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Palladium-Catalyzed Formation of Substituted Tetrahydropyrans: Mechanistic Insights and Structural Revision of Natural Products

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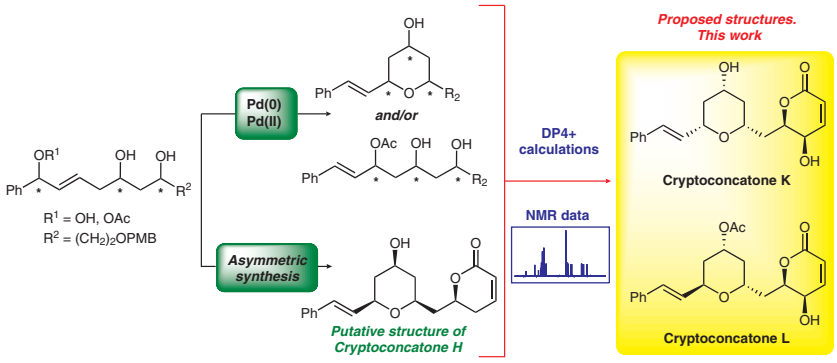
This work is dedicated to Professor Albert J. Kascheres for his guidance and positive example to one of us (R.A.P.).



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Abstract A comprehensive study on the stereochemical outcome of palladium-catalyzed formation of 2,4,6-trisubstituted tetrahydropyrans through cyclization of the corresponding allylic acetates using both Pd(0) and Pd(II) catalysts is presented. We have found that the stereochemical outcome of this cyclization is dependent not only on the stereochemistry of the acyclic precursor but also on the nature of the palladium catalyst. These results were applied to the total synthesis of the putative structure of cryptoconcatone H. Experimental and computational DP4+ NMR results were used to assess the structures proposed for cryptoconcatones K and L.

Key words tetrahydropyran, palladium catalysis, DP4+, structural revision, natural product synthesis

Introduction

The widespread presence of the tetrahydropyran (THP) moiety in Nature has raised interest in the development of stereoselective procedures for its formation, requiring stereochemical control in order to achieve efficiency and scalability.

Several methodologies can be found in the literature for the construction of THP rings.[1] Lewis and Brønsted acids, as well as transition-metal-catalyzed cyclization of allylic alcohols (and/or their respective ester, carbonate or phosphate) to form THPs has taken a major role in the last decade, with the palladium-mediated construction of this motif being one of the most versatile procedures. Both Pd(0) and Pd(II) methodologies can lead to substrate-controlled, regioselective cyclization with retention of configuration (Scheme 1).[2]

In 2002, Trost and co-workers described the enantioselective formation of a series of substituted heterocycles, including tetrahydrofurans and tetrahydropyrans, through a combined Ru-catalyzed ene-yne coupling, followed by a Pd-catalyzed asymmetric allylation.[3]

Hansen and Lee studied the formation of a variety of 2-alkenyl-4-methylene THP derivatives catalyzed by $Pd(PPh_3)_4$, and succeeded in the transfer of stereochemical information from the starting material to the product and gaining access to either 2,6-*cis* or 2,6-*trans* configuration.[4] For the preparation of THPs with an unsubstituted vinyl group, Trost's chiral amine ligand was found to promote formation of the *cis* isomer in up to 10:1 ratio, although for the *trans* isomer selectivity was in the range of 2:1.

Uenishi and co-workers described the use of $PdCl_2(CH_3CN)_2$ to stereospecifically catalyze the formation of either *cis* or *trans* THP from *syn*- or *anti*-2,8-diol, respectively, and they proposed that the stereogenic center in the secondary allylic alcohol transfers stereochemical information to the newly generated stereogenic center in the pyran ring in a *syn*-S_N2' type process.[5]

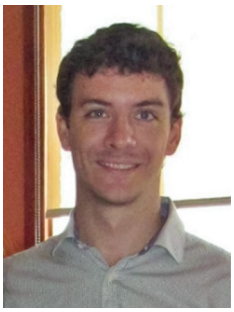
Later, Hanessian and co-workers explored Uenishi's methodology for the cyclization of allylic diols bearing a methyl substituent at C-2 in the allylic alcohol position and they found that a non-stereoselective process took place providing a mixture of *cis*- and *trans*-2,6-dihydropyrans.[6] While other Pd(II) species such as $PdCl_2$ or $PdCl_2(PPh_3)_2$ failed to catalyze the conversion, diastereoselection favoring the 2,6-*cis* dihydropyran could be restored when cationic $Pd(CH_3CN)_4(BF_4)_2$ or a Lewis acid such as $BF_3{\cdot}OEt_2$, $Fe(ClO_4)_2{\cdot}xH_2O$ or $Cu(OTf)_2$, or even a Brønsted acid such as TfOH or *p*-TsOH, were employed. The 2,6-*cis* preference was independent of the configuration at the allylic carbinolic stereogenic center, as demonstrated for the conversion of 1,3-*syn* and *anti* diols into the same 2,6-*cis* dihydropyran in almost the same yields and diastereoselectivities when treated with $BF_3{\cdot}OEt_2$.

Krische and co-workers examined the formation of several 2,6-*cis* and 2,6-*trans* 4-hydroxy-tetrahydropyrans

through the use of chiral palladium and iridium complex catalysts. In accordance with the results of Hansen and Lee, they emphasized that the 2,6-*trans* diastereoisomers were intrinsically more challenging to obtain in high selectivity because of rapid interconversion of the diastereoisomeric π-allyl intermediates.[7]

The three-dimensional disposition of the substituents around the THP ring is crucial for the biological and chemical properties of this class of natural products, and knowing the proper relative stereochemistry in THP-containing compounds is of paramount importance. In this regard, despite the enormous progress in spectrometric techniques available for the characterization of organic compounds over the last decades, structural misassignments are still found in the literature,[8] and total synthesis comes into play as one of the most effective approaches for structural elucidation.[9]

Biographical Sketches

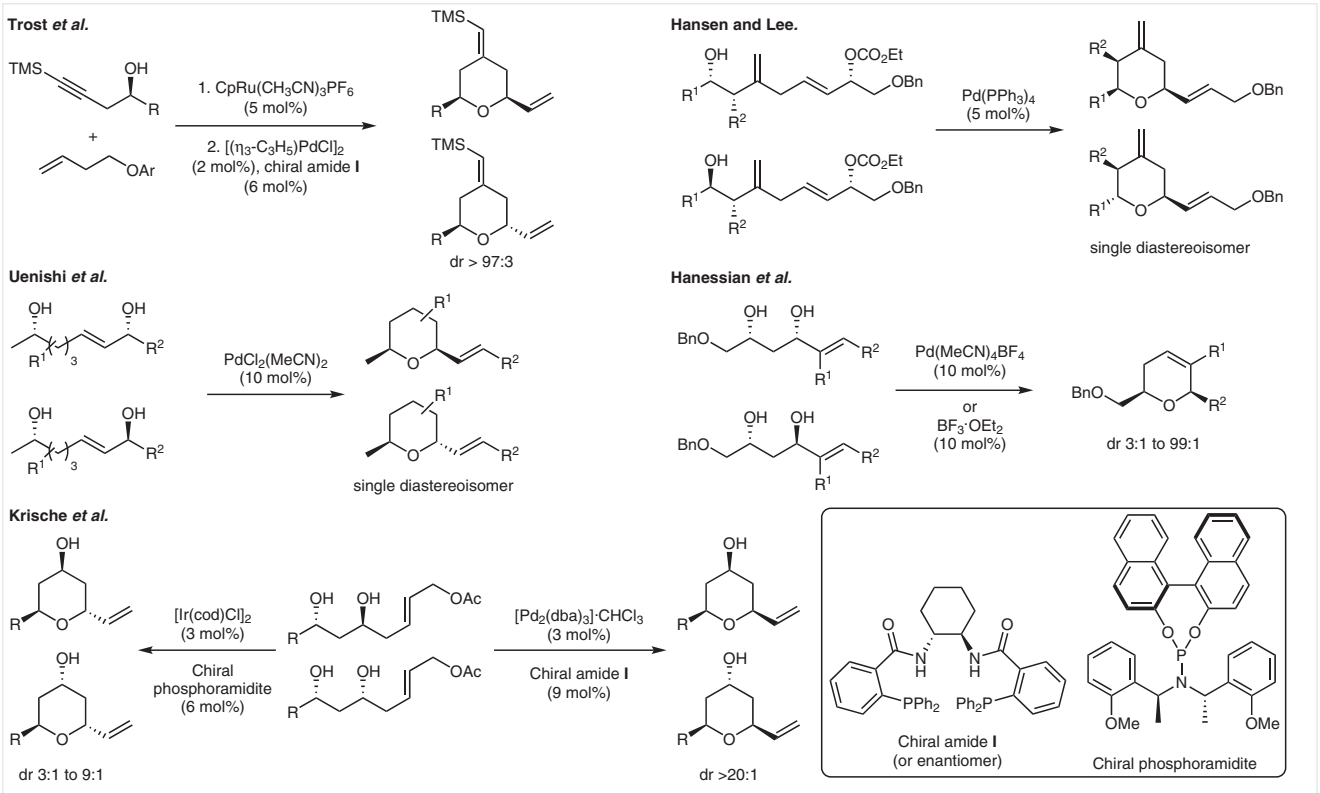


Franco Della-Felice obtained his BSc degree in chemistry at the National University of Rosario (UNR, Argentina) in 2013 under the guidance of Professors Edmundo A. Rúveda and María I. Colombo. In 2014, he joined Professor Ronaldo A. Pilli group at the University of Campinas (Brazil) focusing on synthesis and structural revision of natural products.

Francisco F. de Assis obtained his BSc degree in chemistry at the University of São Paulo (USP) in 2011 and his PhD in Organic Chemistry at the Federal University of São Carlos (UFSCar) in 2016, under the supervision of Professor Kleber T. de Oliveira. In the same year he joined Professor Pilli's research group as postdoctoral fellow to work on the synthesis of molecules with potential antihyperglycemic activity. Between 2017 and 2018 he temporarily joined the group of Professor Eric Meggers at the University of Marburg (Germany) to work on the development of asymmetric visible-light photocatalysis methodologies. Currently, he continues his postdoctoral research in Professor Pilli's group.

Ariel M. Sarotti received his PhD from the National University of Rosario (UNR, Argentina) in 2007, under supervision of Prof Alejandra G. Suárez. After his postdoctoral research in computational chemistry at IQUIR, he became researcher of the Argentine National Council Research (CONICET). Currently, he is Associate Professor of Organic Chemistry at UNR, and Independent Researcher at CONICET. His scientific interests include green and sustainable chemistry, asymmetric synthesis, computational chemistry, NMR spectroscopy and medicinal chemistry.

Ronaldo A. Pilli graduated from the University of Campinas, Brazil in 1977 and got his PhD from the same university in 1981, under the supervision of Professor Albert J. Kascheres working on the reactivity of strained cyclopropenimines. After a post-doctoral stint at the University of California, Berkeley under the supervision of Professor Clayton H. Heathcock, he returned to Campinas to start his independent career working on the stereoselective synthesis of natural products where he is now Professor of Chemistry. His interests include the total synthesis and biological properties of natural compounds and analogues.



Scheme 1 Representative examples of Pd-mediated construction of THPs

Recently, we presented a stereochemical revision of the structure of natural cryptoconcatone H, a trisubstituted tetrahydropyran styryl lactone isolated by Kong, Luo and co-workers from *Cryptocarya concinna* (Figure 1).[10] Altogether, these authors reported twelve new styryl lactones, named cryptoconcatones A–L, with interesting biological activities. Whereas cryptoconcatones D, H and I showed moderate anti-inflammatory activity, as evaluated by NO production, cryptoconcatones K and L were moderately active against Huh7 tumor cell line.[11]

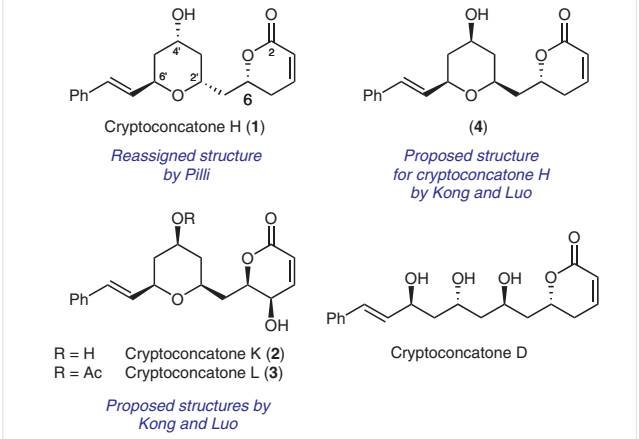


Figure 1 Secondary metabolites isolated from *C. concinna* by Kong, Luo and co-workers

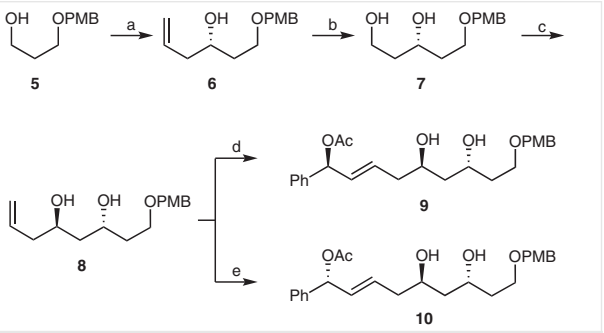
As can be noted, the THP ring in the proposed structures of cryptoconcatones K (**2**) and L (**3**) features the same relative configuration as originally proposed for cryptoconcatone H (**4**). On the other hand, the stereochemical connection between the THP ring and the carbinolic center at the dihydropyranone moiety present in **2** and **3** was assigned the opposite configuration to that in structure **4**.

In our previous synthetic studies on cryptoconcatones, we employed the Pd(II)-catalyzed THP ring formation to stereoselectively secure the formation of the 2,4,6-trisubstituted tetrahydropyran ring of the reassigned structure of cryptoconcatone H (**1**). Further investigation revealed that the stereochemical outcome of the palladium-catalyzed formation of styryl tetrahydropyrans via cyclization of the allylic alcohols or acetates bearing a δ,ζ-diol was dependent not only on the stereochemistry of the acyclic precursor but also on the nature of the palladium catalyst.

Herein, we would like to report a comprehensive study on such reactions and their application to the total synthesis of the putative structure originally assigned to cryptoconcatone H (**4**). In addition, a configurational analysis of the structures proposed for cryptoconcatones K and L (**2** and **3**, respectively) through DFT calculations of NMR chemical shifts is also presented.

Results and Discussion

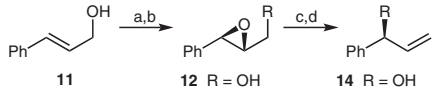
Preparation of the 2,6-*trans* THP ring present in **1** and the 2,6-*cis* THP counterpart present in **2**–**4**, were envisioned through a Tsuji–Trost reaction of allylic acetates **9** and **10** (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) (*S*)-(BINAP-π-allyliridium-C,O-benzoate) catalyst (5 mol%), Cs_2CO_3, 3-Cl-4-NO_2-BzOH, AcOAllyl, THF/H_2O, 110 °C, 40 h, 95% (*ee* ≥ 99%); (b) OsO_4 (1 mol%), $NaIO_4$, 1,4-dioxane/H_2O, r.t., 4 h, then $NaBH_4$, 0 °C, 15 min, 90%; (c) $[Ir(cod)Cl]_2$ (2.5 mol%), (*R*)-BINAP (5 mol%), Cs_2CO_3, 3-Cl-4-NO_2-BzOH, AcOAllyl, THF, 110 °C, 40 h, 72% (dr> 95:5); (d) (*S*)-**15** (150 mol%), Hoveyda–Grubbs II catalyst (3 mol%), CH_2Cl_2, Δ, 2 h, 89%; (e) (*R*)-**15** (150 mol%), Hoveyda–Grubbs II catalyst (3 mol%), CH_2Cl_2, Δ, 2 h, 82%.

These two epimeric structures at the benzylic position were prepared starting from monoprotected PMB ether **5**, followed by Krische asymmetric allylation employing chiral (*S*)-(BINAP-π -allyliridium-C,O-benzoate) catalyst to give **6** in high yields and excellent enantioselectivity.[12] Alkene **6** was next transformed into its corresponding alcohol **7** after a one-pot Lemieux–Johnson oxidation/$NaBH_4$ reduction, followed by a protecting group-free Krische asymmetric allylation[13] to obtain **8** in high selectivity. Finally, cross-metathesis reaction with either (*S*)- or (*R*)-**15** gave **9** or **10**, respectively.

For the preparation of enantiomerically enriched ester **15**, we explored the Sharpless asymmetric epoxidation (SAE) of cinnamyl alcohol (**11**)[14] to introduce the required stereogenic center in high yield and selectivity (**12**, Scheme 3). After conversion into the corresponding bromide **13**, epoxide opening with *n*-BuLi, followed by esterification, provided **15** in 70% overall yield without erosion of the enantiomeric ratio initially obtained from the SAE reaction.

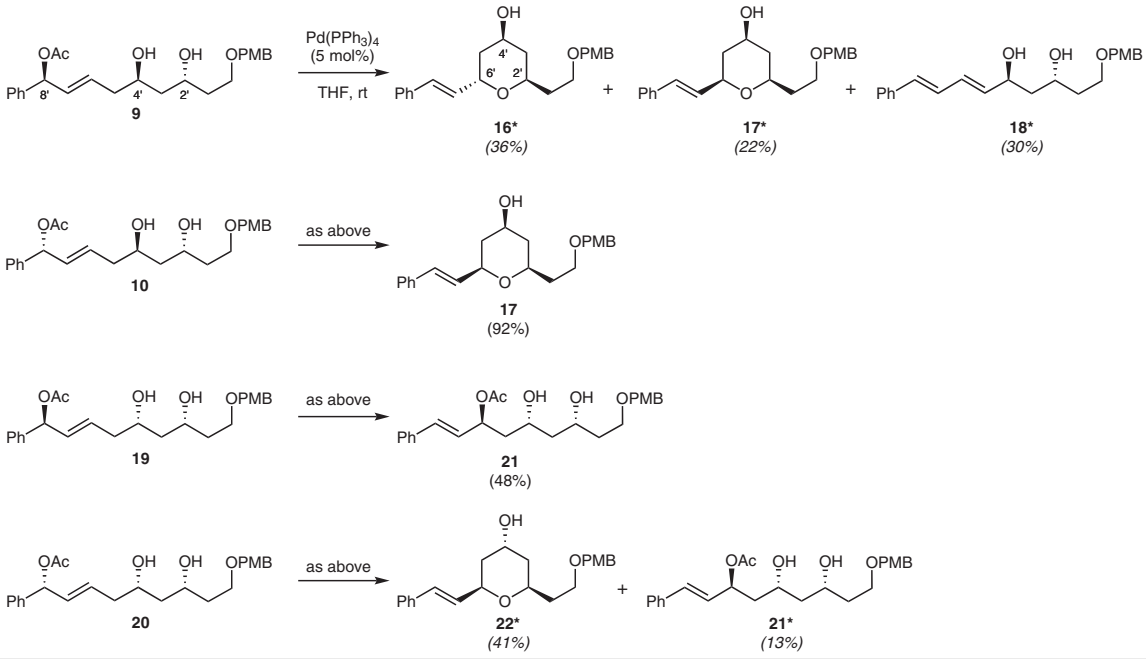


Scheme 3 *Reagents and conditions*: (a) ^tBuOOH, (–)- DIPT (10 mol%), $Ti(O^iPr)_4$ (7.5 mol%), MS 4 Å, CH_2Cl_2, –30 °C, 14 h, 91% (*ee* 90%); (b) CBr_4, PPh_3, CH_2Cl_2, r.t., 30 min, 81%; (c) *n*-BuLi, THF, –78 °C, 1 h, 99%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 1 h, 96% (*ee* 90%).

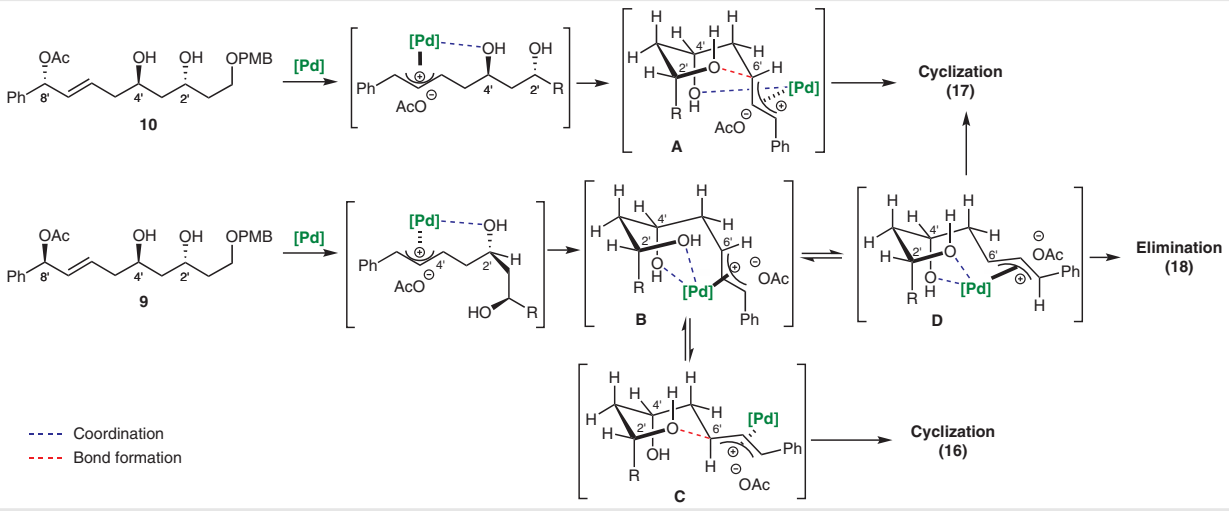
In our previous work,[10] it was reported that **9** gave a complex mixture of products under Tsuji–Trost conditions. After extensive analysis, it was found that the desired 2,6-*trans* THP **16** was formed along with the corresponding isomer **17** and diol **18** (Scheme 4), in a 36:22:30 ratio, respectively.[15] Surprisingly, under the same conditions, precursor **10** gave only the expected 2,6-*cis* THP **17**.

As the mechanism of the Tsuji–Trost reaction involves a Pd-π-allyl carbocation intermediate, we rationalized that the free alcohol at C-4′ (cryptoconcatone numbering) takes a major role in the outcome of the reaction as it can coordinate to the intervening Pd species (Scheme 5). According to this rationale, when the Pd(0) catalyst interacts with **10** and positions itself on the same side as the C-4′ hydroxyl group, the cationic Pd-π-allyl intermediate undergoes coordination with the free hydroxyl group at C-4′, leading to a stereoelectronically favored conformation for the formation of the 2,6-*cis* THP **17** (conformer A). On the other hand, when the cationic Pd-π-allyl intermediate interacts with the hydroxyl at C-4′ in **9**, it leads to a conformation in which the stereoelectronics does not favor the cyclization path (conformer B). This would extend the half-life of the Pd-π-allyl carbocation species, giving rise to either rotation along the C5′–C6′ axis (conformer C), allowing the formation of THP **16**, or isomerization of the Pd-π-allyl carbocation to structure D,[16] thus leading to THP **17**. Additionally, a competitive β-elimination pathway leading to **18** may be operational.[17]

Intrigued by these results, we next focused in changing the stereochemistry at the C-4′ position to further explore the impact of the hydroxyl configuration on the stereochemistry of the THPs to be formed via Tsuji–Trost cyclization. After preparing **19** and **20** in a similar fashion as depicted in Scheme 2, these two new substrates were subjected to the same Pd(0) conditions described earlier (Scheme 4). In this case, whereas **19** gave the rearranged diol **21** in moderate yield as the only isolated product, compound **20** afforded the cyclic product **22** as the major product, along with the formation of the rearranged compound **21** and a minor byproduct that was identify as the C6′-epimer of **21**. In a tentative attempt to rationalize these events, and considering that complexation of the palladium species with the free hydroxyl plays a pivotal role in the stereochemical outcome of these reactions, the behavior observed for compound **19** can be explained through a six-membered-ring conformation involving the palladium species and OH-4′ (conformer E, Scheme 6), which precludes attack of the free OH-2′ to the Pd-π-allyl carbocation. As a result, the cyclization and elimination pathways are not productive, allowing the rearrangement pathway to occur preferentially through the opposite face to that where palladium coordinates, thus providing the rearranged product **21** bearing *S* configuration at the allylic stereogenic center



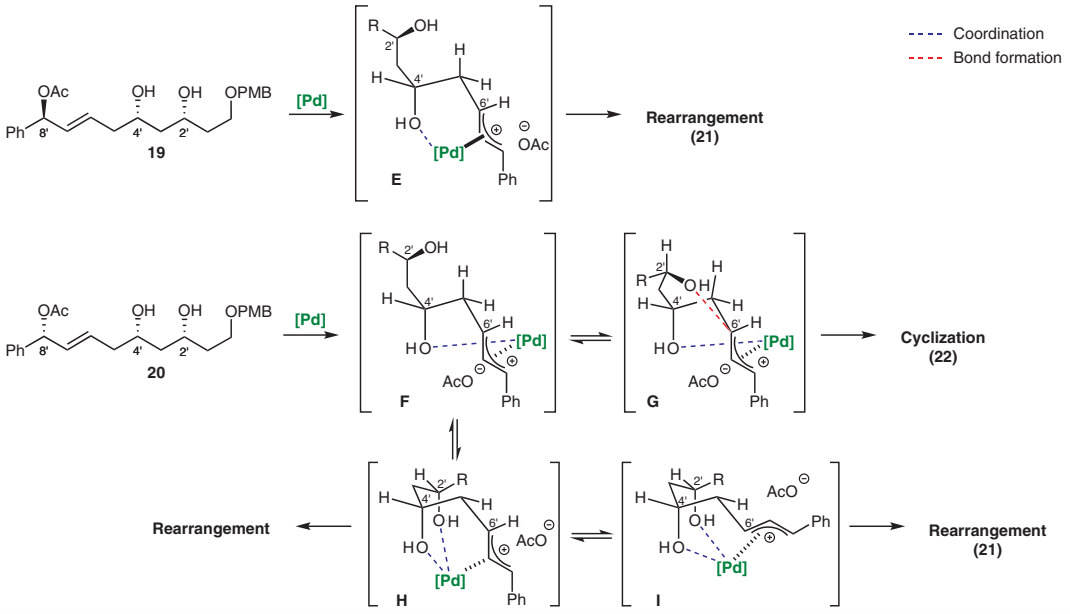
Scheme 4 Pd(0)-mediated reaction of compounds **9**, **10**, **19** and **20**. * Yield estimated based on molar ratio (^{1}H NMR spectroscopic analysis).[15]



Scheme 5 Mechanistic reasoning for the product distribution in the Tsuji–Trost reaction of ζ-hydroxy allylic acetates **9** and **10** (R = CH_2CH_2OPMB)

formed.[18] Compound **20**, epimeric to **19** at the allylic acetate, would also form a six-membered-ring conformer with the palladium catalyst (conformer F). Here, the OH-2′ is either able to equilibrate to conformer G, leading to the formation of **22** as the stereoelectronics required for the cyclization are favorable, or to coordinate with the palladium species and give rise to conformer H, where a rearrangement pathway seems possible, or undergo isomerization of the Pd-π-allyl carbocation to structure I, giving access to the formation of **21** as the minor product observed (Scheme 6).

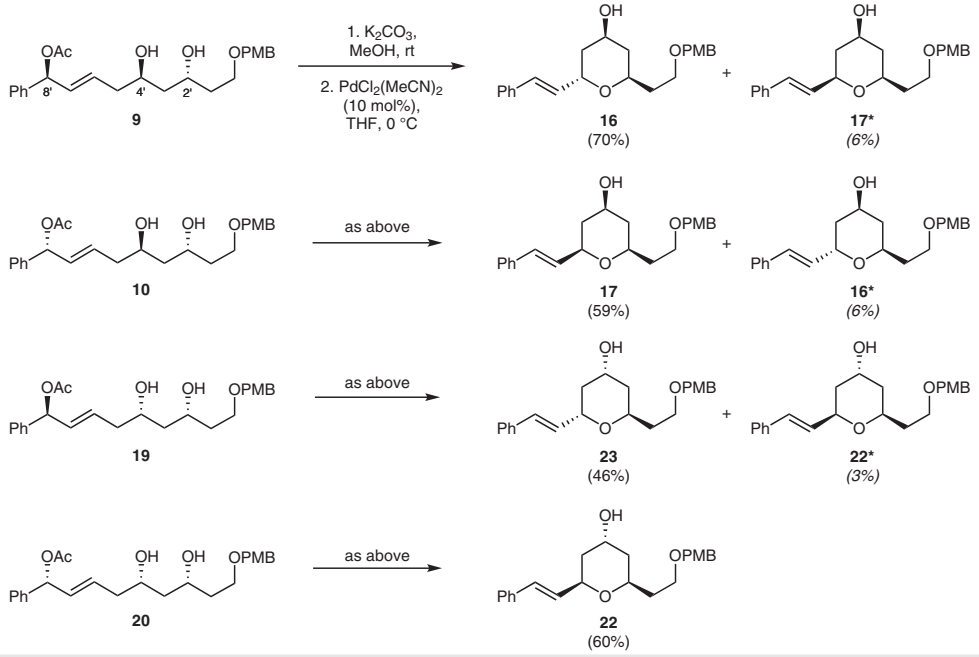
To overcome the complex mixture observed when **9** was treated under Tsuji–Trost conditions, we explored the use of the allylic alcohol corresponding to **9** in a stereospecific Pd(II)-catalyzed cyclization.[5] After a detailed study of this reaction, we found that under Uenishi's conditions the desired THP **16** was formed predominantly, along with small amounts of the all-*cis* THP **17** (Scheme 7). When **10**, epimeric to **9** at the allylic acetate position, was employed, the all-*cis* THP **17** was the major product, with **16** detected as the minor stereoisomer. From **19**, a C-4′ epimer of **9**, tetrahydropyran **23**, was obtained as the major product, with **22**



Scheme 6 Mechanistic reasoning for the formation of **21** and **22** via Tsuji–Trost reaction from **19** and **20** (R = CH_2CH_2OPMB)

formed in small proportion. Finally, starting from **20**, epimeric at C-8′ when compared to **19** or at C-4′ when compared to **10**, only the cyclization product **22** was obtained.

The results above show that, in the Pd(II)-catalyzed cyclization, the configuration at C-6′ is determined by the configuration of the allylic acetate used as the precursor of the reacting allylic alcohol: *S* configuration at C-8′ will lead to THPs bearing *S* configuration at C-6′ as the major product (**16** and **23** from **9** and **19**, respectively) while the opposite configuration is observed when substrates with *R* configuration at C-8′ are employed (**17** and **22** from **10** and **20**, respectively). Most interestingly to note is the formation of the side products observed when using **9**, **10** and **19**.[19] As the overall transformation is described as an S_N2' substitution of



Scheme 7 Pd(II)-mediated reaction of compounds **9**, **10**, **19** and **20**. * Yield estimated based on molar ratio (^{1}H NMR spectroscopic analysis).[15]

an allylic alcohol with an internal alcohol moiety, there are two possible mechanisms to consider that may clarify the observed results.

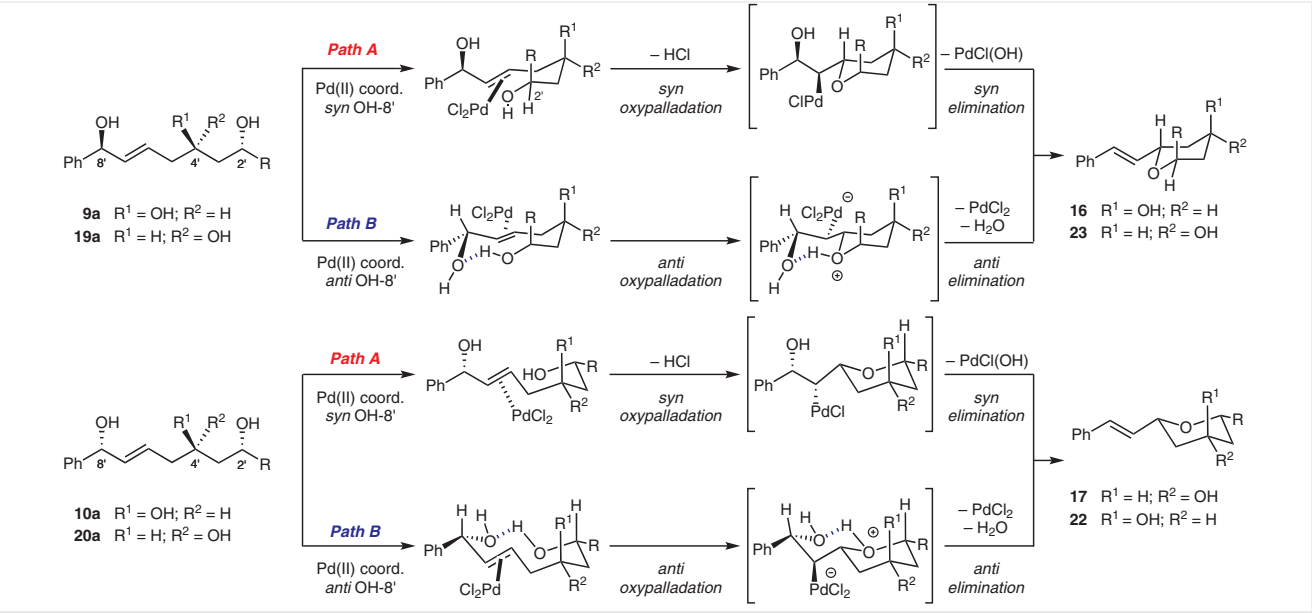
During their work, Uenishi *et al.* proposed a *syn* coordination of the Pd species to the double bond with respect to the free allylic alcohol,[5] followed by a *syn* approximation of the nucleophilic hydroxyl group to the double bond (*Si* face) to form a *syn* oxypalladation intermediate with concomitant formation of HCl (Scheme 8, path A). Finally, *syn* elimination of PdCl(OH) would generate the double bond with *E* configuration. Alternatively, Ess, Aponick and co-workers reported a mechanistic analysis of such reaction supported by DFT calculations.[20] In their study, the lowest energy path would correspond to an *anti* coordination of the Pd species to the double bond with respect to the allylic alcohol, followed by an *anti* oxypalladation process and final *anti* elimination of water, promoted by an internal hydrogen bond between the allylic alcohol and the nucleophilic hydroxyl group (Scheme 8, path B). Both mechanisms account for the observed stereospecificity of the major products obtained in Scheme 8.

Secondary pathways may be involved in the formation of the observed minor products (Scheme 7), bearing the opposite configuration at C-6′ compared to the major products.

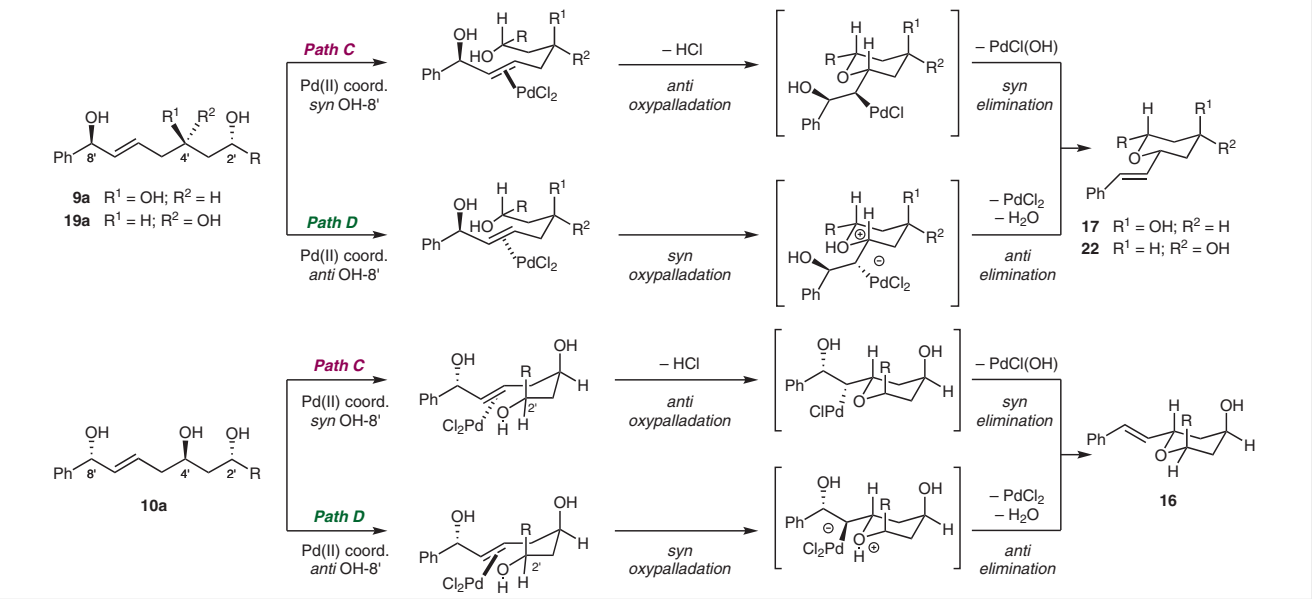
In compounds **9a** and **19a**, if a *syn* coordination is involved, the system can pass through an *anti* oxypalladation process (*Re* face attack) generating HCl, and final *syn* elimination of PdCl(OH) to give access to either **17** or **22**, respectively (Scheme 9, path C). No coordination of the nucleophilic hydroxyl group with the palladium species would take place, a situation disfavored considering the inherent electrophilicity of Pd(II). On the other hand, if the *anti* coordination is to proceed, the system could also experience a *syn* oxypalladation followed by *anti*-elimination of water, giving access to **17** and **22**, respectively (Scheme 9, path D). In this alternative, the allylic alcohol and the nucleophilic hydroxyl group are on opposite sides, interrupting the internal hydrogen bonding between them and disfavoring the elimination step to generate the double bond. No further analysis could be made for the results obtained with compound **20a**, where no formation of side products were detected. As the only difference between **20** and **10** is the stereochemistry at C-4′, possessing all three hydroxyls at the same side, we can only speculate a further interaction of OH-4′ with the Pd-intermediate that would favor cyclization to **22**.

Total Synthesis of the Putative Structure of Cryptoconcatone H and Stereochemical Analyses of Cryptoconcatones K and L

The results from the previous study on the Pd(II)- and Pd(0)-catalyzed cyclization of ζ-hydroxy allylic alcohols and acetates led us to contribute to the structure validation of other representatives of the cryptoconcatone family beyond our previous study of stereochemical revision for cryptoconcatone H (Figure 1).[10] Guided by quantum calculations of NMR shifts, the large discrepancies found between the calculated NMR shifts of **4** (the originally proposed structure of cryptoconcatone H) and the experimen-



Scheme 8 Mechanistic reasoning for the Pd(II)-catalyzed cyclization of the observed major products from the allylic alcohols derived from **9**, **10**, **19** and **20** (R = CH_2CH_2OPMB)

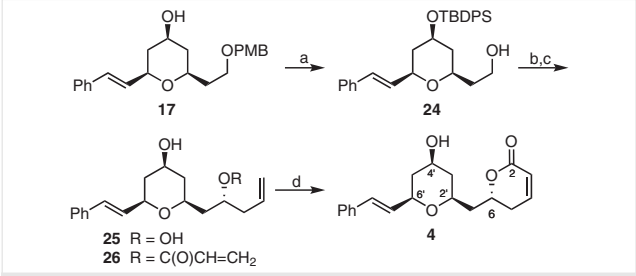


Scheme 9 Mechanistic reasoning for the Pd(II)-catalyzed cyclization of the observed minor products from the allylic alcohols derived from **9**, **10** and **19** (R = CH_2CH_2OPMB)

tal values reported for the natural product, allowed us to settle structure **1** (featuring a 2,4-*cis*/2,6-*trans* substituted THP ring) as the correct isomer for cryptoconcatone H without the requirement for synthesizing first the putative structure **4**.

In 2016, two new related styryl lactones were isolated from *C. concinna*, namely cryptoconcatones L and K.[11b] Based on ROESY correlations, the authors settled the all-*cis* relative configuration at the THP ring of both natural products. In addition, due to the paucity of sample of the natural products, the absolute configuration in the THP ring was arbitrarily assigned as originally described for cryptoconcatone H based on comparison of their NMR spectra. As the structure of natural cryptoconcatone H was shown to be in error, and considering similar biosynthetic pathway for these natural products, we found necessary to validate the relative stereochemistry proposed for THPs **2** and **3** by comparing their reported NMR data with those of **1** and **4**. For this, we took advantage of the stereoselective outcome of the cyclization of ζ-hydroxy allylic alcohol **10** under Tsuji–Trost conditions, which provided the all-*cis* THP **17** to continue up to the synthesis of **4**, having the same proposed relative configuration in the THP moiety as those reported for cryptoconcatones K and L.

Starting from THP **17**, TBDPS protection followed by PMB cleavage provided alcohol **24** (Scheme 10). Subsequent allylation using the Krische protocol provided the corresponding homoallylic alcohol **25** in good yield as an 85:15 diastereoisomeric mixture. Esterification of the newly formed secondary alcohol with acryloyl chloride, followed by RCM of acrylate **26** with Grubbs I catalyst, and deprotection of the silyl group, finally delivered THP **4**.



Scheme 10 *Reagents and conditions*: (a) i. TBDPSCl, imidazole, CH_2Cl_2, r.t., 1 h; ii. CAN, acetone:H_2O, 0 °C, 1 h, 26% (two steps); (b) $[Ir(cod)Cl]_2$ (2.5 mol%), (*R*)-BINAP (5 mol%), Cs_2CO_3, 3-Cl-4-NO_2-BzOH, AcOAllyl, THF, 120 °C, 40 h, 62% (85% brsm; *dr* 85:15); (c) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 2 h, 55%; (d) i. Grubbs I catalyst (10 mol%), CH_2Cl_2, 40 °C, 14 h; ii. TBAF, AcOH, EtOAc, r.t., 20 h, 61% (two steps).

To address the question of whether two different structures may have indistinguishable NMR spectra,[21a,b] and in perfect agreement with our previous computational predictions, comparison of the NMR data of **4** with those of natural cryptoconcatone H clearly showed a low correlation, revealing large differences in the chemical shifts for most of the hydrogens and carbons (differences of 0.78, 0.40, and 0.39 ppm were observed in the ^1H NMR spectrum for H-6′, H-2′, and H-5b′, respectively, and 6.0, 3.6, and 3.5 ppm in the ^{13}C NMR spectrum for C-1′, C-5′, and C-3′, among others), as depicted in Figure 2. Additionally, the specific optical rotation for synthetic **4** {$[\alpha]_D^{20}$ +22 (*c* 0.1, MeOH)} differed greatly from that described for natural cryptoconcatone H {$[\alpha]_D^{25}$ –24 (*c* 0.1, MeOH)}.[21c]

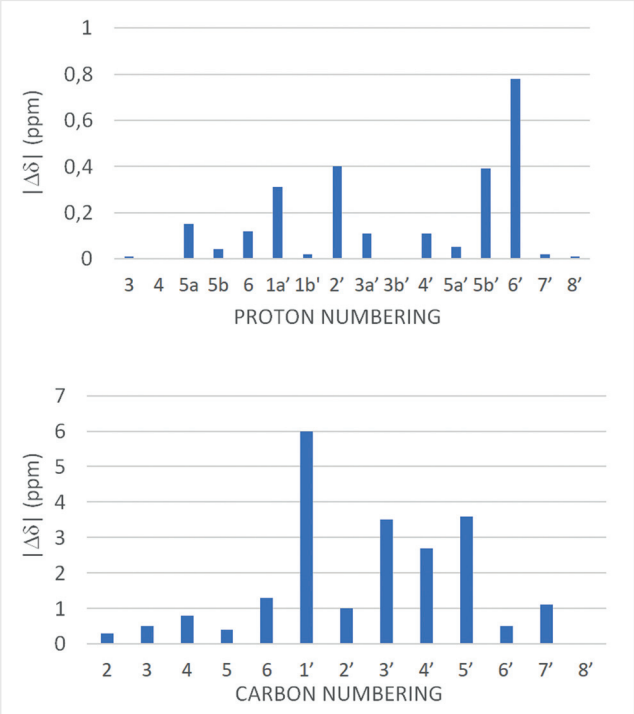


Figure 2 Comparison of selected ^{1}H and ^{13}C NMR data of THP **4** and natural cryptoconcatone H

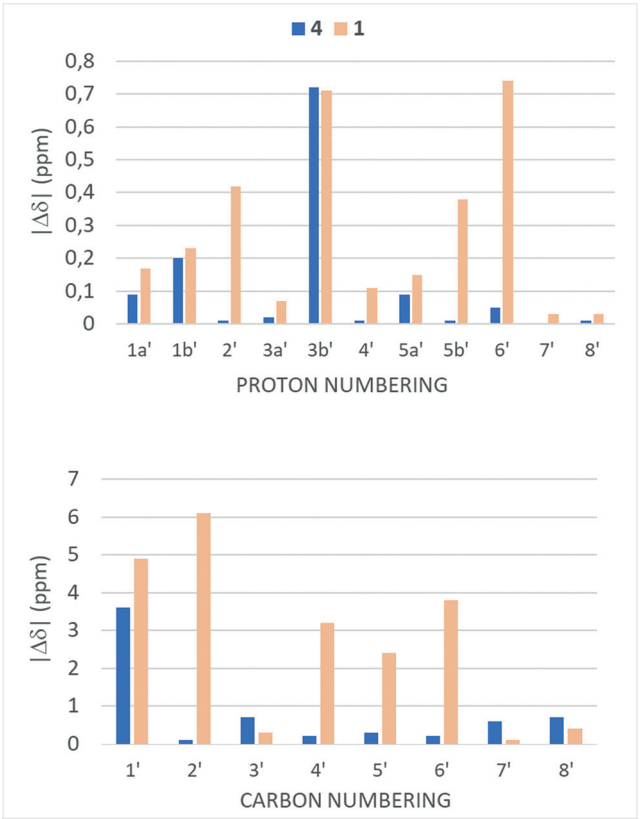


Figure 3 Comparison of selected ^{1}H and ^{13}C NMR data of natural cryptoconcatone K vs. THP **1** and **4**

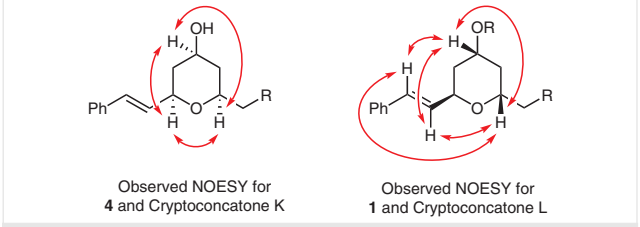


Figure 4 NOESY correlations observed for natural cryptoconcatone K and L, synthetic **4** and **1**

From the NMR data of the reassigned structure of cryptoconcatone H (**1**) and **4**, we turned our attention to the NMR data reported for natural cryptoconcatones K and L, keeping in mind that their structures were proposed based on comparison with the misassigned structure originally proposed for cryptoconcatone H.

Focusing on cryptoconcatone K, comparison of its ^{1}H and ^{13}C NMR data with those for **1** and **4** (Figure 3) revealed small Δδ for natural cryptoconcatone K and synthetic **4**, especially for the carbinolic protons of the THP ring, which supports the proposition that cryptoconcatone K and **4** bear the same relative configuration in the THP ring. Furthermore, the reported ROESY correlations of cryptoconcatone K matched well with an all-*cis* configuration in the THP ring, as observed for **4** (Figure 4), thus supporting the relative stereochemistry found in the THP ring in structure **2** proposed by Kong, Luo and co-workers.

Focusing on cryptoconcatone L, although the presence of the acetyl group in C-4′ influences its spectroscopic properties, comparison of the ^{1}H and ^{13}C NMR chemical shifts of the natural product with those observed for **1** and **4** reveals that the differences are smaller for THP **1**, particularly for H-2′/C-2′ and H-6′/C-6′, suggesting the same stereochemical pattern in the THP moiety for crytoconcatone L and structure **1** (Figure 5).

During the stereochemical description of cryptoconcatone L by the isolation team, ROESY correlations between H-2′/H-4′ and H-4′/H-6′ were described to support the stereochemical assignment of the THP fragment. However, after detailed analysis of the ROESY spectra provided in the Supporting Information of the original reference, clear cross-peaks between the vinylic protons H-7′ and H-8′ with the signals assigned to H-2′ and H-4′ were noted, as found in the NOESY spectra of **1** (Figure 4). Such correlations present strong evidence suggesting that the proposed structure for cryptoconcatone L might be in error.

Considering that the NMR data comparison was carried out from similar, but not stereoisomeric compounds, we undertook computational calculations on the NMR spectra for the assigned structures of cryptoconcatone K and L to

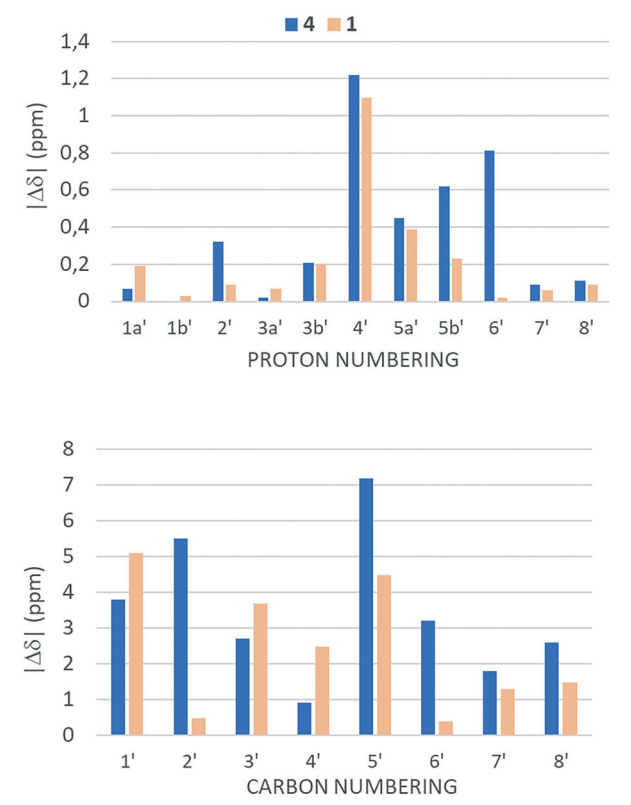


Figure 5 Comparison of selected ^{1}H and ^{13}C NMR data of natural cryptoconcatone L vs. THP **1** and **4**

provide further support for our analysis. For this, quantum chemical calculations of NMR shifts were considered to be a powerful and affordable strategy to facilitate structural elucidation.[22] Among the different strategies available to settle structural issues of organic molecules from a computational point of view,[22b] we decided to use the DP4+ probability, an updated and improved version of the DP4 method,[23] that includes the use of scaled and unscaled chemical shifts computed at higher levels of theory.[24]

To establish the most likely relative configuration at the THP rings in cryptoconcatones K and L, and to provide further confidence to our assignment, we initially carried out a fragment-based approach. Hence, the complete structures of the natural products were simplified to THP fragments displaying similar substitution pattern (compounds **27**–**30** and **31**–**34** for cryptoconcatones K and L, respectively; Figure 6). In addition, given that the experimental NMR data of structures **27**–**30** were available,[7] this approach offered a prime opportunity to test the DP4+ performance for setting the relative configuration of 2,4,6-trisubstituted THP systems.

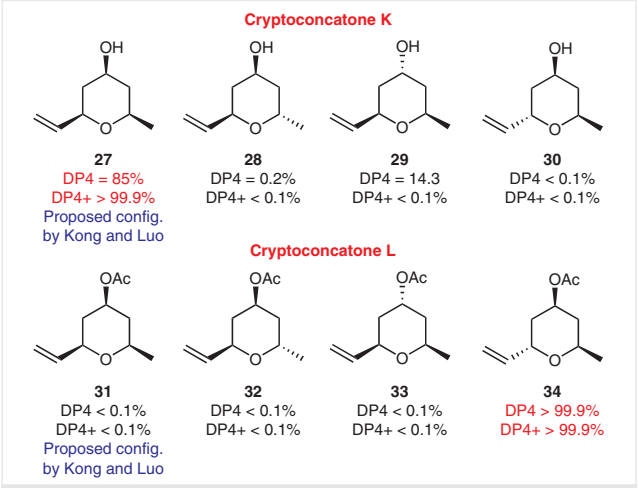


Figure 6 Plausible THP cores for cryptoconcatone K and L and their DP4 and DP4+ probabilities

By following the recommended methodology, and after exhaustive exploration of the conformational space at the MMFF level, the NMR shifts of the simplified systems bearing the THP core of cryptoconcatones K and L were computed at the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level of theory using chloroform as solvent, followed by Boltzmann averaging.[24a] With the theoretical NMR shifts in hand, we next correlated them with the experimental ^{1}H and ^{13}C chemical shifts values reported for the C2′–C6′ region of the natural products. As shown in Figure 6, both DP4 and DP4+ suggested that the originally proposed THP ring **27** of cryptoconcatone K was correct, whereas the original THP ring **31** proposed for cryptoconcatone L was unlikely. Instead, the *cis*/*trans* arrangement present in **34** was the most likely structure, resembling the THP structure found in **1**. Interestingly, when correlating the NMR data calculated for **27**–**30** with the chemical shifts experimentally observed for these compounds, DP4+ correctly identified the corresponding isomer in high confidence (>99.9%), providing support for our previous assignment (see Supporting Information).

Finally, we carried out NMR calculations followed by DP4+ analysis on the full molecular systems of cryptoconcatones K and L. In both cases, the configuration at C-6 was proposed as *R* based on a negative Cotton effect at 250 nm, whereas the configuration at C-5 was also set as *R* based on a small coupling constant observed between H-5 and H-6 (2.4 Hz for cryptoconcatone K and 2.6 Hz for cryptoconcatone L), clearly indicating a *syn* arrangement in these systems.[11b,25] Hence, the corresponding set of eight possible diastereoisomers of cryptoconcatones K and L were built by fixing the configurations at C-5 and C-6 as *R*,*R*. After exhaustive conformational searches at the MMFF level, the geometries were optimized first at the HF/3-21G level, followed by final optimizations at the B3LYP/6-31G* level and NMR calculations at the PCM/mPW1PW91/6-31+G** level.

When using the experimental NMR data of cryptoconcatone K, structures **2** and **35** are the most probable candidates, in line with the calculations on the simplified model system (Figure 7). Although the DP4+ values slightly favored **35** (with all the configurations inverted at the THP ring as originally proposed), it is important to point out that the theoretical NMR shifts of both candidates reflected high similarities. In fact, the corrected mean absolute error (CMAE) values computed for **2** (1.3 ppm and 0.12 ppm for carbon and proton data, respectively) were identical to those calculated for **35**.

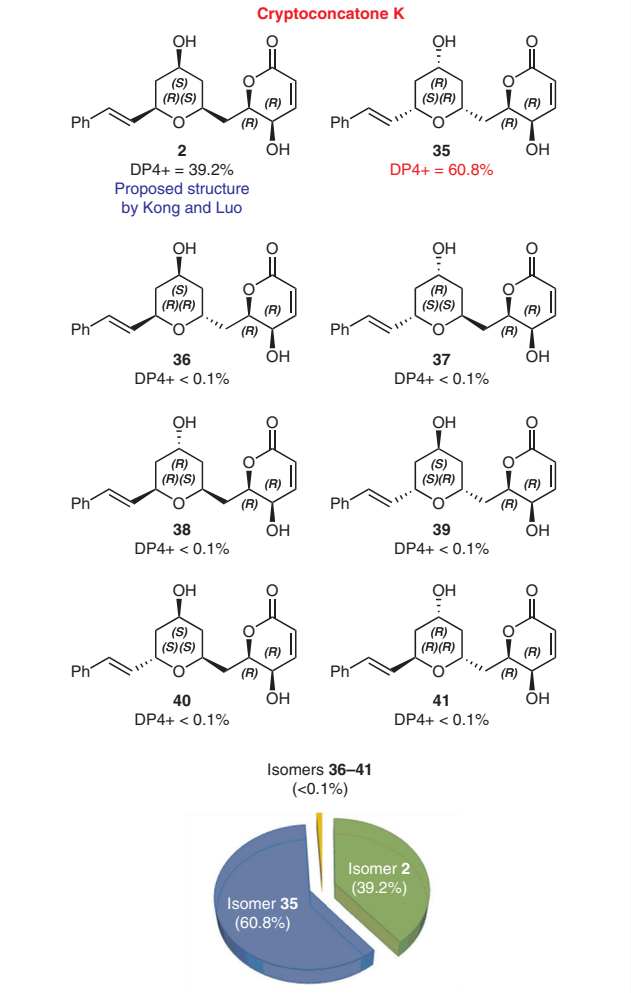


Figure 7 Plausible isomers for cryptoconcatone K and their DP4+ probabilities

On the other hand, when correlating the calculated NMR data of **3**, **42**–**48** with the experimental shifts of natural cryptoconcatone L, the originally proposed structure **3** was the least probable isomer among eight candidates (Figure 8). In its place, and in excellent agreement with our preliminary results obtained with the model system, structures **47** and **48** (featuring a *cis*/*trans* THP system) showed

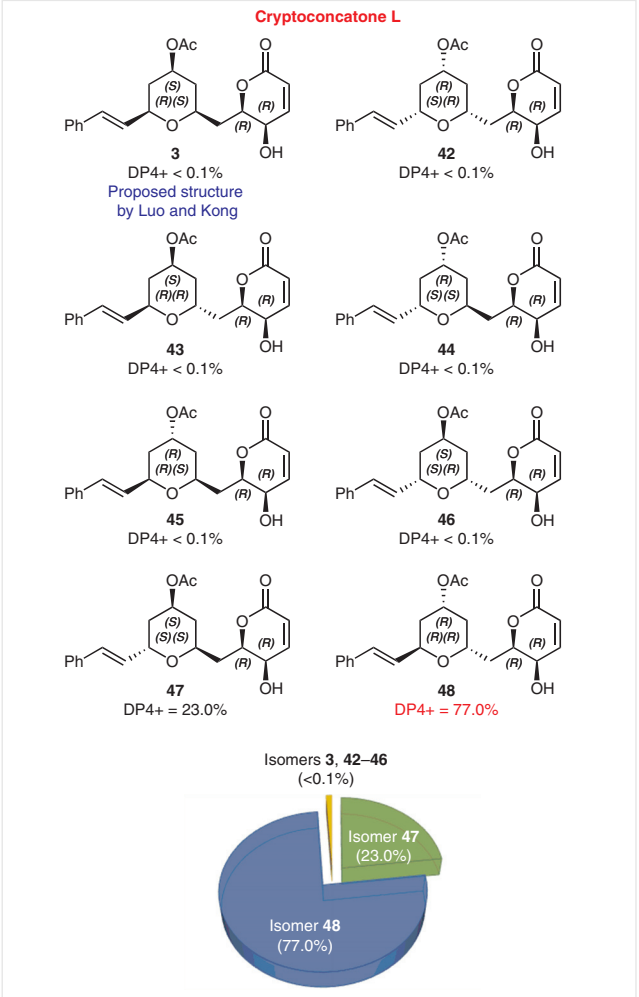


Figure 8 Plausible isomers for cryptoconcatone L and their DP4+ probabilities

the highest DP4+ values. In this case, isomer **48** (with C-2′ and C-4′ configurations inverted as originally reported) was pointed out as the most probable structure of cryptoconcatone L. Here again, minor differences were noted when comparing the calculated NMR shifts of **47** (CMAE = 1.9 ppm and 0.20 ppm for carbon and proton data, respectively) and **48** (CMAE = 1.8 ppm and 0.17 ppm for carbon and proton data, respectively).

Given that the absolute configuration at C-4′ was misassigned by the isolation team when proposing **4** as the structure of cryptoconcatone H, there is a high probability, based on biosynthetic considerations, that C-4′ in cryptoconcatone K and L displays the same stereochemistry at the THP ring as in **1**.

According to the present analysis, structures **35** and **48** can then be proposed for cryptoconcatones K and L, respectively (Figure 7 and Figure 8). Nevertheless, on the basis of a tight stereochemical relationship between the studied isomers, the spectroscopic similarity exhibited between the

first and second ranked candidates, and the known tendency of DP4 (or DP4+) to overestimate the probabilities rates,[10,23] isomers **2** and **47** should not be ruled out as possible structures of cryptoconcatone K and L, respectively.

Conclusion

A comprehensive study on the stereochemical outcome of palladium-catalyzed formation of styryl tetrahydropyrans through cyclization of the corresponding allylic acetates or alcohols using both Pd(0) and Pd(II) catalysts, respectively, was presented wherein coordination of the palladium species with free hydroxyl groups present in the molecule can direct the outcome of the reaction, providing evidence for the role of a stereoelectronic effect when employing Pd(0) or Pd(II) species for THP formation.

We applied these results to the total synthesis of the structure initially proposed for cryptoconcatone H by Kong, Luo and co-workers (structure **4**). Along with DP4+ computational studies, a structural elucidation analysis was performed for two other natural tetrahydropyrans, cryptoconcatones K and L, which had their stereochemistry established only by spectroscopic techniques. Our analyses led us to the conclusion that the relative configuration of the THP moiety shown for structures **2** and **35** is correct for cryptoconcatone K, and to suggest the most probable stereochemistry of the THP ring for cryptoconcatone L is displayed by structures **47** or **48**.

Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. CH_2Cl_2, triethylamine, and 2,6-lutidine were treated with calcium hydride and distilled before use. THF was treated with metallic sodium and distilled before use. Anhydrous reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Progress of the reactions was monitored by thin-layer chromatography (TLC) analysis (silica gel 60 F254 on aluminum plates) and visualized under UV light, *p*-anisaldehyde standard solution and/or $KMnO_4$ standard solution. Flash column chromatography was performed on silica gel (300–400 mesh) applying positive air pressure. Melting points were recorded with a Electrothermal 9100 apparatus. Optical rotations were recorded with a Perkin Elmer 341 polarimeter. FTIR spectra were recorded with a Thermo Nicolet iS5 spectrophotometer and are reported in cm^{-1}. ^1H and ^{13}C NMR and 2D experiments (^1H ^1H COSY, ^1H ^{13}C HSQC, ^1H ^{13}C HMBC, NOESY) were recorded on 250, 400 or 500 MHz equipment; chemical shifts (δ) are reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$ δ = 7.27, 77.0 ppm) unless otherwise specified. Mass spectra were recorded with a Q-Tof equipment operating in electrospray mode (ESI).

Compounds **6–9**, and **16** were synthesized and purified as described previously.[10]

(1*R*,5*R*,7*R*,*E*)-5,7-Dihydroxy-9-((4-methoxybenzyl)oxy)-1-phenylnon-2-en-1-yl Acetate (10)

A solution of diol **8** (66.8 mg, 0.238 mmol, 100 mol%), acetate (*R*)-**15** (62.5 mg, 0.356 mmol, 150 mol%) and Hoveyda–Grubbs 2nd generation catalyst (4.6 mg, 7.1 μmol, 3 mol%) in anhydrous CH_2Cl_2 (2.8 mL, 0.1 M) under nitrogen atmosphere was heated to reflux in an oil bath at 45 °C. After 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (gradient, 5 to 100% EtOAc/Hex) gave acetate (*R*)-**15** (25.0 mg 0.142 mmol; 40% recovered) as a colorless oil, followed by diol **10** (90 mg, 0.21 mmol; 89% yield) as a light-brown oil.

R_f 0.17 (50% EtOAc/Hex); $[\alpha]_D^{22}$ –10 (*c* 1.0, $CHCl_3$).

FTIR (ATR): 3449, 2938, 1733, 1612, 1513, 1371, 1244, 1087, 1031, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.40–7.20 (m, 7 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.28–6.18 (m, 1 H), 5.81–5.71 (m, 2 H), 4.45 (s, 2 H), 4.20–4.08 (m, 1 H), 3.98 (td, *J* = 5.7, 11.6 Hz, 1 H), 3.81 (s, 3 H), 3.76–3.55 (m, 3 H), 3.08–2.85 (m, 1 H), 2.31–2.21 (m, 2 H), 2.10 (s, 3 H), 1.97–1.77 (m, 2 H), 1.63–1.56 (m, 2 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 170.0, 159.3, 139.4, 131.2, 130.2, 129.8, 129.3, 128.5, 128.0, 126.9, 113.8, 76.1, 73.0, 69.4, 69.0, 68.1, 55.2, 42.1, 40.4, 36.2, 21.3.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{32}O_6Na$: 451.2097; found: 451.2116.

(2*S*,3*R*)-2-(Bromomethyl)-3-phenyloxirane (13)

To a solution of epoxy alcohol **12** (796 mg, 5.30 mmol, 100 mol%) and CBr_4 (1.82 g, 5.43 mmol, 102 mol%) in CH_2Cl_2 (10.6 mL, 0.5 M) at 0 °C under nitrogen atmosphere was added a solution of PPh_3 (1.50 g, 5.43 mmol, 102 mol%) in CH_2Cl_2 (4.5 mL, 1.2 M). After 40 min, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2; 0 to 8% EtOAc/Hex). Bromide **13** (901 mg, 4.23 mmol, 80% yield) was obtained as a colorless oil.

R_f 0.63 (30% EtOAc/Hex); $[\alpha]_D^{21}$ +13 (*c* 1.0, $CHCl_3$); antipode: $[\alpha]_D^{21}$ –5 (*c* 1.0, $CHCl_3$); {Lit.[26] $[\alpha]_D^{25}$ +11.3 (*c* 1, $CHCl_3$)}.

FTIR (ATR): 3034, 1497, 1460, 1412, 1246, 1220, 1026, 904, 870, 768, 746, 695 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.40–7.24 (m, 5 H), 3.81 (d, *J* = 1.7 Hz, 1 H), 3.51 (s, 1 H), 3.49 (s, 1 H), 3.31 (dt, *J* = 1.9, 6.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 136.0, 128.6, 125.6, 60.9, 60.2, 31.9.

HRMS (ESI-TOF): *m*/*z* $[M]^+$ calcd for C_9H_9BrO: 212.9915; found: 212.9923.

(*S*)-1-Phenylprop-2-en-1-ol (14)

To a stirred solution of bromide **13** (1.81 g, 8.48 mmol, 100 mol%) in THF (34 mL, 0.25 M) under nitrogen atmosphere at –78 °C was added dropwise *n*-BuLi (6.36 mL, 8.90 mmol, 105 mol%, 1.6 M in THF). After stirring at –78 °C for 1 h, the reaction was quenched with water (17 mL) at –78 °C and the mixture was stirred at r.t. for 30 min. The aqueous layer was extracted (Et_2O), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduce pressure. The resultant residue was purified by flash column chromatography (gradient, 5 to 30% EtOAc/Hex) to give alcohol (*S*)-**14** (1.13 g, 8.40 mmol, 99% yield) as a colorless oil. The spectroscopic properties of this compound were consistent with the data available in the literature.[27a,b]

R_f 0.34 (30% EtOAc/Hex); $[\alpha]_D^{21}$ –3 (*c* 1.0, $CHCl_3$, 90% ee) {Lit. (antipode)[27c] $[\alpha]_D^{20}$ +1.3 (*c* 1.0, $CHCl_3$, > 99% ee)}.

FTIR (ATR): 3358, 3028, 2980, 2867, 1494, 1453, 1409, 1195, 1114, 1024, 989, 927, 761, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.44–7.28 (m, 5 H), 6.07 (ddd, *J* = 6.0, 10.1, 17.1 Hz, 1 H), 5.37 (td, *J* = 1.3, 17.1 Hz, 1 H), 5.27–5.17 (m, 2 H), 1.93 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 142.6, 140.2, 128.4, 127.6, 126.3, 115.0, 75.2.

(*S*)-1-Phenylallyl Acetate (15)

Alcohol (*S*)-**14** (410.7 mg, 3.06 mmol, 100 mol%), DMAP (3.7 mg, 0.03 mmol, 1 mol%) and TEA (1.72 mL, 12.2 mmol, 400 mol%) were dissolved in CH_2Cl_2 (15 mL, 0.2 M) at 0 °C under a nitrogen atmosphere. Acetic anhydride (0.6 mL, 6.1 mmol, 200 mol%) was added dropwise and the mixture was stirred at r.t. for 1 h. The reaction was then quenched with sat. aq $NaHCO_3$, the aqueous layer was extracted (Et_2O), and the combined organic layers dried over $MgSO_4$ and concentrated under vacuo. Purification of the resultant residue by flash column chromatography (gradient, 3 to 12% EtOAc/Hex) gave acetate (*S*)-**15** (510 mg, 2.89 mmol; 96% yield) as a colorless oil. The spectroscopic properties of this compound were consistent with the data available in literature.[28a,b]

R_f 0.68 (30% EtOAc/Hex); $[\alpha]_D^{21}$ +59 (*c* 1.0, $CHCl_3$), antipode: $[\alpha]_D^{21}$ –40 (*c* 1.0, $CHCl_3$); {Lit.[28a] $[\alpha]_D^{25}$ +30.42 (*c* 0.48, $CHCl_3$, 96% ee)}.

FTIR (ATR): 3034, 1740, 1371, 1231, 1020, 936, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.40–7.29 (m, 5 H), 6.28 (br d, *J* = 5.8 Hz, 1 H), 6.02 (ddd, *J* = 5.8, 10.4, 16.4 Hz, 1 H), 5.31 (td, *J* = 1.2, 14.5 Hz, 1 H), 5.25 (td, *J* = 1.2, 7.8 Hz, 1 H), 2.13 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 169.9, 138.9, 136.3, 128.6, 128.1, 127.1, 116.9, 76.2, 21.2.

(2*R*,4*S*,6*R*)-2-(2-((4-Methoxybenzyl)oxy)ethyl)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (17)

To a stirring solution of $Pd(PPh_3)_4$ (65.5 mg, 37.5 μmol, 5 mol%) in THF (3.2 mL, 12 mM) was added dropwise a solution of diol **10** (321.0 mg, 0.749 mmol, 100 mol%) in THF (12.8 mL, 0.06 M) under a nitrogen atmosphere at r.t. After 90 min, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (gradient, 30 to 100% EtOAc/Hex). Alcohol **17** (275 mg, 0.694 mmol; 93% yield) was obtained as a yellow oil.

R_f 0.26 (50% EtOAc/Hex); $[\alpha]_D^{22}$ +47 (*c* 1.0, $CHCl_3$).

FTIR (ATR): 3449, 2938, 1733, 1612, 1513, 1371, 1244, 1087, 1031, 968, 821, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.43–7.19 (m, 7 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 6.21 (dd, *J* = 5.7, 16.0 Hz, 1 H), 4.46 (d, *J* = 1.4 Hz, 2 H), 4.00 (br tdd, *J* = 1.5, 5.8, 11.1 Hz, 1 H), 3.94–3.82 (m, 1 H), 3.77 (s, 3 H), 3.69–3.54 (m, 3 H), 2.10 (br tdd, *J* = 2.1, 4.3, 12.2 Hz, 1 H), 2.00 (br tdd, *J* = 1.6, 4.2, 11.6 Hz, 1 H), 1.94–1.79 (m, 2 H), 1.37 (td, *J* = 11.4, 11.9 Hz, 1 H), 1.24 (td, *J* = 11.6, 12.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 159.1, 136.7, 130.5, 130.1, 129.6, 129.1, 128.4, 127.5, 126.4, 113.7, 75.7, 72.6, 72.5, 68.0, 66.1, 55.1, 41.1, 41.0, 36.1.

HRMS (ESI-TOF): *m*/*z* [M – OH]$^+$ calcd for $C_{23}H_{27}O_3$: 351.1960; found: 351.1971.

Tsuji–Trost Reaction with Compound 9

To a stirring solution of $Pd(PPh_3)_4$ (28.5 mg, 19.6 μmol, 6 mol%) in THF (2 mL, 10 mM) was added dropwise a solution of diol **9** (168 mg, 0.392 mmol, 100 mol%) in THF (5.8 mL, 0.07 M) under nitrogen atmosphere at r.t. After 2 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (gradient, 30 to 100% EtOAc/Hex) to give **16**, **17**, and **18** (127.1 mg) as an inseparable mixture in a 36:22:30 molar ratio (^{1}H NMR), respectively. Semipreparative HPLC separation on C_{18} SiO_2 column [dimensions: 19 mm × 100 mm; particle size: 5 μm; elution: started in 25:75 ACN/H_2O, finished at 85:15 ACN/H_2O in 18 min period, then steady at 85:15 ACN/H_2O for 1 min; flow: 15.5 mL/min; detector: 254 nm; t_R = 11.10 (**16**), 11.51 (**18**), 11.83 (**17**)] furnished isomers **16**,[10] **17** and **18** pure enough for characterization.

Compound 18

White solid; R_f 0.28 (50% EtOAc/Hex); m.p. 77.3–81.5 °C; $[\alpha]_D^{23}$ –7 (*c* 0.5, $CHCl_3$).

FTIR (ATR): 3396, 2937, 2866, 1612, 1513, 1488, 1302, 1248, 1174, 1806, 1033, 991, 820, 749, 692 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.42–7.39 (m, 2 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.26–7.21 (m, 3 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.79 (dd, *J* = 10.6, 15.6 Hz, 1 H), 6.56 (d, *J* = 15.6 Hz, 1 H), 6.46 (br dd, *J* = 10.6, 15.2 Hz, 1 H), 5.89 (dd, *J* = 5.9, 15.2 Hz, 1 H), 4.57 (br s, 1 H), 4.46 (s, 2 H), 4.19 (br t, *J* = 8.8 Hz, 1 H), 3.80 (s, 3 H), 3.74–3.70 (m, 1 H), 3.66 (dt, *J* = 3.9, 9.2 Hz, 1 H), 3.59 (br s, 1 H), 3.19 (br s, 1 H), 1.91 (dtd, *J* = 4.4, 9.0, 14.6 Hz, 1 H), 1.81 (ddd, *J* = 3.5, 8.7, 14.6 Hz, 1 H), 1.72 (br td, *J* = 3.2, 4.6 Hz, 1 H), 1.69 (br td, *J* = 3.1, 4.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.3, 137.3, 136.5, 132.3, 130.0, 129.8, 129.4, 128.6, 128.4, 127.5, 126.3, 113.9, 73.1, 70.0, 69.6, 69.0, 55.3, 42.6, 36.3.

HRMS (ESI-TOF) *m*/*z* [M – OH]$^+$ calcd for $C_{23}H_{27}O_3$: 351.1960; found: 351.1964.

(3*S*,5*R*,7*R*,*E*)-5,7-Dihydroxy-9-((4-methoxybenzyl)oxy)-1-phenylnon-1-en-3-yl Acetate (21)

Compound **21** (31.5 mg, 73.5 μmol, 48% yield) was obtained as a colorless oil from alcohol **19** (65.1 mg, 0.152 mmol) in a similar procedure to that described for THP **17**.

R_f 0.26 (50% EtOAc/Hex); $[\alpha]_D^{20}$ –49 (*c* 2.0, $CHCl_3$).

FTIR (ATR): 3434, 2939, 2918, 2865, 1734, 1613, 1514, 1449, 1372, 1302, 1246, 1174, 1091, 1032, 967, 821, 751, 694 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.37 (m, 2 H), 7.36–7.31 (m, 2 H), 7.30–7.24 (m, 3 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.20 (dd, *J* = 7.0, 16.0 Hz, 1 H), 5.68 (dt, *J* = 6.3, 7.0 Hz, 1 H), 4.48–4.46 (m, 2 H), 4.12–4.04 (m, 1 H), 4.01–3.87 (m, 3 H), 3.82 (s, 3 H), 3.70 (td, *J* = 5.3, 9.3 Hz, 1 H), 3.64 (ddd, *J* = 4.8, 7.6, 9.3 Hz, 1 H), 2.14 (s, 3 H), 1.84–1.81 (m, 2 H), 1.80–1.69 (m, *J* = 0.9 Hz, 2 H), 1.68–1.61 (m, 1 H), 1.60–1.53 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 171.2, 159.2, 136.2, 132.1, 130.0, 129.3, 128.5, 127.9, 127.4, 126.5, 113.8, 72.9, 71.7, 71.5, 68.1, 68.1, 55.2, 43.1, 43.0, 37.0, 21.2.

HRMS (ESI-TOF) *m*/*z*: [M – $C_2H_3O_2$]$^+$ calcd for $C_{23}H_{29}O_4$: 369.2066; found: 369.2070; [M + K]$^+$ calcd for $C_{25}H_{32}O_6K$: 467.1836; found: 467.1859.

Tsuji–Trost Reaction with Compound 20

To a stirring solution of $Pd(PPh_3)_4$ (13.2 mg, 11.4 μmol, 6 mol%) in THF (0.9 mL, 13 mM) was added dropwise a solution of diol **20** (168 mg, 0.392 mmol, 100 mol%) in THF (5.8 mL, 0.07 M) under nitrogen atmosphere at r.t. After 70 min, the reaction mixture was concentrated under reduced pressure to give a yellow oil (complex ^{1}H NMR). Purification by flash column chromatography (gradient, 30 to 70% EtOAc/Hex) gave compound **22** (41% yield, molar ratio by ^{1}H NMR) and **21** (13% yield, molar ratio by ^{1}H NMR).

Compound 22

Yellow oil; R_f 0.36 (50% EtOAc/Hex); $[\alpha]_D^{20}$ +55 (*c* 2.0, $CHCl_3$).

FTIR (ATR): 3348, 2916, 2865, 1612, 1513, 1450, 1363, 1302, 1247, 1174, 1092, 1035, 967, 820, 747, 694 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.38 (m, 2 H), 7.35–7.27 (m, 4 H), 7.27–7.21 (m, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.21 (dd, *J* = 5.9, 16.0 Hz, 1 H), 4.53–4.43 (m, 3 H), 4.30 (br s, 1 H), 4.11–4.03 (m, 1 H), 3.78 (s, 3 H), 3.70–3.57 (m, 2 H), 1.92–1.78 (m, 3 H), 1.74–1.65 (m, 2 H), 1.63–1.53 (m, 1 H).

^{1}H NMR (C_6D_6, 500 MHz): δ = 7.25 (dd, *J* = 8.0, 13.4 Hz, 4 H), 7.10 (t, *J* = 7.5 Hz, 2 H), 7.05–7.00 (m, 1 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.23 (dd, *J* = 5.5, 16.0 Hz, 1 H), 4.56 (br dd, *J* = 5.5, 11.5 Hz, 1 H), 4.36 (dd, *J* = 11.8, 18.7 Hz, 2 H), 4.24–4.17 (m, 1 H), 3.85 (t, *J* = 2.7 Hz, 1 H), 3.70 (ddd, *J* = 6.0, 8.0, 9.0 Hz, 1 H), 3.59 (td, *J* = 5.9, 9.2 Hz, 1 H), 3.28 (s, 3 H), 1.93 (tdd, *J* = 5.7, 8.4, 14.0 Hz, 1 H), 1.80 (dddd, *J* = 4.2, 6.6, 7.7, 14.0 Hz, 1 H), 1.56 (br qd, *J* = 2.3, 13.6 Hz, 1 H), 1.47–1.40 (m, 2 H), 1.31 (ddd, *J* = 2.7, 11.5, 13.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.0, 136.9, 130.6, 130.4, 129.9, 129.2, 128.4, 127.4, 126.4, 113.7, 72.5, 72.0, 68.7, 66.4, 64.5, 55.2, 38.6, 38.5, 36.3.

HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{28}O_4Na$: 391.1885; found: 391.1884.

Methanolysis of 9 and Reaction with $PdCl_2(MeCN)_2$

To a solution of acetate **9** (351 mg, 0.820 mmol, 100 mol%) in MeOH (3.3 mL, 0.25 M) was added K_2CO_3 (567 mg, 4.10 mmol, 500 mol%) in parts at 0 °C. After stirring at r.t. for 12 h, the mixture was diluted with EtOAc (12 mL) and water (12 mL), then the reaction was quenched with $NaHCO_3$ (s). The aqueous phase was extracted (EtOAc), and the combined organic layers were treated with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The remaining colorless oil was used in the next step without further purification.

To a stirring solution of the previous crude oil in THF (1.4 mL) under nitrogen atmosphere at 0 °C was added $PdCl_2(MeCN)_2$ (21.5 mg, 82.9 μmol) in one portion. After 30 min, the reaction mixture was directly concentrated under reduce pressure to give a yellow oil. Purification by flash column chromatography (gradient, 30 to 80% EtOAc/Hex) gave **16** (210 mg, 0.57 mmol, 70% yield) as a light-yellow oil and **17** (6% yield by ^{1}H NMR molar ratio) as a yellow oil.[15,19]

Methanolysis of 10 and Reaction with $PdCl_2(MeCN)_2$

To a solution of acetate **10** (30 mg, 0.070 mmol, 100 mol%) in MeOH (0.27 mL, 0.25 M) was added K_2CO_3 (48.4 mg, 0.350 mmol, 500 mol%) in portions at 0 °C. After stirring at r.t. for 12 h, the mixture was diluted with EtOAc (1 mL) and water (1 mL), and the reaction was quenched with $NaHCO_3$ (s). The aqueous phase was extracted (EtOAc), and the combined organic layers were treated with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The remaining colorless oil was used in the next step without further purification.

To a stirring solution of the previous crude oil in THF (1.4 mL) under nitrogen atmosphere at 0 °C was added $PdCl_2(MeCN)_2$ (1.8 mg, 6.9 μmol) in one portion. After 30 min, the reaction mixture was directly concentrated under reduce pressure to give a yellow oil. Purification by flash column chromatography (gradient, 30 to 60% EtOAc/Hex) gave **17** (15.1 mg, 41.0 μmol, 59% yield) as a light-yellow oil and **16** (6% yield by ^{1}H NMR molar ratio) as a yellow oil.[15,19]

Methanolysis of 19 and Reaction with $PdCl_2(MeCN)_2$

To a solution of acetate **19** (25.0 mg, 58.3 μmol, 100 mol%) in MeOH (0.27 mL, 0.22 M) was added K_2CO_3 (48 mg, 0.35 mmol, 600 mol%) in portions at 0 °C. After stirring at r.t. for 12 h, the mixture was diluted with EtOAc (1 mL) and water (1 mL), and then the reaction was quenched with $NaHCO_3$ (s). The aqueous phase was extracted (EtOAc), and the combined organic layers were treated with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The remaining colorless oil was used in the next step without further purification.

To a stirring solution of the previous crude oil in THF (1.4 mL) under nitrogen atmosphere at 0 °C was added $PdCl_2(MeCN)_2$ (1.8 mg, 6.9 μmol) in one portion. After 40 min, the reaction mixture was directly concentrated under reduce pressure to give a yellow oil. Purification by flash column chromatography (gradient, 30 to 60% EtOAc/Hex) gave **23** (10 mg, 27.1 μmol, 46% yield) as a light-yellow oil and **22** (3% yield by ^{1}H NMR molar ratio) as a light-yellow oil.[15,19]

Compound 23

R_f 0.2 (50% EtOAc/Hex); $[\alpha]_D^{20}$ +18 (*c* 1.0, $CHCl_3$).

FTIR (ATR): 3394, 2919, 2849, 1612, 1513, 1450, 1367, 1302, 1247, 1174, 1091, 1033, 968, 821, 748, 694 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41–7.36 (m, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 7.25–7.21 (m, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 6.58 (d, *J* = 16.1 Hz, 1 H), 6.31 (dd, *J* = 5.9, 16.0 Hz, 1 H), 4.46 (s, 2 H), 4.36–4.29 (m, 2 H), 4.11 (tt, *J* = 4.3, 9.1 Hz, 1 H), 3.78 (s, 3 H), 3.61–3.54 (m, 2 H), 2.13–2.01 (m, 2 H), 1.85 (br td, *J* = 3.8, 13.0 Hz, 1 H), 1.77 (ddd, *J* = 5.0, 7.3, 14.4 Hz, 1 H), 1.70 (ddd, *J* = 5.3, 9.5, 13.0 Hz, 1 H), 1.52 (td, *J* = 9.2, 12.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 159.1, 136.8, 130.5, 130.4, 130.1, 129.3, 128.5, 127.6, 126.5, 113.8, 72.8, 69.8, 68.6, 66.8, 64.6, 55.2, 40.3, 38.2, 32.6.

HRMS (ESI-TOF) *m*/*z* [M–OH]$^+$ calcd for $C_{23}H_{27}O_3$: 351.1960; found: 351.1969.

Methanolysis of 20 and Reaction with $PdCl_2(MeCN)_2$

To a solution of acetate **20** (30 mg, 0.070 mmol, 100 mol%) in MeOH (0.27 mL, 0.25 M) was added K_2CO_3 (48.4 mg, 0.350 mmol, 500 mol%) in portions at 0 °C. After stirring at r.t. for 12 h, the mixture was diluted with EtOAc (1 mL) and water (1 mL), and the reaction was quenched with $NaHCO_3$ (s). The aqueous phase was separated and extracted (EtOAc), and the combined organic layers were treated with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The remaining colorless oil was used in the next step without further purification.

To a stirring solution of the previous crude oil in THF (1.4 mL) under nitrogen atmosphere at 0 °C was added $PdCl_2(MeCN)_2$ (1.8 mg, 6.9 μmol) in one portion. After 30 min, the reaction mixture was directly concentrated under reduce pressure to give a yellow oil. Purification by flash column chromatography (gradient, 30 to 60% EtOAc/Hex) gave **22** (15.5 mg, 41.0 μmol, 60% yield) as a light-yellow oil.

2-((2*R*,4*S*,6*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)ethan-1-ol (24)

To a solution of alcohol **17** (178 mg, 0.483 mmol, 100 mol%) and imidazole (66.4 mg, 0.966 mmol, 200 mol%) in CH_2Cl_2 (1 mL, 0.5 M) at 0 °C under nitrogen atmosphere was added TBDPSCl (0.19 mL, 0.72 mmol, 150 mol%) dropwise. After stirring at r.t. for 1 h, the reaction mixture was poured into sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was then dissolved in a 9:1 mixture of acetone/water (4.8 mL), and CAN (802 mg, 1.45 mmol, 300 mol%) was added in three equal portions every 20 min at 0 °C, with the third addition at r.t. After completion, the mixture was diluted with EtOAc (13 mL) and water (13 mL) and treated with sat. aq $NaHCO_3$ (13 mL). The aqueous phase was extracted (EtOAc), and the combined organic layer was washed with brine,

dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (gradient, 10 to 40% EtOAc/Hex) gave alcohol **24** (60.6 mg, 0.125 mmol; 26% yield for two steps) as a yellow gum.

R_f 0.44 (30% EtOAc/Hex); $[\alpha]_D^{21}$ –32 (*c* 2.0, $CHCl_3$).

FTIR (ATR): 3464, 2932, 2858, 1646, 1428, 1112, 1075, 823, 743, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.67 (m, 4 H), 7.44–7.39 (m, 5 H), 7.38–7.33 (m, 3 H), 7.32–7.28 (m, 2 H), 7.24 (d, *J* = 7.0 Hz, 1 H), 6.48 (d, *J* = 16.1 Hz, 1 H), 6.13 (dd, *J* = 6.0, 16.0 Hz, 1 H), 3.89–3.81 (m, 2 H), 3.79–3.71 (m, 2 H), 3.48 (dddd, *J* = 2.0, 2.8, 8.8, 11.1 Hz, 1 H), 2.56 (br s, 1 H), 1.91 (tdd, *J* = 2.3, 4.7, 12.6 Hz, 1 H), 1.86–1.78 (m, 1 H), 1.78–1.72 (m, 1 H), 1.67 (tdd, *J* = 3.8, 6.0, 14.7 Hz, 1 H), 1.55–1.46 (m, 2 H), 1.07 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 136.6, 135.7, 134.20, 134.17, 130.3, 129.7, 129.4, 128.5, 127.6, 126.4, 76.1, 75.7, 69.1, 61.2, 41.3, 41.1, 37.8, 26.9, 19.1.

HRMS (ESI-TOF) *m*/*z* $[M - OH]^+$ calcd for $C_{31}H_{37}O_2Si$: 469.2563; found: 469.2572.

(*R*)-1-((2*R*,4*S*,6*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)pent-4-en-2-ol (25)

A solution of alcohol **24** (58.7 mg, 120 μmol, 100 mol%) in anhydrous THF (0.6 mL, 0.2 M) was added to a sealed tube charged with $[Ir(cod)Cl]_2$ (2.1 mg, 30 μmol, 2.5 mol%), (*R*)-BINAP (3.8 mg, 60 μmol, 5 mol%), Cs_2CO_3 (7.9 mg, 24 μmol, 20 mol%), 4-Cl-3-NO_2-BzOH (2.5 mg, 12 μmol, 10 mol%) and allyl acetate (131 μL, 1.21 mmol, 1000 mol%) under nitrogen atmosphere. The reaction mixture stirred in an oil bath at 120 °C for 40 h and then concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (gradient, 4 to 20% EtOAc/Hex) gave alcohol **25** (39.2 mg, 74.4 μmol; 62% yield, dr 85:15 according quantitative ^{13}C NMR) as a yellow gum and alcohol **24** (15.6 mg, 32.1 mmol; 27% recovered) as a yellow gum.

R_f 0.63 (30% EtOAc/Hex); $[\alpha]_D^{23}$ –19 (*c* 1.0, $CHCl_3$).

FTIR (ATR): 2934, 2857, 1733, 1428, 1113, 1073, 965, 912, 822, 739, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.70 (d, *J* = 7.7 Hz, 4 H), 7.44–7.39 (m, 6 H), 7.36–7.31 (m, 3 H), 7.31–7.28 (m, 1 H), 7.24 (t, *J* = 7.1 Hz, 1 H), 6.48 (d, *J* = 15.9 Hz, 1 H), 6.13 (dd, *J* = 5.9, 16.0 Hz, 1 H), 5.84 (tdd, *J* = 7.1, 10.0, 17.1 Hz, 1 H), 5.13–5.06 (m, 2 H), 3.90–3.83 (m, 3 H), 3.73 (br s, 1 H), 3.50 (t, *J* = 10.5 Hz, 1 H), 2.26 (td, *J* = 6.8, 14.0 Hz, 1 H), 2.19 (td, *J* = 6.5, 14.0 Hz, 1 H), 1.95–1.91 (m, 1 H), 1.79 (d, *J* = 10.4 Hz, 1 H), 1.73–1.65 (m, 1 H), 1.59–1.52 (m, 2 H), 1.46 (q, *J* = 11.7 Hz, 1 H), 1.08 (s, 9 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 136.5, 135.7, 134.9, 134.2, 134.1, 130.4, 129.7, 129.1, 128.5, 127.7, 127.6, 126.4, 117.2, 76.8, 76.1, 71.2, 68.9, 41.9, 41.8, 41.5, 41.2, 26.9, 19.1.

HRMS (ESI-TOF): *m*/*z* $[M + K]^+$ calcd for $C_{34}H_{42}O_3SiK$: 565. 2540; found: 565.2518.

(*R*)-1-((2*R*,4*S*,6*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)pent-4-en-2-yl Acrylate (26)

Triethylamine (24 μL, 0.17 mmol, 300 mol%) was added to a solution of alcohol **25** (29.5 mg, 56.0 μmol, 100 mol%) in CH_2Cl_2 (0.9 mL, 0.2 M) at 0 °C under nitrogen atmosphere. After stirring for 10 min, acryloyl chloride (9.5 μL, 0.11 mmol, 200 mol%) in CH_2Cl_2 (0.5 mL, 0.2 M) was added dropwise. After 2 h of stirring at r.t., the reaction mixture was treated with sat. aq $NaHCO_3$ and extracted (CH_2Cl_2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (gradient, 0 to 9% EtOAc/Hex; 2% Et_3N) gave ester **26** (17.9 mg, 30.8 μmol; 55% yield) as a light-yellow oil.

R_f 0.56 (10% EtOAc/Hex); $[\alpha]_D^{23}$ –34 (*c* 2.0, $CHCl_3$).

FTIR (ATR): 2931, 2857, 1723, 1428, 1405, 1270, 1195, 1112, 1072, 966, 822, 742, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.71–7.67 (m, 4 H), 7.46–7.37 (m, 6 H), 7.36–7.32 (m, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.1 Hz, 1 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 6.34 (dd, *J* = 1.4, 17.3 Hz, 1 H), 6.11 (dd, *J* = 5.8, 16.0 Hz, 1 H), 6.06 (dd, *J* = 10.4, 17.3 Hz, 1 H), 5.80–5.70 (m, 2 H), 5.18–5.11 (m, 1 H), 5.10–5.04 (m, 2 H), 3.84 (tt, *J* = 4.7, 10.7 Hz, 1 H), 3.75 (dd, *J* = 5.8, 11.3 Hz, 1 H), 3.34 (td, *J* = 6.0, 11.6 Hz, 1 H), 2.42–2.30 (m, 2 H), 1.97 (td, *J* = 7.6, 14.7 Hz, 1 H), 1.90–1.82 (m, 2 H), 1.69 (td, *J* = 4.9, 14.5 Hz, 1 H), 1.48 (q, *J* = 11.5 Hz, 1 H), 1.36 (q, *J* = 12.3 Hz, 1 H), 1.07 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.6, 136.8, 135.7, 134.3, 134.2, 133.4, 130.3, 130.1, 129.69, 129.66, 129.64, 128.8, 128.4, 127.6, 127.6, 127.5, 126.4, 117.9, 75.8, 72.9, 70.9, 69.3, 41.3, 41.1, 39.8, 38.8, 26.9, 19.1.

HRMS (ESI-TOF): *m*/*z* $[M + K]^+$ calcd for $C_{37}H_{44}O_4SiK$: 619.2646; found: 619.2603.

Synthesis of 4

To a solution of ester **26** (16.0 mg, 27.5 μmol, 100 mol%) in CH_2Cl_2 (5.5 mL, 5 mM) was added Grubbs I catalyst (2.3 mg, 2.8 μmol, 10 mol%) in two portions over 1 h, and the mixture was heated to reflux in an oil bath at 45 °C. After 14 h of refluxing, the reaction mixture was concentrated under reduced pressure. The resulting residue was then dissolved in EtOAc (1 mL) and glacial AcOH (1.6 μL, 27.5 μmol, 100 mol%) and then TBAF (82.5 μL, 82.5 mmol, 1 M in THF; 300 mol%) were added at 0 °C and the mixture was stirred at r.t. After 20 h, the reaction mixture was treated with sat. aq $NaHCO_3$ and the aqueous phase was extracted (EtOAc). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (gradient, 50 to 100% EtOAc/Hex, then 3 to 9% MeOH/EtOAc) gave lactone **4** (5.3 mg, 17 μmol; 61% yield over two steps) as a yellow gum.

R_f 0.42 (100% EtOAc); $[\alpha]_D^{23}$ +22 (*c* 0.1, MeOH).

FTIR (ATR): 3404, 2920, 2849, 1715, 1390, 1251, 1607, 1039, 968, 810, 731, 695 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz):[29] δ = 7.38 (br d, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.24 (tt, *J* = 1.9, 7.2 Hz, 1 H), 6.89 (ddd, *J* = 2.5, 6.0, 9.7 Hz, 1 H), 6.58 (d, *J* = 16.0 Hz, 1 H), 6.19 (dd, *J* = 5.8, 16.0 Hz, 1 H), 6.03 (br dd, *J* = 2.5, 9.7 Hz, 1 H), 4.67 (dtd, *J* = 4.1, 6.0, 11.6 Hz, 1 H), 4.01 (tdd, *J* = 1.8, 5.8, 11.3 Hz, 1 H), 3.92 (tt, *J* = 4.3, 11.3 Hz, 1 H), 3.73 (dddd, *J* = 1.8, 5.5, 8.0, 11.3 Hz, 1 H), 2.51 (tdd, *J* = 2.5, 11.6, 18.4 Hz, 1 H), 2.40 (dddd, *J* = 1.9, 4.1, 6.0, 18.4 Hz, 1 H), 2.18 (ddd, *J* = 6.0, 8.0, 14.5 Hz, 1 H), 2.10 (tdd, *J* = 1.8, 4.3, 12.3 Hz, 1 H), 2.04 (tdd, *J* = 1.8, 4.3, 12.3 Hz, 1 H), 1.89 (ddd, *J* = 5.5, 6.0, 14.5 Hz, 1 H), 1.37 (td, *J* = 11.3, 12.3 Hz, 1 H), 1.30 (td, *J* = 11.3, 12.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz):[29] δ = 164.7, 145.7, 136.8, 130.7, 129.5, 128.8, 128.0, 126.7, 121.5, 76.3, 75.2, 71.6, 68.1, 41.4, 40.8, 40.6, 29.5.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}O_4$: 315.1596; found: 315.1592.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037–1611708.

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