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An Approach to *Lauroxanes* by Iterative Use of $Co_2(CO)_6$-Acetylenic Complexes. A Formal Synthesis of (+)-Laurencin[†]

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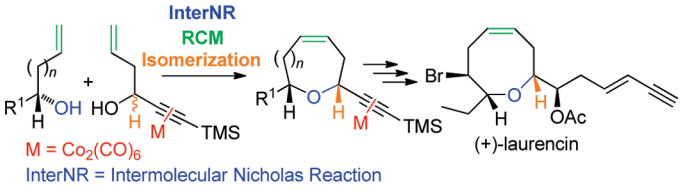

A new approach to lauroxanes by a powerful and highly convergent methodology based on iterative use of $Co_2(CO)_6$-acetylenic complexes is described. The strategy employs an intermolecular Nicholas reaction to form unsaturated branched linear ethers, a ring closing metathesis to obtain the cobalt complex cyclic ethers, and an isomerization promoted by montmorillonite K-10. A short synthesis of cyclic ethers of seven-, eight-, and nine-membered rings is described. Additionally, the methodology is exemplified by the formal synthesis of (+)-laurencin, a red algae metabolite.

Introduction

Medium-ring oxacycles are important structural features present and widespread in many marine natural products such as brevetoxin A and B, yessotoxin, ciguatoxin, gambieric acid A, the eunicellins, and maitotoxin, some of them implicated in massive fish kills and ciguatera seafood poisoning.[1] In addition, an important group of marine natural products, called lauroxanes, contain medium-ring ethers (Figure 1). Lauroxanes are a series of nonterpenoid C_{15}-metabolites derived from fatty acid metabolism (acetogenins) that have been isolated from the *Laurencia* species of red algae, and those marine organisms which feed on *L.* sp. These compounds display a wide range of biological activity including antitumor, antimicrobial, immunosuppressant, antifeedant, pesticide activity, etc.[1] The structural diversity of this kind of molecules is very wide, but all have in common the presence of halogenated cyclic ethers with a defined stereochemistry in the substituents and ring size ranging from five to nine members. Most have *cis* stereochemistry at the positions adjacent (α,α′) to the oxygen atom of the ether. Such cyclic ethers are considered to be biogenetically originated from linear lauredials, which occur in nature as various stereoisomers, through electrophilic cyclizations usually induced by a bromonium ion.[1e]

The fascinating structures and biological activities of such naturally occurring medium-ring oxacycles have stimulated the imagination and have been a challenge for synthetic chemists, and therefore a significant level of effort has been focused on the development of new methodologies for their synthesis. In general terms, the unfavorable entropy and enthalpy of activation associated with the formation of medium sized cyclic ethers have been a disadvantage for their synthesis. However, a plethora of methods have been developed to construct these systems.[2] Essentially, they can be summarized mainly on two major strategies: through the formation of a C−O bond, using a nucleophilic

[†] Dedicated to Professor José Barluenga Mur on the occasion of his 70th birthday.

(1) (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, pp 43−121. (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. V, pp 131−257. (c) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (d) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48. and preceding issues. (e) Kurozawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1972**, 2121–2124.

(2) (a) Alvarez, E.; Candenas, M. L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953–1980. (b) Mori, Y. *Chem.—Eur. J.* **1997**, *3*, 849–852. (c) Hoberg, L. O. *Tetrahedron* **1998**, *54*, 12631–12670. (d) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44–122. (e) Marmsäter, F. P.; West, F. G. *Chem.—Eur. J.* **2002**, *8*, 4346–4353.

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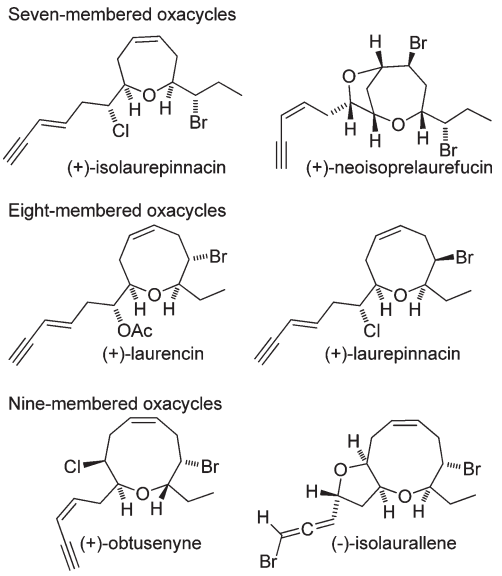
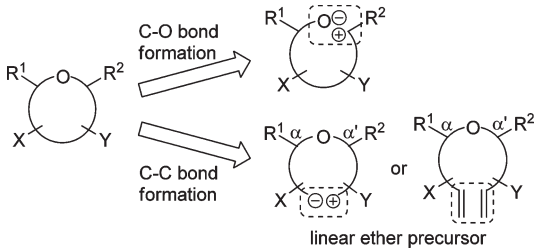


FIGURE 1. Representative C_{15} medium sized cyclic ether marine metabolites.

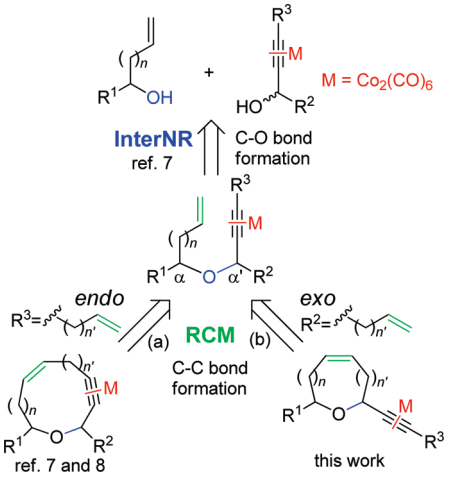
SCHEME 1. Main Strategies Used in the Synthesis of Polyfunctionalized Cyclic Ethers



oxygen, or by C−C bond formation using a linear ether precursor (Scheme 1).[2]

Within the last approach, the combination of the synthesis of the suitable unsaturated branched ether and ring-closing metathesis (RCM) provided a powerful methodology to the synthesis of isolated and fused medium sized cyclic ethers.[3] In consequence, the preparation of the α,α′-disubstituted linear ether precursor has become an intriguing synthetic challenge for the synthesis of the oxacycles. Even more interesting is to develop a tandem strategy that allows us to perform the formation of linear ether precursor and consecutively a RCM. In this sense we focused our attention on an intermolecular Nicholas reaction[4] (interNR) to build up the linear precursor.[5] With the branched linear ethers in hand, the next step would be the synthesis of the medium sized cyclic ethers through a RCM.[6] This tandem strategy has two alternative approaches (Scheme 2): (a) locating the alkyne $Co_2(CO)_6$-complexed moiety in an *endo* position with respect to the cyclic ether or (b) where such functionality is placed in an *exo* position.

SCHEME 2. Retrosynthetic Analysis of Cyclic Ethers Based on Tandem Intermolecular Nicholas Reaction (interNR) and RCM



Recently, using the *endo* strategy, path a in Scheme 2, we were able to obtain the saturated ethers (+)-*cis*- and (−)-*trans*-lauthisan and (+)-*cis*- and (+)-*trans*-obtusan, whose structures represent the basic skeletons present in a number of these naturally occurring nonterpenoid eight- and nine-membered ring ethers.[7,8] However, this approach has two important drawbacks. First, we could not use an allyl group in position R^3 of the $Co_2(CO)_6$-complexed propargylic alcohols, since the double bond of the substrate competes with the incoming oxygen by an intramolecular Nicholas reaction (intraNR). This competition forced us to introduce the allyl group after the linear ether was formed, lengthening the synthesis in several steps. Second, as suggested by our earlier exploratory investigations, with this approach we could not obtain seven-membered oxacycles.

On the basis of the alternative *exo* approach, herein, we report a powerful and highly convergent methodology that

(3) For representative examples, see: (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123–126. (c) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919–6920. (d) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548–7549. (e) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904–1907. (f) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7361–7365. (g) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440. (h) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791. (i) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157–6162. (j) Fujiwara, K.; Yoshimoto, A.; Souma, S.-I.; Mishima, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 6819–6822. (k) Sato, K.; Sasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2518–2522. (l) Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4726–4728. (m) Sasaki, M.; Oyamada, K.; Takeda, K. *J. Org. Chem.* **2010**, *75*, 3941–3943.

(4) (a) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, 4163–4167. (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214. (c) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1996**, *108*, 3128–3130. (d) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809–826. (e) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133–4170. (f) Diaz, D. D.; Betancort, J. M.; Martin, V. S. *Synlett* **2007**, 343–359. (g) Green, J. R. *Eur. J. Org. Chem.* **2008**, 6053–6062.

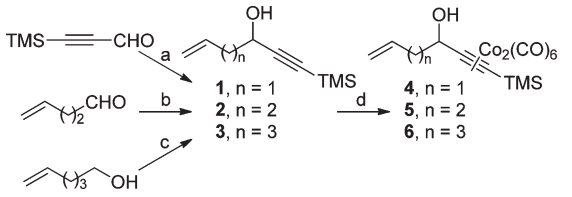
(5) For the synthesis of cyclic ethers by intramolecular Nicholas reactions, see: (a) Mukai, C.; Yamaguchi, S.; Sugimoto, Y.; Miyakoshi, N.; Kasamatsu, E.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6761–6765. and references cited therein. (b) Crisóstomo, F. R. P.; Martín, T.; Martín, V. S. *Org. Lett.* **2004**, *66*, 565–568 and references cited therein. (c) Hamajima, A.; Isobe, M. *Org. Lett.* **2006**, *8*, 1205–1208. and references cited therein. (d) Hamajima, A.; Isobe, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2941–2945. and references cited therein.

(6) For a RCM with cobalt alkyne complex, see: (a) Green, J. R. *Synlett* **2001**, 353–356. (b) Burlison, J. A.; Gray, J. M.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 5363–5365. (c) Young, D. G. J.; Burlison, J. A.; Peters, U. *J. Org. Chem.* **2003**, *68*, 3494–3497. (d) Rosillo, M.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Org. Biomol. Chem.* **2003**, *1*, 1450–1451. (e) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881–7889.

(7) Ortega, N.; Martín, T.; Martín, V. S. *Eur. J. Org. Chem.* **2009**, 554–563.

(8) Ortega, N.; Martín, T.; Martín, V. S. *Org. Lett.* **2006**, *8*, 871–873.

SCHEME 3. Preparation of $Co_2(CO)_6$-Propargylic Alcohols Bearing Remote Terminal Alkene[a]



[a]Reagents and conditions: (a) allylmagnesium bromide, Et_2O, −78 °C, 94%; (b) $Me_3SiC{\equiv}CH$, *n*-BuLi, THF, −78 °C, 89%; (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78 °C → rt, (ii) $Me_3SiC{\equiv}CH$, *n*-BuLi, THF, −78 °C, 87% over two steps; (d) $Co_2(CO)_8$, CH_2Cl_2, rt, quantitative.

allows us a very short synthesis of seven-, eight-, and nine-membered cyclic ethers by a real tandem interNR and RCM. When the target product has a *cis* stereochemical relationship in the α,α′ position, a consecutive isomerization step can be used. Additionally, using this strategy, we disclose a formal synthesis of the enantiomer of the natural product (+)-laurencin.

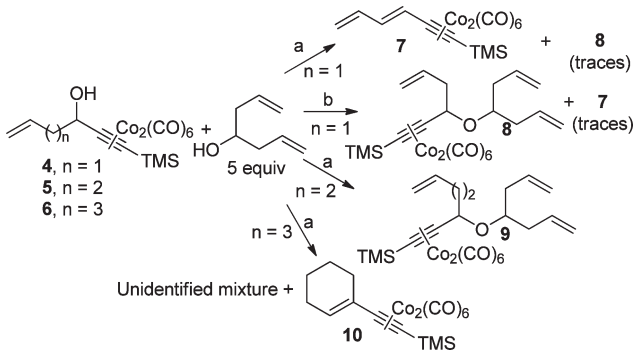
Results and Discussion

Our study started with the exploration of the suitable position of the double bond in R^2 of the cobalt complex in order to avoid undesirable intramolecular Nicholas or elimination reactions. Thus, the synthesis of a series of substrates was achieved, in which propargylic alcohol and a terminal alkene were linked through an alkyl chain with a variable length. To perform the synthesis of these compounds, we used as starting materials the appropriate commercially available aldehydes or alcohols (Scheme 3). In this way, propargylic alcohols **1**,[9] **2**,[6c] and **3** could be obtained by a simple addition of the suitable organometallic compound to aldehydes, and subsequent complexation with $Co_2(CO)_8$ providing the corresponding alkyne complexes **4**, **5**, and **6**.

The next step was to determine in which of these cobalt complexes occurs the interNR. Thus, we selected the 1,6-heptadien-4-ol as a common nucleophile to carry out this reaction (Scheme 4). We found that the cobalt complex **5** was the optimal, since we obtained the desired linear ether **9** with very good yields. Alternatively, the complex **6** gave mixtures including carbocycle **10** via an intramolecular carbon-cyclization reaction instead of the desired interNR. The use of **4** provided mainly the fully conjugated compound **7**, due to the elimination of the propargyl alcohol. Interestingly, **4** gave the desired interNR at lower temperatures (−20 °C), albeit contaminated with some elimination product. Taking into account these results we decided to use the cobalt complex **5** as a model for our *exo* approach to the synthesis of medium-sized cyclic ethers.

With the optimal cobalt complex **5** in hand, the following step was to perform the interNR using the allylic **11**, homoallylic **12**,[10] and bishomoallylic **13**[11] alcohols as nucleophiles

SCHEME 4. Evaluation of the Cobalt Complex in the *exo* Approach[a]



[a]Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2 (0.5 M), 0 °C; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2 (0.5 M), −20 °C.

(Scheme 5). The preparation of the enantiomerically enriched alcohols **11** and **12** has been previously described,[7] and the alcohol **13** was obtained, as a racemic mixture, by addition of *n*-butyllithium to the commercially available 4-pentenal. The optimized conditions for the interNR[7] afforded in very good yields the doubly branched ethers **14**, **15**, and **16**, respectively. At this point of the synthesis, the stereoselection of the newly created stereocenter in compound **14** could be determined by its ^1H NMR spectrum, observing a ratio of approximately 1.0:1.1, as later confirmed, in favor of the α,α′-*anti*-isomer.[12] Although it was very difficult to ensure the stereoselection in compounds **15**, a more elaborated fragment in the synthesis (vide infra) showed us a ratio of approximately 1.1:1.0, in favor of the α,α′-*syn*-isomers.[12] Unfortunately, we were unable to determinate the stereoselection obtained from compound **16**, even using more advanced intermediates.

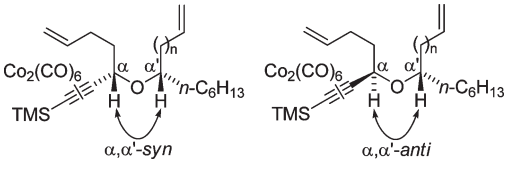
Having accomplished the important task of creating the proper substituted linear ether, we could now embark on the construction of cyclic ethers by the ring-closing metathesis process. Two major advantages can be attained from the use of the cobalt alkyne complex in the RCM process: first, the cobalt complex should avoid the undesirable participation of the triple bond in the metathesis process,[13] and second, the $Co_2(CO)_6$-alkyne in the *exo* position can be used as a functional group for further transformations and also as a stereochemical control agent for a critical isomerization process in the final cyclic product. With the diene complex **14** in hand, closure of the oxepene with the second-generation Grubbs' catalyst was performed. Thus, exposure of diene cobalt complex **14** to 30 mol % of the catalyst in dichloromethane (0.001 M) at reflux cleanly produced the

(9) The physical data are in agreement with the literature values: Darvesh, S.; Grant, A. S.; MaGee, D. I.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 712–722.

(10) The physical data are in agreement with the literature values: Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889–1904.

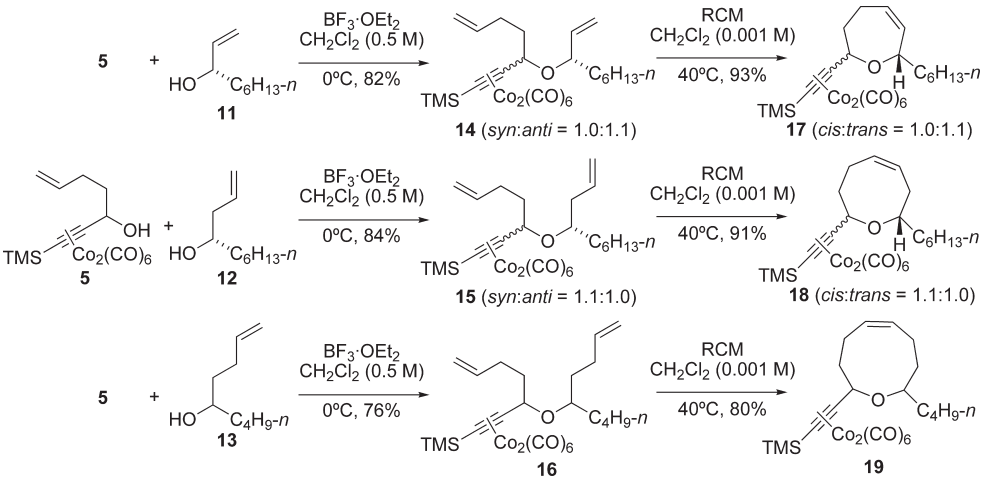
(11) The physical data are in agreement with the literature values: Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991–6994.

(12) Diastereoisomers *anti* and *syn* of the α,α′-disubstituted linear ethers are defined as described below:

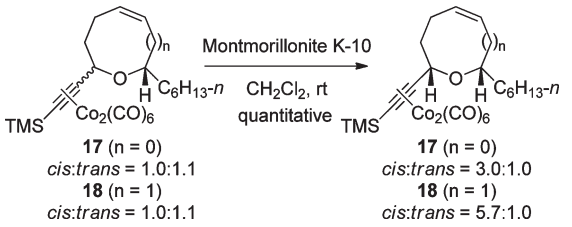


(13) For representative examples of enyne metathesis, see: Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

SCHEME 5. Tandem Process of interNR and RCM To Synthesize the Cobalt Complexes of Medium-Ring Oxacycles



SCHEME 6. Isomerization of 2,7-Disubstituted Oxepene 17 and 2,8-Disubstituted Oxocene 18 $Co_2(CO)_6$ Complexes Promoted by Montmorillonite K-10



desired cycle-complex **17** with excellent yields, as a mixture of isomers (*cis*:*trans* = 1.0:1.1). Using the same experimental conditions we carried out the cyclization of diene cobalt complexes **15** and **16**, obtaining the oxocene **18**, as a mixture of isomers (*cis*:*trans* = 1.1:1.0), and the oxonene **19** in excellent yields (Scheme 5). Interestingly, at this point of the synthesis both diastereoisomers of **17** and **18** were very easily separated by silica gel column chromatography. The stereochemistry of both isomers was clearly determined by NOE studies.

As aforementioned, separation of both diastereoisomers was very simple at this step. However, considering that both isomers were isolated in nearly equimolecular amounts, we pondered the possibility of performing an isomerization to the *cis*-isomer considering that such stereoisomers are usually thermodynamically more stable.[14] The use of our recently reported conditions relative to the use of montmorillonite K-10 as acid in the Nicholas reaction proved to be highly efficient to perform the desired conversion, presumably through a process involving a cation intermediate (Scheme 6).[15] The original mixture evolved quantitatively to a *cis*/*trans* ratio of 3.0:1.0 for the seven-membered ring **17** and a *cis*/*trans* ratio of 5.7:1.0 for the eight-membered ring **18**. Considering that in the oxocene **19** we were unable to distinguish both isomers, *cis* and *trans*, by TLC chromatography or by ^{1}H NMR and ^{13}C NMR, even at low or high temperature, we did not perform the isomerization step.

In an attempt to validate our methodology for the construction of medium-sized cyclic ethers, we decided to carry out the synthesis of the saturated systems. These molecules have served several times as the testing ground for the efficacy of medium-ring oxacycles construction. Therefore, the last steps required to complete the synthesis of the basic skeletons present in a number of these naturally occurring nonterpenoids were decomplexation of the $Co_2(CO)_6$ complexes *cis*-**17** and *cis*-**18**, cleavage of the TMS by TBAF, and further catalytic hydrogenation providing the saturated oxacycles *cis*-**22** and (+)-*cis*-lauthisan (*cis*-**23**) (Scheme 7) in excellent yields. It should be emphasized that, to the best of our knowledge, it is the shortest synthesis of (+)-*cis*-lauthisan, the fully saturated core of the natural derivative (+)-laurencin (Figure 1), and the one with highest overall yields reported up to this date, 53% over six steps from the cobalt complex **5** and the homoallylic alcohol **12**.[16]

Once we had established a methodology that allowed us to synthesize medium size cyclic ethers in a very efficient manner, the next step was to address the synthesis of (+)-laurencin. This compound is one of the most representative members from the group of lauroxanes and it was first isolated from the extracts of the red algae *Laurencia glandulifera* by Irie and Masamune and co-workers in 1965.[17] Its structure was determined by a combination of chemical degradation, spectroscopic methods, and X-ray crystallography, and the absolute configuration was assigned by the

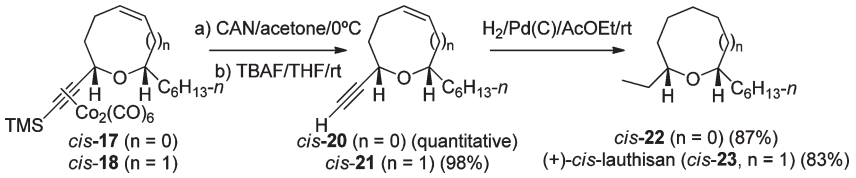
(14) For acid-induced isomerization in fused medium-sized $Co_2(CO)_6$-cycloalkyne ethers, see: (a) Liu, T.-Z.; Li, J.-M.; Isobe, M. *Tetrahedron* **2000**, *56*, 10209–10219. (b) Betancort, J. M.; Martín, T.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **2003**, *68*, 3216–3224.

(15) Crisóstomo, F. R. P.; Carrillo, R.; Martín, T.; Martín, V. S. *Tetrahedron Lett.* **2005**, *46*, 2829–2832.

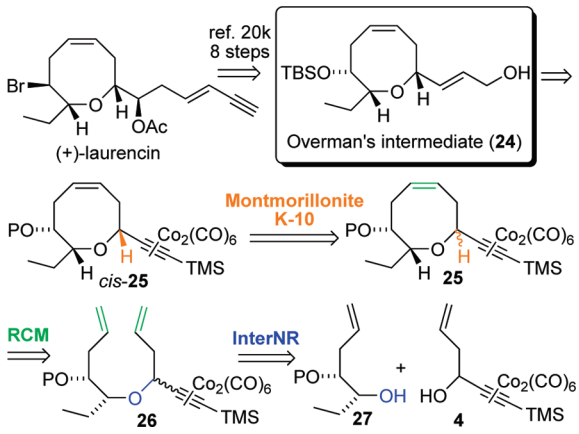
(16) For previously reported syntheses of lauthisan, see: (a) Tripathi, D.; Pandey, S. K.; Kumar, P. *Tetrahedron* **2009**, *65*, 2226–2231. (b) Reference 7. (c) Miyakoshi, N.; Ohgaki, Y.; Masui, K.; Mukai, C. *Heterocycles* **2007**, *74*, 185–189. (d) Reference 8. (e) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladie, G. *Org. Lett.* **2005**, *7*, 2039–2042. (f) Rhee, H. J.; Beom, H. Y.; Kim, H.-D. *Tetrahedron Lett.* **2004**, *45*, 8019–8022. (g) Coster, M. J.; De Voss, J. J. *Org. Lett.* **2002**, *4*, 3047–3050. (h) Suh, Y.-G.; Koo, B.-A.; Kim, E.-N.; Choi, N.-S. *Tetrahedron Lett.* **1995**, *36*, 2089–2092. (i) Kim, H.; Ziani-Cherif, C.; Oh, J.; Cha, J. K. *J. Org. Chem.* **1995**, *60*, 792–793. (j) Udding, J. H.; Giesselink, J. P. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 6671–6682. (k) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83–94. (l) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703–1704. (m) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263–6276. (n) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761–764. (o) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153–5161. (p) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565–567.

(17) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091–1099.

SCHEME 7. Synthesis of the Saturated Oxacycles

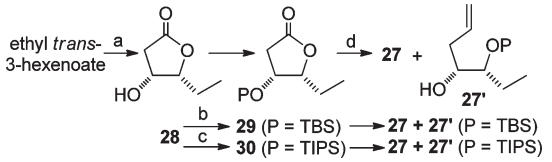


SCHEME 8. Retrosynthetic Analysis for the Stereoselective Synthesis of Overman's Intermediate (24)



Prelog atrolactic acid method on a side-chain degradation product.[17,18,19] Since its isolation as the first medium-ring ether from an algae, (+)-laurencin has been the subject of significant synthetic efforts and has been prepared by several different strategic approaches.[20] Our route to oxocanes seemed well suited to interface with a total synthesis of (+)-laurencin developed by Overman's group.[20k] In this synthesis the oxocene **24** is an advanced intermediate and has been converted in eight steps into the enantiomerically pure (+)-laurencin (Scheme 8). Therefore, this molecular block represents an interesting synthetic target inasmuch as its synthesis achieved in some alternative manner represents a new formal synthesis of the natural compound. As depicted in the retrosynthesis in Scheme 8, we envisaged that oxocene **24** might be secured via a simple sequence of reactions from the cobalt hexacarbonyl complex *cis*-**25**. Alkyne complex *cis*-**25** would be accessible by the three key steps used in our methodology: isomerization of the mixture of diastereomers **25** mediated by montmorillonite K-10 to obtain only the *cis* isomer (*cis*-**25**), RCM of the unsaturated branched ether cobalt complex **26**, and the interNR using the alcohol **27** and the acetylenic cobalt complex **4**. However, we were aware that the cobalt complex **4** is not the ideal substrate for the synthesis of cyclic ethers since, as mentioned above, the interNR needs to be carried out at −20 °C to avoid the formation of the elimination product **7**.

SCHEME 9. First Approach to the Synthesis of Alcohol 27[a]



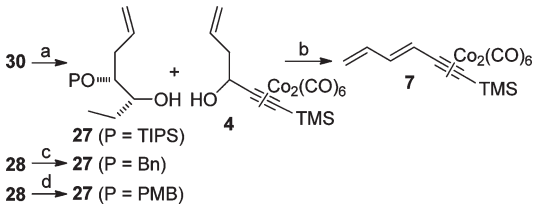
[a]Reagents and conditions: (a) AD-mix-β, $CH_3SO_2NH_2$, ^{t}BuOH:H_2O (1:1), 0 °C; (b) TBSCl, imidazole, CH_2Cl_2, rt, 92% over two steps; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 76% over two steps; (d) (i) DIBAL-H (1 equiv), Et_2O, −78 °C, (ii) $CH_3PPh_3^+Br^-$, *n*-BuLi, THF, −78 to −20 °C, overnight, 72% for **27** + **27**′ (P = TBS) over two steps and 74% for **27** + **27**′ (P = TIPS) over two steps.

Our first aim, therefore, was the preparation of enantiomerically enriched alcohol **27**. As a first approach, we chose as protecting group P the same that is present in the target molecule **24**, i.e. *tert*-butyldimethylsilyl (TBS). The synthesis of **27** (P = TBS) began with the commercially available ethyl *trans*-3-hexenoate, which was submitted to a Sharpless asymmetric dihydroxylation reaction[21] using AD-mix-β yielding the β-hydroxy-γ-lactone **28** (Scheme 9).[22] With this step we simultaneously achieved two important goals: first, we introduced the correct stereochemistry in the two stereocenters of the final molecule, and second, by spontaneous regioselective lactonization we performed the chemical differentiation between the two hydroxy groups. Protection of the free secondary alcohol as a *tert*-butyldimethylsilyl (TBS) ether afforded the γ-lactone **29**. For the completion of the synthesis, the γ-lactone **29** was reduced with 1 equiv of DIBAL-H and the lactol submitted to Wittig olefination with the ylide derived from commercially available methyltriphenylphosphonium bromide. Unsatisfactorily, instead of the expected **27**, a mixture of two alkenes resulting from migration of the silyl group was obtained.[23] In light of this result, we use the triisopropylsilyl ether as the protective

(18) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193–4205.
(19) (a) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1965**, 638. (b) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc. B* **1969**, 559–564.
(20) For a racemic total synthesis of laurencin, see: (a) Murai, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, *18*, 2507–2510. For asymmetric total syntheses of laurencin, see: (b) Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011–2015. (c) Fujiwara, K.; Yoshimoto, S.; Takizawa, A.; Souma, S.; Mishima, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 6819–6822. (d) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75–77. (e) Crimmins, M. T.; Emmitee, K. A. *Org. Lett.* **1999**, *1*, 2029–2032. (f) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. (g) Mújica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728–9729. (h) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483–7498. (i) Krüger, J.; Hoffman, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499–7504. (j) Mújica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983–984. (k) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958–5966. (l) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345–4348.

(21) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Shröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
(22) For a previous synthesis of the β-hydroxy-γ-lactone **28**, see: (a) Wang, Z. M.; Zhang, X. L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407–6410. For synthesis of other β-hydroxy-γ-lactones using Sharpless asymmetric dihydroxylation, see: (b) García, C.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 1420–1428. (c) Martín, T.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 2503–2505. (d) Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2750–2752.
(23) Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431–432.

SCHEME 10. Synthesis of alcohols 27 (P = TIPS, Bn, PMB) and the interNR with 4[a]

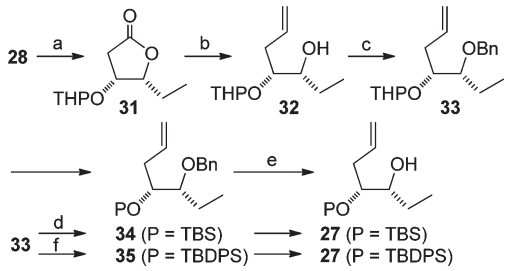


[a]Reagents and conditions: (a) (i) DIBAL-H (1 equiv), Et_2O, −78 °C, (ii) Tebbe reagent, THF, 0 °C, 30% over two steps; (b) $BF_3 \cdot OEt_2$, CH_2Cl_2 (0.5 M), −20 °C; (c) (i) BnBr, Ag_2O, TBAI (cat), DMF, rt, 3 days, 72%, (ii) DIBAL-H (1 equiv), Et_2O, −78 °C, (iii) $CH_3PPh_3^+Br^-$, *n*-BuLi, THF, −78 °C→rt, overnight, 67% over two steps; (d) (i) *p*-$MeOC_6H_4CH_2OC(=NH)CCl_3$, $La(OTf)_3$ (cat), toluene, rt, 73%, (ii) DIBAL-H (1 equiv), Et_2O, −78 °C, (iii) $CH_3PPh_3^+Br^-$, *n*-BuLi, THF, −78 °C→rt, overnight, 75% over two steps.

group, which is well-known to have less propensity to migrate.[24] However, when we carried out the reduction to the lactol of the γ-lactone **30** and tried a variety of conditions in the Wittig homologation, we observed similar results to those described above (Scheme 9). Therefore, we tested as an alternative the methylenation using the Tebbe reagent[25] in the lactol obtained from the γ-lactone **30**. In this way we could obtain, as the only isomer without any migration, the target alcohol **27** (P = TIPS), albeit with low yields (Scheme 10). Unfortunately, this approach failed when we used the lactol obtained from the γ-lactone **29**. Despite the low yield, this method provided us with enough alcohol **27** (P = TIPS) to carry out the interNR with cobalt complex **4**. Disappointingly, even performing the reaction at −20 °C we obtained exclusively the elimination compound **7**. In a similar manner as described in Scheme 9, we also prepared alcohols **27** bearing as protecting groups benzyl (P = Bn)[26] and *p*-methoxybenzyl (P = PMB). In these cases, the interNR of these alcohols with the cobalt complex **4** also failed, affording mainly the elimination product **7**. Having been unable to construct the desired linear ether we had to improve the synthesis of **27** and to look for a synthetic equivalent of **4**.

A new approach was developed to avoid the migration of the silyl-protecting group. In this sense, we used as starting material the previously prepared β-hydroxy-γ-lactone **28**, which after protection of the free secondary alcohol as tetrahydropyranyl ether **31** was converted to the protected homoallylic alcohol **32** by two consecutive steps: reduction with 1 equiv of DIBAL-H and one-carbon homologation by the Wittig-olefination of the lactol obtained. Protection of the free alcohol as benzyl ether gave the compound **33** in excellent yields (Scheme 11). The tetrahydropyranyl ether in **33** was converted directly into a *tert*-butyldimethylsilyl ether, affording **34**.[27] Finally, the cleavage of the benzyl group, using DDQ in a buffer solution at pH 7, provided the desired nucleophilic alcohol **27** (P = TBS) in good overall yield without any migration of the silyl group.

SCHEME 11. Synthesis of alcohols 27 (P = TBS, TBDPS)[a]



[a]Reagents and conditions: (a) DHP, $POCl_3$ (cat), CH_2Cl_2, rt, 92%; (b) (i) DIBAL-H (1 equiv), Et_2O, −78 °C, (ii) $CH_3PPh_3^+Br^-$, *n*-BuLi, THF, −78 °to −20 °C, 3 h, 82% over two steps; (c) NaH, BnBr, TBAI (cat), DMF, 0 °C→rt, overnight, 95%; (d) TBSOTf, Me_2S, CH_2Cl_2, −50 °C, 82%; (e) DDQ, Buffer pH 7, $ClCH_2CH_2Cl$, 40 °C, overnight, 91% for **27** (P = TBS) and 89% for **27** (P = TBDPS); (f) (i) Dowex 50Wx8, MeOH, rt, overnight, (ii) TBDPSCl, imidazole, CH_2Cl_2, rt, overnight, 98% over two steps.

With **27** (P = TBS) in hand, we turned our attention to the design of a new cobalt complex as electrophile for the Nicholas reaction. This cobalt complex should meet two key requirements: first, to have a lower tendency for elimination reactions, and second, to have a suitable terminal functional group in order to transform it into a double bond in later stages. Considering the above requirements, we synthetized two alternative cobalt complexes **36** and **37** (Figure 2).

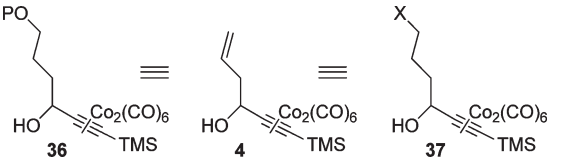


FIGURE 2. New synthetic equivalents of **4**.

Analyzing the retrosynthetic plan described in Scheme 8 and considering the structure of the target **24**, we should avoid the silyl-protection group in **36**, considering as plausible the alternative use of benzyl as the protecting group (P = Bn). The synthesis of the cobalt complex **36** (P = Bn) started with a selective monobenzylation of commercially available butane-1,4-diol, providing the alcohol **38**, which was oxidized by a Swern reaction,[28] and the crude aldehyde treated with the lithium acetylide of (trimethylsilyl)acetylene providing the propargylic alcohol **39**. Further complexation of the acetylene moiety by direct reaction with $Co_2(CO)_8$ in CH_2Cl_2 afforded the complexed alcohol **36** (P = Bn) (Scheme 12). Cobalt complex **37** was easily prepared from commercially available ethyl 4-bromobutyrate, which was reduced to the corresponding aldehyde and treated with the lithium acetylide of (trimethylsilyl)acetylene providing the propargylic alcohol **40**. Complexation of **40** with $Co_2(CO)_8$ afforded the complexed alcohol **37** (X = Br) (Scheme 12).

Once we had successfully synthesized the cobalt complex **36** (P = Bn), we examined the interNR with the alcohol **27** (P = TBS) at different temperatures. Unfortunately, when the reaction was conducted at 0 °C, the unprotected diol **41** and the elimination product **42** were obtained. Interestingly, when the interNR was carried out at −20 °C, the reaction delivered the desire branched ethers **43**, as a mixture of protected and free

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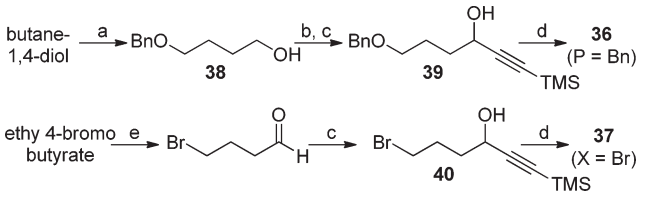
(25) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.

(26) Crimmins and co-workers synthesized the protected homoallylic alcohol **27** (P = Bn) using asymmetric glycolate alkylation of an acyl oxazolidinone, see ref 20e.

(27) Kim, S.; Kee, I. S. *Tetrahedron Lett.* **1990**, *31*, 2899–2900.

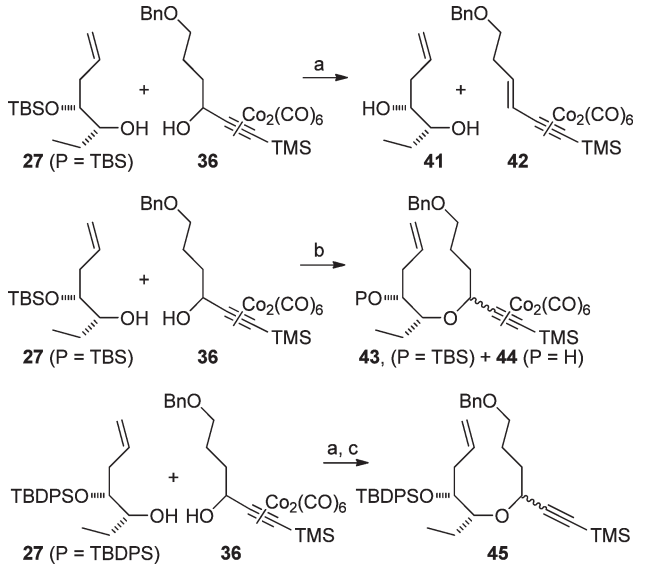
(28) Swern, D.; Mancuso, A. J.; Huang, S. *J. Org. Chem.* **1978**, *43*, 2480–2482.

SCHEME 12. Synthesis of the Cobalt Complex 36 (P = Bn) and 37 (X = Br)[a]



[a]Reagents and conditions: (a) NaH, BnBr, TBAI (cat), THF, 0 °C, 3 h, 85%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78 °C→rt; (c) $Me_3SiC{\equiv}CH$, *n*-BuLi, THF, −78 °C, 75% over two steps for **39** and 51% over two steps for **40**; (d) $Co_2(CO)_8$, CH_2Cl_2, rt, quantitative; (e) DIBAL-H (1 equiv), Et_2O, −78 °C.

SCHEME 13. Synthesis of the Branched Ethers Using the Alcohols 27 (P = TBS, TBDPS) and the Cobalt Complex 36[a]

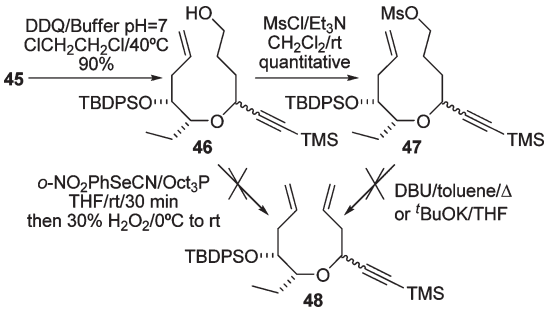


[a]Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2 (0.5 M), 0 °C; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2 (0.5 M), −20 °C; (c) CAN, acetone, 0 °C, 81% for **45** over two steps.

secondary alcohol **44**, probably due to the Lewis acid presence. It is noteworthy that the elimination product was not detected (Scheme 13). Once we established that the cobalt complex **36** (P = Bn) worked properly, we pondered the use of alcohol **27** with a more robust silyl-protecting group stable to the Nicholas reaction conditions. Therefore, we synthesized the alcohol **27** (P = TBDPS) in accordance with Scheme 11. In such a synthesis we used compound **33**, previously used for the synthesis of the alcohol **27** (P = TBS). Removal of the tetrahydropyranyl ether in **33**, followed by protection of the free secondary alcohol as a *tert*-butyldiphenylsilyl ether provided **35**, which after further cleavage of the benzyl ether delivered the alcohol **27** (P = TBDPS) in good overall yields. Gratifyingly it was found that the interNR took place, with very good yields, when the alcohol **27** (P = TBDPS) was used as nucleophile (Scheme 13).

With this satisfactory result in our hands the next step was the elimination reaction to obtain the dienes **48** required for the RCM. First we used DDQ in the presence of a buffer

SCHEME 14. Approach to the Synthesis of the Dienes 48



solution at pH 7 to obtain the free alcohols **46**, which were submitted to the one-pot protocol described by Grieco et al. in a fruitless manner (Scheme 14).[29] Alternatively, the alcohols **46** were converted to the methanesulfonates **47**, and treated under standard elimination conditions. However, these reactions also failed.

In light of these results we focused our attention on the cobalt complex **37** (X = Br) hoping that the elimination reaction could be carried out on the brominated derivative. It should be mentioned that based on our previous studies, halogen atoms are compatible with the Nicholas conditions providing a very convenient method to obtain halo-substituted ethers.[7,30] Gratifyingly, when the interNR was applied to **37** (X = Br) using as incoming alcohol **27** (P = TBDPS) the corresponding ethers **49**, after complex cleavage, were obtained as a mixture of isomers, ca. 1.0:1.0 (Scheme 15). Dienes **48** were readily elaborated from bromide derivatives **49** using a variant of the Grieco reaction.[31] Before the cyclization step by RCM, the complexation of the alkyne group was carried out with $Co_2(CO)_8$, affording the cobalt complexes **26** (P = TBDPS). This complexation generated a series of advantages that were described above. With the key linear precursors in hand, we proceeded to address the construction of the oxocene core by using a RCM reaction. Exposure of dienes **26** (P = TBDPS) to the RCM conditions using the second-generation Grubbs' catalyst gave the eight-membered ring ethers in 99% yields. The oxocenes **25** (P = TBDPS) were obtained as a mixture of *cis* and *trans* diastereomers in the propargyl carbon (ca. 1.0:1.0). This mixture of isomers *cis* and *trans* was transformed into the *cis* isomer quantitatively by treatment with montmorillonite K-10 in CH_2Cl_2 under reflux for 48 h.

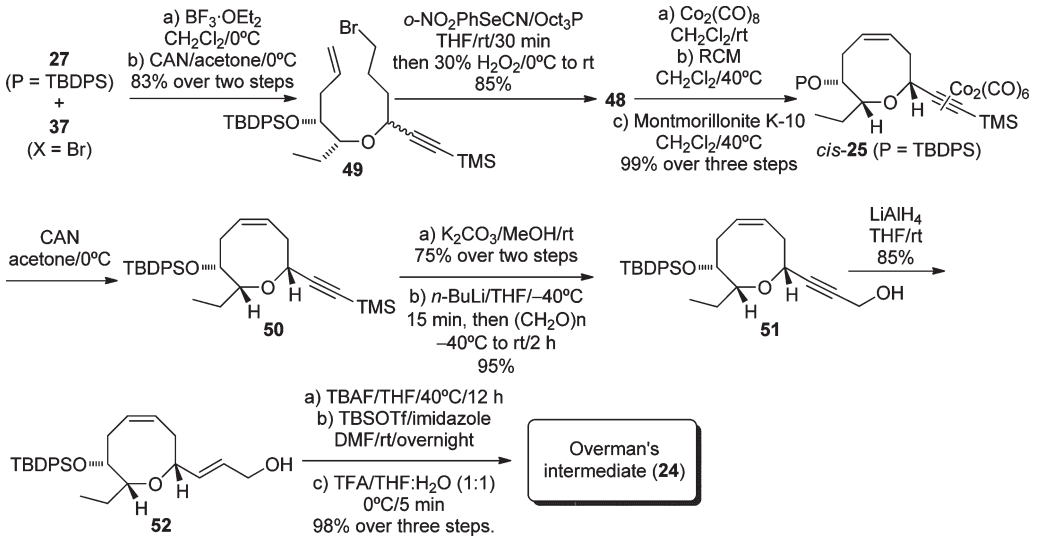
The completion of the formal synthesis from alkyne-cobalt complex *cis*-**25** (P = TBDPS) dealt with the transformation of the terminal alkyne to an allylic alcohol. To achieve this goal, an oxidative demetalation was performed to obtain the alkyne **50**. Selective removal of the trimethylsilyl protecting group under basic conditions followed by coupling of paraformaldehyde with the lithium salt of the terminal alkyne furnished the propargylic alcohol **51** in excellent yields (Scheme 15). Finally, the reduction of **51** to the allylic alcohol **52**, with $LiAlH_4$, provided an analogue of Overman's intermediate. Although compound **52** has a protective group of the same nature as Overman's intermediate, and therefore, it could be used to complete the

(29) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(30) Díaz, D. D.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 9993–9996.

(31) (a) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1974**, *40*, 947–949. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, 237–240.

SCHEME 15. Synthesis of the Overman's Intermediate (24)



synthesis of the natural product, in order to check the structure of this compound and to achieve the formal synthesis of (+)-laurencin a change in the protecting group in the secondary alcohol should be performed. Thus, cleavage of the TBDPS group with TBAF at 40 °C provided the corresponding diol, which was treated with TBSOTf to give the diprotected compound. The last step was a selective deprotection of the primary silyl ether with trifluoroacetic acid to give Overman's intermediate (**24**) with excellent yields, whose spectroscopic and physical data were in good agreement with those reported from Overman and co-workers.[20k]

Conclusion

The iterative use of the $Co_2(CO)_6$ acetylenic complex provides a powerful synthetic methodology to address the synthesis of medium-sized cyclic ethers. The strategy is based on three key steps: intermolecular Nicholas reaction, ring closing metathesis, and isomerization. One of the main goals of this methodology was the finding of the suitable position of the double bond in the cobalt complex in order to avoid undesirable intramolecular Nicholas or elimination reactions. In this manner a tandem strategy could be applied to the synthesis of seven-, eight-, and nine-membered cyclic ethers. We also validated our strategy by a formal synthesis of (+)-laurencin, one of the most representative lauroxanes. Current efforts are focused on the expansion of this strategy to the synthesis of other natural products containing medium ring ethers in their structures.

Experimental Section

Dicobalt Hexacarbonyl Complex of Trimethyl (3-((*S*)-Non-1-en-3-yloxy)hept-6-en-1-yn-1-yl)silane (14). Solid $Co_2(CO)_8$ (376 mg, 1.1 mmol) was added to a solution of 1-(trimethylsilyl)hept-6-en-1-yn-3-ol (**2**) (188 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 atmosphere. The dark solution was stirred at room temperature until TLC showed the formation of the complex to be completed (ca. 2 h). The reaction mixture was cooled to 0 °C, and the alcohol **11** was added (710 mg, 5 mmol), followed by the slow addition of $BF_3 \cdot OEt_2$ (317 μL, 2.5 mmol). After the addition, the reaction mixture was stirred for an additional 2 h. The mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude was purified by chromatographic column to give **14** as a dark red oil with a 1.0:1.1 mixture of isomers (488 mg, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.30 (s, 18H), 0.86 (m, 6H), 1.25−1.38 (m, 16H), 1.39−1.97 (m, 8H), 2.05−2.39 (m, 4H), 3.87 (m, 1H), 4.03 (dd, J = 6.7, 12.0 Hz, 1H), 4.55 (m, 2H), 5.12 (m, 8H), 5.62 (m, 2H), 5.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.77 (q), 13.8 (q), 22.3 (t), 22.3 (t), 24.7 (t), 25.1 (t), 29.0 (t), 29.1 (t), 29.7 (t), 30.2 (t), 31.5 (t), 31.5 (t), 34.6 (t), 35.1 (t), 36.3 (t), 39.0 (t), 74.2 (d), 74.8 (d), 79.5 (d), 80.3 (d), 114.7 (t), 114.9 (t), 117.9 (t), 118.4 (t), 137.4 (d), 137.8 (d), 138.9 (d), 139.1 (d), 200.23 (s); IR (film, NaCl plates) 2930, 2087, 2048, 841, 520 cm^{-1}.

Dicobalt Hexacarbonyl Complex of (2*S*)- and (2*R*)-(((7*S*)-Hexyl-2,3,6,7-tetrahidrooxepine-2-yl)etinyl)trimethylsilane (17). To a stirred solution of cobalt complexes **14** (400 mg, 0.67 mmol) in dry CH_2Cl_2 (670 mL, 0.001 M) was added 30 mol % of second generation Grubbs catalyst (172 mg, 0.20 mmol). The reaction was warmed at 40 °C and kept at that temperature until TLC showed complete conversion. Then, the solvent was evaporated and the residue was purified by column chromatography yielding 531 mg of **17** as a mixture of *cis*/*trans* isomers (93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 18H), 0.87 (m, 6H), 1.26−1.42 (m, 16H), 1.51−1.80 (m, 6H), 2.15−2.55 (m, 6H), 4.20 (s, 1H), 4.57 (s, 1H), 4.70 (m, 1H), 5.04 (dd, J = 5.1, 11.2 Hz, 1H), 5.58 (d, J = 14.9 Hz, 2H), 5.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.5 (q), 0.6 (q), 13.8 (q), 22.4 (t), 24.7 (t), 24.7 (t), 25.1 (t), 27.1 (t), 29.2 (t), 29.3 (t), 31.5 (t), 31.6 (t), 35.2 (t), 35.8 (t), 36.4 (t), 37.3 (t), 71.2 (d), 78.1 (d), 79.1 (d), 80.3 (d), 129.7 (d), 130.1 (d), 132.6 (d), 134.40 (d); IR (film, NaCl plates) 2931, 2087, 2019, 841 cm^{-1}.

Dicobalt Hexacarbonyl Complex of (((2*S*,7*S*)-7-Hexyl-2,3,-4,7-tetrahydrooxepin-2-yl)ethynyl)trimethylsilane (*cis*-17). To a solution of the $Co_2(CO)_6$ complexes **17** (*cis*:*trans*, 1.0:1.1) (300 mg, 0.53 mmol) in CH_2Cl_2 (53 mL) was added montmorillonite K-10 (900 mg) and the mixture was refluxed overnight. Then, the mixture was filtered and concentrated and the residue was purified by flash column chromatography, yielding *cis*-**17** (214 mg) and *trans*-**17** (71 mg) (95% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.29 (s, 9H), 0.87 (m, 3H), 1.26 (m, 6H), 1.42 (m, 2H), 1.59 (m, 2H), 1.75 (m, 1H), 2.17 (m, 2H), 2.52 (m, 1H), 4.22 (s, 1H), 4.73 (dd, J = 5.0, 11.0 Hz, 1H), 5.61 (d, J = 14.0 Hz, 1H), 5.83 (ddd, J = 5.0, 7.5, 12 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.5 (q), 13.8 (q), 22.4 (t), 24.7 (t), 25.1 (t), 29.2 (t), 31.5 (t), 35.8 (t), 37.3 (t), 79.1 (d), 80.3 (d), 129.7 (d), 134.40 (d); IR (film, NaCl plates) 2931, 2087, 2019, 841 cm^{-1}.

(2*S*,7*S*)-2-Ethynyl-7-hexyl-2,3,4,7-tetrahydrooxepine (*cis*-20). $Co_2(CO)_6$ complex *cis*-**17** (180 mg, 0.32 mmol) was dissolved in 3.2 mL of reagent grade acetone at 0 °C. Ceric ammonium nitrate (702 mg, 1.28 mmol) was added in small portions with stirring until evolution of CO ceased and the CAN color persisted (20 min). The solvent was removed under vacuum and the pink solid residue was then partitioned between Et_2O and H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding the free alkyne (89 mg, quantitative) as an oil: $[\alpha]^{25}_D$ −21.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 0.87 (m, 3H), 1.34 (m, 7H), 1.42−1.69 (m, 2H), 1.86 (m, 1H), 1.75 (m, 1H), 2.11 (m, 2H), 2.47 (m, 1H), 4.00 (s, 1H), 4.41 (dd, J = 5.8, 9.3 Hz, 1H), 5.52 (ddd, J = 2.0, 3.9, 14.7 Hz, 1H), 5.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.3 (q), 13.9 (q), 22.4 (t), 24.9 (t), 25.3 (t), 28.9 (t), 31.6 (t), 34.9 (t), 35.9 (t), 70.9 (d), 77.7 (d), 105.6 (s), 130.8 (d), 134.2 (d); IR (film, NaCl plates) 2956, 2857, 1101, 1074, 845 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 278 $(M)^+$ (2.4), 263 $(M - CH_3)^+$ (6.5), 219 (100), 193 $(M - C_6H_{13})^+$ (32.7); HRMS (EI) calcd for $C_{17}H_{30}OSi$ $(M)^+$ 278.2066, found 278.2078.

To a solution of free alkyne (62 mg, 0.22 mmol) in THF (2.2 mL, 0.1 M) at room temperature was added nBu$_4$NF (440 μL of a 1 M solution) dropwise. Then the reaction mixture was stirred at room temperature until TLC showed complete conversion, and then the mixture was poured into water and extracted with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding the terminal alkyne *cis*-**20** (45 mg, quantitative) as an oil: $[\alpha]^{25}_D$ −2.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.54−1.72 (m, 8H), 1.93 (m, 1H), 2.17 (m, 2H), 2.48 (s, 2H), 2.53 (m, 2H), 4.06 (s, 1H), 4.46 (s, 1H), 5.55 (dd, J = 1.2, 11.0 Hz, 1H), 5.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (q), 22.6 (t), 25.0 (t), 25.5 (t), 29.2 (t), 26.7 (d), 30.3 (t), 34.9 (t), 36.3 (t), 70.4 (d), 77.9 (d), 84.1 (s), 130.9 (d), 134.3 (d); IR (film, NaCl plates) 2954, 2876, 1677, 731 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 205 $(M - H)^+$ (14.8), 135 $(M - C_5H_{11})^+$ (10.1), 121 $(M - C_6H_{13})^+$ (100); HRMS (EI) calcd for $C_{14}H_{22}O$ $(M)^+$ 206.1671, found 206.1673.

(2*R*,7*S*)-2-Ethyl-7-hexyl-2,3,4,7-tetrahydrooxepine (*cis*-22). To a stirred solution of *cis*-**20** (30 mg, 0.14 mmol) in dry ethyl acetate (1.4 mL, 0.1 M) was added 10% Pd(C) (8 mg, 0.011 mmol) at room temperature under H_2 atmosphere (1 atm). The reaction mixture was stirred for 12 h, after which time TLC showed the end of the reaction. The solution was filtered through a pad of Celite and the filter was washed with EtOAc. The combined organic phases were concentrated, and the crude obtained was purified by flash chromatography to yield *cis*-**22** (26 mg, 87% yield): $[\alpha]^{25}_D$ +0.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83−0.95 (m, 6H), 1.24−1.58 (m, 14H), 1.60−1.85 (m, 6H), 3.35 (m, 1H), 3.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6 (q), 14.1 (q), 22.6 (t), 24.0 (t), 26.3 (t), 27.1 (t), 29.5 (t), 29.8 (t), 31.9 (t), 33.3 (t), 33.6 (t), 37.0 (t), 79.6 (d), 81.1 (d); IR (film, NaCl plates) 2926, 2857, 1459, 1090 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 197 $(M - CH_3)^+$ (21), 168 $(M - C_3H_8)^+$ (9), 97 $(C_6H_9O)^+$ (68), 55 (100); HRMS (EI) calcd for $C_{12}H_{23}O$ $(M - C_2H_5)^+$ 183.1749, found 183.1744.

Dicobalt Hexacarbonyl Complex of (3-((*S*)-Dec-1-en-4-yloxy)-hept-6-en-1-yn-1-yl)trimethylsilane (15). Solid $Co_2(CO)_8$ (376 mg, 1.1 mmol) was added to a solution of 1-(trimethylsilyl)hept-6-en-1-yn-3-ol (**2**) (188 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 atmosphere. The dark solution was stirred at room temperature until TLC showed the formation of the complex to be completed (ca. 2 h). The reaction mixture was cooled to 0 °C, and the alcohol **12** was added (781 mg, 5 mmol), followed by the slow addition of $BF_3 \cdot OEt_2$ (317 μL, 2.5 mmol). After the addition, the reaction mixture was stirred for an additional 2 h. The mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude was purified by chromatographic column to give **15** as a dark red oil with a mixture of isomers (1.1:1.0) (509 mg, 84% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32 (s, 18H), 0.88 (m, 6H), 1.18−1.79 (m, 22H), 1.80−1.99 (m, 2H), 2.15−2.45 (m, 8H), 3.63 (m, 2H), 4.55 (dd, J = 7.8, 15.6 Hz, 2H), 5.15 (m, 8H), 5.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.8 (q), 13.8 (q), 22.4 (t), 24.7(t), 24.8 (t), 25.4 (t), 28.9 (t), 29.3 (t), 29.3 (t), 29.8 (t), 29.9 (t), 31.5 (t), 31.6 (t), 33.1 (t), 35.8 (t), 36.8 (t), 37.2 (t), 37.8 (t), 37.8 (t), 75.1(d), 75.5 (d), 75.6 (d), 114.93 (t), 114.9 (t), 116.5 (t), 116.9 (t), 134.5 (d), 134.8 (d), 137.3 (d), 137.4 (d); IR (film, NaCl plates) 2931, 2859, 2087, 2020, 841, 520 cm^{-1}.

Dicobalt Hexacarbonyl Complex of (2*S*,5*Z*)- and (2*R*,5*Z*)-((8*R*-Hexyl-3,4,7,8-tetrahydro-2*H*-oxocin-2-yl)ethynyl)trimethylsilane (18). To a stirred solution of cobalt complexes **15** (450 mg, 0.74 mmol) in dry CH_2Cl_2 (740 mL, 0.001 M) was added 30 mol % of second generation Grubbs catalyst (188 mg, 0.22 mmol). The reaction was warmed at 40 °C and kept at that temperature until TLC showed complete conversion. Then, the solvent was evaporated and the residue was purified by column chromatography yielding 389 mg of **18** as a mixture of *cis*:*trans* isomers (1.1:1.0) (91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 18H), 0.87 (m, 6H), 1.28 (m, 16H), 1.55−2.55 (m, 16H), 3.43 (m, 1H), 3.91 (m, 1H), 4.66 (dd, J = 9.5, 9.5 Hz, 1H), 4.84 (dd, J = 3.8, 13.8 Hz, 1H), 5.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.6 (q), 0.7 (q), 13.8 (q), 22.3 (t), 23.7 (t), 24.5 (t), 25.5 (t), 26.4 (t), 29.1 (t), 29.2 (t), 31.0 (t), 31.4 (t), 31.5 (t), 32.6 (t), 32.7 (t), 35.9 (t), 39.1 (t), 41.1 (t), 71.9 (d), 78.8 (d), 80.9 (d), 127.6 (d), 128.4 (d), 130.9 (d), 131.7 (d), 200.3 (s); IR (film, NaCl plates) 2931, 2087, 2047, 841 cm^{-1}.

(((2*S*,8*S*,*Z*)-8-Hexyl-3,4,7,8-tetrahydro-2*H*-oxocin-2-yl)ethynyl)trimethylsilane (*cis*-18). To a solution of the $Co_2(CO)_6$ complexes **18** (350 mg, 0.6 mmol) in CH_2Cl_2 (121 mL) was added montmorillonite K-10 (1.05 g) and the mixture was stirred at room temperature overnight. Then, the mixture was filtered and concentrated and the residue was purified by flash column chromatography, yielding 295 mg of the *cis* isomer **18** (85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.31 (s, 9H), 0.89 (m, 3H), 1.28 (m, 9H), 1.58 (m, 2H), 1.71 (m, 1H), 1.85 (m, 2H), 2.12 (m, 2H), 2.62 (m, 1H), 3.45 (m, 1H), 4.67 (dd, J = 8.8, 8.8 Hz, 1H), 5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.8 (q), 14.0 (q), 22.6 (t), 23.9 (t), 25.6 (t), 29.4 (t), 31.8 (t), 32.8 (t), 36.1 (t), 39.3 (t), 79.1 (d), 81.1 (d), 128.6 (d), 131.2 (d); IR (film, NaCl plates) 2931, 2087, 2047, 841 cm^{-1}.

(2*S*,8*S*,*Z*)-2-Ethynyl-8-hexyl-3,4,7,8-tetrahydro-2*H*-oxocine (*cis*-21). $Co_2(CO)_6$ complex *cis*-**18** (200 mg, 0.34 mmol) was dissolved in 3.4 mL of reagent grade acetone at 0 °C. Ceric ammonium nitrate (745 mg, 1.28 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (20 min). The solvent was removed under vacuum and the pink solid residue was then partitioned between Et_2O and distilled H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding the free alkyne (97 mg, 98% yield) as an oil: $[\alpha]^{25}_D$ −38.9 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 0.87 (m, 3H), 1.34 (m, 8H), 1.54 (m, 2H), 1.64 (m, 1H), 1.97 (m, 3H), 2.27 (m, 1H), 2.48 (m, 1H), 3.31 (dd, J = 11.0, 11.0 Hz, 1H), 4.18 (m, 1H), 5.63 (ddd, J = 9.6, 12.4, 14.0 Hz, 1H), 5.78 (ddd, J = 10.8, 10.8, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.3 (q), 13.9 (q), 22.4 (t), 22.7 (t), 26.0 (t), 28.9 (t), 31.8 (t), 34.5 (t), 35.8 (t), 36.4 (t), 69.1 (d), 82.12 (d), 106.0 (s), 128.7 (d), 130.0 (d); IR (film, NaCl plates) 2956, 2930, 2174, 1086, 844 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 292 $(M)^+$ (0.2), 277 $(M - CH_3)^+$ (1.0), 109 $(C_7H_9O)^+$ (51.8),

73.0 $(C_3H_9Si)^+$ (100); HRMS (EI) calcd for $C_{18}H_{32}OSi$ $(M)^+$ 292.2222, found 292.2216.

To a solution of the free alkyne (90 mg, 0.31 mmol) in THF (3.1 mL, 0.1 M) at room temperature was added TBAF (620 μL of a 1 M solution) dropwise. The reaction mixture was stirred at room temperature until TLC showed complete conversion, and then was poured into water and extracted with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding *cis*-**21** as a colorless oil (68 mg, quantitative): $[\alpha]^{25}_D$ −19.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.37 (m, 8H), 1.53 (m, 2H), 1.69 (m, 1H), 2.05 (m, 3H), 2.29 (m, 1H), 2.45 (s, 1H), 2.55 (m, 1H), 3.33 (m, 1H), 4.21 (d, J = 14.5 Hz 1H), 5.65 (ddd, J = 9.2, 12.8, 13.6 Hz, 1H), 5.80 (ddd, J = 10.4, 10.8, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (q), 22.4 (t), 22.7 (t), 25.9 (t), 28.9 (t), 31.6 (d), 34.3 (t), 35.9 (t), 36.4 (t), 68.4 (d), 72.4 (s), 82.41 (d), 84.1 (s), 128.7 (d), 130.0 (d); IR (film, NaCl plates) 2920, 1737, 733, 485 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 220 $(M)^+$ (1.3), 106 $(C_8H_{10})^+$ (100), 91 $(C_7H_7)^+$ (85.9); HRMS (EI) calcd for $C_{15}H_{24}O$ $(M)^+$ 220.1827 found, 220.1834.

(+)-*cis*-Lauthisan (*cis*-23). To a stirred solution of *cis*-**21** (55 mg, 0.25 mmol) in dry ethyl acetate (2.5 mL, 0.1 M) was added 10% Pd(C) (13.6 mg, 0.019 mmol) at room temperature under H_2 atmosphere (1 atm). The reaction mixture was stirred for 15 h, after which time TLC showed the end of the reaction. The solution was filtered through a pad of Celite and the filter washed with EtOAc. The combined organic phases were concentrated, and the crude obtained was purified by flash chromatography to yield (+)-*cis*-Lauthisan (*cis*-**23**) (56.6 mg, 83% yield), whose spectroscopic and physical data were in good agreement with those reported previously:[16e] $[\alpha]^{25}_D$ +6.0 (*c* 0.2, $CHCl_3$) [lit. $[\alpha]^{25}_D$ +4.0 (*c* 0.15, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (m, 6H), 1.15−1.72 (m, 22H), 3.53 (m, 1H), 3.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6 (q), 13.9 (q), 22.4 (t), 23.8 (t), 26.1 (t), 26.8 (t), 29.2 (t), 29.5 (t), 31.7 (t), 33.1 (t), 33.3 (t), 36.8 (t), 79.4 (d), 81.8 (d).

Dicobalt Hexacarbonyl Complex of Trimethyl(3-(non-1-en-5-yloxy)hept-6-en-1-yn-1-yl)silane (16). Solid $Co_2(CO)_8$ (376 mg, 1.1 mmol) was added to a solution of 1-(trimethylsilyl)hept-6-en-1-yn-3-ol (**2**) (188 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 atmosphere. The dark solution was stirred at room temperature until TLC showed the formation of the complex to be completed (ca. 2 h). The reaction mixture was cooled to 0 °C, and the alcohol **13** was added (711 mg, 5 mmol), followed by the slow addition of $BF_3 \cdot OEt_2$ (317 μL, 2.5 mmol). After the addition, the reaction mixture was stirred for an additional 2 h. The mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude was purified by chromatographic column to give **16** as a dark red oil (450 mg, 76% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 9H), 0.89 (dd, J = 6.3, 6.3 Hz, 3H), 1.31 (m, 4H), 1.50−1.67 (m, 6H), 1.93 (m, 2H), 2.21 (m, 2H), 3.58 (m, 1H), 4.52 (dd, J = 5.1, 5.7 Hz, 1H), 5.00 (m, 4H), 5.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.86 (q), 13.7 (s), 22.7 (t), 27.0 (t), 27.2 (t), 29.2 (t), 29.9 (t), 32.1 (t), 32.7 (t), 32.9 (t), 36.8 (t), 75.1 (d), 75.7 (d), 114.2 (t), 114.3 (t), 115.0 (t), 137.3 d), 138.2 (d), 138.7 (d); IR (film, NaCl plates) 2936, 2088, 2048, 841 cm^{-1}.

Dicobalt Hexacarbonyl Complex of (*Z*)-((9-Butyl-2,3,4,7,8,9-hexahydrooxonin-2-yl)ethynyl)trimethylsilane (19). To a stirred solution of cobalt complexes **16** (400 mg, 0.67 mmol) in dry CH_2Cl_2 (670 mL, 0.001 M) was added 30 mol % of second generation Grubbs catalyst (172 mg, 0.20 mmol). The reaction was refluxed until TLC showed complete conversion (1 h). Then, the solvent was evaporated and the residue was purified by column chromatography yielding 305 mg of the complex **19** (80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (s, 9H), 0.92 (m, 3H), 1.23−1.68 (m, 8H), 1.87 (m, 4H), 2.73 (m, 2H), 3.75 (dd, J = 4.4, 8.8 Hz, 1H), 4.78 (dd, J = 5.2, 5.2 Hz, 1H), 5.56 (dd, J = 5.6, 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.82 (q), 0.86 (q), 13.9 (s), 19.9 (t), 20.7 (t), 23.0 (t), 28.1 (t), 29.5 (t), 29.7 (t), 34.1 (t), 34.9 (t), 72.6 (d), 73.7 (d), 129.9 (d), 130.3 (d); IR (film, NaCl plates) 2932, 2087, 2047, 839 cm^{-1}.

(4*R*,5*R*)-5-Ethyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)dihydrofuran-2(3*H*)-one (31). The γ-lactone **28** was dissolved in CH_2Cl_2 (47 mL, 0.3 M) in a flask under nitrogen, and then DHP (2.5 mL, 28 mmol) and a catalytic amount of $POCl_3$ were added. After 1 h the TLC showed that the reaction finished, then it was quenched with Et_3N and concentrated under vacuum. The resulting residue was purified by column chromatography yielding **31** (2.7 g, 92% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (m, 6H), 1.51 (m, 8H), 1.77 (m, 8H), 2.45−2.67 (m, 2H), 2.68 (d, J = 3.6 Hz, 2H), 3.43 (dd, J = 5.1, 5.6 Hz, 2H), 3.72 (m, 2H), 4.28 (m, 3H), 4.43 (dd, J = 4.4, 4.8 Hz, 1H), 4.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8 (q), 10.1 (q), 19.1 (t), 19.1 (t), 21.8 (t), 25.1 (t), 25.1 (t), 30.4 (t), 35.8 (t), 37.7 (t), 62.4 (t), 62.5 (t), 70.8 (t), 74.9 (t), 85.5 (t), 85.7 (t), 95.5 (t), 100.4 (t), 175.3 (s), 175.6 (s); IR (film, NaCl plates) 3536, 2943, 1777 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 215 $(M + H)^+$ (2), 113 $(C_6H_9O_2)^+$ (48), 85 $(C_5H_9O)^+$ (100); HRMS (ESI) calcd for $C_{11}H_{18}O_4Na$ $(M + Na)^+$ 237.1103, found 237.1108.

(3*R*,4*R*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)hept-6-en-3-ol (32). The γ-lactone **31** (2.6 g, 12.13 mmol) was disolved in Et_2O (121 mL, 0.1 M) at −78 °C under nitrogen, and DIBAL-H (12.1 mL of a 1 M solution) was added dropwise. After 30 min the TLC showed that the reaction was complete, and the reaction mixture was quenched with water. Then the reaction was warmed at room temperature, and a white precipitate was observed. The reaction mixture was dried with $MgSO_4$ and filtrated through a pad of Celite, then the aldehyde obtained was used in the next step without further purification. Ph_3PCH_3Br (13 g, 36.4 mmol) was placed in a dry flask at −20 °C under nitrogen with THF (60 mL) and *n*BuLi (13.8 mL of a solution 2.2 M in hexano) was added dropwise. The reaction mixture was stirred at this temperature for 30 min, and then the stirring was stopped to let the salts precipitate. In another flask the aldehyde obtained previously was dissolved in dry THF (60 mL) and was cooled at −20 °C. Then the orange solution of the ylide was added dropwise, and the reaction mixture was stirred for 3 h. The reaction was quenched with H_2O (100 mL) and the aqueous phase was extracted with Et_2O. The combined organic layers where dried with $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic column to give **32** (2.1 g, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (m, 6H), 1.28−2.65 (m, 22H), 3.45 (m, 6H), 3.88 (m, 2H), 4.42 (d, J = 3.6 Hz, 1H), 4.63 (d, J = 2.8 Hz, 1H), 4.98 (m, 4H), 5.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (q), 19.6 (t), 20.9 (t), 21.0 (t), 25.0 (t), 25.3 (t), 25.3 (t), 25.3 (t), 25.4 (t), 25.6 (t), 26.2 (t), 30.6 (t), 30.9 (t), 31.0 (t), 31.1 (t), 32.1 (t), 33.4 (t), 35.7 (t), 36.3 (t), 62.3 (t), 64.7 (t), 73.4 (d), 73.9 (d), 80.8 (d), 82.8 (d), 100.1 (d), 100.5 (d), 116.9 (t), 117.3 (t), 134.4 (d), 134.8 (t); IR (film, NaCl plates) 3441, 2941, 1641, 1028 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 199 $(M - CH_3)^+$ (2), 185 $(M - C_2H_5)^+$ (3), 85 $(C_5H_9O)^+$ (100); HRMS (EI) calcd for $C_{11}H_{19}O_3$ $(M - CH_3)^+$ 199.1334, found 199.1335.

2-(((4*R*,5*R*)-5-(Benzyloxy)hept-1-en-4-yl)oxy)tetrahydro-2*H*-pyran (33). NaH (409 mg, 10.2 mmol) was placed in a dry flask at 0 °C under nitrogen with DMF (47 mL, 0.2 M). Then the alcohol **32** (2 g, 9.33 mmol) was added slowly and after 5 min benzyl bromide (1.3 mL, 11.1 mmol) and a catalytic amount of TBAI were added. After 12 h the TLC showed that the reaction was complete, then the reaction was quenched with 50 mL of water and extracted with ether (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude was purified by chromatographic column to give **33** (2.7 g, 95% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (m, 6H), 1.45−1.92 (m, 16H), 2.21 (m, 2H), 2.52 (m, 2H), 3.52 (m, 4H), 3.93 (m, 4H), 4.66 (m, 6H), 5.14 (m, 4H), 5.95 (m, 2H), 7.37 (m,

10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (q), 10.8 (q), 19.7 (t), 19.8 (t), 22.4 (t), 22.8 (t), 25.5 (t), 25.6 (t), 30.8 (t), 31.1 (t), 34.0 (t), 35.8 (t), 62.5 (t), 62.6 (t), 72.5 (t), 72.7 (t), 98.9 (d), 99.1 (d), 116.4 (t), 116.7 (t), 127.4 (d), 127.4 (d), 127.5 (d), 127.6 (d), 127.7 (d), 127.7 (d), 127.8 (d), 127.9 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.6 (d), 135.7 (d), 135.8 (d), 138.9 (s), 139.1 (s); IR (film, NaCl plates) 2929, 1720, 1026, 484 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 219 $(M - C_5H_9O)^+$ (3), 197 $(M - C_7H_7O)^+$ (4), 91 $(C_7H_7)^+$ (77), 85 $(C_5H_9O)^+$ (100); HRMS (EI) calcd for $C_{19}H_{28}O_3$ $(M)^+$ 304.2038, found 304.2031.

(((4*R*,5*R*)-5-(Benzyloxy)hept-1-en-4-yl)oxy)(*tert*-butyl)diphenylsilane (35, P = TBDPS). To a solution of **33** (2.6 g, 8.54 mmol) in MeOH (43 mL, 0.2 M) was added Dowex 50Wx8 and the reaction mixture was stirred at room temperature until the TLC showed that the reaction was completed. The mixture was filtrated through a pad of Celite and concentrated under vacuum. The resulting oil was purified by chromatographic column to give the secondary alcohol (1.88 g, quantitative): $[\alpha]^{25}_D$ −3.9 (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (dd, *J* = 7.2, 7.6 Hz, 3H), 1.64 (ddd, *J* = 7.0, 7.0, 13.0 Hz, 1H), 1.76 (ddd, *J* = 7.0, 7.0, 14.0 Hz, 1H), 2.28 (m, 1H), 2.36 (m, 1H), 3.31 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.69 (m, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 5.11 (s, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 5.89 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 9.4 (q), 22.7 (t), 38.1 (t), 71.5 (d), 72.3 (t), 82.4 (d), 117.2 (t), 127.7 (d), 127.8 (d), 127.9 (d), 128.4 (d), 128.5 (d), 135.0 (d), 138.4 (s); IR (film, NaCl plates) 3417, 2932, 2857, 1112, 703 cm^{-1}.

The secondary alcohol obtained above (1.8 g, 8.17 mmol) was dissolved in CH_2Cl_2 (27 mL, 0.3 M) under nitrogen at room temperature, and then TBDPSCl (3.2 mL, 12.3 mmol) and imidazole (1.7 g, 24.5 mmol) were added. The reaction mixture was stirred until TLC showed that the reaction was finished (ca. 12 h) then it was quenched with 20 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers where dried with $MgSO_4$, filtrated, and concentrated. The crude was purified by chromatographic column to give **35** (P = TBDPS) (3.7 g, 98% yield): $[\alpha]^{25}_D$ +3.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (dd, *J* = 7.2, 7.6 Hz, 3H), 1.06 (s, 9H), 1.44 (m, 1H), 1.77 (m, 1H), 2.18 (m, 1H), 2.37 (m, 1H), 3.11 (m, 1H), 3.93 (dd, *J* = 4.4, 8.0 Hz, 1H), 5.71 (d, *J* = 10.0 Hz, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 4.91 (m, 2H), 5.73 (m, 1H), 7.13−7.45 (m, 10H), 7.68 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (q), 19.4 (t), 21.8 (t), 26.8 (q), 27.1 (q), 36.3 (t), 71.9 (t), 72.9 (d), 83.4 (d), 116.4 (t), 127.3 (d), 127.4 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.1 (d), 128.1 (d), 134.1 (s), 135.5 (d), 136.0 (d), 136.1 (d), 136.2 (d), 138.9 (s); IR (film, NaCl plates) 3070, 2933, 2858, 1109, 702 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 401 $(M - {}^t\mathrm{Bu})^+$ (4.1), 233 $(M - C_{13}H_{17}OSi)^+$ (66.6), 105 (C_6H_5Si) (100); HRMS (EI) calcd for $C_{26}H_{29}O_2Si$ $(M - {}^t\mathrm{Bu})^+$ 401.1937, found 401.1925.

(3*R*,4*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)hept-6-en-3-ol (27, P = TBDPS). 35 (P = TBDPS) (3.6 g, 7.85 mmol) was dissolved in 1,2-dichloroethane (157 mL, 0.05 M) and then a buffer solution at pH 7 (66.7 mL, 8.5 mL × mmol of starting material) and DDQ (7.13 g, 31.4 mmol) were added. The reaction mixture was stirred at 40 °C until TLC showed complete conversion of the starting material (ca. 12 h). Then it was cooled at room temperature, poured into a saturated aqueous $NaHCO_3$ (200 mL), and stirred vigorously for 12 h to give a dark red solution. The layers where separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers where dried with $MgSO_4$, filtrated, and concentrated. The crude was purified by chromatographic column to give **27** (P = TBDPS) (2.6 g, 89% yield): $[\alpha]^{25}_D$ −9.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.10 (s, 9H), 1.48 (m, 2H), 1.59 (s, 1H), 2.14 (m, 1H), 2.40 (m, 1H), 3.41 (dd, *J* = 2.4, 2.4 Hz, 1H), 3.64 (dd, *J* = 4.0, 8.0 Hz, 1H), 4.91 (m, 2H), 5.58 (m, 1H), 7.45 (m, 6H), 7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (q), 19.5 (s), 26.8 (t), 27.1 (q), 38.1 (t), 73.9 (d), 75.6 (d), 117.5 (t), 127.6 (d), 127.8 (d), 129.8 (d), 129.9 (d), 133.4 (s), 134.0 (d), 134.1 (d), 135.9 (d), 136.0 (d); IR (film, NaCl plates) 3466, 2934, 1428, 1110, 703 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 311 $(M - {}^t\mathrm{Bu})^+$ (12.7), 199 $(C_{12}H_{11}OSi)^+$ (100); HRMS (EI) calcd for $C_{19}H_{23}O_2Si$ $(M - {}^t\mathrm{Bu})^+$ 311.1467, found 311.1471.

6-Bromo-1-(trimethylsilyl)hex-1-yn-3-ol (40). To a solution of ethyl 4-bromobutyrate (1 g, 5.12 mmol) in dry Et_2O (51 mL, 0.1 M) at −78 °C under nitrogen was added DIBAL-H (5.1 mL of a 1 M solution) dropwise. After 30 min the TLC showed that the reaction was complete, and the reaction mixture was quenched with water. Then the reaction mixture was warmed at room temperature, and a white precipitate was observed. The reaction mixture was dried with $MgSO_4$ and filtrated with Celite, then the aldehyde obtained was used in the next step without further purification. On the other hand, ethynyltrimethylsilane (739 μL, 5.27 mmol) was dissolved in dry THF (26 mL, 0.1 M) at 0 °C under nitrogen. Afterward, *n*BuLi was added (3.3 mL of a solution 2.1 M in hexane) and the reaction mixture was stirred for 15 min. Then, the mixture was cooled at −78 °C and the crude aldehyde was added dissolved in dry THF (5 mL). The reaction was kept at that temperature until TLC showed complete conversion, and then was poured into saturated NH_4Cl and extracted with ethyl ether (2 × 25 mL). The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding **40** (650 mg, 51% overall yield): ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.81 (br s, 1H), 1.88 (m, 2H), 2.08 (m, 2H), 3.50 (m, 2H), 4.44 (dd, *J* = 5.2, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −0.17 (q), 28.4 (t), 33.3 (t), 36.0 (t), 62.0 (d), 90.1 (s), 106.0 (s); HRMS (ESI) calcd for $C_9H_{17}{}^{79}BrOSiNa$ $(M + Na)^+$ 271.0130, found 271.0129.

Preparation of (7*R*,8*R*)-8-Allyl-5-(3-bromopropyl)-7-ethyl-2,2,11,11-tetramethyl-10,10-diphenyl-6,9-dioxa-2,10-disiladodec-3-yne (49). The general procedure for the preparation of cobalt-complexed propargyl alcohols described above was applied to **40** (336 mg, 1.35 mmol). The dark solution was stirred at room temperature until TLC showed the formation of the complex to be completed (ca. 1 h), yielding the complex **37** (X = Br). The reaction mixture was cooled to 0 °C, and the alcohol **27** (P = TBDPS) (2.5 g, 6.75 mmol) was added followed by the slow addition of $BF_3 \cdot OEt_2$ (257 μL, 2 mmol). After the addition, the reaction mixture was stirred for an additional 6 h. The mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The cobalt complex was then dissolved (14 mL, 0.1 M) in reagent grade acetone at 0 °C. Ceric ammonium nitrate (2.9 g, 5.4 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (20 min). The solvent was removed under vacuum and the pink solid residue was then partitioned between Et_2O and distilled H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding **49** as a mixture 1.0:1.0 of isomers (672 mg, 83% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 0.18 (s, 9H), 0.82 (dd, *J* = 7.2, 7.6 Hz, 3H), 1.00 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.12 (s, 18H), 1.30−2.41 (m, 18H), 2.51 (m, 1H), 3.15 (dd, *J* = 4.0, 4.0 Hz, 2H), 3.30−3.51 (m, 5H), 3.65 (dd, *J* = 5.6, 6.0 Hz, 2H), 4.28 (m, 1H), 4.99 (m, 4H), 5.78 (m, 2H), 7.44 (m, 12H), 7.75 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.1 (q), −0.1 (q), 10.7 (q), 10.8 (q), 19.4 (t), 19.5 (t), 21.1 (t), 21.5 (t), 27.0 (q), 27.1 (q), 28.6 (t), 33.2 (t), 33.5 (t), 34.2 (t), 34.7 (t), 36.2 (t), 67.5 (d), 68.2 (d), 72.7 (d), 72.9 (d), 81.3 (d), 82.8 (d), 89.8 (s), 89.9 (s), 105.3 (s), 105.5 (s), 116.3 (t), 116.5 (t), 127.5 (d), 127.5 (d), 127.5 (d), 127.6 (d), 127.6 (d), 127.6 (d), 127.7 (d), 129.6 (d), 129.7 (d), 129.7 (d), 129.8 (d), 133.8 (s), 133.9 (s), 134.2 (s), 134.4 (s), 135.9 (d), 136.0 (d), 136.0 (d), 136.0 (d), 136.1 (d), 136.1 (d), 136.2 (d),

136.3 (d), 136.4 (d); IR (film, NaCl plates) 2961, 1251, 1108, 844, 703 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 541 $(M - {}^tBu)^+$ (1.1), 311 (61.2), 135 $(C_9H_{11}O)^+$ (100), 73 $(C_3H_9Si)^+$ (45.2); HRMS (EI) calcd for $C_{28}H_{39}{}^{79}BrO_2Si_2$ $(M + H - {}^tBu)^+$ 542.1672, found 542.1671.

Preparation of (7*R*,8*R*)-5,8-Diallyl-7-ethyl-2,2,11,11-tetramethyl-10,10-diphenyl-6,9-dioxa-2,10-disiladodec-3-yne (48). To a solution of *o*-NO_2PhSeCN (257 mg, 1.13 mmol) in ethanol (10.3 mL, 0.1 M) at 0 °C was added slowly $NaBH_4$ (46 mg, 1.24 mmol). After 15 min **49** (620 mg, 1.03 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. After this time, the TLC showed that the reaction was not complete, and an additional 0.04 equiv of *o*-NO_2PhSeCN and 0.1 equiv of $NaBH_4$ were added. After 5 h the reaction was complete, and the reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding **48** as a colorless oil (498 mg, 85% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 0.18 (s, 9H), 0.81 (dd, *J* = 7.2, 7.6 Hz, 3H), 0.98 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.10 (s, 18H), 1.39 (m, 3H), 1.82 (m, 2H), 2.27 (m, 6H), 2.51 (m, 1H), 3.14 (d, *J* = 4.4 Hz, 1H), 3.41 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.62 (d, *J* = 6.8 Hz, 1H), 3.68 (dd, *J* = 4.0, 4.0 Hz, 1H), 4.15 (dd, *J* = 3.2, 4.0 Hz, 1H), 5.03 (m, 8H), 5.77 (m, 4H), 7.43 (m, 12H), 7.74 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.2 (q), −0.1 (q), 10.7 (q), 10.8 (q), 19.4 (t), 19.5 (t), 21.2 (t), 21.5 (t), 27.0 (q), 27.1 (q), 36.0 (t), 36.2 (t), 40.2 (t), 40.8 (t), 68.5 (d), 68.9 (d), 81.5 (d), 82.9 (d), 89.6 (s), 105.4 (s), 105.6 (s), 116.2 (t), 116.4 (t), 117.2 (t), 117.4 (t), 127.4 (d), 127.5 (d), 127.6 (d), 127.6 (d), 127.6 (d), 129.5 (d), 129.6 (d), 129.7 (d), 133.9 (d), 133.9 (d), 133.9 (d), 134.5 (s), 136.0 (d), 136.0 (d), 136.1 (d), 136.1 (d), 136.1 (d), 136.2 (d), 136.4 (d), 136.6 (d); IR (film, NaCl plates) 2961, 2859, 1251, 1108, 843, 703 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 477 $(M - C_3H_5)^+$ (1.7), 311 $(C_{19}H_{23}O_2Si)^+$ (68.8), 135 $(C_9H_{11}O)^+$ (100), 73 $(C_3H_9Si)^+$ (78.5); HRMS (EI) calcd for $C_{29}H_{41}O_2Si_2$ $(M - C_3H_5)^+$ 477.2645, found 477.2658.

Preparation of the Hexacarbonyl Dicobalt Complex of *tert*-Butyl(((2*R*,3*R*,8*R*,*Z*)-2-ethyl-8-((trimethylsilyl)ethynyl)-3,4,7,8-tetrahydro-2*H*-oxocin-3-yl)oxy)diphenylsilane (*cis*-25, P = TBDPS). The general procedure for the preparation of cobalt-complexed propargyl alcohols described above was applied to **48** (470 mg, 0.9 mmol), to yield a mixture of cobalt complexes (729 mg, quantitative). To a stirred solution of cobalt complexes (470 mg, 0.9 mmol) in dry CH_2Cl_2 (450 mL, 0.002 M) was added 30 mol % of second generation Grubbs catalyst (229 mg, 0.27 mmol). The reaction was warmed at 40 °C and kept at that temperature until TLC showed complete conversion. Then, the solvent was evaporated and the residue was purified by column chromatography yielding 692 mg of **25** (P = TBDPS) as a mixture of *cis*:*trans* isomers (1.0:1.0) (99% yield). To a solution of the $Co_2(CO)_6$ complexes **25** (P = TBDPS) (1.0:1.0) (692 mg, 0.89 mmol) in CH_2Cl_2 (356 mL, 0.0025 M) was added montmorillonite K-10 (2.1 g) and the mixture was refluxed for 48 h. Then, the mixture was filtered and concentrated and the residue was purified by flash column chromatography, yielding 692 mg of *cis*-**25** (P = TBDPS) (quantitative): ^1H NMR (400 MHz, $CDCl_3$) δ 0.45 (s, 9H), 0.89 (m, 3H), 0.99 (s, 9H), 1.59 (m, 1H), 1.77 (m, 1H), 2.01 (m, 1H), 2.32 (m, 1H), 2.68 (m, 1H), 2.85 (m, 1H), 3.59 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.72 (dd, *J* = 8.4, 13.2 Hz, 1H), 4.47 (d, *J* = 10.0 Hz, 1H), 5.54 (ddd, *J* = 7.6, 8.4, 9.2 Hz, 1H), 5.79 (ddd, *J* = 7.6, 8.3, 9.2 Hz, 1H), 7.42 (m, 6H), 7.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.9 (q), 11.1 (q), 19.4 (s), 25.6 (t), 26.9 (q), 29.7 (t), 33.5 (t), 39.4 (t), 75.7 (d), 80.9 (d), 83.2 (d), 127.2 (d), 127.5 (d), 127.6 (d), 128.7 (d), 129.3 (d), 129.6 (d), 130.7 (d), 133.6 (s), 136.0 (d), 136.1 (d).

Preparation of *tert*-Butyl(((2*R*,3*R*,8*R*,*Z*)-2-ethyl-8-((trimethylsilyl)ethynyl)-3,4,7,8-tetrahydro-2*H*-oxocin-3-yl)oxy)diphenylsilane (50). $Co_2(CO)_6$ complex *cis*-**25** (P = TBDPS) (670 mg, 0.86 mmol) was dissolved in reagent grade acetone (8.6 mL, 0.1 M) at 0 °C. Ceric ammonium nitrate (1.9 g, 3.44 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (20 min). The solvent was removed under vacuum and the pink solid residue was then partitioned between Et_2O and distilled H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic layers were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding the alkyne **50** (317 mg, 75% yield) as an oil: $[\alpha]^{25}{}_D$ −12.5 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 9H), 0.94 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.04 (s, 9H), 1.39 (m, 1H), 1.91 (m, 2H), 2.26 (m, 1H), 2.75 (m, 2H), 3.23 (m, 1H), 3.71 (m, 1H), 3.94 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.39 (m, 1H), 5.68 (m, 1H), 7.40 (m, 6H), 7.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0 (q), 10.8 (q), 19.5 (s), 25.9 (t), 27.1 (q), 33.4 (t), 36.4 (t), 73.4 (d), 85.6 (d), 88.1 (s), 105.8 (s), 127.6 (d), 127.6 (d), 128.4 (d), 129.4 (d), 129.6 (d), 130.2 (d), 134.8 (s), 135.9 (d), 136.2 (d); IR (film, NaCl plates) 2961, 2858, 1074, 848, 705 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 433 $(M - {}^tBu)^+$ (36.6), 199 $(C_{12}H_{11}OSi)^+$ (79.8), 135 $(C_9H_{11}O)^+$ (100), 73 $(C_3H_9Si)^+$ (78.5); HRMS (EI) calcd for $C_{30}H_{42}O_2Si_2$ $(M)^+$ 490.2723, found 490.2726.

Preparation of 3-((2*R*,7*R*,8*R*,*Z*)-7-((*tert*-Butyldiphenylsilyl)oxy)-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)prop-2-yn-1-ol (51). To a solution of the alkyne **50** (300 mg, 0.61 mmol) in methanol (6.1 mL, 0.1 M) at room temperature was added K_2CO_3 (42 mg, 0.31 mmol). After TLC showed complete conversion, the reaction mixture was filtrated through a Celite pad and concentrated, yielding the terminal alkyne (quantitative). Then, the terminal alkyne was dissolved in dry THF (6.1 mL, 0.1 M) and cooled at −40 °C. Then *n*-BuLi (419 μL of a 1.6 M solution) was added and 15 min later paraformaldehyde (37 mg, 1.22 mmol). The reaction mixture was warmed at room temperature and after 2 h the TLC showed complete conversion. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The combined organic layers were dried with $MgSO_4$, filtrated, concentrated, and subjected to silica gel flash chromatography yielding **51** as a colorless oil (260 mg, 95% yield): $[\alpha]^{25}{}_D$ −17.8 (*c* 2.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.04 (s, 9H), 1.26 (s, 1H), 1.35 (m, 1H), 1.94 (m, 2H), 2.25 (m, 1H), 2.74 (m, 2H), 3.28 (d, *J* = 8.8 Hz, 1H), 3.68 (m, 1H), 3.99 (d, *J* = 10.4 Hz, 1H), 4.35 (s, 2H), 5.40 (m, 1H), 5.64 (m, 1H), 7.38 (m, 6H), 7.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (q), 19.5 (s), 25.9 (t), 27.1 (q), 33.4 (t), 36.3 (t), 51.3 (t), 72.7 (d), 76.8 (d), 82.5 (s), 85.3 (d), 85.8 (s), 127.3 (d), 127.6 (d), 128.2 (d), 129.4 (d), 129.7 (d), 130.4 (d), 133.6 (s), 134.7 (s), 136.0 (d), 136.1 (d); IR (film, NaCl plates) 3045, 2932, 2859, 1072, 704 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{27}O_3Si$ $(M - {}^tBu)^+$ 391.1729, found 391.1723.

Preparation of (*E*)-3-((2*R*,7*R*,8*R*,*Z*)-7-((*tert*-Butyldiphenylsilyl)oxy)-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)prop-2-en-1-ol (52). To a solution of **51** (240 mg, 0.53 mmol) in dry THF (5.3 mL, 0.1 M) under nitrogen and at room temperature was added $LiALH_4$ (802 μL of a 1 M solution) dropwise. After 12 h the TLC showed complete conversion and the reaction mixture was quenched with water. The mixture was dried, filtered, concentrated, and subjected to silica gel flash chromatography to yield 203 mg of **52** (85% yield): $[\alpha]^{25}{}_D$ −37.6 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.04 (s, 9H), 1.33 (m, 1H), 1.79 (m, 1H), 1.91 (dd, *J* = 5.6, 6.0 Hz, 1H), 2.06 (m, 2H), 2.42 (m, 1H), 2.74 (ddd, *J* = 10.8, 10.8, 10.8 Hz, 1H), 3.39 (ddd, *J* = 3.2, 3.2, 6.4 Hz, 1H), 3.76 (m, 2H), 4.20 (d, *J* = 5.2 Hz, 2H), 5.40 (dd, *J* = 1.6, 6.8 Hz, 1H), 5.67 (m, 1H), 5.85 (m, 1H), 5.92 (m, 1H), 7.38 (m, 6H), 7.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (q), 19.6 (s), 26.2 (t), 27.1 (q), 33.3 (t), 35.2 (t), 63.3 (t), 76.9 (d), 81.5 (d), 84.0 (d), 127.2 (d), 127.5 (d), 128.7 (d), 129.1 (d), 129.3 (d), 129.6 (d), 129.6 (d), 133.5 (d), 135.0 (s), 135.9 (d), 136.1 (d); IR (film, NaCl plates) 3381, 2932,

2858, 1071, 704 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 307 $(C_{19}H_{19}O_2Si)^+$ (7.2), 199 $(C_{12}H_{11}OSi)^+$ (100), 135 $(C_9H_{11}O)^+$ (48.7); HRMS (EI) calcd for $C_{24}H_{29}O_3Si$ $(M - {}^tBu)^+$ 393.1886, found 393.1874.

Preparation of (*E*)-3-((2*R*,7*R*,8*R*,*Z*)-7-((*tert*-Butyldimethylsilyl)-oxy)-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)prop-2-en-1-ol (24). To a solution of **52** (100 mg, 0.22 mmol) in dry THF (2.2 mL, 0.1 M) under nitrogen at room temperature was added TBAF (333 μL of a 1 M solution) dropwise. The reaction mixture was stirred at 40 °C for 12 h, when the TLC showed complete conversion. The reaction was then quenched with water and extracted with ether. The combined organic layers were dried with $MgSO_4$, filtrated, and concentrated. The crude was dissolved in dry DMF (2.2 mL, 0.1 M) and imidazole (45 mg, 0.7 mmol) and TBSOTf (0.15 mL, 0.5 mmol) were added. The reaction mixture was stirred for 12 h, and the TLC showed complete protection of the secondary alcohol. The reaction was quenched with an aqueous solution of HCl at 5%, and extracted with ether. The combined organic layers were dried on $MgSO_4$, filtrated, and concentrated under vacuum. The crude was dissolved in a mixture THF/H_2O (1:1) (1.1 mL of THF and 1.1 mL of H_2O) at 0 °C and CF_3CO_2H was added dropwise (8 μL, 0.11 mmol). After 5 min the TLC showed the complete cleavage of the primary alcohol, and the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic layers were dried, filtered, concentrated, and subjected to silica gel flash chromatography to yield **24** (70 mg, 98%), whose spectroscopic and physical data were in good agreement with those reported for Overman and co-workers:[20k] $[\alpha]^{25}_D$ −4.3 (*c* 0.26, $CHCl_3$) [lit. $[\alpha]^{25}_D$ −6.3 (*c* 0.85, $CHCl_3$)]; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.30 (m, 3H), 1.59 (s, 1H), 1.65 (m, 2H), 2.11 (m, 2H), 2.55 (m, 1H), 2.76 (ddd, J = 11.0, 11.0, 11.0 Hz, 1H), 3.44 (ddd, J = 3.0, 3.0, 9.5 Hz, 1H), 3.75 (m, 2H), 4.18 (d, J = 4.5 Hz, 2H), 5.32−589 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7 (q), −4.2 (q), 10.9 (d), 18.3 (s), 26.0 (q), 33.6 (t), 35.1 (t), 63.3 (t), 76.1 (d), 81.8 (d), 84.1 (d), 128.9 (d), 129.4 (d), 129.5 (d), 133.5 (d).

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**−**3**, **11**−**13**, and **28**, as well as copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.