A Pericyclic Cascade to the Stereocontrolled Synthesis of 9-*cis*-Retinoids

Beatriz Iglesias, Alicia Torrado, and Angel R. de Lera*

Departamento de Química Física e Química Orgánica, Universidade de Vigo, 36200 Vigo, Spain

Susana López

Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15706 Santiago, Spain

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A domino reaction that is pericyclic in nature is thought to be triggered upon treatment of alkenynol **10** with arylsulfenyl chlorides. The process comprises an ordered sequence of sigmatropic rearrangements: a reversible [2,3]-allyl sulfenate to allyl sulfoxide shift, followed by a [2,3]-propargyl sulfenate to allenyl sulfoxide rearrangement, and last a stereodifferentiating [1,5]-sigmatropic hydrogen migration leading to polyene **13**. The occurrence of the C7 to C11 hydrogen migration has been demonstrated by labeling experiments. The double diastereoselection of the [1,5]-sigmatropic hydrogen shift to afford a single isomer of the final polyene **13** is thought to arise from a combination of the electronic effect of the sulfoxide at one terminus, and the steric effect imparted by the bulky trimethylcyclohexenyl substituent at the other terminus. The overall process thus constitutes a stereoselective synthesis of an *E,Z,Z*-triene fragment from an alkenynol and, in particular, a retinoid with the 7*E*,9*Z*,11*Z*,13*E* configuration on the conjugated polyenic side chain. Application of this method to the synthesis of retinoids, including labeled analogues, is straightforward.

Introduction

Sequential transformations constitute important synthetic strategies for the construction of complex molecules from simple precursors.[1] In particular, transformations that arise as a consequence of functionality introduced by a previous fragmentation, bond formation or rearrangement, termed *tandem*, *domino*, or *cascade* reactions, are powerful bond-forming reaction sequences that also enjoy the added benefit of being atom-economical.[1a] A systematic classification of domino processes has been proposed and is based on the type of chemical reaction involved in the first and subsequent step of the global sequence.[1a] Most of the pericyclic−pericyclic tandem processes described in the literature have been mainly based on the venerable Diels−Alder and Claisen rearrangements, as well as their variants, as the key functional group-forming steps. The exploitation of the full synthetic potential inherent in pericyclic processes, including the high diastereoselectivities predicted by the Woodward−Hoffmann rules, has yet to be fully realized.[1] In this regard, the [1,j]-H subset of sigmatropic rearrangements is one of the least exploited pericyclic reactions from the synthetic perspective. This neglect is perhaps due to the fact that both [1,5]-H and [1,7]-H migrations entail polyene isomerization processes. When the polyene includes a cumulene bond (in particular an allene bond),[2] the gain in complexity, for example the extended conjugation of the resulting polyene, is remarkable, and this finding has not escaped the attention of chemists. The thermally induced suprafacial [1,5]-sigmatropic hydrogen shift of vinylallenes (model transformation **1** → **2**) has been extensively studied by Okamura in elegant approaches to the triene and pentaene conjugated systems of vitamin D analogues (**3** → **4**) and 11-*cis*-retinoids (**5** → **6**, Scheme 1).[3] In the case of compound **5** the pericyclic nature of the [1,5]-hydrogen shift ensures the *Z* geometry of the central double bond, but control over the geometry of the ensuing polyene terminus in **6** could not be achieved. Intense efforts have been directed toward finding substituents with the ability to influence the stereochemical course of the rearrangement at the termini of the conjugated system in order to fully realize the synthetic benefit of stereocontrolled polyene synthesis via [1,5]-H shifts. In this regard, Okamura discovered that the sulfoxide group not only accelerated the [1,5]-sigmatropic hydrogen shift of vinylallene sulfoxides, but also directed the migrating hydrogen anti to its location.[4] Upon treatment of propargylic alcohols **7** with PhSCl, the intermediate vinylallene sulfoxides **8** stereoselectively provided triene sulfoxides **9** (Scheme 1) regardless of the size of the R group, by a [1,5]-H migration that is, however, inconsequential for the geometry of the terminal

* Corresponding author. Phone: + (34) 986 812316. Fax: + (34) 986 812382. e-mail: qolera@uvigo.es.

(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Parson, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (c) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159.

(2) For reviews on allenes, see (a) *The Chemistry of Ketenes, Allenes and Related Compounds*, Patai, S., Ed.; John Wiley & Sons: New York, 1980; Part II. (b) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: New York, 1982. (c) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81−88. (d) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis;* Wiley-Interscience: New York, 1984. (e) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805−2827. (f) Bruneau, C.; Dixneuf, P. Allenes and Cumulenes. In *Comprehensive Organic Funcional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C., Roberts, S., Eds.; Pergamon Press: Oxford, 1995; Volume 1, Chapter 1.20, pp 953−995.

(3) (a) Reference 2c. (b) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877−1952.

(4) (a) Okamura, W. H.; Shen, G. Y.; Tapia, R. *J. Am. Chem. Soc.* **1986**, *108*, 5018−5019. (b) Shen, G. Y.; Tapia, R.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 7499−7505.

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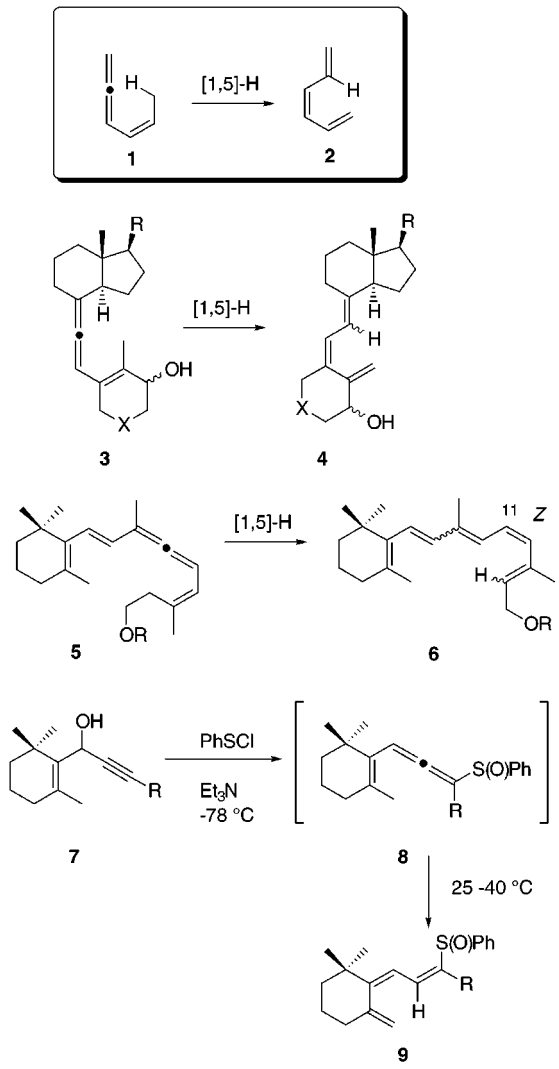
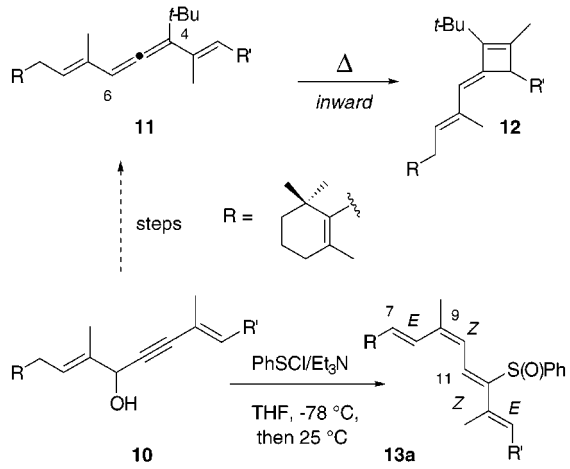
Scheme 1



olefin. However, other sulfur substituents (PhS, PhO_2S) that also accelerate the rearrangement failed to induce stereoselectivity on the sulfoxide-substituted olefin geometry in **9**.

The synthesis of 11-*cis*-retinoids (**5** → **6**) depicted in Scheme 1 is one of the relatively few existing studies on the pericyclic reactions of divinylallenes that have olefins of differing substitution patterns on either side of the allene. We have recently reported that bulky substituents at the allene unit are capable of influencing the regio- and stereoselectivity of the electrocyclic ring closure of divinylallenes **11** to functionalized alkylidenecyclobutenes **12** (Scheme 2).[5] The torquoselectivity,[6] i.e., the stereoselectivity arising from a preferred mode of rotation of substituents during electrocyclization (indicated as C6-*inward* for **11**), was mainly steric in nature and was enhanced by the presence of an electron-withdrawing

Scheme 2



group at one of the termini experiencing cyclization (from *E*/*Z* 86:14 for **12**, R′ = CH_2OH to *E*/*Z* > 99:1 for **12**, R′ = CHO).

Within this context,[5] we became interested in the study of the effect that heteroatoms attached to the internal position (C4 in **11**, vide infra) might have on the thermal behavior of divinylallenes. In a preliminary communication we described the unprecedented isomerization of alkenynol **10** to polyene **13a** upon treatment with phenylsulfenyl chloride and Et_3N (Scheme 2), which was suspected to involve a divinylallene sulfoxide.[7] We report here a detailed mechanistic study of this remarkable approach to 9-*cis*-retinoic acid,[8] the native ligand of the RXR nuclear receptors,[9] and its extension to the stereocontrolled synthesis of retinoids with 9*Z* geometry. This process takes advantage of the directing effect of the phenylsulfoxide group to control double-bond geometry in a [1,5]-sigmatropic hydrogen shift.

Results and Discussion

Treatment of a solution of known alcohol **10** (obtained in two steps from *β*-ionone)[10] in THF/Et_3N with freshly prepared[11] phenylsulfenyl chloride at −78 °C and stirring of the mixture for 1 h at −78 °C and then for 1 h at ambient temperature gave compound **13a** in 61% yield after chromatographic purification on silica gel impregnated with Et_3N. The polyenic nature of the product was suggested, in comparison to **10**, by the increase in the number of signals in the vinyl region and the absence of signals due to the methylene at C7 of **10** in the ^1H NMR spectrum of **13a**. Extensive NOE experiments suggested the 7*E*,9*Z*,11*Z*,13*E* geometry for the conjugated polyene structure shown in **13a**. The *Z* geometry about the C11−C12 double bond was unequivocally established after

(5) (a) García Rey, J.; Rodríguez, J.; de Lera, A. R. *Tetrahedron Lett.* **1993**, *34*, 6293−6296. (b) López, S.; García Rey, J.; Rodríguez, J.; de Lera, A. R. *Tetrahedron Lett.* **1995**, *36*, 4669−4672. (c) López, S.; Rodríguez, J.; García Rey, J.; de Lera, A. R. *J. Am. Chem. Soc.* **1996**, *118*, 1881−1891. (d) de Lera, A. R.; Torrado, A., García Rey, J.; López, S. *Tetrahedron Lett.* **1997**, *38*, 7421−7424. (e) de Lera, A. R.; García Rey, J.; Hrovat, D. A.; Iglesias, B.; López, S. *Tetrahedron Lett.* **1997**, *38*, 7425−7428.

(6) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471−477.

(7) de Lera, A. R.; Castro, A.; Torrado, A.; López, S. *Tetrahedron Lett.* **1998**, *39*, 4575−4578.

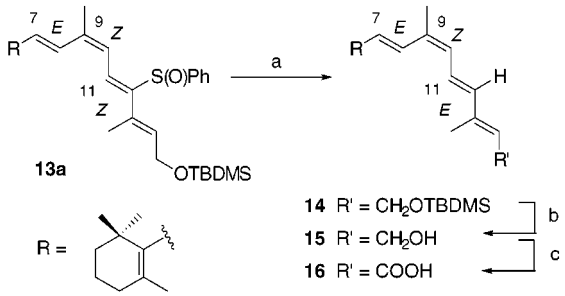
(8) For details on the nomenclature and numbering of retinoids, see: IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). *Eur. J. Biochem.* **1982**, *129*, 1−5. Note that the cis and trans notations are used for the geometry of the polyene side chain, regardless of the substituents.

(9) For reviews on biological implications of 9-*cis*-retinoic acid, see (a) Evans, R. M. *Science* **1988**, *240*, 889−895. (b) Mangelsdorf, D. A.; Evans, R. M. *Cell* **1995**, *83*, 841−850. (c) Rosen, J.; Day, A.; Jones, T. K.; Jones, E. T. T.; Nadzan, A. M.; Stein, R. B. *J. Med. Chem.* **1995**, *38*, 4855−4874.

(10) Isler, O.; Huber, W.; Ronco, A.; Kofler, M. *Helv. Chim. Acta* **1947**, *30*, 1911−1927.

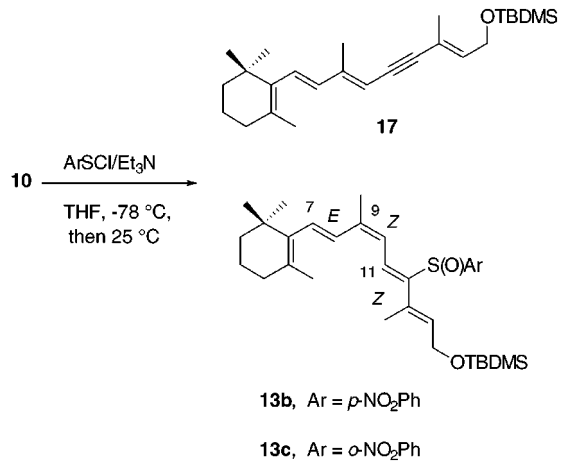
(11) Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J. *Org. Synth.* **1990**, *68*, 8−13.

Scheme 3[a]



[a] (a) *t*-BuLi, MeLi, MeOH, THF, −78 °C, 67%. (b) *n*-Bu_4NF, THF, 25 °C, 93%. (c) Ag_2O, MnO_2, MeOH, 1 M NaOH, 60 °C, 72%.

Scheme 4



stereoselective desulfuration, using a modification[12] of Okamura's procedure[13] (*t*-BuLi, MeLi,[12] MeOH, THF, −78 °C, 67%), and spectroscopic analysis of the product **14** (Scheme 3). Additional evidence for the structure of **13a** came from deprotection of **14** (TBAF, 25 °C) to provide 9-*cis*-retinol **15**[14] (93% yield) and oxidation of **15** with Ag_2O/MnO_2/MeOH[15] to yield 9-*cis*-retinoic acid **16** (72% yield).

Reaction of **10** with *p*-nitrophenylsulfenyl chloride likewise provided compound **13b** (79% yield) together with a second product, which was easily identified as silyl ether **17** (15% yield). The use of *o*-nitrophenylsulfenyl chloride gave instead compound **17** as the major component (60%) together with pentaene **13c** (40%). The silyl ether of 11,12-didehydroretinol **17** most likely arises by vinylogous elimination of the 10-arylsulfenate group derived from **10** (see **18**, Scheme 5), a process favored when the NO_2 substituent slows down the alternative pathway leading to **13b**,**c** through steric and inductive effects (Scheme 4).

The overall transformation **10** → **13** involves the unprecedented one-step synthesis of stereodefined tetraenes (ignoring the cyclohexenyl double bond) from alkenynols and is presumed to originate from sulfenate ester **18**, which is the primary derivative of **10** formed upon treatment with phenylsulfenyl chloride (Scheme 5). A further insight into the mechanism of the overall transformation is provided by analysis of the configuration of the product. Both the facile [2,3]-sigmatropic rearrangement of propargylic sulfenates to allenyl sulfoxides[16] and the aforementioned effect of the allenyl sulfoxide on the kinetics and stereodifferentiation of the [1,5]-H shift[4] are key factors suggesting the involvement of allenyl sulfoxide **19** in the overall conversion. Given the rate-accelerating effect, as well as the control of facial selectivity imparted by the sulfoxide group in [1,5]-sigmatropic hydrogen migrations of vinylallene phenyl sulfoxides,[4] which directs the migrating hydrogen anti, the geometries of the C9−C10 (*Z*) and C11−C12 (*Z*) double bonds of **13a** can be properly justified (Scheme 5). Moreover, the severe steric interactions imparted by the bulky trimethylcyclohexenyl group at the migration origin would favor the transition state leading stereoselectively to the C7−C8 *E* geometry. However, for the system to accommodate the [1,5]-H shift, an isomerization of the 8*E* to the 8*Z* geometry in **19** would be required, and this stereochemical issue will be addressed subsequently.

To corroborate the presumed involvement of a C7 to C11 [1,5]-sigmatropic hydrogen migration, we turned our attention to the analysis of the reaction product arising from the isotopologous C7-dideuterated enynol, **10**-C7-d_2. Propargylic alcohol **10**-C7-d_2, with the desired label at C7,[8] was prepared as shown in Scheme 6. Incorporation of deuterium into commercially available 2-(2,2,6-trimethylcyclohexenyl)ethanal (**20**) with NaH in D_2O/Pyr[17] was followed by Horner−Emmons condensation with diethyl 1-(ethoxycarbonyl)ethanephosphonate to provide ester **21** in 73% yield as a 62:38 mixture of *E*/*Z* isomers, which were separated by chromatography. DIBAL-H reduction of **21** afforded quantitatively allylic alcohol **22**, and oxidation of the latter with activated MnO_2 provided dideuterated aldehyde **23** in 89% yield. Finally, condensation of aldehyde **23** and the acetylenic anion originating from treatment of enyne **24**[5c] with *n*-BuLi provided the desired target **10**-C7-d_2 in 75% yield.

Subjecting alkenynol **10**-C7-d_2 to the appropriate reaction conditions afforded a polyenic sulfoxide in 77% yield. ^1H NMR analysis of this compound showed a high level of isotope incorporation at C11, and quantification provided a value of 95% label at this position, which further attests to the postulated C7 to C11 [1,5]-H shift (Scheme 5) through the mediation of the dideuterated divinylallene sulfoxide **19**-C7-d_2.

If a [1,5]-sigmatropic hydrogen migration was indeed operating in the overall sequence **10** → **13a**, and the vinylallene sulfoxide intermediate (8*E*)-**19** lacks the cis geometry required for such a shift, the isomerization of (8*E*)-**19** to (8*Z*)-**19** under the reaction conditions is a prerequisite for the success of the entire sequence (Scheme 5). Among the thermal noncatalyzed mechanisms known to produce double bond isomerization,[18] the first to be considered was a reversible allylic rearrange-

(12) Neef, G.; Eder, U.; Seeger, A. *Tetrahedron Lett.* **1980**, *21*, 903−906.

(13) (a) Theobald, P. G.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 741−750. (b) Theobald, P. G.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 6565−6568. (c) Park. G.; Okamura, W. H. *Synth. Commun.* **1991**, *21*, 1047−1054.

(14) Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931−1969.

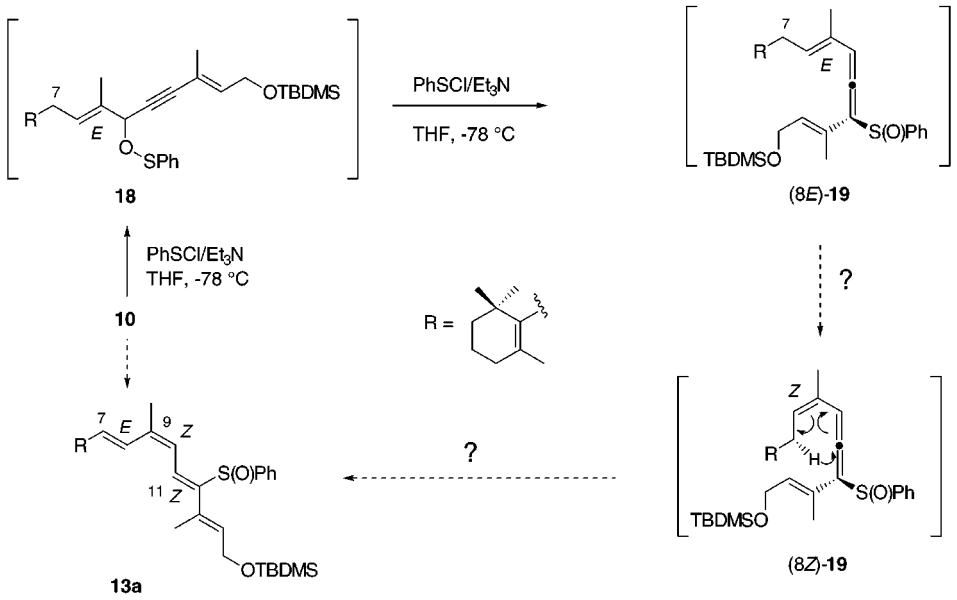
(15) Liebman, A. A.; Burger, W.; Malarek, D. H.; Serico, L.; Muccino, R. R.; Perry, C. W.; Choudhry, S. C. *J. Labeled Compound Radiopharm.* **1989**, *28*, 525−541.

(16) (a) Horner, L.; Binder, V. *Liebigs Ann. Chem.* **1972**, *757*, 33−68. (b) VanRheenen, V.; Shephard, K. P. *J. Org. Chem.* **1979**, *44*, 1582−1584. (c) Cutting, I.; Parsons, P. J. *Tetrahedron Lett.* **1983**, *24*, 4463−4464. See also ref 4.

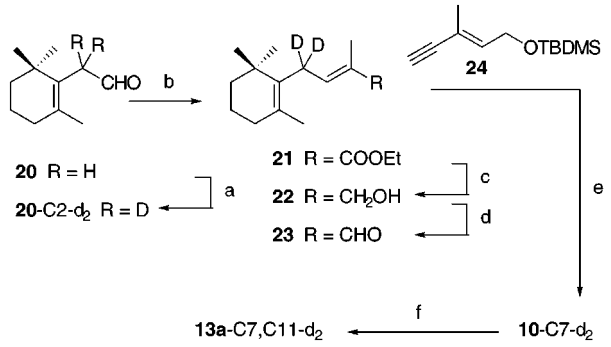
(17) Fransen, M. R.; Palings, I.; Lugtenburg, J.; Jansen, P. A. A.; Groenendijk, G. W. T. *Recueil Trav. Chim. Pays-Bas* **1980**, *99*, 384−391.

(18) Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557−604.

Scheme 5



Scheme 6[a]



[a] (a) NaH, pyridine, D_2O, 25 °C (repeat three times), 99%; (b) diethyl 1-(ethoxycarbonyl)ethanephosphonate, *n*-BuLi, THF, −78 °C, then 25 °C, 73%; (c) DIBAL-H, THF, 0 °C, 99%; (d) MnO_2, CH_2Cl_2, 25 °C, 89%; (e) *n*-BuLi, **24**, then **23**, 1.5 h at −78 °C, then 25 °C, 75%; (f) PhSCl, Et_3N, THF, −78 °C, then 25 °C, 1 h, 77%.

ment[19] of the primary product, i.e., sulfenate ester to allyl sulfoxide, since [2,3] shifts of that nature generally have low activation energies.[20] Indeed, Okamura and van Krutchen had previously isolated the allyl sulfoxide **27** upon treatment of the simple alkenynols **25** ($R_1 = R_2 = R_3 = R_4 = H$) with PhSCl.[21] Interestingly, although the geometry of the double bond in the primary product **27** is *E*, heating a benzene solution of (*E*)-**27** ($R_1 = R_2 = R_3 = R_4 = H$) afforded a mixture of (*E*)-**27**, (*Z*)-**27** and vinylallene sulfoxide **28**. This observation led to the conclusion that the allyl sulfenate to allyl sulfoxide rearrangement (**26** → **27**) was reversible in that case; the allyl sulfoxides **27** were the kinetic products, whereas the vinylallenyl sulfoxide **28** was thermodynamically favored. However, methyl substitution might alter the course of the rearrangement ([2,3]-propargylic vs [2,3]-allylic). The allyl sulfoxides **27** were the exclusive or major products (i.e., when $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, a 4:1 **27**/**28** mixture was obtained) starting from the monomethylated alkenynols, whereas the presence of a terminal dimethylated double bond ($R_1 = R_2 = CH_3$) led only to vinyallene sulfoxides **28** (Scheme 7).

In keeping with these observations, alkenynol **29** (Scheme 8), which was obtained in 87% yield by addition of the alkynyl anion derived from **24** to acrolein, was treated with PhSCl under the standard reaction conditions to afford a single product. This compound showed a characteristic trans coupling pattern ($J = 15.6$ Hz) in the vinylic region, together with two groups of signals resonating at 3.55 and 3.63 ppm characteristic of an allylic sulfoxide, in its ^1H NMR spectrum. These spectroscopic data suggested structure (*E*)-**31** for the primary [2,3]-allylic rearrangement product, a situation that is in agreement with the behavior exhibited by simple systems such as **26**. Signals due to a minor (<10%) compound were also present in the ^1H NMR spectrum, and these increased in intensity upon standing. Moreover, heating a solution of (*E*)-**31** in C_6D_6 to 50 °C in a sealed tube cleanly led to an equilibrium mixture consisting of (*E*)-**31** and its (*Z*)-**31** isomer in a 1:2 ratio after 25 h, the same ratio observed upon heating the isolated (*Z*)-**31** under the same conditions. At higher temperatures (80 °C) complex mixtures were obtained from which the desired vinylallene sulfoxide could not be isolated. However, in independent experiments, indirect support for the formation of a vinylallene by [2,3]-propargylic rearrangement was based on the observation that treatment of **10** or acetal **33**[22] with Ph_2PCl/Et_3N[23] afforded alle-

(19) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869−4875. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100−2103. (c) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Org. Chem.* **1995**, *60*, 6682−6683. (d) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147−155. (e) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563−572. (f) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1995**, *117*, 9077−9078. (g) Amaudrut, J.; Pasto, D. J., Wiest, O. *J. Org. Chem.* **1998**, *63*, 6061−6064.

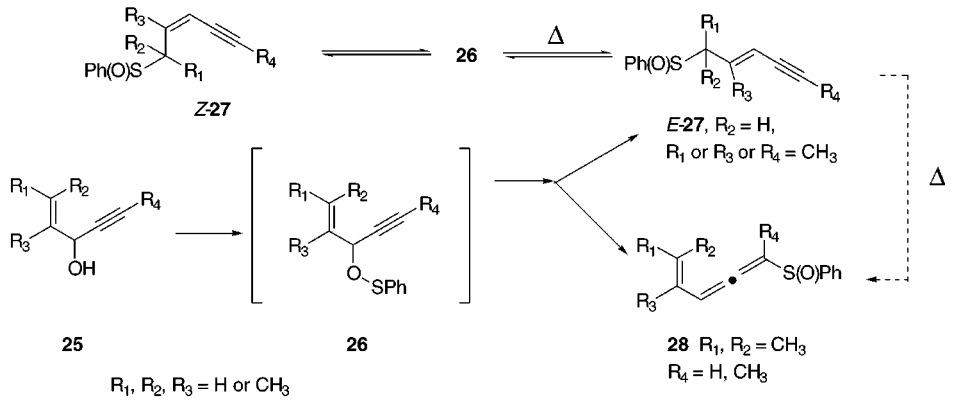
(20) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001−3020.

(21) van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 1019−1023.

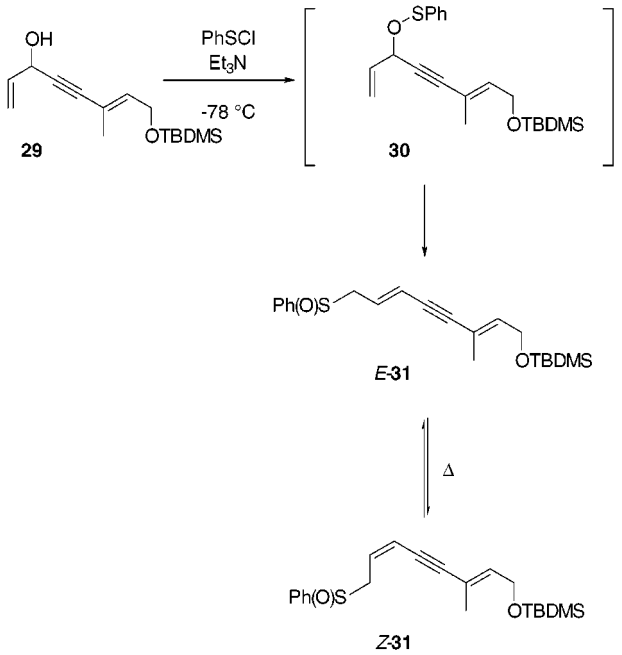
(22) Acetal **33** was prepared following the general synthetic scheme previously described,[5] starting from the corresponding acetal derived from known 3-methylpent-4-yn-2-enal (Derguini, F.; Nakanishi, K.; Balogh-Nair, V. *Tetrahedron Lett.* **1979**, 4899−4502).

(23) (a) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825−7826. (b) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603−626.

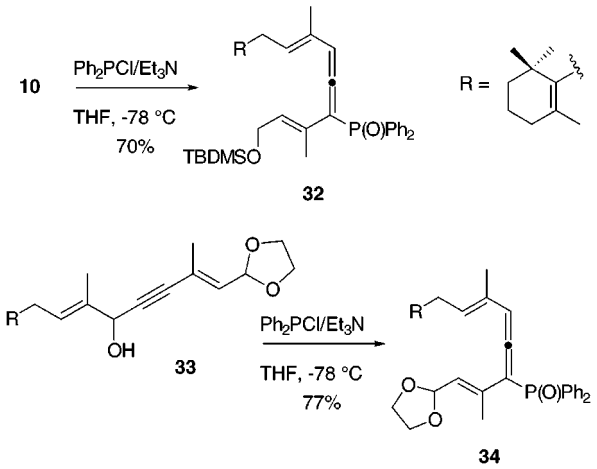
Scheme 7



Scheme 8



Scheme 9



nylphosphine oxides **32** and **34**, respectively (Scheme 9).[24] From (*E*)-vinylallene sulfoxide (*E*)-**19** (Scheme 10), however, an alternative mechanistic proposal of electrocyclic nature was also considered. The electrocyclic ring-closure of dienes (vinylallenes) followed by electrocyclic ring-opening of cyclobutenes (alkylidenecyclobutenes) in the same conrotatory sense could also account for the double-bond isomerization, which might even profit from the torquoelectronic effects of the substituents.[6] We were, however, unable to demonstrate by NMR the involvement of alkylidenecyclobutenes upon heating simple vinylallene sulfoxides at high temperatures.[25]

The thermal behavior of the model systems depicted in Scheme 7 led us to postulate the likely formation of vinylallene sulfoxides by rearrangement of allyl propargylic sulfenate esters and, by inference, their mediation in the rearrangement of **10** to **13a**, a hypothesis awaiting further confirmation.

Supported by the experiments described above, a detailed mechanism can be proposed for the isomerization of alkenynol **10** to TBDMS-protected 9-*cis*-12-phenylsulfinylretinol **13a**. The sequence of events in this domino reaction includes reversible[19] [2,3]-sigmatropic shift of allyl sulfenate ester (*E*)-**18** to allyl sulfoxide **35** (with concomitant double bond isomerization arising from conformer **35′**),[19,20] followed by propargylic sulfenate to vinylallene sulfoxide rearrangement[16,21] from (*Z*)-**18**[26] to provide (*Z*)-**19** and, finally, irreversible doubly stereoselective [1,5]-sigmatropic hydrogen migration to **13a** (Scheme 10). Although vinylallene sulfoxide (*Z*)-**19** could not be isolated due to the facile [1,5]-H rearrangement induced by the sulfoxide group, its involvement was inferred from the stereoselective generation of the C11−C12 *Z* olefin geometry as well as by the isolation of allenylphosphine oxides **32** and **34** described above. The facile (−78 °C) conversion of **10** to **13a** without the isolation of intermediates **35** and **19** stands in contrast to their isolation in simple systems (Schemes 8 and 9). It is likely that the sterically bulky ring additionally contributes to the acceleration of both the reversible [2,3]-allylic as well as the [2,3]-propargylic rearrangements.

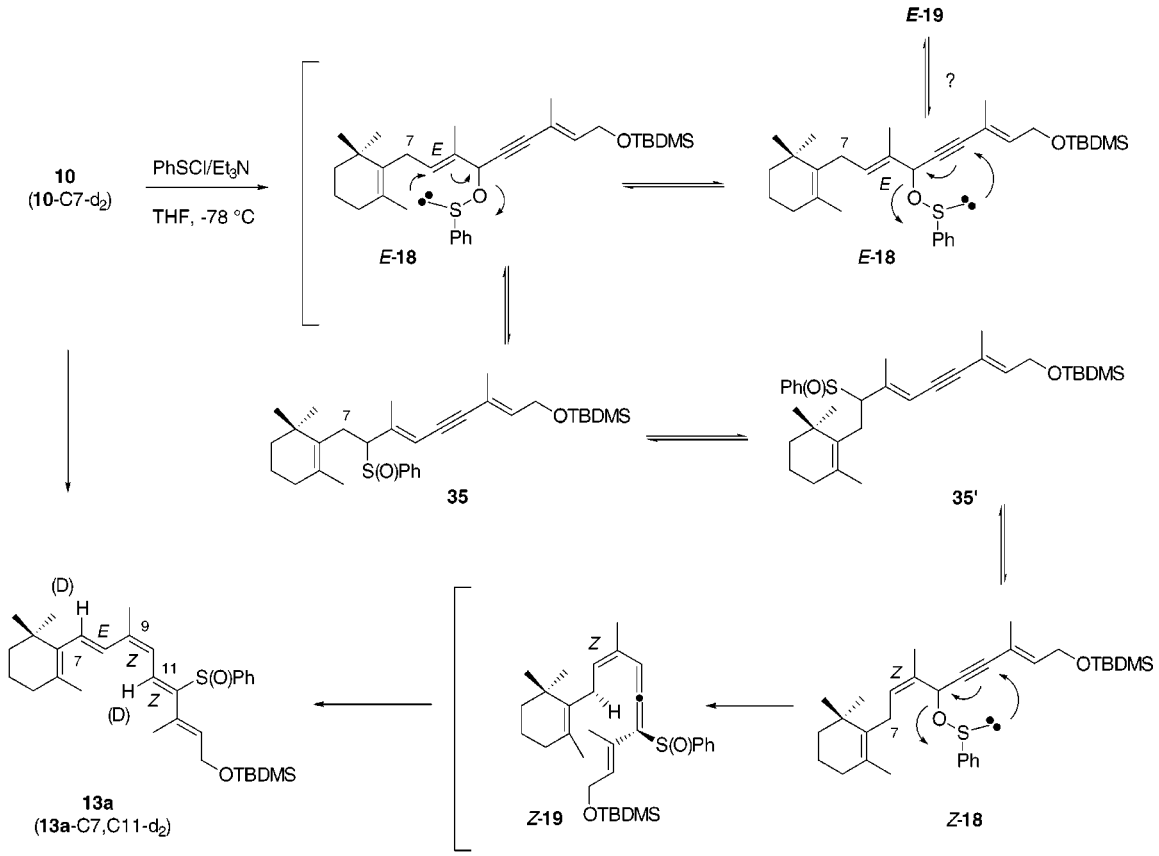
The unprecedented cascade of sigmatropic rearrangements described in Scheme 10 allows the highly stereo-

(24) Allenyl phosphine oxides **32** and **34** were thermally stable, and they could be recovered unaltered after heating to 140 °C in C_6D_6 (^{1}H NMR monitoring), thus providing evidence of the rate-retarding effect of a heteroatom at C4 on the electrocyclization of these model divinylallenes compared to analogues (Scheme 2) in which a *t*-Bu is present at the same position.

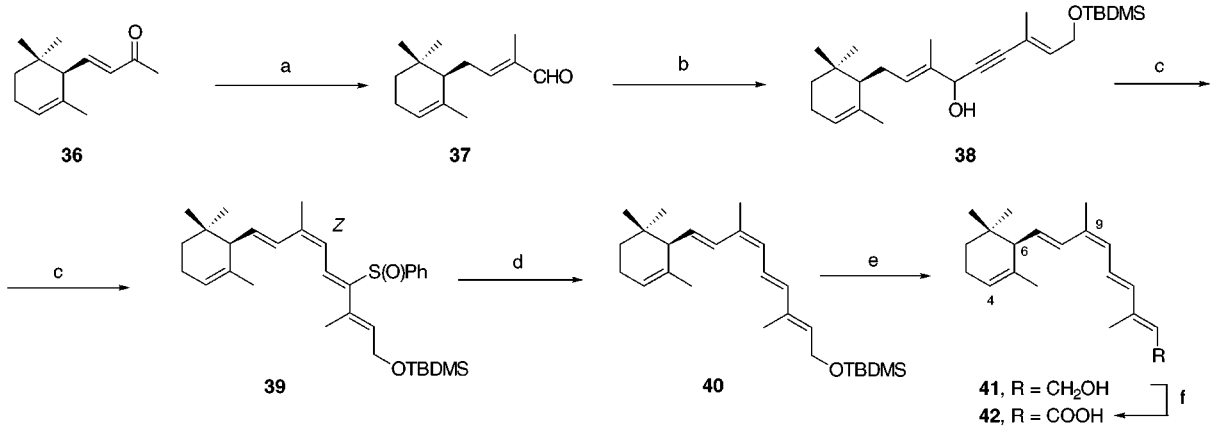
(25) T. Costas, unpublished.

(26) A referee suggested that interception of the *Z*-allyl alcohol (*Z*)-**10** by displacement of the allylsulfoxide **35′** to allylsulfenate (*Z*)-**18** equilibrium (Scheme 10) with a thiopile might constitute additional support for the proposed mechanism. However when, in separate experiments, excess $P(OMe)_3$ was added to a reaction flask containing **10** and PhSCl (Et_3N, CH_2Cl_2, −78 °C) after 15, 30, and 60 min reaction time, a mixture of (*E*)-**10** and **13a** was obtained in all cases with no detectable presence of isomer (*Z*)-**10**.

Scheme 10



Scheme 11[a]

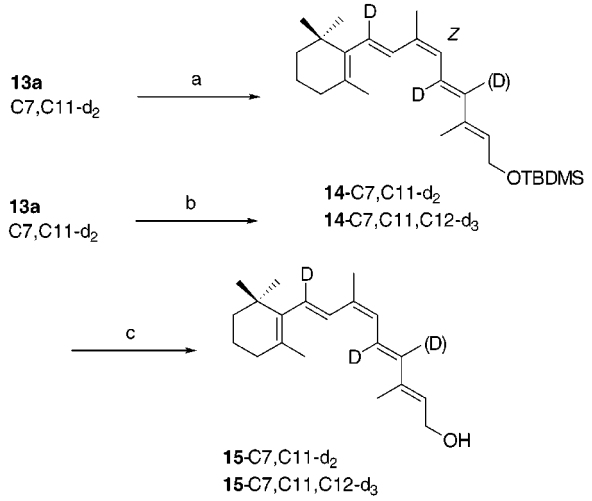


[a] (a) $ClCH_2CO_2Me$, MeOH, MeONa, 0 °C, then 25 °C, 58%; (b) *n*-BuLi, **24**, then **37**, 1.5 h at −78 °C, then 25 °C, 56%; (c) PhSCl, Et_3N, THF, −78 °C, then 25 °C, 1 h, 40%; (d) *t*-BuLi, MeLi, MeOH, THF, −78 °C, 73%; (e) *n*-Bu_4NF, THF, 25 °C; (f) Ag_2O, MnO_2, MeOH, 1 M NaOH, 60 °C, 53% (two steps).

selective generation of the C7−C12 triene fragment of 9-*cis*-retinoids in a one-pot reaction starting from alkenynol **10**. The complete control of the side-chain geometry of 9-*cis*-retinoids can be extended to the preparation of ring-modified 9-*cis*-retinoids, according to the general scheme indicated for the parent compound 9-*cis*-retinoic acid **16** (Scheme 2 and Scheme 3). As an example of an application, the synthesis of the (9*Z*)-4,6-*retro*retinoic[8] acid **42** was undertaken. Darzen's glycidic acid condensation[10] of racemic α-ionone **36** led to unsaturated aldehyde **37** in 58% yield. Alkenynol **38** was obtained in 56% yield by addition of the lithium anion derived from **24** to aldehyde **37**. The key sequence of pericyclic reactions afforded, as anticipated from the results described above, the protected 9-*cis*-12-arylsulfinyl-4,6-*retro*retinol **39** (40%). Stereospecific sulfoxide reduction provided **40** in 73% yield, and this step was followed by elaboration of the final carboxylic acid **42** through deprotection of **40** (TBAF) followed by oxidation of alcohol **41** with Ag_2O/MnO_2 in a combined yield of 53% (Scheme 11).

In conclusion, it has been shown that retinoids with the 9-cis geometry are accessible in one step from enynol **10**. The mechanism is another example of a pericyclic domino reaction, in which the product of the first thermal transformation serves as a starting material for the subsequent step(s) of the same overall transformation. In contrast to other pericyclic cascades described in the literature, our sequence does not build complexity, but

Scheme 12[a]



[a] (a) *t*-BuLi, MeLi, MeOH, THF, −78 °C, 77%; (b) *t*-BuLi, MeLi, MeOD, THF, −78 °C, 63%; (c) *n*-Bu_4NF, THF, 25 °C, 65−67%.

provides stereochemically defined polyenes from precursors that are not fully conjugated. In a more fundamental sense, the reaction could be described as a doubly stereoselective [1,5]-sigmatropic hydrogen shift. Whereas the "sulfoxide effect"[4] secures the 11*Z* geometry of **13**, the exclusive formation of the 7*E* geometry is most likely ascribed to the severe steric hindrance enforced by the highly substituted cyclohexenyl ring.

Given the paucity of stereocontrolled methods for the synthesis of retinoids with the 9*Z* geometry,[27] as well as the increasing importance of these geometric isomers in vision studies[28] and as ligands of the RXR subfamily of nuclear receptors,[9] the pericyclic cascade described here should find application in retinoid research. The potential utility of these compounds as biological tools may be enhanced by incorporation of labels in the stereoselective reduction step. As an additional application, the synthesis of C7,C11-dideuterated-retinol **15**-C7,C11-d_2 and C7,-C11,C12-trideuterated-retinol **15**-C7,C11,C12-d_3 is shown in Scheme 12.

Experimental Section

General. Solvents were dried according to published methods and distilled before use. HPLC grade solvents were used for the HPLC purification. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed using Merck silica gel 60 (particle size 0.040−0.063 μm). All operations involving synthesis and/or manipulation of retinoids were done under subdued light.

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*Z*,13*E*)-12-(Phenylsulfinyl)retinyl Ether (13a). General Procedure for the Reaction of Propargyl Alcohols with Phenylsulfenyl Chloride.** To a cooled (−78 °C) solution of propargyl alcohol **10**[5c] (0.90 g, 2.16 mmol) in THF (40 mL) was added, dropwise, Et_3N (0.90 mL, 6.50 mmol). After stirring for 15 min, a solution of phenylsulfenyl chloride (0.94 g, 6.50 mmol) in THF (20 mL) was added. The resulting orange solution was stirred at −78 °C for 1 h and at 25 °C for an additional 1 h. Saturated aqueous Na_2CO_3 was added, and the aqueous layer was extracted with ether (3×). The combined organic layers were washed with H_2O (3×) and brine (3×), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel (90:8:2 hexane/EtOAc/Et_3N) to provide 0.69 g (61%) of sulfoxide **13a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 6H), 0.85 (s, 9H), 1.05 (s, 6H), 1.4−1.6 (m, 4H), 1.61 (d, J = 0.9 Hz, 3H), 1.75 (s, 3H), 1.83 (s, 3H), 2.04 (t, J = 6.0 Hz, 2H), 4.15 (m, 2H), 5.66 (tq, J = 6.0, 0.9 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 6.67 (d, J = 16.0 Hz, 1H), 6.89 (d, J = 12.1 Hz, 1H), 7.12 (d, J = 12.1 Hz, 1H), 7.4−7.6 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (2×), 17.3, 18.7, 19.6, 21.8, 22.3, 26.3 (3×), 29.4 (2×), 33.5, 34.6, 39.9, 60.7, 121.6, 124.7 (2×), 129.1 (2×), 129.3, 129.9, 131.1, 131.4, 132.0, 132.3, 133.4, 138.3, 142.0, 144.1, 144.2; UV (MeOH) λ_{max} 234, 334 nm; HRMS calcd for $C_{32}H_{48}O_2SSi$ 524.3144, found 524.3141.

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*E*,13*E*)-Retinyl Ether (14). General Procedure for the Desulfuration Reaction.** To a cooled (−78 °C) stirred solution of sulfoxide **13a** (0.20 g, 0.39 mmol) in THF (20 mL) containing MeOH (0.05 mL, 1.22 mmol), was added, dropwise, MeLi (0.06 mL, 1.6 M in Et_2O, 0.10 mmol) followed by *t*-BuLi (1.03 mL, 1.7 M in pentane, 1.76 mmol) using a syringe pump at a rate of 2.1 mL/h, and the resulting mixture was stirred for 10 min at −78 °C. MeOH (10 mL) and H_2O (10 mL) were added, and the mixture was allowed to reach 25 °C. The aqueous layer was extracted with Et_2O (3×), and the combined organic layers were washed with H_2O (2×) and brine (2×), dried (Na_2SO_4), and evaporated. Purification by chromatography on neutral alumina (2.4% H_2O) (100% hexane) afforded 0.10 g (67%) of 9-*cis*-retinyl ether **14**. ^{1}H NMR (400 MHz, C_6D_6) δ 0.06 (s, 6H), 0.99 (s, 9H), 1.11 (s, 6H), 1.4−1.6 (m, 4H), 1.58 (s, 3H), 1.82 (s, 3H), 1.9−2.0 (m, 2H), 1.93 (s, 3H), 4.26 (d, J = 6.3 Hz, 2H), 5.77 (t, J = 6.3 Hz, 1H), 6.07 (d, J = 11.3 Hz, 1H), 6.29 (d, J = 15.0 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.92 (dd, J = 15.0, 11.3 Hz, 1H), 7.04 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ −4.8 (2×), 12.8, 18.7, 19.8, 21.1, 22.4, 26.4 (3×), 29.3 (2×), 33.4, 34.7, 39.9, 60.7, 123.7, 129.6, 130.2, 131.1, 132.8, 134.3, 135.0, 137.0, 137.1, 138.8; UV (MeOH) λ_{max} 254, 322 nm; HRMS calcd for $C_{26}H_{44}OSi$ 400.3161, found 400.3156.

(7*E*,9*Z*,11*E*,13*E*)-Retinol (15). General Procedure for the Deprotection of Silyl Ethers. TBAF (0.30 mL, 1 M in THF, 0.30 mmol) was added to a solution of retinyl ether **14** (0.10 g, 0.25 mmol) in THF (4.2 mL). After stirring at 25 °C for 1.5 h, the mixture was poured over saturated $NaHCO_3$, and it was extracted with Et_2O (3×). The combined organic layers were washed with saturated $NaHCO_3$ (2×), dried (Na_2SO_4) and evaporated. Purification by chromatography (SiO_2, 77:20:3 hexane/AcOEt/Et_3N) afforded 0.06 g (93%) of 9-*cis*-retinol **15**.[14] ^{1}H NMR (400 MHz, C_6D_6) δ 1.22 (s, 6H), 1.4−1.6 (m, 4H), 1.64 (s, 3H), 1.93 (s, 3H), 2.0−2.1 (m, 2H), 2.05 (s, 3H), 4.10 (d, J = 6.6 Hz, 2H), 5.73 (t, J = 6.6 Hz, 1H), 6.20 (d, J = 11.3 Hz, 1H), 6.37 (d, J = 15.0 Hz, 1H), 6.43 (d, J = 16.1 Hz, 1H), 7.03 (dd, J = 15.0, 11.3 Hz, 1H), 7.14 (d, J = 16.1 Hz, 1H).

(7*E*,9*Z*,11*E*,13*E*)-Retinoic Acid (16). General Procedure for the Oxidation of Primary Alcohols to Carboxylic Acids. A solution of 9-*cis*-retinol **15** (0.05 g, 0.17 mmol) in dry MeOH (3.5 mL) was added to a suspension of activated MnO_2 (0.09 g, 1.05 mmol) and Ag_2O (0.24 g, 1.05 mmol) in a mixture of H_2O (4.9 mL), MeOH (4.9 mL) and 1 M NaOH (0.87 mL) at 60 °C, under an Ar atmosphere. After stirring at 60 °C for 2 h, the mixture was cooled to 25 °C and filtered through Celite into a flask contaning ice-cooled H_2O (2.3 mL), CH_2Cl_2 (11.4 mL), and 3 M H_3PO_4 (1.25 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O containing brine (0.08 mL/mL H_2O), dried (Na_2SO_4), and evaporated. Purification by chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH) afforded 0.04 g (72%) of retinoic acid **16**.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 6H), 1.5−1.7 (m, 4H), 1.76 (s, 3H), 2.02 (s,

(27) (a) Bennani, Y. L. *J. Org. Chem.* **1996**, *61*, 3542−3544. (b) Bennani, Y. L.; Boehm, M. F. *J. Org. Chem.* **1995**, *60*, 1195−1200. (c) Wada, A.; Hiraishi, S.; Takamura, N.; Date, T.; Aoe, K.; Ito, M. *J. Org. Chem.* **1997**, *62*, 4343−4348. (d) Pazos, Y.; de Lera, A. R. *Tetrahedron Lett.* **1999**, *40*, 8287−8290.

(28) For recent reviews, see: (a) Corson, D. W.; Crouch, R. K. *Photochem. Photobiol.* **1996**, *64*, 595−600. (b) Crouch, R. K.; Chader, G. J.; Wiggert, B.; Pepperberg, D. R. *Photochem. Photobiol.* **1996**, *64*, 613−621.

3H), 2.06 (t, J = 6.4 Hz, 2H), 2.36 (s, 3H), 5.81 (s, 1H), 6.07 (d, J = 11.2 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 6.29 (d, J = 15.8 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 7.13 (dd, J = 15.0, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.2, 20.9, 21.9, 29.0 (2×), 33.0, 34.2, 39.4, 117.2, 127.9, 129.4, 130.2, 130.5, 130.6, 134.2, 137.9, 139.0, 155.3, 170.8; IR (NaCl) υ 3600−3100 (br, O−H), 1679 (s, C=O) cm^{-1}; UV (MeOH) λ_{max} 340 nm; HRMS calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2103.

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*Z*,13*E*)-12-(4-Nitrophenylsulfinyl)retinyl Ether (13b) and *tert*-Butyldimethylsilyl (7*E*,9*E*,13*E*)-11,12-Didehydroretinyl Ether (17).** In accordance to the general procedure described above, the reaction of propargyl alcohol **10** (0.05 g, 0.12 mmol) with *p*-nitrophenylsulfenyl chloride (0.07 g, 0.36 mmol) provided 0.05 g (79%) of sulfoxide **13b** as a yellow oil and 7 mg (15%) of product **17**. (See Supporting Information for **13b** characterization data). **Data for 17**: ^{1}H NMR (250 MHz, $CDCl_3$) δ −0.09 (s, 6H), 0.91 (s, 9H), 1.01 (s, 6H), 1.4−1.6 (m, 4H), 1.69 (s, 3H), 1.84 (s, 3H), 1.9−2.0 (m, 2H), 2.05 (s, 3H), 4.27 (d, J = 6.4 Hz, 2H), 5.52 (s, 1H), 5.92 (t, J = 6.4 Hz, 1H), 6.09 (d, J = 16.3 Hz, 1H), 6.25 (d, J = 16.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2 (2×), 15.0, 17.7, 18.3, 19.2, 21.6, 25.9 (3×), 28.9 (2×), 33.0, 34.2, 39.6, 60.1, 86.2, 98.9, 108.7, 119.4, 129.3, 130.0, 135.6, 136.1, 137.6, 147.1; UV (MeOH) λ_{max} 318 nm; HRMS calcd for $C_{26}H_{42}OSi$ 398.3005, found 398.3001.

Author: Just one 3× for C-13 NMR shift at 25.9 ppm for compound above?

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*Z*,13*E*)-12-(2-Nitrophenylsulfinyl)retinyl Ether (13c) and *tert*-Butyldimethylsilyl (7*E*,9*E*,13*E*)-11,12-Didehydroretinyl Ether (17).** In accordance to the general procedure described above, the reaction of propargyl alcohol **10** (0.05 g, 0.12 mmol) with *o*-nitrophenylsulfenyl chloride (0.07 g, 0.36 mmol) provided 0.03 g (40%) of sulfoxide **13c** as a yellow oil and 0.03 g (60%) of **17**. (See Supporting Information for **13c** characterization data).

2,2-Dideutero-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanal (20-C2-d_2). A solution of 2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanal (2.50 g, 12.05 mmol) in pyridine (14 mL) containing D_2O (6.50 mL, 0.36 mol) was added, dropwise, to a suspension of NaH (46 mg, 1.81 mmol) in pyridine (4 mL). After stirring at 25 °C for 2 h, the final mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and evaporated. The whole process was repeated twice more, until the complete disappearance of the starting material was confirmed by ^{1}H NMR, finally isolating 2.02 g (99.9%) of dideuterated aldehyde **20**-C2-d_2 (> 95% D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 6H), 1.4−1.5 (m, 2H), 1.58 (s, 3H), 1.5−1.6 (m, 2H), 2.02 (t, J = 6.1 Hz, 2H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 20.1, 28.0 (2×), 32.8, 34.5, 39.1, 43.1, 128.3, 132.5, 201.4; IR (NaCl) υ 1720 (s, C=O) cm^{-1}; HRMS calcd for $C_{11}H_{16}D_2O$ 168.1483, found 168.1482.

Ethyl (2*E*)-4,4-Dideutero-2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-2-enoate ((*E*)-21) and Ethyl (2*Z*)-4,4-Dideutero-2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-2-enoate ((*Z*)-21). To a cooled (−78 °C) solution of diethyl 1-(ethoxycarbonyl)ethanephosphonate (0.94 g, 3.93 mmol) in THF (7 mL) was added *n*-BuLi (1.50 mL, 2.93 M in hexane, 4.28 mmol). After stirring at −78 °C for 30 min, a solution of aldehyde **20** (0.60 g, 3.57 mmol) in THF (4 mL) was added, and the final mixture was stirred at −78 °C for 3 h and at 25 °C for an additional 2 h. A 0.5 M HCl solution was then added until neutral pH was reached, and the mixture was extracted with Et_2O (3×). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification by chromatography (SiO_2, 97:3 hexane/ethyl acetate) afforded 0.41 g of (*E*)-**21** (95% D) and 0.25 g of (*Z*)-**21** (>95% D) (73% overall yield). **Data for (*E*)-21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.4−1.5 (m, 2H), 1.53 (s, 3H), 1.5−1.6 (m, 2H), 1.89 (d, J = 1.3 Hz, 3H), 1.94 (t, J = 6.2 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 6.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.2, 19.4, 19.7, 27.4, 28.1 (2×), 32.8, 34.8, 39.4, 60.3, 126.1, 129.1, 134.6, 143.3, 168.3; IR (NaCl) υ 1710 (s, C=O) cm^{-1}; HRMS calcd for $C_{16}H_{24}D_2O_2$ 252.2058, found 252.2065. **Data for (*Z*)-21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.32 (t, J = 7.1 Hz, 3H), 1.4−1.5 (m, 2H), 1.5−1.6 (m, 2H), 1.60 (s, 3H), 1.89 (d, J = 1.3 Hz, 3H), 1.93 (t, J = 6.2 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.4, 19.6, 20.5, 28.1 (2×), 28.3, 32.7, 34.9, 39.6, 59.9, 125.5, 128.2, 136.1, 144.9, 168.0; IR (NaCl) υ 1714 (s, C=O) cm^{-1}; HRMS calcd for $C_{16}H_{24}D_2O_2$ 252.2058, found 252.2055.

(2*E*)-4,4-Dideutero-2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-2-en-1-ol (22). To a cooled (0 °C) solution of ethyl ester (*E*)-**21** (0.14 g, 0.55 mmol) in THF (3 mL) was added DIBAL-H (1.60 mL, 1.0 M in toluene, 1.60 mmol). After stirring at 0 °C for 3 h, H_2O was added and the mixture was extracted with Et_2O (5x). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried (Na_2SO_4), and evaporated. Purification of the residue by chromatography (SiO_2, 85:15 hexane/ethyl acetate) afforded 0.12 g (99.9%) of alcohol **22** (>95% D) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 6H), 1.4−1.5 (m, 2H), 1.54 (s, 3H), 1.5−1.6 (m, 2H), 1.72 (d, J = 1.1 Hz, 3H), 1.92 (t, J = 6.1 Hz, 2H), 3.99 (d, J = 5.5 Hz, 2H), 5.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.5, 19.6, 26.3, 28.2 (2×), 32.8, 34.8, 39.7, 68.9, 127.3, 127.8, 133.0, 136.1; IR (NaCl) υ 3600−3100 (br, OH) cm^{-1}; HRMS calcd for $C_{14}H_{22}D_2O$ 210.1953, found 210.1958.

(2*E*)-4,4-Dideutero-2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-2-enal (23). To a solution of alcohol **22** (0.26 g, 1.24 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (1.72 g, 19.81 mmol), and the mixture was stirred at 25 °C for 3 h. It was then filtered through Celite, and the solvent was evaporated. Purification by chromatography (SiO_2, 98:2 hexane/ethyl acetate) afforded 0.23 g (89%) of aldehyde **23** (95% D) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.4−1.5 (m, 2H), 1.54 (s, 3H), 1.5−1.6 (m, 2H), 1.81 (d, J = 1.1 Hz, 3H), 1.96 (t, J = 6.2 Hz, 2H), 6.34 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.15, 19.3, 19.7, 27.8, 28.1 (2×), 32.8, 34.8, 39.4, 129.7, 134.2, 138.0, 155.8, 195.1; IR (NaCl) υ 1690 (s, C=O) cm^{-1}; HRMS calcd for $C_{14}H_{20}D_2O$ 208.1796, found 208.1797.

(2*E*,7*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-1,1-dideutero-3,7-dimethyl-1-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,7-dien-5-yn-4-ol (10-C7-d_2). General Procedure for the Preparation of Propargylic Alcohols. To a cooled (−78 °C) solution of alkyne **24** (0.12 g, 0.58 mmol) in THF (2 mL) was added, dropwise, *n*-BuLi (0.25 mL, 2.36 M in hexane, 0.58 mmol). After stirring at −78 °C for 15 min and at 0 °C for 20 min, the mixture was cooled to −78 °C, and a solution of aldehyde **23** (0.11 g, 0.53 mmol) in THF (2 mL) was then added. After stirring at −78 °C for 1.5 h, a saturated aqueous NH_4Cl solution was added and stirring at 25 °C was continued for 10 min. The mixture was then extracted with Et_2O (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Purification by chromatography (SiO_2, 93:7 hexane/ethyl acetate) afforded 0.17 g (75%) of propargylic alcohol **10**-C7-d_2 (>95% D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 0.96 (s, 3H), 0.97 (s, 3H), 1.4−1.6 (m, 4H), 1.53 (s, 3H), 1.77 (d, J = 1.4 Hz, 3H), 1.80 (d, J = 1.1 Hz, 3H), 1.91 (t, J = 6.1 Hz, 2H), 4.24 (dq, J = 6.2, 0.6 Hz, 2H), 4.84 (d, J = 5.6 Hz, 1H), 5.43 (s, 1H), 5.91 (tq, J = 6.2, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2×), 12.1, 17.4, 18.2, 19.4, 19.6, 25.8 (3×), 26.4, 28.2 (2×), 32.8, 34.7, 39.6, 59.8, 68.4, 86.1, 87.9, 118.1, 128.1, 128.8, 132.6, 135.6, 137.0; IR (NaCl) υ 3600−3100 (br, OH) cm^{-1}; HRMS calcd for $C_{26}H_{42}D_2O_2Si$ 418.3236, found 418.3221.

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*Z*,13*E*)-7,11-Dideutero-12-(phenylsulfinyl)retinyl Ether (13a-C7,C11-d_2).** In accordance to the general procedure described above, reaction of propargylic alcohol **10**-C7-d_2 (0.15 g, 0.36 mmol) with Et_3N (0.15 mL, 1.08 mmol) and phenylsulfenyl chloride (0.16 g, 1.08 mmol) in THF (9 mL) provided, after purification by chromatography (SiO_2, 96:3:1 hexane/ethyl acetate/Et_3N), 0.15 g (77%) of retinyl ether **13a**-C7,C11-d_2 (95% D). An analytical sample for characterization was further purified by chromatography on Al_2O_3 (4.8% H_2O) (95:5 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 6H), 0.84 (s, 9H), 1.04 (s, 6H), 1.4−1.6 (m, 4H), 1.61 (s, 3H), 1.74 (s, 3H), 2.04 (t, J = 6.1 Hz, 2H),

2.07 (d, J = 0.8 Hz, 3H), 4.1−4.2 (m, 2H), 5.66 (tq, J = 6.0, 1.3 Hz, 1H), 6.65 (s, 1H), 6.88 (s, 1H), 7.4−7.6 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (2×), 16.8, 18.2, 19.1, 21.3, 21.9, 25.9 (3×), 29.0 (2×), 33.1, 34.2, 39.4, 60.2, 121.1, 124.2 (2×), 128.5, 128.8 (2×), 129.8, 130.7, 131.0, 132.9, 137.7, 141.6, 143.6 (2×); HRMS calcd for $C_{32}H_{46}D_2O_2SSi$ 526.3270, found 526.3262.

(6*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6-methylocta-1,6-dien-4-yn-3-ol (29). According to the general procedure described above, the reaction of alkyne **24** (0.41 g, 1.96 mmol), acrolein (0.10 g, 1.78 mmol), and *n*-BuLi (0.72 mL, 2.84 M in hexane, 2.05 mmol) afforded, after purification by flash chromatography on silica gel (88:10:2 hexane/EtOAc/Et_3N), 0.45 g (87%) of alkenynol **29**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.79 (d, J = 0.8 Hz, 3H), 4.25 (d, J = 6.0 Hz, 2H), 5.00 (br s, 1H), 5.23 (d, J = 10.1 Hz, 1H), 5.47 (d, J = 16.9 Hz, 1H), 5.95 (t, J = 6.0 Hz, 1H), 6.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (2×), 18.0, 18.8, 26.3 (3×), 60.4, 64.0, 85.5, 89.0, 116.9, 118.3, 137.4, 138.1; IR (NaCl) υ 3600−3100 (br, O−H) cm^{-1}; UV (MeOH) λ_{max} 230 nm; HRMS calcd for $C_{15}H_{26}O_2Si$ 266.1702, found 266.1696.

***tert*-Butyldimethylsilyl (2*E*,6*E*)-6-Methyl-1-(phenylsulfinyl)octa-2,6-dien-4-yn-8-yl Ether ((*E*)-31)**. In accordance to the general procedure described above, the reaction of Et_3N (0.16 mL, 1.11 mmol), alkenynol **29** (0.10 g, 0.37 mmol), and phenylsulfenyl chloride (0.16 g, 1.11 mmol) in THF (10 mL) afforded, after purification by flash chromatography (83:15:2 hexane/EtOAc/Et_3N), 0.12 g (89%) of sulfoxide (*E*)-**31** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.78 (d, J = 1.2 Hz, 3H), 3.55 (ddd, J = 12.8, 7.8, 0.8 Hz, 1H), 3.63 (ddd, J = 12.8, 7.8, 0.8 Hz, 1H), 4.25 (d, J = 6.2 Hz, 2H), 5.65 (d, J = 15.6 Hz, 1H), 5.85 (dt, J = 15.6, 7.8 Hz, 1H), 5.92 (td, J = 6.3, 1.2 Hz, 1H), 7.5−7.6 (m, 5H); ^{1}H NMR (400 MHz, C_6D_6) δ 0.00 (s, 6H), 0.93 (s, 9H), 1.62 (s, 3H), 2.85 (ddd, J = 12.8, 7.8, 1.1 Hz, 1H), 2.98 (ddd, J = 12.8, 7.8, 1.1 Hz, 1H), 4.07 (d, J = 6.2 Hz, 2H), 5.47 (d, J = 15.7 Hz, 1H), 5.76 (dt, J = 15.7, 7.8 Hz, 1H), 6.14 (td, J = 6.2, 1.4 Hz, 1H), 6.9−7.0 (m, 3H), 7.3−7.5 (dd, J = 7.8, 2.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (2×), 17.9, 26.3 (3×), 38.0, 60.4, 60.9, 84.9, 94.2, 118.9, 124.7 (2×), 129.0, 129.5, 129.6 (2×), 131.8, 138.2, 142.9; UV (MeOH) λ_{max} 278 nm; HRMS [M − *t*-Bu] calcd for $C_{17}H_{21}O_2SSi$ 317.1032, found 317.1026. ^{1}H NMR for (*Z*)-**31** (400 MHz, C_6D_6) δ 0.01 (s, 6H), 0.94 (s, 9H), 1.60 (s, 3H), 3.47 (dd, J = 12.7, 7.8 Hz, 1H), 3.57 (dd, J = 12.7, 7.8 Hz, 1H), 4.08 (d, J = 6.2 Hz, 2H), 5.5−5.6 (m, 2H), 6.00 (t, J = 6.2 Hz, 1H), 7.0−7.2 (m, 3H), 7.44 (d, J = 7.8 Hz, 2H).

***tert*-Butyldimethylsilyl (8*E*,13*E*)-12-(Diphenylphosphinoyl)-11,7-*retro*retinyl Ether (32)**. **General Procedure for the Preparation of Allenylphosphine Oxides.** To a cooled (−78 °C) solution of propargylic alcohol **10** (0.10 g, 0.24 mmol) in THF (1.3 mL) was added, dropwise, Et_3N (0.10 mL, 0.73 mmol), followed by chlorodiphenylphosphine (0.02 mL, 0.3 mmol). After stirring at −78 °C for 3 h and at 25 °C for an additional 3 h, the solvent was evaporated. The residue was purified by flash chromatography on silica gel (82:15:3 hexane/EtOAc/Et_3N) to provide, in order of elution, 0.07 g (70%) of allene **32** as a colorless oil, and 0.03 g of unreacted starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.11 (s, 6H), 0.76 (s, 9H), 0.83 (s, 3H), 0.91 (s, 3H), 1.4−1.6 (m, 4H), 1.42 (s, 3H), 1.51 (s, 3H), 1.78 (s, 3H), 1.88 (t, J = 6.1 Hz, 2H), 2.65 (br s, 2H), 4.21 (d, J = 6.0 Hz, 2H), 5.00 (m, 1H), 5.80 (d, $^4J_{H-P}$ = 10.5 Hz, 1H), 6.14 (t, J = 6.0 Hz, 1H), 7.4−7.5 (m, 6H), 7.6−7.7 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (2×), 14.3, 16.9, 17.0 ($^3J_{C-P}$ = 5.2 Hz), 18.6, 19.9, 20.1, 26.2 (3×), 28.1, 28.6, 28.8, 33.3, 35.3, 40.1, 60.9, 103.7 ($^3J_{C-P}$ = 13.5 Hz), 107.1 ($^1J_{C-P}$ = 101.3 Hz), 126.3 ($^3J_{C-P}$ = 7.1 Hz), 128.2 ($^3J_{C-P}$ = 7.0 Hz), 128.4 ($^3J_{C-P}$ = 9.0 Hz), 128.5, 128.6, 128.7 ($^3J_{C-P}$ = 9.0 Hz), 131.9, 132.0 ($^2J_{C-P}$ = 9.0 Hz, 2×), 132.0 ($^2J_{C-P}$ = 10.4 Hz, 2×), 132.7 ($^3J_{C-P}$ = 4.9 Hz), 132.8 ($^4J_{C-P}$ = 4.7 Hz), 133.8, 136.2, 213.0 ($^2J_{C-P}$ = 5.9 Hz); IR (NaCl) υ 1910 (w, C=C=C) cm^{-1}; UV (MeOH) λ_{max} 224, 246 nm; HRMS calcd for $C_{38}H_{53}O_2PSi$ 600.3552, found 600.3551.

(8*E*,13*E*)-14-[1,3]-Dioxolan-2-yl}-12-(diphenylphosphinoyl)-11,7-*retro*retinyl Ether (34). In accordance to the general procedure described above, treatment of propargylic alcohol **33** (0.24 g, 0.70 mmol) with Et_3N (0.29 mL, 2.10 mmol) and chlorodiphenylphosphine (0.25 mL, 2.10 mmol) provided 0.28 g (77%) of allene **34**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.93 (s, 3H), 1.4−1.6 (m, 4H), 1.43 (s, 3H), 1.49 (s, 3H), 1.90 (t, J = 6.2 Hz, 2H), 1.93 (s, 3H), 2.67 (br s, 2H), 3.8−3.9 (m, 2×, 4H), 5.04 (br t, 1H), 5.56 (d, J = 6.4 Hz, 1H), 5.85 (d, $^4J_{H-P}$ = 10.4 Hz, 1H), 6.12 (d, J = 6.4 Hz, 1H), 7.4−7.5 (m, 6H), 7.6−7.7 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 18.1 ($^3J_{C-P}$ = 5.0 Hz), 20.4, 20.7, 28.7, 29.1, 29.3, 33.8, 35.8, 40.6, 65.7 (2×), 101.3, 104.5 ($^3J_{C-P}$ = 13.2 Hz), 107.2 ($^1J_{C-P}$ = 99.7 Hz), 126.6 ($^3J_{C-P}$ = 7.0 Hz), 129.1 ($^3J_{C-P}$ = 13.0 Hz), 129.3 ($^3J_{C-P}$ = 3.9 Hz), 132.5 ($^2J_{C-P}$ = 9.9 Hz), 132.6 ($^4J_{C-P}$ = 5.8 Hz), 132.7, 133.0, 133.9, 135.1, 136.7, 214.2 ($^2J_{C-P}$ = 5.9 Hz); IR (NaCl) υ 1900 (w, C=C=C) cm^{-1}; UV (MeOH) λ_{max} 224, 246 nm; HRMS calcd for $C_{34}H_{41}O_3P$ 528.2793, found 528.2782.

(2*E*)-2-Methyl-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-2-enal (37). To a three-necked Morton flask equipped with a mechanical stirrer and a solid addition funnel were added α-ionone **36** (10.0 g, 52 mmol), methyl chloroacetate (12.25 mL, 0.14 mol), and MeOH (20 mL). The solution was cooled to −10 °C, and MeONa (9.6 g, 0.18 mol) was added in small portions for 2 h. After stirring at 0 °C for 3 h, a solution of 15% NaOH in MeOH (50 mL) was added and the resulting mixture was stirred at 5 °C for 2 h, after which time it was allowed to reach 25 °C. Water was added (60 mL) and the final solution was stirred for 30 min at 25 °C. The two layers were separated, and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with water (3×), dried (Na_2SO_4), filtered and evaporated. Purification by flash chromatography on silica gel (95:5 hexane/EtOAc) afforded 6.20 g (58%) of aldehyde **37** as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 3H), 0.82 (s, 3H), 1.0−1.2 (m, 1H), 1.2−1.4 (m, 1H), 1.59 (d, J = 1.8 Hz, 3H), 1.67 (d, J = 1.1 Hz, 3H), 1.71 (br t, J = 5.1 Hz, 1H), 1.8−2.0 (m, 2H), 2.38 (td, J = 6.2, 0.9 Hz, 2H), 5.34 (br s, 1H), 6.50 (td, J = 7.1, 1.3 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2, 22.8, 23.2, 27.4 (2×), 30.0, 31.5, 32.4, 49.2, 121.9, 134.5, 138.0, 155.8, 195.0; HRMS calcd for $C_{14}H_{22}O$ 206.1671, found 206.1667.

(2*E*,7*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-3,7-dimethyl-1-(2,6,6-trimethylcyclohex-2-en-1-yl)nona-2,7-dien-5-yn-4-ol (38). According to the general procedure described above, the reaction of aldehyde **37** (0.5 g, 2.43 mmol), alkyne **24** (0.57 g, 2.70 mol), and *n*-BuLi (1.27 mL, 2.55 M in hexane, 3.24 mmol) in THF (8 mL), afforded, after flash chromatography on silica gel (90:10 hexane/EtOAc), 0.56 g (56%) of propargylic alcohol **38** as a yellow oil. (See Supporting Information for characterization data).

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*Z*,13*E*)-12-(Phenylsulfinyl)-4,6-*retro*retinyl Ether (39).** Following the general procedure described above, treatment of propargylic alcohol **38** (0.22 g, 0.53 mmol) with phenylsulfenyl chloride (0.23 g, 1.59 mmol) and Et_3N (0.20 mL, 1.59 mmol) in THF (18 mL) afforded, after flash chromatography on silica gel (93:6:1 hexane/EtOAc/Et_3N), 0.11 g (40%) of sulfoxide **39**. An analytical sample for characterization was purified by HPLC (85:15 hexane/EtOAc). (See Supporting Information for characterization data).

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*E*,13*E*)-4,6-*retro*Retinyl Ether (40).** Following the general procedure described above, the reaction of sulfoxide **39** (0.03 g, 0.06 mmol) in THF (4 mL) with MeOH (13 μL, 0.31 mmol), MeLi (40 μL, 1.6 M in Et_2O, 0.06 mmol), and *tert*-BuLi (0.36 mL, 1.7 M in pentane, 0.62 mmol) afforded, after purification by chromatography (C18, 100% CH_3CN), 0.02 g (73%) of silyl ether **40**. (See Supporting Information for characterization data).

(7*E*,9*Z*,11*E*,13*E*)-4,6-*retro*Retinoic Acid (42). Following the general procedure described above, compound **40** (0.01 g, 0.03 mmol) was deprotected by treatment with TBAF (33 μL, 1.0 M in THF, 0.03 mmol) to afford alcohol **41**. The residue was immediately oxidized, according to the general procedure, with MnO_2 (14 mg, 0.16 mmol) and Ag_2O (38 mg, 0.16 mmol) to provide, after purification by chromatography (SiO_2, 98:2 CH_2Cl_2/MeOH), 4 mg (53%) of carboxylic acid **42**. (See Supporting Information for characterization data).

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*E*,13*E*)-7,11-Dideuterioretinyl Ether (14-C7,C11-d_2).** According to the general procedure described above, treatment of sulfoxide **13a**-C7,C11-d_2 (0.05 g, 0.09 mmol) in THF (5 mL) with MeOH (18 μL, 0.45 mmol), MeLi (42 μL, 1.6 M in Et_2O, 0.07 mmol), and *tert*-BuLi (0.42 mL, 1.7 M in pentane, 0.71 mmol) afforded, after purification by chromatography (SiO_2, 99.6:0.4 hexane/Et_3N), 0.03 g (77%) of retinyl ether **14**-C7,C11-d_2, which was immediately converted into the corresponding retinol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.04 (s, 6H), 1.5−1.7 (m, 4H), 1.75 (s, 3H), 1.80 (s, 3H), 1.96 (s, 3H), 2.04 (t, J = 6.2 Hz, 2H), 4.35 (d, J = 6.3 Hz, 2H), 5.60 (t, J = 6.3 Hz, 1H), 6.00 (s, 1H), 6.22 (s, 1H), 6.63 (s, 1H);^{1}H NMR (400 MHz, C_6D_6) δ 0.08 (s, 6H), 1.00 (s, 9H), 1.12 (s, 6H), 1.4−1.6 (m, 4H), 1.60 (s, 3H), 1.83 (s, 3H), 1.9 (m, 2H), 1.94 (s, 3H), 4.27 (d, J = 6.3 Hz, 2H), 5.77 (t, J = 6.3 Hz, 1H), 6.08 (s, 1H), 6.29 (s, 1H), 7.02 (s, 1H).

***tert*-Butyldimethylsilyl (7*E*,9*Z*,11*E*,13*E*)-7,11,12-Trideuterioretinyl Ether (14-C7,C11,C12-d_3).** In accordance to the general procedure described above, sulfoxide **13a**-C7,-C11-d_2 (0.05 g, 0.09 mmol) in THF (5 mL) was treated with CD_3OD (18 μL, 0.44 mmol), MeLi (56 μL, 1.6 M in Et_2O, 0.09 mmol), and *tert*-BuLi (0.42 mL, 1.7 M in pentane, 0.71 mmol) to afford, after purification by chromatography (SiO_2, 99.6:0.4 hexane/Et_3N), 0.02 g (63%) of retinyl ether **14**-C7,C11,C12-d_3, which was immediately converted into the corresponding retinol.^{1}H NMR (400 MHz, C_6D_6) δ 0.07 (s, 6H), 0.99 (s, 9H), 1.11 (s, 6H), 1.4−1.6 (m, 4H), 1.60 (d, J = 0.4 Hz, 3H), 1.81 (s, 3H), 1.90 (m, 2H), 1.93 (d, J = 0.7 Hz, 3H), 4.27 (d, J = 6.4 Hz, 2H), 5.76 (t, J = 6.4 Hz, 1H), 6.07 (s, 1H), 7.01 (s, 1H).

(7*E*,9*Z*,11*E*,13*E*)-7,11-Dideuterioretinol (15-C7,C11-d_2). In accordance to the general procedure described above, retinyl ether **14**-C7,C11-d_2 (0.03 g, 0.06 mmol) in THF (1.3 mL) was treated with TBAF (79 μL, 1.0 M in THF, 0.08 mmol) to afford, after purification by chromatography (SiO_2, 95:13:2 hexane/ethyl acetate/Et_3N), 12 mg (65%) of retinol **15**-C7,C11-d_2 (90% D). A sample for characterization was purified by HPLC (Prep Nova-Pak HR Silica [19 × 300 mm], 4 mL/min, 80:20 hexane/ethyl acetate, 43 min). ^{1}H NMR (400 MHz, C_6D_6) δ 1.11 (s, 6H), 1.4−1.6 (m, 4H), 1.54 (s, 3H), 1.81 (s, 3H), 1.9−2.0 (m, 2H), 1.94 (s, 3H), 3.96 (d, J = 6.6 Hz, 2H), 5.58 (t, J = 6.6 Hz, 1H), 6.09 (s, 1H), 6.24 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.4, 19.7, 20.8, 22.0, 29.2 (2×), 33.3, 34.5, 39.8, 59.4, 129.6, 129.8, 130.7, 131.8, 134.3, 135.9, 136.6, 138.5; IR (NaCl) υ 3600−3100 (br, OH) cm^{-1}; HRMS calcd for $C_{20}H_{28}D_2O$ 288.2422, found 288.2419.

(7*E*,9*Z*,11*E*,13*E*)-7,11,12-Trideuterioretinol (15-C7,C11,-C12-d_3). In accordance to the general procedure described above, retinyl ether **14**-C7,C11,C12-d_3 (0.02 g, 0.06 mmol) in THF (1.2 mL) was treated with TBAF (0.07 mL, 1.0 M in THF, 0.07 mmol) to afford, after purification by chromatography (SiO_2, 95:13:2 hexane/ethyl acetate/Et_3N), 11 mg (67%) of retinol **15**-C7,C11,C12-d_3 (95% D). A sample for characterization was purified by HPLC (Prep Nova-Pak HR Silica [19 × 300 mm], 4 mL/min, 80:20 hexane/ethyl acetate, 44 min). ^{1}H NMR (400 MHz, C_6D_6) δ 1.18 (s, 6H), 1.4−1.6 (m, 4H), 1.61 (s, 3H), 1.88 (s, 3H), 1.9−2.0 (m, 5H), 4.03 (d, J = 6.7 Hz, 2H), 5.64 (tq, J = 6.7, 1.0 Hz, 1H), 6.15 (s, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.4, 19.6, 20.8, 22.0, 29.1 (2×), 33.2, 34.5, 39.8, 59.4, 129.5, 129.7, 130.7, 131.7, 134.3, 135.9, 138.5; IR (NaCl) υ 3600−3100 (br, OH) cm^{-1}; HRMS calcd for $C_{20}H_{27}D_3O$ 289.2485, found 289.2486.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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