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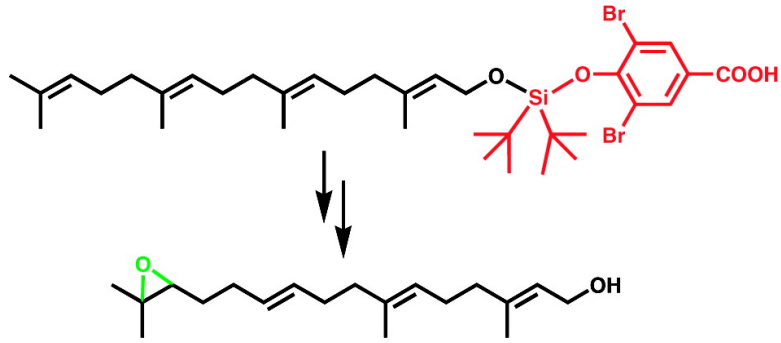

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A Strategy for Position-Selective Epoxidation of Polyprenols

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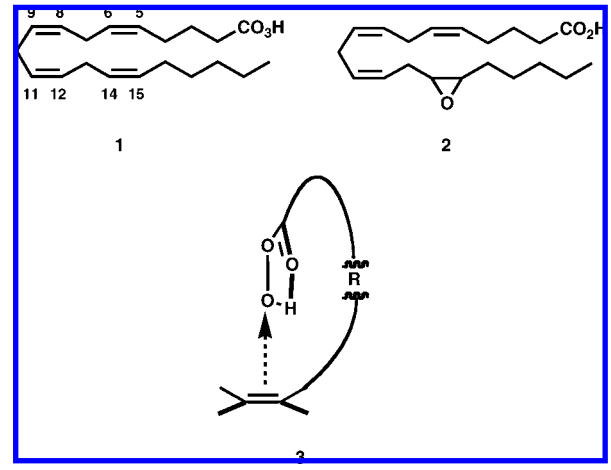
Abstract: An effective strategy has been developed for the efficient site-selective epoxidation of poylolefinic isoprenoid alcohols, based on the use of an internal control element for intramolecular reaction. The approach is illustrated by application to a series of polyisoprenoid alcohols (polyprenols) at substrate concentration of 0.5 mM. With polyprenol substrates having the hydroxyl function at one terminus, the internal epoxidation can be directed at the double bond of the polyprenol, which is either four or five away from the terminal hydroxyprenyl subunit.

Introduction

The site-selective epoxidation of poly-unsaturated substrates is a key process in the biosynthesis of several families of natural products, including steroids and triterpenoids (from 2,3-(*S*)-oxidosqualene),[1] insect juvenile hormones (farnesoate or homofarnesoate terminal epoxides),[2] and eicosanoids (e.g., leukotriene-A_4[3] or (11*R*,12*S*)-oxidoarachidonic acid).[4] The selective introduction of an oxirane unit in polyenes by chemical means remains a relatively undeveloped area of chemical synthesis. Only a few examples of such reactions are currently known: (1) the terminal hydroxybromination of farnesol esters or squalene (neither of which is highly selective),[5] (2) the bromolactonization of poly-unsaturated fatty acids (e.g., arachidonic acid at the Δ^5-double bond),[6] (3) the internal epoxidation of peroxyarachidonic acid **1**, which generates the 14,15-epoxide **2** with high efficiency,[7] and (4) the terminal epoxidation of geraniol and farnesol esters by $OsO_4-K_3Fe(CN)_6$ in the presence of the Noe-Lin,[8] Zhang,[9] or Huang[10] cinchona-based catalyst.

The selective formation of **2** from **1** can be ascribed to the stereoelectronic constraints for intramolecular oxygen transfer arising from attack by the C=C π-orbital electrons backside to the O−O bond (σ^*-orbital) of the internally hydrogen-bonded peroxycarbonyl group, with the C=C σ plane approximately perpendicular to the peroxycarbonyl ring, as shown in **3**. Such structures for internal transfer of oxygen to the Δ^5-, Δ^8-, or Δ^{11}-double bonds in **1** would involve appreciably more ring strain.[11] The present paper describes the application of this model to the development of a strategy for the position-selective epoxidation of poly-unsaturated alcohols, specifically polyisoprenoid alcohols (polyprenols).

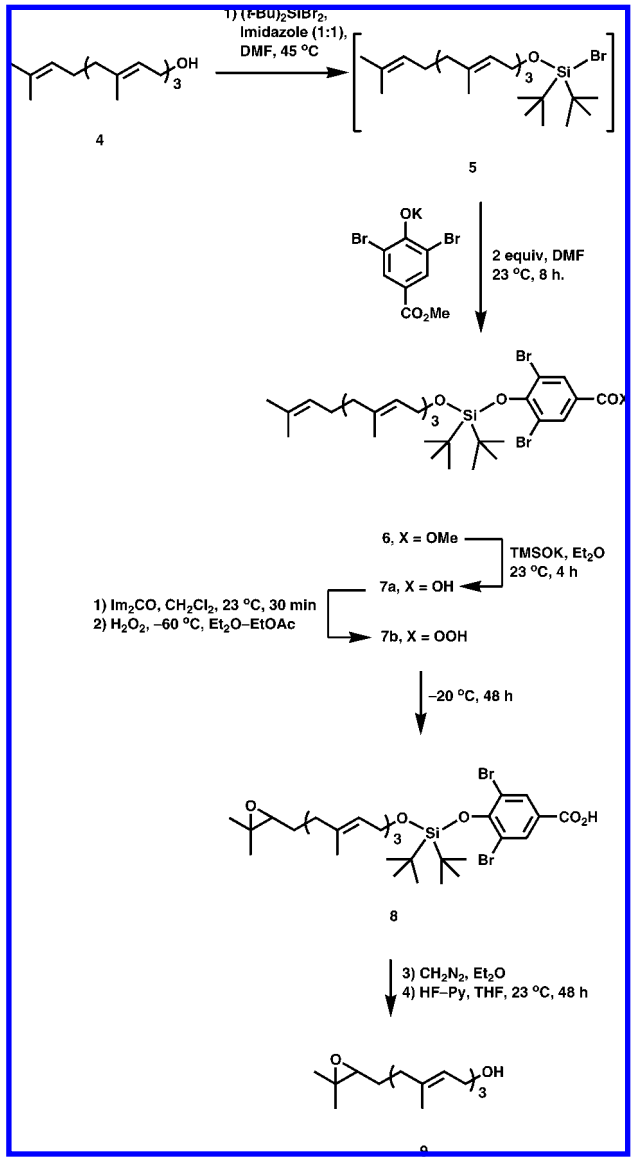


Results and Discussion

The tetra-unsaturated acid **7a** was synthesized from all-*E*-tetraprenol **4** (geranylgeraniol) by the following sequence: (1) mono coupling with 1 equiv of di-*tert*-butyldibromosilane (imidazole catalyst in DMF at 45 °C); (2) further coupling of the monobromosilyl ether **5** with the potassium salt of methyl 3,5-dibromo-4-hydroxybenzoate to form methyl ester **6** (DMF,

(1) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750–4751.
(2) Röller, H.; Dahm, K. H.; Sweeley, C. C.; Trost, B. M. *Angew. Chem., Int. Ed.* **1967**, *6*, 179–182.
(3) (a) Hammarström, S.; Samuelsson, B.; Clark, D. A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1266–1272. (b) Corey, E. J.; Arai, Y.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748–6749.
(4) (a) Node, K.; Huo, Y.; Ruan, X.; Yang, B.; Spiecker, M.; Ley, K.; Zeldin, D. C.; Liao, J. K. *Science* **1999**, *285*, 1276–1279. (b) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433–1434. (c) Han, X.; Crane, S. N.; Corey, E. J. *Org. Lett.* **2000**, *2*, 3437–3438.
(5) Van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, *3*, 121–124.
(6) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435–1436.
(7) Corey, E. J.; Niwa, H.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 1586–1587.
(8) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741–8744.
(9) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211–3214.
(10) Huang, J.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3455–3458.
(11) Structural oxygen transfer in poly-unsaturated peroxy acid is also somewhat more facile when the intervening double bonds have *Z* rather than *E* geometry, see: Liau, B. B.; Gnanadesikan, V.; Corey, E. J. *Org. Lett.* **2008**, *10*, 1055–1057.

Scheme 1

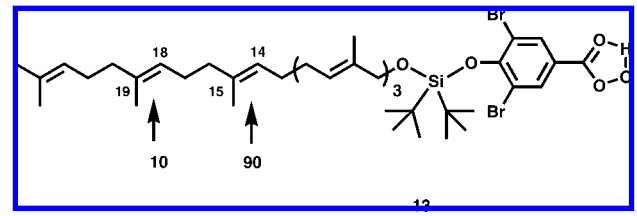


23 °C, 7 h, 73% overall yield); and (3) demethylation of **6** with Me_3SiOK in ether (Scheme 1).[12]

The acid **7a** was transformed into the peroxy acid **7b** by sequential reaction with carbonyldiimidazole in CH_2Cl_2 at 23 °C to form the corresponding *N*-acylimidazole and with a dry solution of H_2O_2 in $Et_2O-EtOAc$ at −60 °C.[7] When a solution of **7b** (0.5 mM concentration) was brought to −20 °C and maintained there, internal epoxidation occurred to form the terminal epoxide **8** with *>20:1 selectivity* . Methyl esterification of **8** and desilylation (HF−Py in THF at 23 °C)[13] gave solely the terminal epoxide **9** of all-*E*-tetraprenol, identical in all respects with the known compound.[14] We determined experimentally that the internal epoxidation competes very favorably with intermolecular epoxidation at an initial substrate concentration of 0.5 mM, and this protocol was employed in all the experiments described herein.

The nona-unsaturated peracid **10** (Scheme 2) was prepared from all-*E*-nonaprenol (solanesol) under the same conditions as used for **7b** (Scheme 1), with essentially identical yields. The peracid solution of **10** in CH_2Cl_2 (0.5 mM concentration) was maintained at −20 °C for 48 h and then treated with excess Me_2S. The resulting carboxylic acid product was methylated with CH_2N_2. For analytical purposes, a small quantity of epoxy silyl methyl ester **11** was subjected to the following sequence: (1) desilylation with HF−Py in THF and (2) oxirane cleavage with $H_5IO_6-Bu_4NIO_4$ in a $CH_2Cl_2-H_2O$ mixture. The oxidative cleavage products were isolated by extraction, filtration through a small pad of flash silica gel, and removal of solvent. The cleavage products, produced by the process oxirane → 1,2-diol → methyl ketone + aldehyde, were then subjected to GC−MS analysis, which revealed the formation of three methyl ketones arising from C−C cleavage at bonds 14−15 (92%), 18−19 (5%), and 10−11 (3%), leading to the distribution of oxirane products shown in formula **10** in Scheme 2. Preparative isolation of the methyl ester **11** was readily accomplished by column chromatography of the bulk of the reaction product on flash silica gel impregnated with $AgNO_3$. Desilylation of **11** provided the 14,15-epoxide of nonaprenol, **12** (Scheme 2).

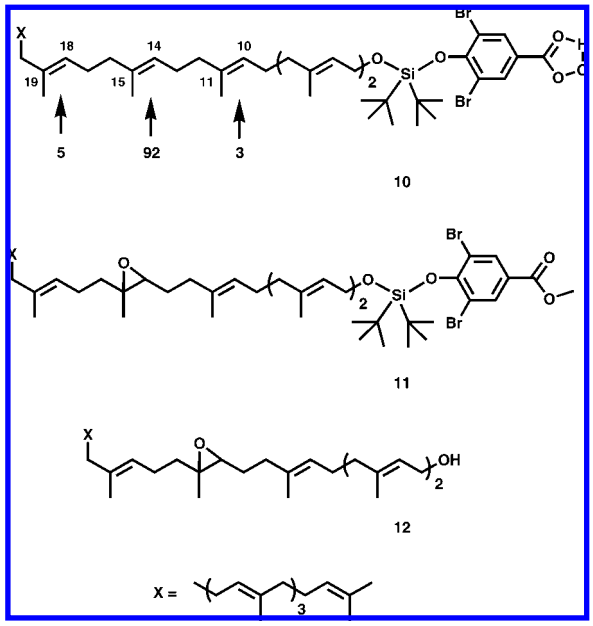
The above results with the 4-silyloxybenzoic acid controller in the substrates **7b** and **10** demonstrate that this controller effectively directs internal epoxidation to the double bond of the fourth prenyl unit from the prenyl−OH subunit (Δ^{14}). This same mode of selectivity also operates with an isoprenoid substrate that does not have all the prenyl groups arranged head-to-tail, as shown for the 1-hydroxylated squalene derivative **13**.[15] The peroxy acid **13** underwent internal epoxidation mainly at the double bond four removed from the controller (Δ^{14}). A small amount of epoxidation occurred at the double bond five away from the controller (Δ^{18}, ca. 10%), but none could be observed at the more proximate or remote olefinic units.[16]



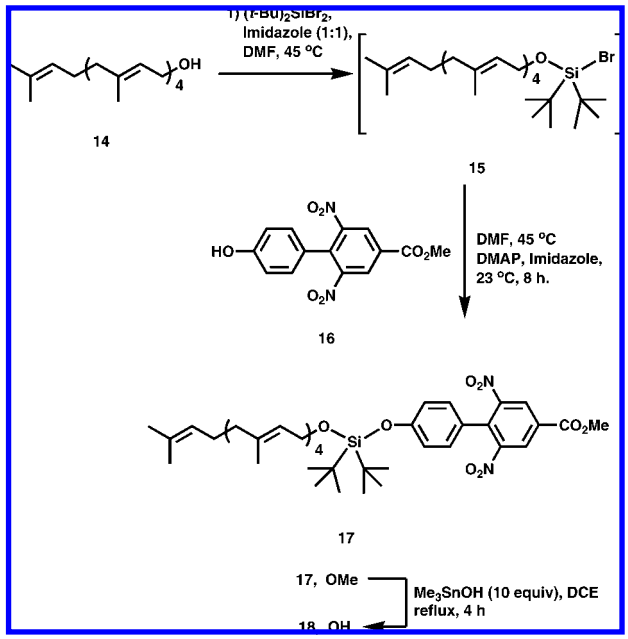
We have also designed a spacer/controller for the selective internal delivery of oxygen to the double bond five removed from the controller of a polyprenol (Δ^{18}). The pentanoic acid **18** was synthesized from all-*E*-pentaprenol **14** (geranylfarnesol)[17] by the following sequence: (1) mono coupling with 1 equiv of di-*tert*-butyldibromosilane, using imidazole catalyst in DMF at 45 °C for 8 h to give **15**; (2) a second coupling of **15** with the dinitro phenol **16**, DMAP (2 equiv), and imidazole (2 equiv) in dry DMF at 45 °C for 8 h, leading to 74% overall yield of **17**; and (3) demethylation of **17** with excess Me_3SnOH in refluxing dichloroethane (DCE), as shown in Scheme 3.[18] The pentaprenol peroxyacid **19** (see below for more detail) was

(12) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831–5834.
(13) For details, see Supporting Information.
(14) Corey, E. J.; Luo, G.; Lin, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 9927–9928.
(15) 1-Hydroxysqualene was prepared by SeO_2 oxidation of squalene with TBHP in CH_2Cl_2, see: Sen, S. E.; Prestwich, G. D. *J. Med. Chem.* **1989**, *32*, 2152–2158.
(16) The analysis of the internal epoxidation product from **13** and **22** was carried out by GC−MS measurements of the products of oxirane cleavage as described above for the products from **10** and **11**.
(17) McDonald, B. F.; Neiwert, F. T.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487–4489.
(18) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.

Scheme 2



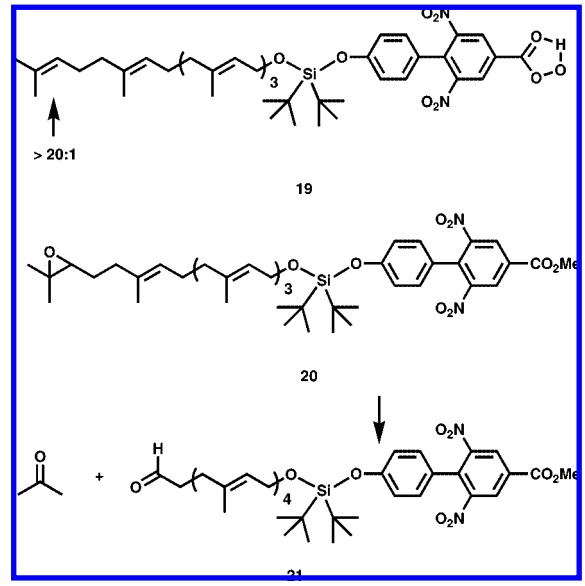
Scheme 3



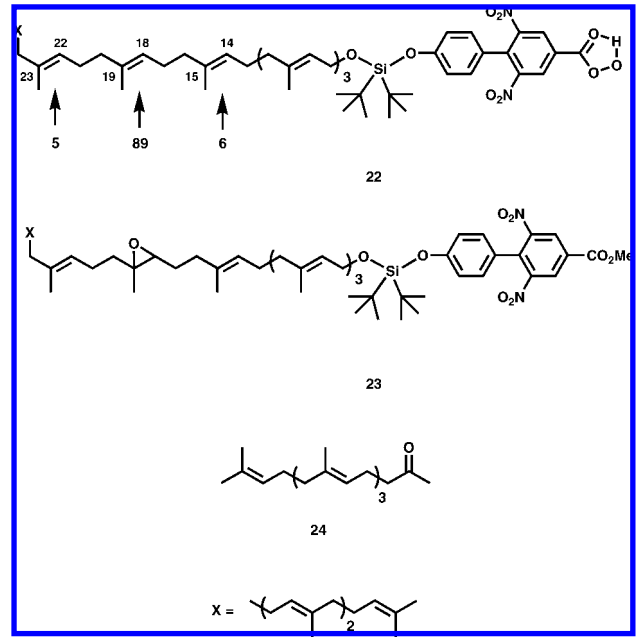
synthesized from **18** and allowed it to transfer oxygen internally in 0.5 mM solution in CH_2Cl_2 at −20 °C. The product was a single epoxide (81% yield) arising from the delivery of oxygen selectively to the terminal olefinic unit (fifth from the controller, as anticipated). Again the product was transformed to the methyl ester **20** and analyzed by GC−MS after oxidative cleavage of the oxirane subunit to form silyloxy aldehyde **21** and acetone (see Scheme 4).

We have also examined the application of the biphenyl spacer **16** to the selective internal epoxidation of nonaprenol. The nona-unsaturated biphenyl-linked peroxy acid **22** was prepared from all-*E*-nonaprenol by applying the methodology described above for **18** (61% overall yield from nonaprenol to the carboxylic acid corresponding to **22**, Scheme 3). The peracid solution **22** in CH_2Cl_2 (0.5 mM concentration, −20 °C) also underwent internal epoxidation mainly at the double bond five removed

Scheme 4



Scheme 5



from the controller, forming the 18,19-epoxide **23** after methylation (67% yield). The structure of **23** was proven by oxidative cleavage to methyl ketone **24** (Scheme 5). A minor amount of epoxidation occurred at the double bond four away (6%, Δ^{14}) and that six away (5%, Δ^{22}) from the controller, but no other epoxides could be detected.[16]

The results described above show that it is possible to achieve site-selective internal epoxidation of a double bond in a polyunsaturated substrate by the application of an appropriate spacer/controller group that also serves as the peroxy acid component. More specifically, the data support the stereomechanistic model for internal epoxidation in which the peroxy acid function approaches the reacting double bond in accord with the following constraints on the transition-state geometry: (1) oxygen is delivered in a synchronous fashion to both olefinic carbons, (2) the midpoint of the C=C π-bond aligns with the O−O σ^*-orbital (behind the O−O bond being broken in the

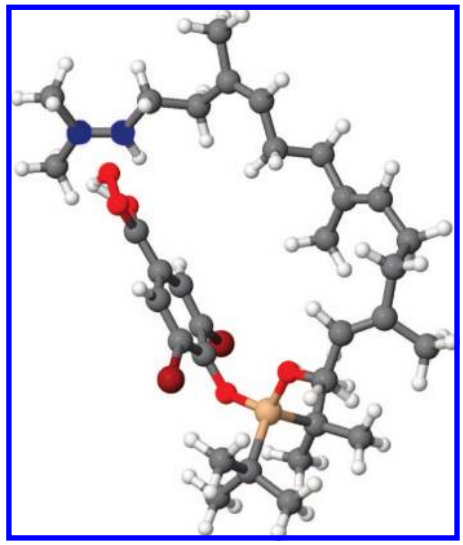


Figure 1. Approximate depiction of the internal epoxidation reaction of the peroxy acid **7b** derivative of tetraprenol that delivers oxygen selectively to the terminal isopropylidene group.

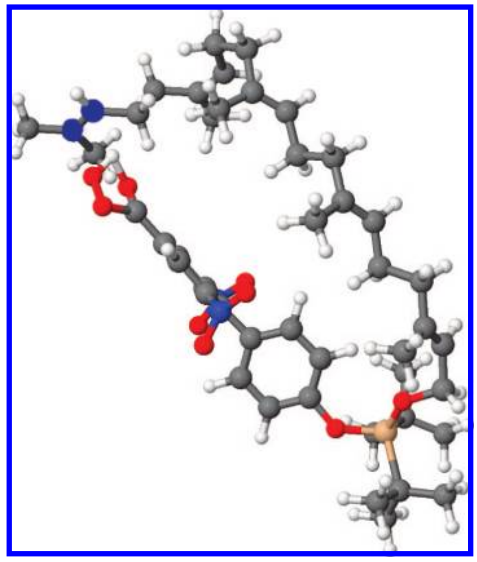


Figure 2. Representation of the internal epoxidation reaction of pentaprenol, showing the geometry for oxygen transfer from the peroxy acid function of the pentaprenol derivative **19** to the terminal isopropylidene unit, which is the farthest removed of the five double bonds.

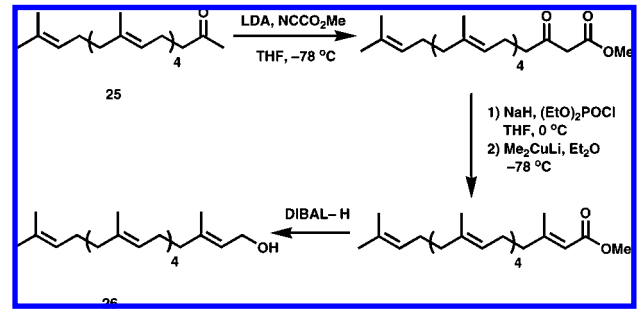
transition state), and (3) the plane of the internally H-bonded peroxy group is approximately orthogonal to the σ-plane of the olefinic partner.

The ball-and-stick model displayed in Figure 1 illustrates this geometrically favorable transition-state geometry for the internal epoxidation of tetraprenol (geranylgeraniol) using the 4-*tert*-butylsilyoxy peroxybenzoic acid spacer that delivers oxygen to the terminal isopropylidene group of **7b**.

Similarly, Figure 2 shows the favorable geometry that leads from the pentaprenol peroxy acid derivative **19** to the terminal epoxy acid corresponding to the methyl ester **20**.

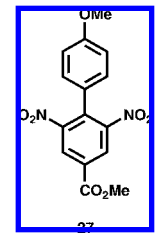
The availability of various epoxy polyprenols by the routes described above provides access to a range of interesting polyprenoids. For instance, the 14,15-epoxide **11** derived from the peroxy acid **10** affords the methyl ketone **25** by oxidative cleavage with $H_5IO_6-Bu_4NIO_4$ in a $CH_2Cl_2-H_2O$ mixture. This

Scheme 6



ketone was readily transformed into all-*E*-hexaprenol (farnesylfarnesol, **26**) in four high-yielding steps with an overall yield of 75%, as shown in Scheme 6.[19,20]

This study has concentrated on the use of the α-disubstituted 4-silyloxybenzoic and 4′-silyloxybiphenic acid spacers/controllers. These have the advantage of leading to highly reactive peroxy acids that possess the appropriate length for selective targeted internal epoxidation, axial symmetry (which reduces the conformational flexibility of the cyclic transition state), and also synthetic availability. The hydroxybiphenic ester **16**, required in the synthesis of peracids **19** and **22**, was made starting from 4-iodoanisole by the following sequence: (1) conversion to 4-lithioanisole (1 equiv of BuLi, THF, −78 °C, 30 min); (2) addition of 1 equiv of a solution of anhydrous $ZnCl_2$ in THF; (3) slow addition of this solution over 8 h to a solution of $(PPh_3)_4Pd$ and methyl 4-chloro-3,5-dinitrobenzoate in THF at 45 °C; and (4) isolation and demethylation of **27** with 3 equiv of BBr_3 in CH_2Cl_2 at −40 °C.



The di-*tert*-butylsilyl group was chosen for the controller since the required precursor t-Bu_2SiBr_2 is readily available (from t-$BuSiH_2$ and Br_2) and very suitable for successive coupling with the polyprenol and phenolic ester components. In addition, the di-*tert*-butylsilyloxy subunit is stable to isolation by extraction and chromatography on silica gel. An additional advantage of using the t-Bu_2Si subunit in the linker is that it serves to orient the aromatic peroxy group moiety and the polyprenol part in proximity to one another because of its steric bulk.

Conclusions

The research described herein shows the feasibility of applying internal epoxidation quite generally to the selective oxidation of a single, double bond in a polyene. Even when the olefinic units have the same intrinsic reactivity, the transition-state model shown as **3** above provides a reliable guide for the design of suitable controller/linker groups for the realization of useful site selectivity in epoxidation.

(19) For precedent, see: Chen, K. M.; Semple, J. E.; Joullie, M. M. *J. Org. Chem.* **1985**, *50*, 3997–4005.
(20) For a different approach to the synthesis of such oligoprenols, see: Radetich, B.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 2430–2432.

The entropy of activation of the internal epoxidation reactions can be expected to be quite negative, which clearly will diminish the rate of the reaction. However, with the reactions described above, the use of a highly reactive peroxy acid at concentrations of ca. 0.5 mM in CH_2Cl_2 can lead to a favorable rate of *intramolecular* epoxidation relative to *intermolecular* reaction and overcome the unfavorable entropic factor.

Acknowledgment. We thank Dr. L. Kürti and Dr. B. Czakó for help with the modeling studies.

Supporting Information Available: Experimental procedures for the reactions described herein and characterization data of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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