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Stereoselective Synthesis of *cis*- and *trans*-2,3-Disubstituted Tetrahydrofurans via Oxonium−Prins Cyclization: Access to the Cordigol Ring System

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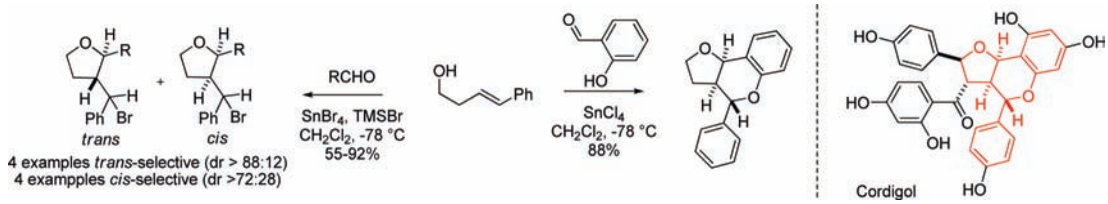
ABSTRACT



$SnBr_4$-promoted oxonium−Prins cyclizations to form 2,3-disubstituted tetrahydrofurans (THFs) are reported. In the absence of an internal nucleophile, the carbocation intermediates are trapped by bromide to give 2,3-*cis*- and 2,3-*trans*-configured products; two variations with intramolecular trapping are also reported. One of these allows a single-step stereocontrolled synthesis of the core 2,3-*cis*-THF ring system of cordigol, a fungicidal polyphenol from the stem bark of *Cordia goetzei*. For this latter transformation, a stepwise oxonium−Prins/cation trapping pathway rather than orthoquinonemethide formation/hetero-Diels−Alder cycloaddition is supported computationally.

The intramolecular addition of an alkene to a pendent oxonium ion via the Prins/ene mechanistic manifold constitutes a powerful strategy for the formation of cyclic ethers such as tetrahydropyrans (THPs) and tetrahydrofurans (THFs).[1] These cyclizations have been classified into types I−III depending on the tether topology.[2] In type III oxonium−Prins reactions, the alkene-bearing side chain is tethered to the oxonium ion oxygen and two modes of ring-closure are possible; for the case of an ethylene tether (i.e., γ,δ-unsaturated oxonium ions) these give rise to THP and THF rings, respectively. The Prins and ene reaction manifolds converge if the resulting carbocation induces an elimination, but trapping of the carbocation with a range of inter- and intramolecular nucleophiles can also occur (Scheme 1).[1] The type III oxonium ion substrates are most directly accessed by Lewis/Brønsted acid mediated aldehyde−homoallylic alcohol/TMS ether condensations[3,4] but can also be formed from α-acetoxy ethers,[5] α-stannyl ethers,[6] acetals,[7,8] and 1-oxa-2-silacyclohept-4-enes.[9] Irrespective of the mode of generation, 6-membered vs 5-membered ring-

(1) For an excellent review, see: (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. See also: (b) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261. (c) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045.

(2) This classification was introduced by Oppolzer and Snieckus; see: (a) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. More recently, Mikami has proposed an alternative nomenclature; see: (b) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403. (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, 1021.

(3) For THP formation, see, e.g.: (a) Zhou, H.; Loh, T.-P. *Tetrahedron Lett.* **2009**, *50*, 4368. (b) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605. (c) Yadav, J. S.; Chakravarthy, P. P.; Borkar, P.; Reddy, B. V. S.; Sarma, A. V. S. *Tetrahedron Lett.* **2009**, *50*, 5998. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, Y. J.; Reddy, N. S. *Tetrahedron Lett.* **2009**, *50*, 2877. (e) Liu, F.; Loh, T.-P. *Org. Lett.* **2007**, *9*, 2063. (f) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491. (g) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231. (h) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (i) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576. (j) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.

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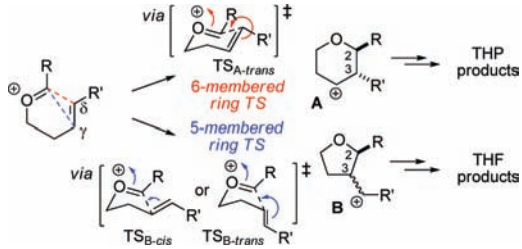
Scheme 1. Type III γ,δ-Unsaturated Oxonium-Prins Cyclizations

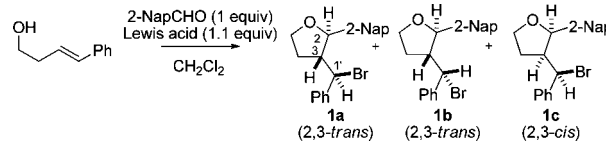


closure is dictated by the relative energies of the indicated transition states, which in turn reflect the stabilities of carbocations **A** and **B**. This means that for the terminal and monoalkyl-substituted alkene-containing systems which are most commonly employed (i.e., R′ = H, alkyl), THP products are formed exclusively.[3] By contrast, THF products are formed exclusively with dialkyl terminally substituted alkenes,[4c,d] with enols/enol ethers (i.e., R′ = OH, OR),[4a,e,7e,f] and with allylsilanes (i.e., R′ = CH_2SiR_3)[4b,6,9] due to the stabilization these substituents impart upon the exocyclic carbocation **B**. Good 2,3-stereocontrol can be achieved for stereodefined enols/enol ethers and allylsilane nucleophiles, and moderate *trans*-2,3-stereoselectivity is observed with dimethyl terminally substituted alkenes.[4c,10]

Intrigued by the absence in the chemical literature of type III oxonium−Prins cyclizations in which the γ,δ-unsaturated alkene is that of a styrene (i.e., R′ = Ar), we considered that these substrates could be valuable precursors for the stereocontrolled synthesis of 2,3-substituted THFs. In particular, we envisaged that *E*-configured styrenes would undergo cyclization to THFs driven by the stability of the resulting benzylic cations (cf. **B**, Scheme 1) and that 2,3-*cis*- rather than 2,3-*trans*-configured products might be preferred via a dipseudoequatorial transition state TS$_{B\text{-}cis}$ (Scheme 1). Herein, we describe our exploration of this reaction manifold.

Using (*E*)-4-phenylbut-3-en-1-ol[11] as the homoallylic alcohol component and 2-naphthylcarboxaldehyde (2-NapCHO) as the aldehyde component, we initially explored the use of $SnBr_4$ and $InBr_3$/TMSBr as Lewis acid promotors in CH_2Cl_2 as described by Rychnovsky[5a] and Loh,[3e] respectively, for the formation of THPs via oxonium−Prins cyclizations (Table 1). The use of $SnBr_4$ (1.1.equiv) led to the formation of three isomeric, bromine-containing THF products with dr 75:14:11 if the reaction mixture was allowed to warm to rt and dr 75:18:7 if the reaction mixture was maintained at low temperature (cf. entries 1 and 2). However, these reactions were slow, particularly the one at low temperature (entry 2). $InBr_3$ (1.1 equiv)/TMSBr (1.1 equiv) induced a more rapid reaction which gave just two isomers but with lower selectivity even at low temperature (dr 62:38:0, entry 3). The optimal conditions employed $SnBr_4$ in conjunction with TMSBr (1 equiv)[12] and led to full conversion within 4 h at −78 °C (dr 90:10:0, entry 4). As expected, the products were those of trapping the carbocation at C1′ with bromine following a Prins cyclization to give a THF ring. There was no evidence of elimination, but at this stage

Table 1. Oxonium Prins Cyclizations: Optimization of Reaction Conditions



entry	time (h)	conditions	conv (%)	dr (**1a/1b/1c**[a])
1	6	$SnBr_4$, −78 °C to rt	70	75:14:11
2	24	$SnBr_4$, −78 °C	20	75:18:7
3	4	$InBr_3$, TMSBr, −78 °C	70	62:38:0
4	4	$SnBr_4$, TMSBr, −78 °C	100	90:10:0[b]

[a] Ratios by integration of ^{1}H NMRs of the crude reaction mixtures; assignment of 2,3-stereochemistry is via NOESY (see the Supporting Information); the configuration at C1′ in the major 2,3-*trans* and 2,3-*cis* isomers is assumed to be that of **a/c** by analogy with that determined by X-ray for **6c** (Scheme 2). [b] The isolated yield of this inseparable mixture of isomers was 55%.

(4) For THF formation, see, e.g.: (a) Ünaldi, S.; Özlügedik, M.; Fröhlich, R.; Hoppe, D. *Adv. Synth. Catal.* **2005**, *347*, 162. (b) Sarkar, T. K.; Haque, S. A.; Basak, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1417. (c) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669. (d) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (e) Hoppe, D.; Krämer, T.; Erdbrügger, C. F.; Egert, E. *Tetrahedron Lett.* **1989**, *30*, 1233.

(5) See, e.g.: (a) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640. (b) Vitale, J. P.; Wolckenhauer, S. A.; Do, N. M.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 3255. (c) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1589. (d) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217.

(6) See, e.g.: Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 3252.

(7) See, e.g.: (a) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485. (b) Smith, A. B., III.; Safonov, I.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (c) Smith, A. B., III; Safonov, I.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426. (d) Smith, A. B., III.; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (e) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 785. (f) Takano, S.; Samizu, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 1032.

(8) See, e.g.: (a) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. (b) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223. Note: These oxonium−Prins reactions give ring closure to a THP cation (cf. **A**, Scheme 1) which undergoes pinacol rearrangement to a THF final product.

(9) (a) Miles, S. M.; Marsden, S. P.; Leatherbarrow, R. J.; Coates, W. J. *J. Org. Chem.* **2004**, *69*, 6874. (b) Miles, S. M.; Marsden, S. P.; Leatherbarrow, R. J.; Coates, W. J. *Chem. Commun.* **2004**, 2292. (c) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411. (d) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861.

(10) Racemisation via various mechanisms can plague oxonium−Prins reactions involving homoallyic alcohols; see ref 5a and references cited therein.

(11) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

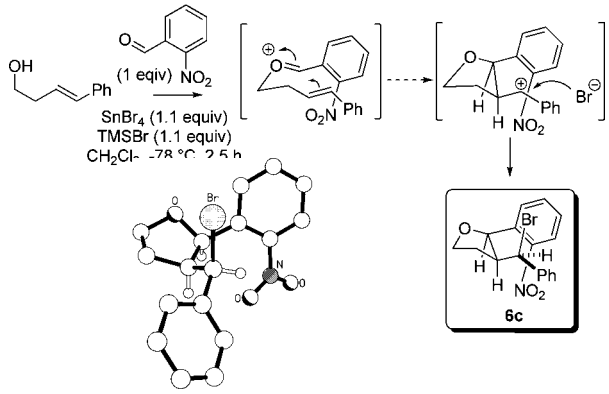
(12) TMSBr appears to serve as a bromide source (cf. ref 3e). Trace product formation occurred using only TMSBr as promoter.

(13) The isomeric ratios were unchanged after resubjection to the reaction conditions (Table 2, entry 7), suggesting the products are formed under kinetic control.

(14) The H2−H3 ^3J coupling constants vary significantly and are not diagnostic in THFs. Additionally, all the products/product mixtures (from Table 2, entry 7, and Table 2, entries 1−7) were subject to debromination (using $NiCl_2{\cdot}6H_2O$/$NaBH_4$, cf. Khurana, J. M.; Kumar, S.; Nand, B. *Can. J. Chem.* **2008**, *86*, 1052). The results were consistent with the assignments made by NOESY. For example, di-debromination of **5a** and **5c** gave the same products as mono-debromination of **4a/b** and **4c**, respectively (compounds **12** and **11**, see the Supporting Information).

the relative stereochemistry of the diastereomeric products **1a**, **1b**, and **1c** was unknown (vide infra).

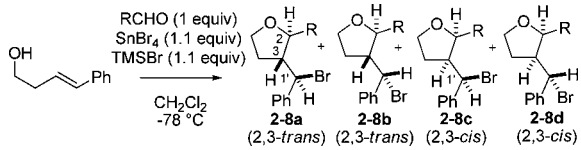
Scheme 2. Molecular Structure of **6c** and a Probable Pathway for its Formation



These conditions were then applied to a range of aldehydes to test the scope of the reaction (Table 2). Both alkyl (entries 1 and 2) and aryl (entries 3−7) aldehydes cyclized successfully to give THF products with a single major isomer constituting >60% of the crude isomer mixture in all cases. The (2*R**,3*S**,1′*R**) relative stereochemistry of compound **6c** isolated from the reaction involving *o*-nitrobenzaldehyde (entry 5) was established from a single-crystal X-ray structure determination (Scheme 2).The 2,3-*cis* configuration is consistent with a dipseudoequatorial "envelope" transition state for cyclization (cf. $TS_{B\text{-}cis}$, Scheme 1, above), and the configuration at C1′ is consistent with trapping of the carbocation following cyclization by bromide from the accessible face opposite to the aldehyde-derived aryl ring in the conformation drawn.[13] The 2,3-*cis* configuration of compound **6c** allows for a cross-peak between H2 and H1′ in its NOESY spectrum. The presence or absence of this diagnostic NOESY cross-peak was used to assign the 2,3-stereochemistry in all the other isomers.[14] Apparently, 2,3-*trans* isomers are favored for THFs **1**, **3**, **6**, and **7**, whereas 2,3-*cis* isomers are favored for THFs **2**, **3**, **5**, and **6**, suggesting that the respective transition states for ring closure (i.e., $TS_{B\text{-}trans}$ and $TS_{B\text{-}cis}$, Scheme 1, above) are close in energy under these conditions.[15]

9-Anthraldehyde underwent a particularly clean reaction to form a single product **9** that did not contain bromine. The identity of this product was established from a single-crystal X-ray structure determination as being that in which the intermediate carbocation, following cyclization to a 2,3-*cis*-THF, has been trapped intramolecularly by the anthracene ring (Scheme 3). Although the intramolecular trapping of the secondary benzylic carbocation intermediate by a proximal aryl ring was unexpected, Friedel−Crafts trapping of this type has close literature precedent in both an intramolecular[16] and intermolecular[3b] context.

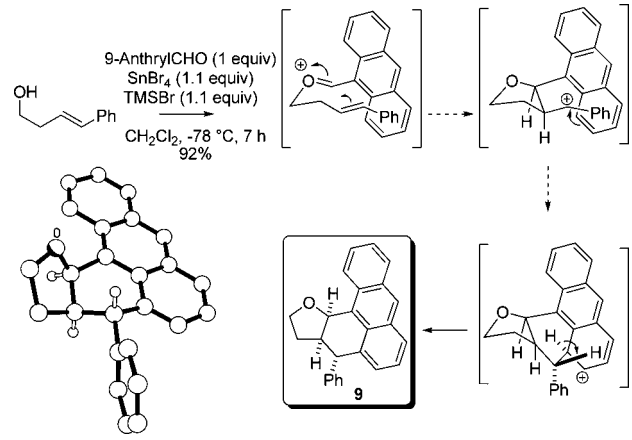
Table 2. Oxonium Prins Cyclizations: Exploration of the Scope with Respect to the Aldehyde Component



entry	R	prod.	time (h)	yield[a] (%)	dr (**a**/**b**/**c**/**d**[b])
1	Me	**2**	1.5	55	0:0:60:40
2	*i*-Pr	**3**	3	92	8:0:80:12
3	Ph	**4**	1.5	60	77:12:11:0
4	*o*-BrC_6H_4	**5**	2	71[c]	28:0:72:0
5	*o*-$NO_2C_6H_4$	**6**	2.5	83	0:0:100:0
6	*o*-$MeOC_6H_4$	**7**	4	58[d]	87:13:0:0
7	*p*-BrC_6H_4	**8**	2	55	68:20:12:0

[a] The yield is that of the inseparable mixture of isomers unless otherwise indicated. [b] Ratios by integration of ^1H NMRs of the crude reaction mixtures; assignment of 2,3-stereochemistry is via NOESY (see the Supporting Information); the configuration at C1′ in the major 2,3-*trans* and 2,3-*cis* isomers is assumed to be that of **a**/**c** by analogy with that determined by X-ray for **6c** (Scheme 2). [c] **5c** 44%, **5d** 27%, separable. [d] **5a** 58%, **5b** not isolated, separable.

Scheme 3. Molecular Structure of **9** and a Probable Pathway for its Formation



Inspired by this result, we speculated that a suitably positioned nucleophilic heteroatom could also be induced to intercept the C1′ benzylic cation and allow the formation other ring systems. In particular, we considered that the

(15) That these TSs are likely to be close in energy is consistent with our calculations on the formation of compound **10**; see ref 21.

(16) See, e.g.: Craig, D.; Meadows, J. D.; Pécheux, M. *Tetrahedron Lett.* **1998**, *39*, 141.

(17) For the isolation and characterization of cordigol, see: Marston, A.; Zagorski, M. G.; Hostettmann, K. *Helv. Chim. Acta* **1988**, *71*, 1210.

(18) The same core ring system is also found in the *Lophira lanceolata* natural product lophirone H; see: Tih, R. G.; Sondengam, B. L.; Martin, M. T.; Bodo, B. *Phytochemistry* **1990**, *29*, 2289.

(19) Use of $SnBr_4$ led to the formation of a mixture of compound **10** (40% yield) and a product tentatively assigned as that of intermolecular trapping by bromide (19% yield). This result is consistent with an oxonium−Prins pathway.

phenol group of an *o*-hydroxybenzaldehyde (salicylaldehyde) reaction partner should be perfectly located to act in this capacity and that this would allow expedient access to the core ring system of the fungicidal polyphenol cordigol.[17,18] Cordigol was first isolated by Hostettmann et al. from the stem bark of the *Cordia goetzei* Guerke (Boraginaceae) in 1988 and displays fungicidal activity against *Cladosporium cucumerinium*.[16] The relative stereochemistry of this hexahydro-2*H*-furano[3,2-*c*]benzopyran-based natural product was established by NOESY, and there have been no reported syntheses to date (Figure 1). Using $SnCl_4$ as the Lewis acid promoter,[19] we were

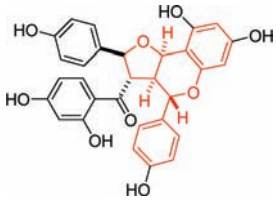
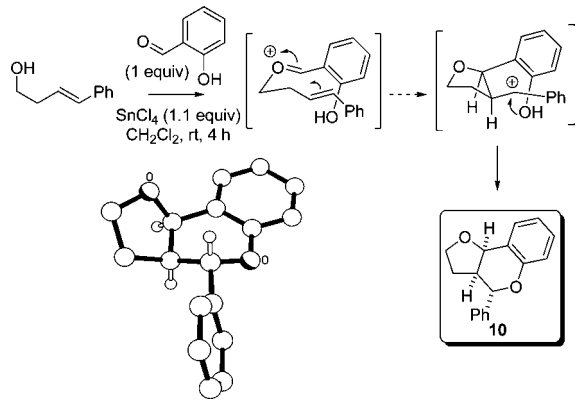


Figure 1. Structure of cordigol.

pleased to observe that (*E*)-4-phenylbut-3-en-1-ol condensed with salicylaldehyde to give the desired 2,3-*cis*-furano[3,2-*c*]-benzopyran **10** as the only product in 88% yield. The identity of this product was secured by a single-crystal X-ray structure determination (Scheme 4). The formation of a related furano[3,2-*c*]benzopyran (dr 85:15 2,3-*trans*/2,3-*cis*) by reaction of salicylaldehyde with 4-methyl-3-penten-1-ol mediated by CH(OMe)$_3$/*p*-TsOH has been reported by Inoue et al.[20a] who proposed a pathway involving *o*-quinonemethide formation[21] and then a hetero-Diels−Alder reaction.

Scheme 4. Molecular Structure of **10** and a Probably Pathway for Its Formation



To distinguish between a stepwise pathway via asynchronous formation of C−C and then C−O bonds (i.e., oxonium−Prins/cation trapping)[22] and a concerted pathway via formal $\pi_{2s} + \pi_{4s}$ cycloaddition (i.e., *o*-quinonemethide formation/hetero-Diels−Alder reaction), the potential energy surface was explored at the B3LYP/6-31G(d)/SCRF(CPCM) level using Gaussian 09. Both H and $SnCl_3$ were input as the activating species (X, Web Table 1). Transition states for initial C−C bond formation (i.e., TS^1_{cis}) were located for both X = H and $SnCl_3$, but a discrete intermediate could only be located for X = $SnCl_3$ from which a second (rate limiting) transition state forming the C−O bond could be located (i.e., TS^2_{cis}). A kinetic free energy barrier of 15.8 kcal/mol was calculated which corresponds to a facile room temperature reaction, as is observed experimentally. An Atoms-in-Molecules (AIM) analysis of the electron density for TS^2_{cis} reveals bond critical points (BCPs) for both forming bonds, the C−C having ρ 0.23, indicating it to be fully formed, and the C−O having ρ 0.073, indicating only partial formation. The calculations therefore indicate that the oxonium−Prins stepwise mechanism is the most likely for this reaction.

In summary, a method for the diastereoselective synthesis of 2,3-disubstituted THFs via an oxonium−Prins pathway driven by the preference of a styrenyl alkene to ring close via a benzylic cation has been described. The utility of this reaction for the facile synthesis of a natural product core has also been demonstrated.

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Supporting Information Available: . Experimental procedures and characterization for compounds **1-12** and details of the crystallographic analyses, including CIF files, of structures **6c**, **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See: (a) Miyazaki, H.; Honda, K.; Asami, M.; Inoue, S. *J. Org. Chem.* **1999**, *64*, 9507. Related transformations have been used to form pyrano[2,3-*c*]benzopyrans; see: (b) Yadav, J. S.; Reddy, B. V. S.; Sadashiv, K.; Padmavani, B. *Adv. Synth. Catal.* **2004**, *346*, 607. (c) Yadav, J. S.; Reddy, B. V. S.; Aruna, M.; Thomas, M. *Synthesis* **2002**, 217. Related transformations have been used to form pyrano[2,3-*c*]benzothiopyrans, see: (d) Inoue, S.; Wang, P.; Nagao, M.; Hoshino, Y.; Honda, K. *Synlett* **2005**, 469. (e) Saito, T.; Horikoshi, T.; Otani, T.; Matsuda, Y.; Karakasa, T. *Tetrahedron Lett.* **2003**, *44*, 6513.

(21) For an excellent review of *o*-quinonemethide chemistry, see: Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

(22) Stepwise C−O then C−C bond formation was also explored computationally. No new TSs were located. Additionally, the energy for a 2,3-*trans*-cyclization via TS^1_{trans} (X = $SnCl_3$) was calculated and found to be only 0.1 kcal/mol higher in energy than that via TS^1_{cis} although the requirement for an O−Sn−O bridge, which is geometrically precluded, prevented location of a TS^2_{trans}.