent-controlled, zinc-mediated acetylide addition developed by Carreira and coworkers[47] that recently has been successfully used in the addition of TMS−acetylene to 2-formyltetrahydrofuran derivatives.[48] We were pleased to find that the addition proceeded in a highly stereocontrolled manner under standard conditions using Zn(OTf)$_2$/(−)-NME to give the desired propargylic alcohol in good yield (83%, dr > 95:5 [49]) (Scheme 10).

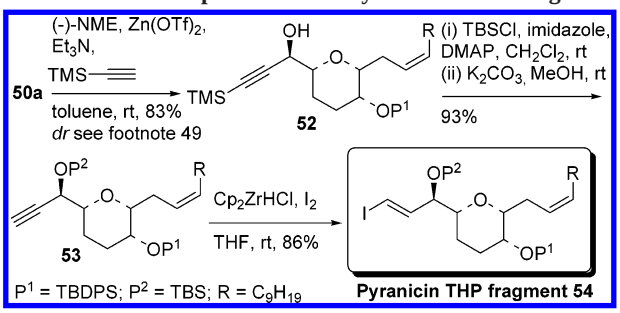
A one-pot TBS protection of the propargylic alcohol using TBSCl, imidazole, and DMAP in CH_2Cl_2 at room temperaure followed by removal of the TMS group by quenching the reaction with methanol and K_2CO_3 then gave the protected propargylic alcohol **53** in good yield (93%). Hydrozirconation with the Schwartz reagent in THF at room temperature followed by addition of elemental iodine thereafter gave exclusively the

(41) Feixas, J.; Capdevila, A.; Guerrero, A. *Tetrahedron* **1994**, *50*, 8539−8550.
(42) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739−5752.
(43) Yang, W.-Q.; Kitahara, T. *Tetrahedron Lett.* **1999**, *40*, 7827−7830.
(44) Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 2025−2028.
(45) Michelet, V.; Adiey, K.; Tanier, S.; Dujardin, G.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 2947−2958.
(46) To simplify the determination of the diastereoselecitivty of the addition, the saturated aldehyde **85** was used as a model.



(47) (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688.
(48) (a) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Eur. J.* **2004**, *10*, 672−680. (b) Kojima, N.; Maezaki, N.; Tominaga, H.; Asai, M.; Yanai, M.; Tanaka, T. *Chem. Eur. J.* **2003**, *9*, 4980−4990.
(49) Since intermediates **52**−**54** and **76** were carried through the synthesis as mixtures of (*E*):(*Z*) isomers, an exact quantification of the stereochemical outcome of the addition could not be made. However, we did not observe a minor diastereomer derived from this transformation in any of the remaining steps of the synthesis. The relative configuration of **52** was assigned by analogy with literature.[47]

SCHEME 10. Completion of the Pyranicin THP Fragment[26]



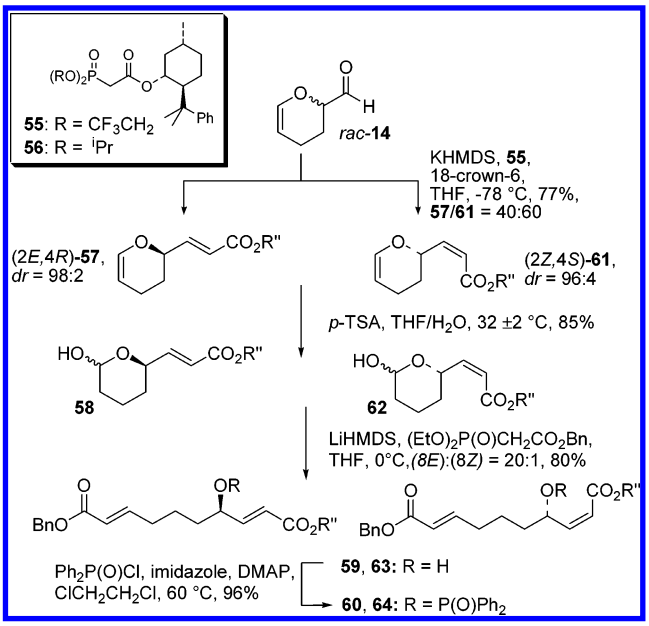
(*E*)-vinyl iodide in 86% yield, thus completing the pyranicin THP fragment **54**.

Synthesis of the Butenolide Precursor 65. The synthesis of the butenolide fragment began with an asymmetric HWE parallel kinetic resolution (PKR) of racemic acrolein dimer **14**, in which the substrate enantiomers are known to form products with opposite alkene geometry (Scheme 11).[50] We have previously performed a PKR with this substrate using a mixture of the (*E*)-selective phosphonate **56** and the (*Z*)-selective phosphonate **55** in excellent yield and with good diastereoselectivity.[20]

We were however pleased to find that a simpler protocol, using slow addition of phosphonate **55** to a slight excess (1.3 equiv) of *rac*-**14** in THF at −78 °C, provided better results in terms of diastereoselectivity. The olefinated products were obtained as a 60:40 mixture[51] of (2*Z*,4*S*)-**61** (dr = 96:4) and (2*E*,4*R*)-**57** (dr = 98:2), respectively, in 77% combined yield. It should be pointed out that although **57** and **61** are readily separable at this stage, we chose not to separate the isomers, but carried them through the subsequent three steps as mixtures, with similar or better results in terms of yield, since later intermediates **60** and **64** give the *exact* same product in the Pd-(0)-catalyzed step.

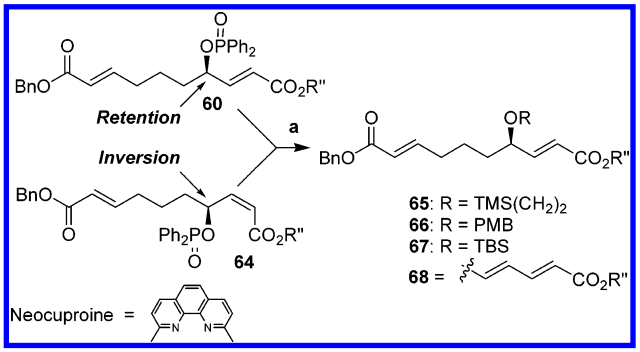
The subsequent acid-catalyzed addition of water to vinyl ethers **57** and **61** using 1 M HCl was sluggish, but changing the proton source to *p*-TSA provided reproducible conditions in 1:1 water/THF, giving the hemiacetals **58** and **62** in good combined yields (85%) as inseparable 34:66 mixtures of diastereomers. It could be noted that precise temperature control is of the essence; the reaction was slow at room temperature, and at 40 °C mainly an unidentified byproduct was isolated, while a reaction at 32 ± 2 °C gave the desired products. Next, an HWE olefination using a benzyl ester phosphonate served to trap the ring-open forms of the hemiacetals, while incorporating a functionality that could be readily cleaved in the presence of the 8-phenylmenthol ester. Due to the predisposition of **62**/**63** to lactonize under basic conditions, extensive optimization of the reaction conditions of this step was needed. Using KHMDS as the base, lactonization could not be suppressed; with the sodium base the reaction proceeded slowly at −20 °C with some lactonization, but to our delight the use of LiHMDS almost completely suppressed the ring closure. When running at 0 °C in THF, the reaction went to completion overnight. The secondary alcohols were then activated for the Pd-catalyzed allylic substitution by conversion into the corresponding phosphinate esters **60** and **64** using $Ph_2P(O)Cl$, imidazole and DMAP in a mixture of 1:1 $ClCH_2CH_2Cl$/THF at 60 °C in excellent yield (96%).

SCHEME 11. Synthesis of the Butenolide Precursor Intermediates[a,26]



[a] Yields are given for the mixtures. See Supporting Information for details regarding the pure isomers.

SCHEME 12. Stereoconvergent Step[a,26]



[a] Reagents and conditions: (a) **60**/**64**, Pd_2dba_3 (0.2−0.4 equiv Pd), ligand (0.4−0.6 equiv), cosolvent/R−OH (1:1), rt.

Stereoconvergent Step. In a palladium-catalyzed allylic substitution (*Z*)-alkenes are known to often react with soft nucleophiles with inversion of both the alkene geometry and the allylic stereocenter through a $\pi-\sigma-\pi$ rearrangement, whereas (*E*)-alkenes are known to react with overall retention at both stereogenic units. By exposing our mixture of (2*E*,4*R*)-**60** and (2*Z*,4*S*)-**64** to a Pd(0) catalyst with a suitable primary alcohol as nucleophile, we expected, on the basis of our previous results, both substrate isomers to converge into a single O-protected product. The reaction proved to be highly dependent on the reaction conditions, the main byproduct being diene **68** formed via β-elimination of the intermediate π-allyl complex. To suppress this side reaction, a large excess of the nucleophile was needed; typically a 1:1 mixture of nucleophile[52] and a cosolvent was used (Scheme 12, Table 1).

(50) For mechanistic insight into the asymmetric HWE reaction see: Norrby, P.-O.; Brandt, P.; Rein, T. *J. Org. Chem.* **1999**, *64*, 5845−5852.

(51) This should be compared to a 54:46 (Z):(E) mixture using a 50:50 mixure of phosphonates **55** and **56**; see footnote 20.

(52) It should be noted that the excess $TMS(CH_2)_2OH$ could be recovered in 80% by bulb-to-bulb distillation of the reaction crude.

TABLE 1. Representative Results of the Stereoconvergent Step

nucleophile	ligand	cosolvent	(2*E*,4*R*):(2*E*,4*S*)[a]	product	product:**68**	yield, %
$(TMS)(CH_2)_2OH$	neocuproine	CH_2Cl_2	97:3[b]	**65**	94:6[b]	72
$(TMS)(CH_2)_2OH$	neocuproine	THF	97:3[c]	**65**	87:13[c]	65
$(TMS)(CH_2)_2OH$	DPPE	THF	98:2[b]	**65**	52:48[c]	d
$(TMS)(CH_2)_2OH$	DPPP	THF	94:6[b]	**65**	61:39[c]	d
PMBOH	neocuproine	CH_2Cl_2	97:3[b,e]	**66**	d	89
TBSOH	neocuproine	THF	−	(**67**)	0:100	0

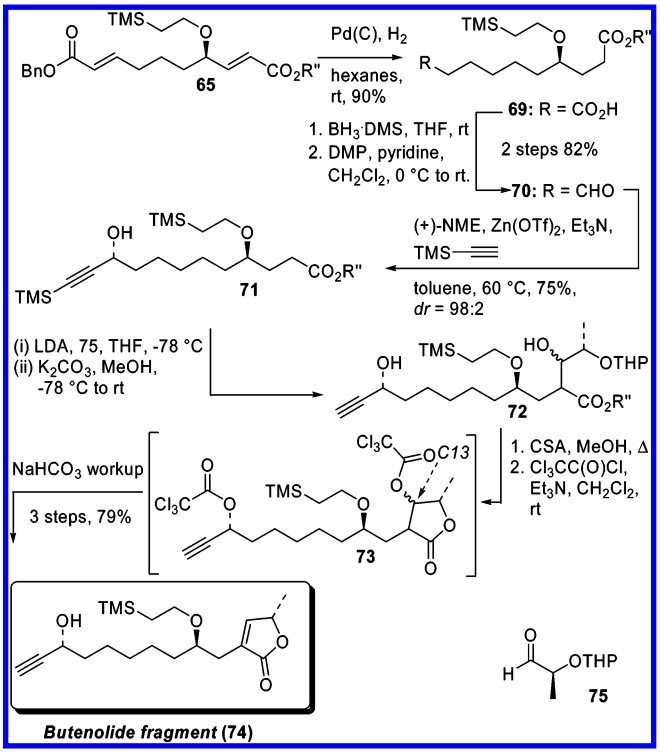
[a] The dr of the product in all cases matches that of the starting material. [b] Determined by ^1H NMR of the crude product. [c] Determined by ^1H NMR after filtration through a short plug of silica. [d] Not recorded. [e] Separable by flash chromatography.

When evaluating ligands, neocuproine was found superior to phosphine-based ligands, both in terms of reaction times and yield. Using neocuproine, the reaction times could be shortened to 4 h using 5 mol % Pd_2dba_3, compared to 3 days with DPPE using 20 mol % Pd_2dba_3. On a gram scale, as little as 1.25% of Pd catalyst was used; however a prolonged reaction time (16 h) was required. The cosolvent also had a large impact on the ratio between the desired product and the elimination product **68**, and CH_2Cl_2 was found superior to THF without affecting the diastereoselectivity of the reaction. To evaluate the scope of this step as a means to introduce protected hydroxyl functionalities in an allylic position, the reaction was carried out with a set of alcohols: $(TMS)(CH_2)_2OH$, PMBOH and TBSOH. The reaction proceeded similarly well with $(TMS)(CH_2)_2OH$ and PMBOH, the difference in yield mainly reflecting the tedious purification of the $(TMS)(CH_2)_2O-R$ reaction. The TBSOH failed completely to give product, probably for steric reasons. It could be noted that although $(TMS)(CH_2)_2O-R$ is an established protective group for acids, it has rarely been utilized for secondary alcohols;[53] one might speculate this is partly because of its difficult introduction. This methodology provides a convenient way to introduce PMBO- and $(TMS)(CH_2)_2O$- in allylic positions. For our purpose the highly robust $(TMS)(CH_2)_2$- group proved ideal to carry through the remaining steps of the synthesis.

Completion of the Shared Butenolide Fragment. With the C4 stereocenter in place we focused on the completion of the butenolide fragment (Scheme 13). Hydrogenation/hydrogenolysis of **65** was performed with Pd(C) in hexanes. Although the reaction was slow at room temperature, it provided the saturated acid in good yield (90%). The use of THF as solvent in this reaction surprisingly resulted in partial reductive removal of the C4 oxygen, and Rh (5% on alumina) also in THF caused extensive ring hydrogenation. A subsequent borane reduction followed by Dess−Martin oxidation provided aldehyde **70** in good overall yield (82%).

To install the C10 stereocenter, we once again utilized the Carreira methodology to add TMS−acetylene stereoselectively. This transformation proved more challenging than the corresponding addition to 2-formyl-THP **50a**; it appears that an α-oxy substituent is an activating factor for this transformation. Under standard conditions ($Zn(OTf)_2$, (+)-NME, and Et_3N in toluene at room temperature) only traces of product could be isolated. We were however pleased to find that raising the temperature to 60 °C in a sealed vessel with an excess of TMS−acetylene increased the conversion significantly, and the propargylic alcohol **71** was isolated in 75% yield with excellent diastereoselectivity (dr = 98:2).[54] For the conversion of aldehyde **70** into propargylic alcohol **71** this reaction proved reliable and should provide a significant improvement over the more common three-step procedure involving a nonselective addition of TMS−acetylene followed by an oxidation/reduction sequence. For a thorough discussion of the performance of this reaction in various complex settings, see ref 55 and references therein.

SCHEME 13. Completion of the Shared Butenolide Fragment[26]



The butenolide was contructed using classical methodology, beginning with an aldol reaction of a preformed enolate derived from **71** and aldehyde **75**, readily available from (*S*)-lactic acid methyl ester in two steps.[56] The aldol product was isolated as a mixture of isomers and carried through the subsequent two steps as such. The THP group was then cleaved with subsequent ring closure to the corresponding lactone under acidic conditions using catalytic amounts of CSA in refluxing methanol. To access the completed butenolide, we then needed to perform a bis-

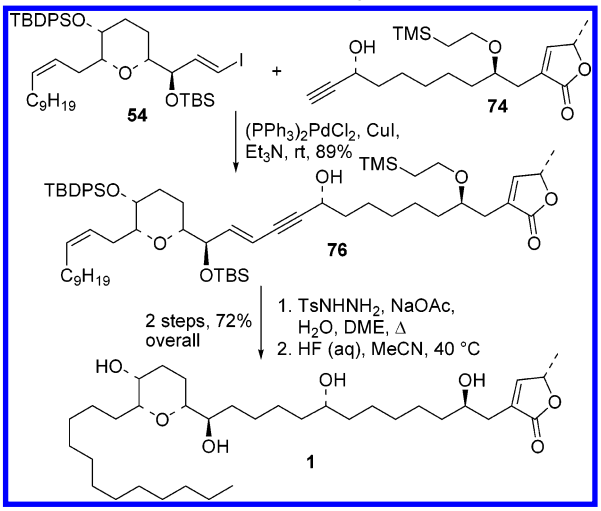
(53) (a) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345−3348. (b) Paquette, L. A.; Backhaus, D.; Braun, R. *J. Am. Chem. Soc.* **1996**, *118*, 11990−11991.

(54) The diastereomeric ratio of **71** was determined by ^1H and ^{19}F analysis of the corresponding (+)- and (−)-MTPA derivatives. The relative configuration was assigned by analogy with literature.[47]

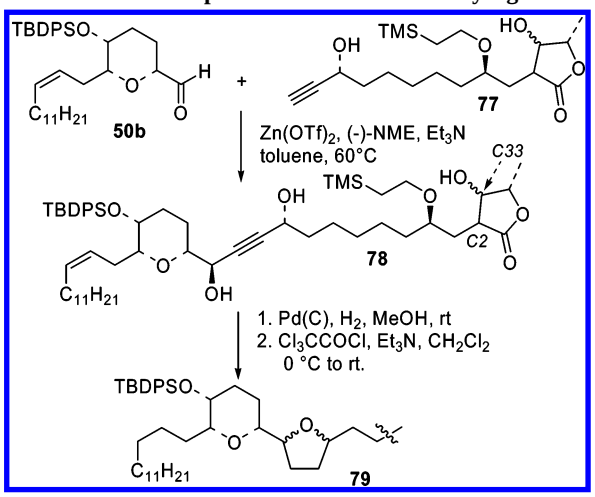
(55) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219−7232.

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

SCHEME 14. End Game toward Pyranicin



SCHEME 15. Attempted End Game toward Pyragonicin



activation under conditions where only the C13-ester of **73** was eliminated. We were pleased to find that the formed lactone was converted into butenolide **74** under conditions described by Marshall and co-workers[57] using TFAA and E_3N. Due to the purification problems caused by the oxidation byproduct formed in the reaction between Et_3N and TFAA,[58] a slightly modified protocol was used where the TFAA was exchanged for Cl_3CCOCl. The C10 alcohol could then be released during a mild workup with $NaHCO_3$ without affecting the now epimerization-prone C34 stereocenter[59] to give the completed butenolide fragment **74** ready for coupling to either of **50b** or **54**.

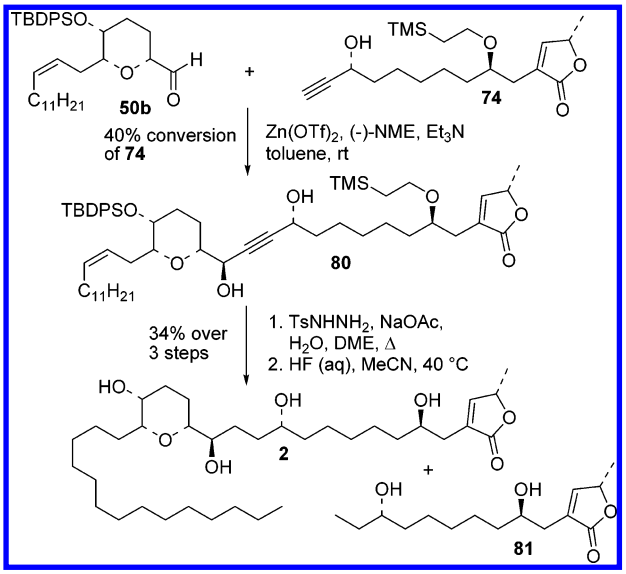
End Game toward Pyranicin. A Sonogashira cross-coupling of **54** and **74** giving ene−yne **76** provided the completed pyranicin framework in good yield (89%) using $(PPh_3)_2PdCl_2$ and CuI in neat Et_3N, without interference from the unprotected butenolide C10 hydroxy center (Scheme 14). Previously, these cross-coupling conditions have been used in the final stages of acetogenin syntheses and shown not to cause epimerization of the butenolide.[57] The subsequent removal of the chain unsaturations could not be accomplished using hydrogenation with Wilkinsons catalyst; instead an inseparable mixture of alkenes was obtained. In sharp contrast, reduction with diimide generated in situ from $TsNHNH_2$ and NaOAc in DME/H_2O at reflux[60] provided triprotected pyranicin in good yield (89%).

A final stage global deprotection would then furnish pyranicin (**1**). Using $BF_3{\cdot}Et_2O$ in CH_2Cl_2 and gradually increasing the temperature from 0 °C to room temperature resulted in rapid complete removal of the TBS and $(TMS)(CH_2)_2$ ethers but left the TBDPS group untouched, and a further increase of temperature resulted in decomposition of the substrate. We also evaluated a protocol of in-situ generation of HF from $BF_3{\cdot}Et_2O$ and salic aldehyde[61] with similar results. On the other hand, the use of HF (40% aq) in MeCN at room temperature resulted in rapid selective removal of the TBS and TBDPS groups leaving the $(TMS)(CH_2)_2$ ether untouched. We were however, delighted to find that HF(aq) at a slightly elevated temperature (40 °C) enabled us to obtain unprotected pyranicin (**1**) in good yield (85%). Spectroscopic properties of our synthetic material were in all respects identical to those reported by Takahashi. Takahashi et al. confirmed McLaughlin's original assignment of the relative and absolute configuration of pyranicin by preparing the known corresponding (+)- and (−)-MTPA derivatives of **1**. There is, however, a strong discrepancy in the optical rotation reported for the natural product and that of the synthetic material: natural material, $[\alpha]^{23}_D$ −9.7 (c = 0.008, $CHCl_3$);[62] synthetic material (Takahashi), $[\alpha]^{23}_D$ +19.5 (c = 0.55, $CHCl_3$); our synthetic material, $[\alpha]^{23}_D$ +21.1 (c = 0.24, $CHCl_3$). A sample of pyranicin was not available to us for purposes of direct comparison to establish the origin of this discrepancy. To ensure that the butenolide stereocenter was not epimerized, we employed Figadères method.[63]

End Game toward Pyragonicin. The Carreira methodology has been used for the construction of 1,4-diols with unprotected propargylic hydroxyl groups present.[64] A direct stereoselective coupling of **50b** and **74** would give the pyragonicin core while at the same time installing the C13 stereocenter. To circumvent the possibility of epimerization of the butenolide moiety, we chose to use the noneliminated lactone **77** for the initial studies (Scheme 15). At 60 °C the coupling of **50b** and **77** proceeded as expected using an excess of reagents.[65] Full conversion of the aldehyde **50b** was achieved; however, the pyragonicin core **78** was isolated as an inseparable mixture with remaining lactone **77**. Since the product was obtained as a mixture of stereoisomers at C2, C33, and the C20 olefin, an exact quantification of the selectivity could not be accomplished. Hydrogenation of the mixture of **78** and **77** resulted in a still inseparable mixture of saturated products. The crude mixture from the hydrogenation was then exposed to the same elimination conditions as were used in the final step in the synthesis of butenolide **74** (vide

(57) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971−975.
(58) Schreiber, S. L. *Tetrahedron Lett.* **1980**, *21*, 1027−1030.
(59) Mild conditions such as TBDMSOTf, pyridine, and 4-DMAP have been shown to cause partial epimerisation;[63] see also: (b) Yu, Q.; Wu, Y.; Wu, Y.-L.; Xia, L.-J.; Tang, M.-H. *Chirality* **2000**, *12*, 127−129. (c) Duret, P.; Figadere, B.; Hocquemiller, R.; Cave, A. *Tetrahedron Lett.* **1997**, *38*, 8849−8852.
(60) Hart, D. J.; Hong, W. P.; Hsu, L. Y. *J. Org. Chem.* **1987**, *52*, 4665−4673.
(61) Mabic, S.; Lepoittevin, J. P. *Synlett* **1994**, 851−852.
(62) One might speculate that the very low concentration used in this analysis would render the outcome sensitive to experimental error and impurities.
(63) Latypov, S.; Franck, X.; Jullian, J.-C.; Hocquemiller, R.; Figadere, B. *Chem. Eur. J.* **2002**, *8*, 5662−5666.
(64) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, *43*, 2691−2694.
(65) Due to the small scale an excess of reagents was used under otherwise standard conditions: $Zn(OTf)_2$, 3.0 equiv; (−)-NME, 5.0 equiv; Et_3N, 10.0 equiv; butenolide **77**, 1.3 equiv; and aldehyde **50b**, 1.0 equiv.

SCHEME 16. End Game toward Pyragonicin



supra). Unfortunately we obtained, besides the desired elimination, an unwanted cyclization of the C10/C13 positions in a 71:29 ratio.[66]

Encouraged by the successful joining of **50b** and **77**, we chose to evaluate the more straightforward direct coupling of the completed butenolide **74** with THP-fragment **50b**. It has been shown that Et_3N does not cause epimerization of butenolides at ambient temperature in aprotic solvents;[67] therefore to further minimize the risk of epimerization, we chose to run the coupling at ambient temperature. Pleasingly, the reaction proceeded cleanly, albeit to 40% conversion[68] using an excess of reagents,[69] 1.5 equiv of aldehyde **50b** and 1.0 equiv of acetylene **74**. It should be noted that unreacted **74** was recovered from the reaction mixture, unfortunately as an inseparable mixture with the desired product product **80**, which in this case prevented recycling. The stereoselectivity could not be directly measured due to the (*E*):(*Z*) mixture of the alkene and the presence of **74**, but at no point in the subsequent steps could we detect any minor diastereomer attributed to the C13 stereocenter. A coupling reaction of this kind involving unprotected propargylic alcohols is known to be favored by high concentration and elevated temperature;[64] thus, on a larger scale, with potentially recoverable substrates, we expect this reaction type to be an even more efficient alternative for coupling of sensitive and highly functionalized substrates with or without unprotected hydroxyl functionalities.

The final steps proceeded as expected, and diimide reduction of a mixture of **80** and **74** gave a still inseparable mixture of reduced products (Scheme 16). Global deprotection under identical conditions as were used in the pyranicin synthesis afforded pyragonicin (**2**) in 34% yield over three steps, along with readily separated butenolide **81** (51%), thus accounting for 85% of the total amount of butenolide fragment **74** used in the coupling. The spectroscopic properties of **2** (IR, ^{1}H and ^{13}C NMR) were identical in all respects to those reported by Takahashi[16] and McLaughlin.[11] However, a strong discrepancy was found in the optical rotation for the synthetic products compared to that of the natural material, similar to what was found for pyranicin; natural material, $[\alpha]^{25}_D$ −25.6 (*c* 0.008, $CHCl_3$);[62] synthetic material (Takahashi), $[\alpha]^{24}_D$ +13.8 (*c* 0.11, $CHCl_3$); our synthetic material, $[\alpha]^{25}_D$ +10.5 (*c* 0.125, $CHCl_3$). To ensure that the C34 stereocenter was not epimerized in the coupling step, we again employed Figadère's method[63] to confirm that within the limits of detection no epimerization had occurred.[70] Takahashi and co-workers further investigated the origin of the discrepancy in optical rotation, by preparing the corresponding (+)- and (−)-MTPA esters of pyragonicin.[16] Discrepancies for these derivatives were found in the chemical shift of C10, prompting the authors to synthesize 10-epi-pyragonicin. This product had however significant deviances from the corresponding data reported by McLaughlin. Although derivatives of **2** clearly fit the data reported by McLaughlin better than 10-epi-**2**, there remains some room for ambiguity regarding the relative stereochemistry of the natural product. To clarify this matter, access to the natural product would be necessary; unfortunately, a sample was not available to us for purposes of direct comparison.

Conclusions. In summary, we have accomplished convergent stereoselective syntheses of the proposed structures of pyranicin (**1**) and pyragonicin (**2**) through a common synthetic route. The longest linear sequence to pyranicin comprises 19 isolated intermediates starting from cyclohexadiene, with an overall yield of 6.3%. The longest linear sequence to pyragonicin comprises 16 isolated intermediates from acrolein dimer (**14**) with an overall yield of 5.5% (16 isolated intermediates, 6.4% overall from cyclohexadiene). Highlights of the syntheses are (i) an asymmetric HWE desymmetrization and subsequent diastereoselective transformations to provide access to all eight stereoisomers of the 2,3,6-substituted THP-ring system; (ii) a stereoconvergent sequence to directly install a protected hydroxyl group using an uncommon, yet highly efficient, protective group ($(TMS)(CH_2)_2$); (iii) the employment of Carreiras asymmetric acetylide additions to construct 1,4- and 1,6-diols, including a stereoselective coupling reaction involving sensitive functionalities and unprotected adjacent hydroxyl groups. Further studies toward the synthesis of related acetogenins as well as investigations of their biological properties will be reported in due course.

Experimental Section

(1*S*,2*R*)-2-(1-Methyl-1-phenylethyl)cyclohexyl (2*Z*,4*R*,7*S*)-4,7-Bis{[*tert*-butyl(diphenyl)silyl]oxy}-8-oxooct-2-enoate (16). To a stirred solution of phosphonate **20** [71] (1.48 g, 2.94 mmol) in THF (130 mL) was added NaHMDS (4.45 mL, 2.67 mmol, 0.6 M in

(66) Determined by ^{1}H NMR of the reaction crude. The isomers are separable by flash but were not identified. One might expect that this cyclization could be circumvented by reversing the order of reactions, starting with elimination of **78** and then performing a diimide reduction of the product.

(67) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971−975.

(68) The conversion was estimated as the ratio of unreacted butenolide **74** to the coupled product **80** from the ^{1}H NMR spectrum after filtration through a short plug of silica to remove any remaining aldehyde.

(69) Due to the small scale, an excess of reagents was used: $Zn(OTf)_2$, 2.0 equiv; (−)-NME, 3.0 equiv; and Et_3N, 5.0 equiv.

(70) For further details, see Supporting Information.

(71) Prepared using a protocol similar to that used in: Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713−2716. Selected data: Yield 93%; IR (film, cm^{-1}) 2964, 2918, 1730, 1300, 1268, 1180, 1070, 960; ^{1}H NMR (500 MHz, selected data) δ 7.31−7.28 (m, 4H), 7.16−7.11 (m, 1H), 4.81 (ddd [app td], J = 10.5, 4.5, 1H), 4.45−4.27 (m, 4H), 2.27 (ddd, J = 26.0, 20.5, 16 Hz, 2H), 2.12 (app td, J = 11.5, 3.5 Hz, 1H), 1.94 (br d, J = 13 Hz, 1H), 1.87−1.82 (m, 1H), 1.77−1.67 (m, 2H), 1.30 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz) δ 164.1, 151.9, 128, 1, 125.3, 125.1, 123.7, 121.1, 76.3, 62.4 (qd, J = 19.6, 5.5 Hz), 62.3 (qd, J = 19.6, 5.5 Hz), 50.5, 39.5, 39.5, 33.4, (d, J = 14.4 Hz), 32.9, 30.0, 26.6, 25.8, 24.6, 22.1. See also: Vares, L. Ph.D. Thesis, Tartu University, Estonia, 2000.

toluene) dropwise at −78 °C. The resulting solution was stirred for 30 min and then transferred to a precooled solution of dialdehyde **15** (2.00 g, 3.21 mmol) in THF (70 mL). After 4 h the reaction was quenched by addition of AcOH (1 M in MeOH) followed by phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (6.25% EtOAc/heptane) furnished olefin **16**, a single detected stereoisomer, as a clear oil (2.00 g, 77% based on **20** [72]): $[\alpha]_D^{23}$ −21.8 (c = 0.91, CH_2Cl_2); IR (film) 3072 (w), 2931 (s), 2858 (s), 1753 (s), 1710 (s), 1427 (s), 1191 (s), 1110 (s), 700 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, J = 1.4 Hz, 1H), 7.63−7.70 (m, 4H), 7.62−7.55 (m, 4H), 7.49−7.42 (m, 2H), 7.43−7.35 (m, 6H), 7.35−7.19 (m, 8H), 7.27−7.18 (m, 1H), 5.95 (dd, J = 11.7, 8.0 Hz, 1H), 5.43−5.35 (m, 1H), 4.83 (dd, J = 11.7, 0.7 Hz, 1H), 4.64 (dt, J = 10.4, 4.2 Hz Hz, 1H), 4.07 (t, J = 4.7 Hz, 1H), 2.02−1.94 (m, 1H), 1.88−0.81 (m, 12H), 1.23 (s, 3H), 1.18 (s, 3H), 1.15 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 164.8, 151.9, 151.8, 136.25, 136.22, 136.1, 134.4, 134.2, 133.5, 133.4, 130.3, 130.0, 129.9, 128.3, 128.2, 128.1, 127.9, 127.8, 125.7, 125.4, 118.9, 78.4, 74.6, 69.8, 51.3, 40.2, 33.7, 32.5, 28.4, 27.6, 27.49, 27.42, 26.3, 26.0, 25.1, 19.8, 19.7; HRMS (ES+, M + Na^+) calcd for $C_{55}H_{68}O_5Si_2$-Na 887.4503, found 887.4523.

{(2*S*,3*R*,6*R*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-6-{[*tert*-butyl-(diphenyl)silyl]oxymethyl}tetrahydro-2*H*-pyran-2-yl}acetic Acid (1*S*,2*R*)-2-(1-Methyl-1-phenylethyl)cyclohexyl Ester (28). To a solution of secondary alcohol **19** (28 mg, 0.032 mmol) in a mixture of toluene (2 mL) and *t*-BuOH (1.5 mL) at 0 °C was added *t*-BuOK (16 μL, 0.1 mmol, 1.0 M in THF). The reaction was stirred for 15 min and then brought to room temperature. After an additional 2 h, the reaction was quenched by pouring onto water and partitioned between EtOAc and water. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (3.13−6.25% EtOAc/heptane) gave the cyclized product **28** as a clear oil (21 mg, 75%): Diastereomeric ratio (2*S*:2*R*) ≥ 98:2; $[\alpha]_D^{23}$ −8.3 (c = 0.67, CH_2Cl_2); IR (film) 3070 (m), 2931 (s), 2858 (m), 1727 (s), 1471 (m), 1427 (m), 1110 (s), 1031 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.61 (m, 8H), 7.47−7.32 (m, 12H), 7.23−7.12 (m, 4H), 7.08−7.02 (m, 1H), 4.70 (dt, J = 10.5, 4.3 Hz, 1H), 3.92 (td, J = 9.6, 4.7 Hz, 1H), 3.72−3.63 (m, 2H), 3.59−3.50 (m, 1H), 3.40 (m, 1H), 2.05 (dd, J = 14.4, 4.3 Hz, 1H), 1.96 (dt, J = 11.5, 3.3 Hz, 1H), 1.86−0.81 (m, 13H), 1.24 (s, 3H), 1.16 (s, 3H), 1.05 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 151.9, 136.24, 136.23, 136.06, 136.00, 134.6, 134.2, 134.0, 133.9, 130.08, 130.02, 130.00, 128.2, 128.0, 127.9, 125.8, 125.3, 75.0, 74.9, 71.5, 70.4, 65.2, 51.1, 40.2, 37.4, 33.6, 27.9, 27.5, 27.3, 27.2, 26.3, 25.6, 25.0, 23.7, 19.68, 19.64; HRMS (FAB, M + Na^+) calcd for $C_{55}H_{70}NaO_5Si_2$ 889.4659, found 889.4668.

{(2*R*,3*R*,6*R*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-6-{[*tert*-butyl-(diphenyl)silyl]oxymethyl}tetrahydro-2*H*-pyran-2-yl}acetic Acid (1*S*,2*R*)-2-(1-Methyl-1-phenylethyl)cyclohexyl Ester (29). To a solution of secondary alcohol **19** (or a mixture of secondary/primary alcohol **19**:**19a** (92:8)) (440 mg, 0.597 mmol) in toluene (10 mL) at 0 °C was added *t*-BuOK (99 μL, 0.1 mmol, 1.0 M in THF) dropwise over 5 min. The reaction was stirred for 50 min, then quenched by addition of phosphate buffer (pH 7), and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the cyclized product **29** as a clear oil, pure by NMR (440 mg, quant.): Diastereomeric ratio (2*R*:2*S*) = 96:4; $[\alpha]_D^{23}$ −0.8 (c = 1.0, CH_2Cl_2); IR (film) 3070 (w), 2931 (s), 2851 (s), 1725 (s), 1427 (m), 1110 (s), 701 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.65 (m, 8H), 7.50−7.34 (m, 13 H), 7.26−7.22 (m, 2H), 7.18−7.12 (m, 2H), 4.71 (dt, J = 10.5, 4.3 Hz, 1H), 3.96 (td, J = 9.2, 4.6 Hz, 1H minor diastereomer), 3.72 (dd, J = 10.2, 4.8 Hz, 1H), 3.61−3.54 (m, 2H), 3.44−3.36 (m, 1H major diastereomer), 3.20 (dd, J = 9.1, 3.5 Hz, 1H), 2.28 (dd, J = 15.7, 9.0 Hz, 1H), 2.02 (dt, J = 11.8, 3.4, 1H), 1.86−0.86 (m, 11H), 1.28 (s, 3H), 1.16 (s, 3H), 1.08 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 151.9, 135.97, 135.95, 135.6, 135.5, 134.4, 133.89, 133.85, 133.6, 129.6, 129.55, 129.52, 129.4, 127.7, 127.59, 127.53, 127.4, 125.3, 124.8, 78.0, 76.6, 74.4, 67.8, 67.2, 50.8, 39.6, 38.3, 33.0, 31.8, 30.2, 28.0, 27.1, 26.9, 26.8, 26.0, 24.6, 24.3, 22.6, 22.3, 19.6, 19.2; HRMS (FAB, M + H^+) calcd for $C_{55}H_{71}O_5Si_2$ 867.4840, found 867.4852.

(2*R*,3*R*,6*R*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-6-{[*tert*-butyl-(diphenyl)silyl]oxymethyl}-2-[(*Z*)-dodec-2-enyl]tetrahydro-2*H*-pyran (48a). To a stirred solution of ester **29** (100 mg, 0.116 mmol) in CH_2Cl_2 (2 mL) at − 78 °C was added DIBAL-H (90.8 μL, 0.136 mmol, 1.5 M in toluene) dropwise over 5 min. The resulting mixture was stirred for 35 min, after which a preformed (30 min) solution of decyltriphenylphosphonium bromide (164 mg, 0.340 mmol) and NaHMDS (0.45 mL, 0.227 mmol, 0.6 M in toluene) in THF (4 mL) at 0 °C was added via a cannula. The temperature was raised to 0 °C over 12 h, and the reaction was then quenched by evaporation onto silica. Purification by flash chromatography (0.78−3.13% EtOAc/heptane) furnished olefin **48a** as a clear oil (69 mg, 75%): (*E*):(*Z*) ∼1:10; $[\alpha]_D^{23}$ +19.0 (c = 1.0, CH_2Cl_2); IR (film) 3070 (w), 2927 (s), 2856 (s), 1471 (m), 1427 (m), 1112 (s), 701 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.63 (m, 8H), 7.48−7.29 (m, 12H), 5.39−5.21 (m, 2H), 3.82 (dd, J = 10.3, 5.3 Hz, 1H), 3.71 (s, 1H), 3.66 (dd, J = 10.2, 5.4 Hz, 1H), 3.51−3.42 (m, 1H), 3.17 (dd, J = 8.3, 5.2 Hz, 1H), 2.48−2.24 (m, 1H), 2.21−1.98 (m, 1H), 1.95−1.68 (m, 4H), 1.57−1.35 (m, 3H), 1.35−0.99 (m, 13H), 1.10 (s, 9H), 1.09 (s, 9H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 136.0, 135.7, 136.0, 134.5, 134.0, 133.9, 133.88, 133.81, 133.6, 132.7, 132.6, 131.1, 129.4, 128.6, 128.5, 128.48, 128.44, 128.3, 127.53, 127.47, 127.40, 127.3, 126.2, 80.5, 78.1, 68.0, 67.3, 31.9, 30.7, 30.5, 29.6, 29.57, 29.56, 29.35, 29.33, 27.4, 27.1, 26.8, 22.6, 22.5, 19.6, 19.2, 14.1; HRMS (FAB, M + Na^+) calcd for $C_{50}H_{70}NaO_3Si_2$ 797.4761, found 797.4762.

(1*R*)-1-{(2*R*,5*R*,6*R*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-6-[(*Z*)-dodec-2-en-1-yl]tetrahydro-2*H*-pyran-2-yl}-3-(trimethylsilyl)-prop-2-yn-1-ol (52). To a solution of zinc triflate (97 mg, 0.256 mmol) and (1*S*, 2*R*)-*N*-(−)-methylephedrine (57 mg, 319 mmol) in toluene (1 mL) was added Et_3N (88.8 μL, 0.637 mmol). The resulting slurry was stirred 1 h 45 min, and the trimethylsilylacetylene (150 μL, 1.06 mmol) was added. After 15 min a solution of aldehyde **50a** (120 mg, 0.212 mmol) in toluene (1 mL) was added via a cannula (rinsed with 0.5 mL toluene).[73] After stirring for 20 h at room temperature the reaction mixture was evaporated onto silica. Purification by flash chromatography (6.25% EtOAc/heptane) afforded propargylic alcohol **52** as a clear oil (110 mg, 83%); $[\alpha]_D^{23}$ +19.8 (c = 1.0, CH_2Cl_2); IR (film) 3478 (br, w), 2956 (s), 2927 (s), 2856 (s), 2177 (w), 1427 (w), 1249 (m), 1110 (s), 842 (s), 701 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.65 (m, 4H), 7.50−7.37 (m, 6H), 5.43−5.20 (m, 2H), 4.32 (d, J = 7.7 Hz, 1H), 3.76−3.70 (m, 1H), 3.40 (ddd, J = 10.1, 7.9, 2.0 Hz, 1H), 3.23 (dd, J = 9.1, 4.3 Hz, 1H), 2.98 (s, 1H), 2.53−2.44 (m, 1H), 2.02−1.68 (m, 5H), 1.67−1.52 (m, 2H), 1.41−0.99 (m, 14H), 1.13 (s, 9H), 0.92 (t, J = 6.9 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 134.2, 132.1, 130.0, 128.00, 127.96, 126.0, 103.4, 91.2, 81.1, 80.7, 68.2, 66.8, 32.3, 30.9, 30.8, 30.06, 30.00, 29.79, 29.76, 27.8, 27.5, 23.1, 22.1, 20.0, 14.5, 0.2; HRMS (FAB, M + Na^+) calcd for $C_{39}H_{61}NaO_3Si_2$ 633.4159, found 633.4153.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*E*)-3-[(2*R*)-3,4-Dihydro-2*H*-pyran-2-yl]acrylate (57) and (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*Z*)-3-[(2*S*)-3,4-

(72) Alternatively, the crude **16** obtained after filtration through a short plug of silica could be directly subjected to reduction/protective group migration. This protocol afforded **18** in 70% overall yield, based on **20**.

(73) Due to the higher reactivity of aldehyde **50a** compared to that of aldehyde **70**, the reaction could be run at room temperature using standard inert techniques.

Dihydro-2*H*-pyran-2-yl]acrylate (61). To a stirred solution of phosphonate **55** (1.97 g, 3.80 mmol) and 18-crown-6 (2.61 g, 9.88 mmol) in THF (150 mL) was added KHMDS (7.24 mL, 3.62 mmol, 0.5 M in toluene) dropwise at −78 °C. The resulting solution was stirred for 30 min and then added via a cannula to a precooled solution of acrolein dimer *rac*-14 (533 mg, 4.94 mmol) in THF (70 mL) over 5 h at −78 °C. After an additional 2 h the reaction was quenched by addition of AcOH (1 M, MeOH) followed by phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (3.13−6.25% EtOAc in heptane) afforded a 60:40 mixture of (2*Z*,4*S*)-61 and (2*E*,4*R*)-57 as a clear oil (1.54 g, 77% based on 55): dr 61, (2*Z*,4*S*):(2*Z*,4*R*) = 96:4; 57, (2*E*,4*R*):(2*E*,4*S*) = 98:2.[74]

10-Benzyl 1-[(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl] (2*E*,4*R*,8*E*)-4-[2-(trimethylsilyl)ethoxy]deca-2,8-dienedioate (65). Neocuproine (427 mg, 0.608 mmol) and Pd_2dba_3 (15.7 mg, 0.015 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature and stirred for 30 min. The resulting clear orange-red solution was transferred to a stirred solution of **60** or **64** (or a mixture of the two), dissolved in 2-(trimethylsilyl)ethanol (2 mL) and CH_2Cl_2 (1 mL) at room temperature. The resulting clear yellow solution was then stirred at room temperature for 3 h during which time the color changed to light brown. The reaction mixture was poured onto phosphate buffer (pH 7) and partitioned between CH_2Cl_2 and phosphate buffer (pH 7). The combined organic phases were dried ($MgSO_4$) followed by removal of CH_2Cl_2 under reduced pressure. Recovery of 2-(trimethylsilyl)ethanol was accomplished using bulb-to-bulb distillation (0.01 mmHg, 60 °C) to give 1.50 g, 80%. Repeated purification by flash chromatography (10% Et_2O/heptane) furnished the (2*E*,8*E*)-diene **65** as a clear oil (263.4 mg, 72%): Diastereomeric ratio (4*R*):(4*S*) = 97:3; $[\alpha]_D^{23}$ +16.4 (*c* = 1.0, CH_2Cl_2); IR (film) 3058 (w), 2952 (s), 2925 (s), 1714 (s), 1652 (m), 1440 (m), 1230 (m), 1230 (s), 1199 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 9H), 7.13−7.07 (m, 1H), 7.01 (td, *J* = 15.6, 6.9 Hz, 1H), 6.53 (dd, *J* = 15.8, 6.5 Hz, 1H major diastereomer), 6.35 (dd, *J* = 15.8, 6.3 Hz, 1H minor diastereomer), 5.89 (td, *J* = 15.6, 1.5, 1H), 5.44 (dd, *J* = 15.8, 1.1 Hz, 1H), 5.18 (s, 2H), 4.87 (dt, *J* = 10.7, 4.4 Hz, 1H), 3.70 (q, *J* = 5.5 Hz, 1H), 3.49 (ddd, *J* = 10.1, 9.4, 6.1 Hz, 1H), 3.29 (ddd, *J* = 10.2, 9.4, 6.3 Hz, 1H), 2.26−2.18 (m, 2H), 2.03 (ddd, *J* = 12.3, 10.6, 3.2 Hz, 1H), 1.96−1.89 (m, 1H), 1.76−0.74 (m, 12H), 1.31 (s, 3H), 1.23 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.7, 166.7, 152.7, 150.6, 149.3, 137.4, 129.8, 129.55, 129.50, 129.2, 126.7, 126.3, 123.6, 122.7, 79.4, 75.9, 67.9, 67.4, 51.8, 43.0, 41.1, 35.9, 35.8, 33.4, 32.6, 28.3, 28.0, 27.4, 25.1, 23.1, 19.7, 0.0; HRMS (FAB, M + H$^+$) calcd for $C_{38}H_{54}O_5Si$ 619.3819, found 619.3822.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4*R*,-10*R*)-10-Hydroxy-12-(trimethylsilyl)-4-[2-(trimethylsilyl)ethoxy]-dodec-11-ynoate (71). To a solution of zinc triflate (79.7 mg, 0.21 mmol) and (1*R*,2*S*)-*N*-(+)-methylephedrine (46.9 mg, 0.26 mmol) in toluene (1 mL) was added Et_3N (73 μL, 0.52 mmol) through a septum.[75] The resulting slurry was stirred 1 h 45 min and then trimethylsilylacetylene (246 μL, 1.744 mmol) was added. After 15 min a solution of aldehyde **70** (90 mg, 0.17 mmol) in toluene (1 mL) was added via a cannula (rinsed with 0.5 mL of toluene). The reaction vessel was then sealed with a screw cap and heated to 60 °C. After 20 h the reaction mixture was evaporated onto silica. Purification by flash chromatography (12.5−25% EtOAc/heptane) afforded propargylic alcohol **71** as a clear oil (80 mg, 75%): Diastereomeric ratio (10*R*:10*S*) = 98:2;[76] $[\alpha]_D^{23}$ −2.8 (*c* = 1.0, CH_2Cl_2); IR (film) 3436 (br, s), 2952 (s), 2929 (s), 2961 (s), 2169 (w), 1727 (s), 1249 (s), 1174 (m), 840 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.27 (m, 4H), 7.18−7.11 (m, 1H), 4.84 (dt, *J* = 10.7, 4.4 Hz, 1H), 4.38 (t, *J* = 6.5 Hz, 1H), 3.52−3.40 (m, 2H), 3.17−3.08 (m, 1H), 2.06−1.98 (m, 1H), 1.97−0.81 (m, 27H), 1.34 (s, 3H), 1.23 (s, 3H), 0.20 (s, 9H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 152.0, 128.3, 125.8, 125.4, 107.2, 89.7, 78.3, 74.3, 66.3, 63.2, 50.7, 42.2, 40.1, 38.1, 34.9, 34.2, 31.7, 30.7, 29.8, 29.1, 28.1, 27.0, 25.7, 25.6, 25.5, 22.2, 19.0, 0.3, −0.8; HRMS (FAB, M + H$^+$) calcd for $C_{36}H_{63}O_4Si_2$ 615.4265, found 615.4269.

(5*S*)-3-{(2*R*,8*R*)-8-Hydroxy-2-[2-(trimethylsilyl)ethoxy]dec-9-yn-1-yl}-5-methylfuran-2(5*H*)-one (74). To a solution of ester **71** (100 mg, 0.17 mmol) in THF (5 mL) at −78 °C was added LDA (249 μL, 0.499 mmol, 2 M). The resulting mixture was stirred for 35 min and a precooled solution (−78 °C) of **76** (131 mg, 0.83 mmol) in THF (3 mL) was added dropwise via a cannula. After stirring for 1 h the reaction was quenched by addition of MeOH (2 mL). The reaction was then brought to room temperature, and K_2CO_3 (200 mg, 1.44 mmol) was added. The resulting suspension was stirred another 12 h after which the reaction mixture was poured into HCl (1 M, aq). The mixture was partitioned between EtOAc and HCl (1 M, aq). The combined organic phases were then dried ($MgSO_4$) and concentrated in vacuo. The crude product **72** was dissolved in MeOH and 10-camphorsulfonic acid (cat.) was added. The resulting mixture was heated to reflux. After 60 min the reaction was cooled to room temperature and partitioned between EtOAc and $NaHCO_3$(sat.,aq). The combined organic phases were dried ($MgSO_4$) and filtered through a short plug of silica (50% EtOAc/heptane) to remove (−)-8-phenylmenthol. The resulting crude oil (59.9 mg) was isolated as a mixture of diastereomers. Of this crude lactone 44 mg was dissolved in CH_2Cl_2 (3 mL) and Et_3N (159.2 μL, 0.572 mmol) was added, followed by trichloroacetyl chloride (38.3 μL, 0.343 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 24 h after which THF (6 mL) followed by $NaHCO_3$ (5 mL, sat., aq) was added. The resulting mixture was stirred for 3 h and then partitioned between EtOAc and water. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (12.5−50% EtOAc/heptane) afforded butenolide **74** as a clear oil (33 mg, 79% overall from **71**): $[\alpha]_D^{23}$ +17.7 (*c* = 0.82, CH_2Cl_2); IR (film) 3430 (br, m), 3297 (w), 2935 (s), 2859 (m), 1752 (s), 1319 (m), 1247 (m), 1076 (s), 1076 (s), 837 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.3 Hz, 1H), 5.08−5.00 (m, 1H), 4.39 (dq, *J* = 6.6, 2.1 Hz, 1H), 3.58−3.46 (m, 3H), 2.50−2.45 (m, 3H), 1.85 (d, *J* = 5.6 Hz, 1H), 1.80−1.66 (m, 2H), 1.58−1.25 (m, 11H), 0.99−0.82 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 151.4, 130.7, 84.9, 77.5, 76.6, 72.8, 66.3, 62.2, 37.5, 34.0, 29.8, 29.2, 25.1, 24.8, 19.1, 18.6, −1.3; HRMS (FAB, M + H$^+$) calcd for $C_{20}H_{35}O_4Si$ 367.2305, found 367.2308.

Pyranicin (1). To a stirred solution of triprotected pyranicin **84** (12.0 mg, 0.0114 mmol) in MeCN (1.2 mL) was added HF (50 μL, 40%, aq) at room temperature. The reaction was heated to 45 °C during 22 h and then quenched by addition of $NaHCO_3$ (sat., aq) and partitioned between EtOAc and $NaHCO_3$. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (3−5% MeOH/EtOAc) afforded unprotected pyranicin (**1**) as a clear oil (5.7 mg, 85%): $[\alpha]_D^{23}$ +21.1 (*c* = 0.24, $CHCl_3$); IR (film) 3392 (br, m), 2921 (s), 2850 (s), 1757 (m), 1743 (m), 1644 (m), 1467 (m), 1321 (m), 1205 (w), 1079 (s), 1027 (m); ^{1}H NMR (500 MHz, CDCl3) δ 7.19 (dd, 2.5, 1.2 Hz, 1H), 5.07 (dq, *J* = 6.8, 1.3 Hz, 1H), 3.89−3.82 (m, 1H), 3.65−3.58 (m, 2H), 3.49−3.43 (m, 1H), 3.35 (dd, *J* = 8.1, 5.6 Hz, 1H), 3.20 (ddd, *J* = 10.8, 7.0, 2.2 Hz, 1H), 2.69 (s, 1H), 2.54 (tdd, *J* = 15.1, 3.1, 1.4 Hz, 1H), 2.41 (tdd, *J* = 15.2, 8.3, 1.2 Hz, 1H), 2.3 (br s, 1H), 2.01 (ddd, *J* = 13.0, 5.9, 3.0 Hz, 1H), 1.84 (d, *J* = 8.2 Hz, 1H), 1.77−1.10 (m, 45H), 1.44 (d, *J* = 6.8 Hz,

(74) For analytical data of **57** and **61**, see: Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535−538.

(75) Sealing the reaction vessel using a septum was not sufficient to prevent TMS−acetylene from escaping from the reaction.

(76) As determined by ^{1}H and ^{19}F analysis of the corresponding (+)- and (−)-MTPA derivatives.

3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 151.8, 131.1, 81.2, 80.0, 77.9, 74.0, 71.7, 69.9, 66.1, 37.35, 37.30, 37.2, 33.4, 32.2, 31.9, 31.6, 30.5, 29.67, 29.66, 29.65, 29.63, 29.60, 29.57, 29.50, 29.3, 25.63, 25.60, 25.51, 25.3, 22.6, 21.5, 19.1, 14.1; HRMS (FAB, M + H^+) calcd for $C_{35}H_{65}O_7$ 597.4730, found 597.4732.

Pyragonicin (2). To a solution of zinc triflate (16.6 mg, 0.046 mmol) and (1*S*,2*R*)-*N*-(−)-methylephedrine (12.3 mg, 0.068 mmol) in toluene (100 μL) was added Et_3N (16 μL, 0.11 mmol). The resulting slurry was stirred for 1 h 45 min, and then butenolide **74** (8.4 mg, 0.022 mmol) in toluene (100 μL) was added. After 15 min, a solution of aldehyde **50b** (19.3 mg, 0.034 mmol) in toluene (100 μL) was added. The reaction was stirred for 20 h, and the reaction mixture was filtered through a plug of silica (25−37.5% EtOAc/heptane) to remove remaining aldehyde. The crude oil (∼10.0 mg) was dissolved in DME (2.4 mL) and tosylhydrazine (300 mg, 1.6 mmol) was added. The reaction was heated to reflux, and sodium acetate (160 mg, 2.0 mmol) in water (3.0 mL) was added over 4 h using a syringe pump. The reaction was then poured onto water and partitioned between EtOAc and water. The combined organic phases were dried ($MgSO_4$), filtered, concentrated in vacuo, and filtered through a plug of silica (25−37.5% EtOAc/heptane). The remaining crude oil was dissolved in MeCN (2.5 mL) and HF (50 μL, 40%, aq) was added at room temperature. The reaction was heated to 40 °C during 22 h and then quenched by addition of $NaHCO_3$(sat.,aq) and partitioned between EtOAc and $NaHCO_3$. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (0−5% MeOH/EtOAc) afforded unprotected pyragonicin (**2**) as a clear oil (4.6 mg, 34%): $[\alpha]_D^{23}$ + 10.3 (c = 0.13, $CHCl_3$); IR (film) 3409 (br, m), 2915 (s), 2848 (s), 1741 (s), 1461 (m), 1317 (w), 1081 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (q, J = 1.5 Hz, 1H), 5.07 (qq, J = 6.7, 1.2 Hz, 1H), 3.88−3.81 (m, 1H), 3.69−3.58 (m, 2H), 3.51 (dt, J = 7.5, 2.5 Hz, 1H), 3.36 (dd, J = 7.6, 5.8 Hz, 1H), 3.24 (ddd, J = 10.5, 7.4, 2.3 Hz, 1H), 2.53 (dt, J = 15.1, 3.2, 1.6, 1H), 2.40 (ddt J = 15.1, badly resolved, 1H), 2.02 (ddd, J = 13.4, 5.7, 3.0 Hz, 1H), 1.83−1.18 (m, 47H), 1.44 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6(weak), 151.8, 131.2, 81.0, 80.1, 78.0, 74.3, 71.6, 69.9, 66.0, 37.3, 37.2, 33.4, 33.3, 31.9, 31.6, 30.5, 29.69, 29.66, 29.64, 29.61, 29.5, 29.4, 29.3, 28.4, 25.63, 25.61, 25.5, 22.7, 21.6, 19.1, 14.1; HRMS (FAB, M + H^+) calcd for $C_{35}H_{65}O_7$ 597.4730, found 597.4739.

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Supporting Information Available: Characterization data and experimental procedures for compounds **18**, **82**, **19**, **86**, **22**, **27**, **48b**, **49a**,**b**, **50a**,**b**, **53**, **54**, **58**, **62**, **59**, **63**, **60**, **64**, **66**, **69**, **83**, **70**, **76**, **84**, and **81**. ^{1}H and ^{13}C NMR spectra for compounds **16**, **28**, **29**, **48a**, **52**, **65**, **71**, **74**, **1**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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