DOI: 10.1002/ejoc.200801063

Synthesis of α,α′-Disubstituted Linear Ethers by an Intermolecular Nicholas Reaction – Application to the Synthesis of (+)-*cis*/(–)-*trans*-Lauthisan and (+)-*cis*/(+)-*trans*-Obtusan

Nuria Ortega,[a] Tomás Martín,*[a,b] and Víctor S. Martín*[a]

Keywords: Cobalt / Natural products / Oxygen heterocycles / Total synthesis / Isomerization

A new and efficient methodology to prepare α,α′-disubstituted linear ethers through an intermolecular Nicholas reaction (interNR) is described. *cis*-2,8-Disubstituted oxocanes, *cis*-2,9-disubstituted oxonanes, their *trans* isomers, and their parent unsaturated precursors were prepared from the corresponding $Co_2(CO)_6$–cycloalkynic ethers. Key steps in such syntheses were the ether linkage formation by interNR, RCM of the suitable acyclic dienyl ether, and montmorillonite K-10 induced isomerization of the complexed cycloalkyne. By taking advantage of the developed methodology a short synthesis of (+)-*cis*- and (–)-*trans*-lauthisan and (+)-*cis*- and (+)-*trans*-obtusan are described.

Introduction

The structure of polyfunctionalized, medium-sized cyclic ethers is widespread in marine natural products such as brevetoxin A and B, yessotoxin, ciguatoxin, gambieric acid A, the eunicellins, and maitotoxin. In addition, an important group of marine natural products, called lauroxanes, contain medium-ring ethers (Figure 1). Lauroxanes are a series of nonterpenoid C15 metabolites derived from fatty acid metabolism (acetogenins) that have been isolated from red algae and species that feed on *Laurencia*. These compounds display a wide range of biological activities, including antitumor, antimicrobial, immunosuppressant, antifeedant, pesticide activity, and so on.[1] The structural diversities of these molecules are very wide, but all have in common the presence of halogenated cyclic ethers with a defined stereochemistry in the substituents and ring sizes ranging from five to nine members. Such cyclic ethers are considered to be biogenetically derived from laurediols through electrophilic cyclizations usually induced by a bromonium ion.[1]

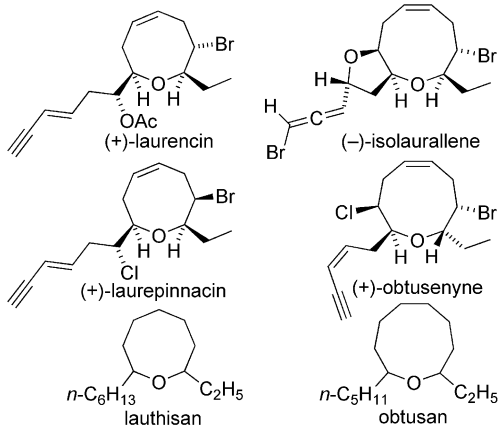
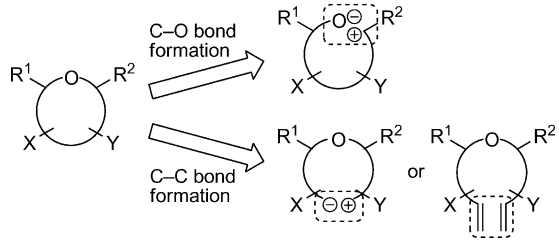


Figure 1. Representative C15 medium-sized ring ether marine metabolites and their basic skeletons.

The fascinating structures and biological activities of such naturally occurring medium-sized cyclic ethers have stimulated the imagination of synthetic chemists, and a significant level of effort has been focused on the development of new methodologies for their synthesis. There are essentially two strategies for the direct synthesis of medium-sized cyclic ethers: through the formation of a C–O bond by using a nucleophilic oxygen reagent or by C–C bond formation by using a linear ether precursor (Scheme 1).[2] Within the last approach, the combination of the synthesis of the suitably unsaturated branched ether and ring-closing metathesis (RCM) provides a powerful method for 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 a challenge for the synthesis of oxacycles.

[a] Instituto Universitario de Bioorgánica "Antonio González", Universidad de La Laguna
Avenida Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Islas Canarias, Spain
Fax: +34-922318571
E-mail: vmartin@ull.es
[b] Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas,
Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Islas Canarias, Spain
Fax: +34-922260135
E-mail: tmartin@ipna.csic.es
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

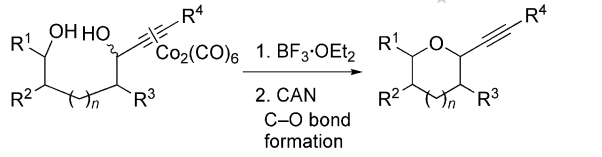


Scheme 1. Main strategies used in the synthesis of polyfunctionalized cyclic ethers.

With the realization that the approach to the branched ether linkage by a direct displacement strategy fails,[4] diverse alternatives have been used for the stereoselective synthesis of these precursors. Accordingly, asymmetric glycolate alkylations or aldolic additions were employed, both following the Evans protocol, and in consequence with the use of a chiral auxiliary.[5] Although the use of a chiral auxiliary works well, it represents an increase in the total number of synthetic steps. Recently, a stereoselective glycolate alkylation was reported without the use of a chiral auxiliary.[6] However, these reactions are not useful when the ethers are sensitive to basic conditions, such as, for instance, halogenated ethers, due to collateral elimination reactions. The development of methodologies oriented toward the synthesis of ethers under neutral or acidic conditions is highly desirable. For instance, a stereoselective synthesis of α,α′-disubstituted linear ethers by intermolecular allylation of an α-acetoxy ether with allyltributyltin and boron trifluoride diethyl ether was reported.[7] Likewise, a ring-opening reaction of a 1,3-dioxolanone with bis(trimethylsily)acetylene promoted by Lewis acid[4] and the use of a D-galactose derivative for the stereoselective introduction of allyl groups and further cleavage of the hexose ring are additional examples of a such strategy.[8]

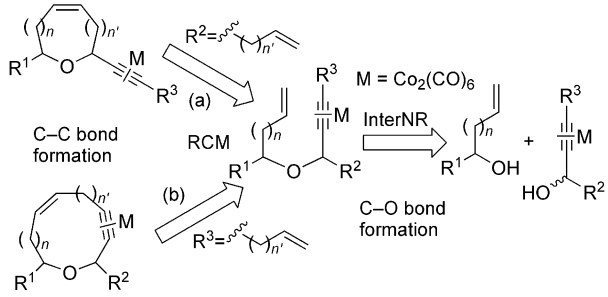
We developed a general procedure for the preparation of cyclic ethers based on an intramolecular Nicholas reaction (intraNR). A hydroxy group located in a suitable chain attacks a carbocation generated by acid treatment of *exo*-$Co_2(CO)_6$–propargylic alcohols to afford six-to-nine-membered cyclic ethers (C–O bond formation strategy) ($R^1 = R^2 = R^3 = H$, Scheme 2).[9,10] Using this methodology, we can also gain access to an oxane–oxepan system (R^1–R^2 = $CH_2CH_2CH_2O$, R^3 = H or OBn, n = 2). However, this methodology provided poor yields and conversions when $R^1 \neq H$ or $R^3 \neq H$ to obtain isolated eight-membered cyclic ethers (n = 3).[11] Moreover, to obtain fused eight-membered cyclic ethers, such as an oxane–oxocane system (R^1–R^2 = $CH_2CH_2CH_2O$, R^3 = OBn, n = 3), we need at least two geometric control elements: a ring and a *Z* double bond in the linear chain.[11]

Taking into account this limitation, we considered the possibility to develop a new strategy based on an intermolecular Nicholas reaction (interNR). Because RCM reactions have become the most powerful methodology to provide cyclic products, we envisioned formation of the cyclic ethers through a tandem interNR and RCM (C–C bond



Scheme 2. Synthesis of cyclic ethers based on the intramolecular Nicholas reaction (intraNR).

formation strategy). With this strategy, we can take advantage of the bending in the acetylenic system when forming the cobalt complex.[12,13] In addition, the cobalt complex should avoid the undesirable participation of the triple bond in the metathesis process.[14] Two alternative approaches can be planned for the synthesis of the oxacycles with the use of these considerations (Scheme 3): (a) locating the $Co_2(CO)_6$–alkyne complexed moiety *exo* to the cyclic ether or (b) including such functionality in an *endo* position. Considering that the presence of the $Co_2(CO)_6$–alkyne complex in the chain possessing one of the terminal alkenes could overcome the entropic disadvantages involved in the cyclization step[15] and the increasing number of known transformations of cyclic alkyne cobalt complexes, the last route seemed more attractive.[16]



Scheme 3. Retrosynthetic analysis of cyclic ethers based on tandem intermolecular Nicholas reaction (interNR) and RCM.

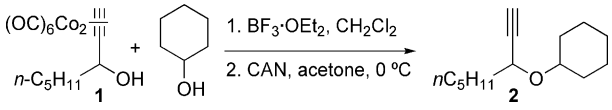
In this paper we report on a simple method for the preparation of α,α′-disubstituted linear ethers through an intermolecular Nicholas reaction (interNR) by treating secondary alcohols with secondary $Co_2(CO)_6$ complexed propargylic alcohols under acidic conditions. In addition, we account full details of the total synthesis of (–)-*trans*- and (+)-*cis*-lauthisan[17] and (+)-*trans*- and (+)-*cis*-obtusan from these linear precursors by taking advantage of the chemical and structural properties induced by the formation of $Co_2(CO)_6$ complexes in propargylic systems.

Results and Discussion

To perform the synthesis of the necessary linear ether precursors, we initially applied our previously reported methodology based on the trapping of $Co_2(CO)_6$–propargylic cations by using alcohols as nucleophiles.[18] Initial investigations began with the cobalt complex of commercially available racemic 1-octyn-3-ol (**1**) and cyclohexanol as test substrates. However, these reported conditions worked well to obtain un- or monosubstituted linear ethers in the α or

α′ position but failed to achieve the desired α,α′-disubstituted linear ethers (Table 1, Entry 1). Considering that the C–O coupling reaction is intermolecular, it is reasonable to expect that the yields could be improved by increasing the concentration. A test regarding the concentration influence on autocoupling and/or elimination of complexed alkyne **1** was performed. Satisfactorily, even at a concentration of 0.5 M over 2 h at 0 °C only trace amounts of the dimeric species was detected. However, longer reaction times (ca. 24 h) provided substantial elimination of the propargylic alcohol providing the corresponding $Co_2(CO)_6$ complex of (*E*)-oct-3-en-1-yne (**3**) as the main isolated product.

Table 1. Optimization of the intermolecular Nicholas reaction.



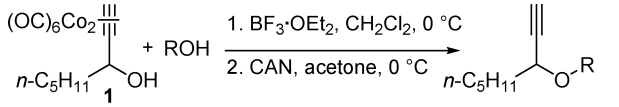
Entry	Cyclohexanol [equiv.]	Conc. [M]	BF_3·OEt_2 [equiv.]	*T* [°C]	*t* [h]	Yield[a] [%]
1	3	0.05	1	–20	3	trace
2	2	0.1	2.5	0	2	53
3	2	0.2	2.5	0	2	66
4	2	0.2	2.0	0	2	56
5	2	0.5	2.5	0	2	77
6	5	0.5	2.5	0	1	82
7	5	0.5	1.5	0	1	80
8	5	0.5	1.5	25	1	79

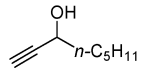
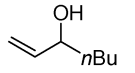
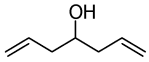
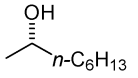
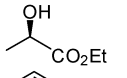
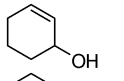
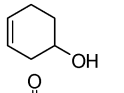
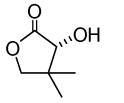
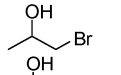
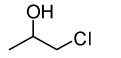
[a] Isolated yield after flash chromatography.

Once ensured that the conditions to avoid dimerization and/or elimination of the starting $Co_2(CO)_6$–propargylic alcohol were met, a variety of concentrations and relative amounts of cyclohexanol and Lewis acid were screened (Table 1). As a result of this study, we found that increasing the amounts of the secondary alcohol and the Lewis acid improved the yield and reduced the reaction time. We also established that raising the temperature diminished the yields (Table 1, Entry 8). Best conditions were achieved by using a relatively high concentration (0.5 M), 5 equivalents of cyclohexanol, and 2.5 equivalents of Lewis acid at 0 °C (Table 1, Entry 6).

A variety of substrates possessing a secondary alcohol were examined with the use of the optimized conditions (Table 2). A wide substrate tolerance was observed. We found the procedure to be highly general, affording the corresponding α,α′-disubstituted linear ethers in good yields. Interestingly, the interNR can be achieved by using unsaturated alcohols as nucleophiles, without the participation of the double and triple bonds in the reaction (Table 2, Entries 1–3, 6, and 7). Dimeric ether **4** was obtained in excellent yield by using 1-octyn-3-ol as the incoming alcohol. In addition, the ester and γ-lactone functions remain unaffected under these conditions (Table 2, Entries 5 and 8). One significant feature of our method is the compatibility with halogenated substrates (Table 2, Entries 9 and 10), providing a very convenient method to obtain halo-substituted ethers in good yields.[19] Noteworthy, the reaction takes place, albeit with moderate yields, even with a sterically hindered secondary alcohol (Table 2, Entry 8). Interestingly, when a tertiary alcohol such as *tert*-butyl alcohol is used as the incoming alcohol, the interNR takes place, although with poor yield (Table 2, Entry 11). Nevertheless, the reaction shows a poor level of stereoselectivity affording an *anti*/*syn* mixture of α,α′-disubstituted linear ethers.[20]

Table 2. Exploring the scope and limitations of the interNR.



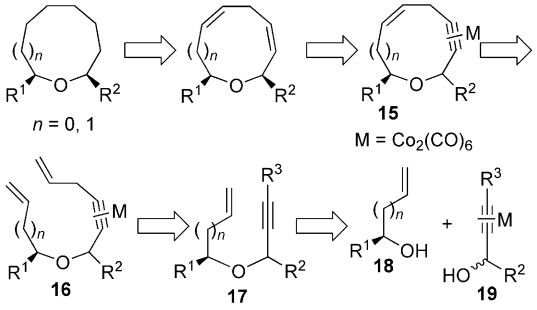
Entry[a]	ROH[b]	Time [h]	Product	Yield[c] [%]	*dr*[d]
1		1	**4**	97	1.5:1.0
2		1	**5**	76 (80)[e]	2.1:1.0
3		1	**6**	79	-
4		1	**7**	60	1.2:1.0
5		1	**8**	61	1.9:1.0
6		1	**9**	92	1.0:1.0
7		1	**10**	95	1.0:1.0
8		1.5	**11**	70	1.4:1.0
9		1	**12**	70	1.2:1.0
10		1	**13**	86	1.0:1.0
11	*t*BuOH	1.5	**14**	38	-

[a] General reaction conditions: ROH (5 equiv.) and BF_3·OEt_2 (2.5 equiv.) in CH_2Cl_2 (0.5 M) at 0 °C. [b] The excess amount of the nucleophilic alcohol can be easily recovered in the purification process. [c] Yield given for isolated material after flash chromatography. [d] Diastereoisomeric ratio of an indistinguishable mixture of *anti* and *syn* isomers determined by ^1H NMR spectroscopy. [e] Numbers in parenthesis denote the yield when the reaction was performed at a concentration of 0.2 M.

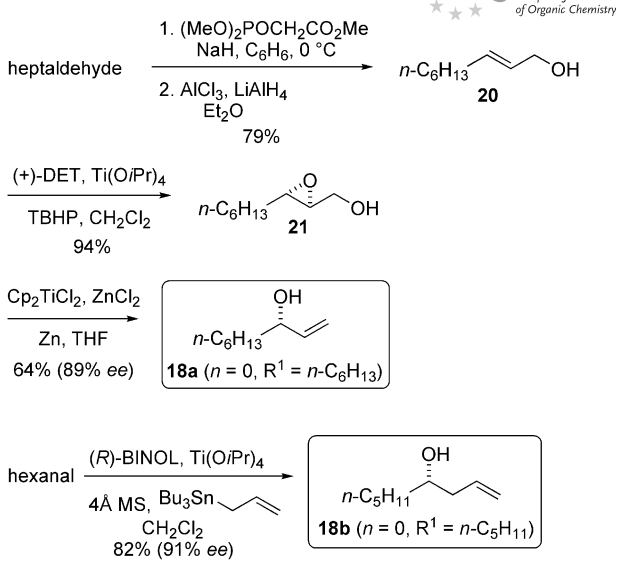
Having developed a suitable protocol to achieve the synthesis of the branched linear ethers, we decided to apply it to the synthesis of medium-sized cyclic ethers trough a tandem interNR and RCM. As targets, we chose the saturated ethers lauthisan[21] and obtusan,[22] whose structures represent the basic skeletons present in a number of these naturally occurring nonterpenoid eight- and nine-membered ring ethers like (+)-laurencin, (+)-laurepinnacin, (+)-obtusenyne, (–)-isolaurallene, and so on. (Figure 1). These molecules have served several times as the testing ground for the efficacy of oxocane and oxonane construction.[21,22]

We envisioned the synthesis of these heterocycles through $Co_2(CO)_6$–cycloalkynic ether **15**, which could be synthe-

sized from unsaturated alkyne–cobalt **16** by RCM. This precursor is easily available from alkyne **17** (R^3 = $CH_2CH{=}CH_2$). Finally, this propargylic ether, having two stereogenic centers close to the oxygen atom, was disassembled to secondary allylic or homoallylic alcohol **18** and complexed propargylic alcohol **19** through an interNR (Scheme 4).



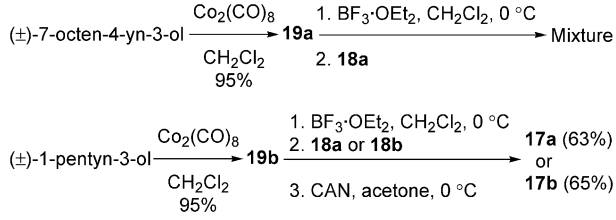
Scheme 4. Retrosynthetic analysis for the stereoselective synthesis of *cis*-2,8-dialkyloxocanes and *cis*-2,9-dialkyloxonanes.



Scheme 5. Preparation of enantiomerically enriched alcohols **18a** (n = 0, R^1 = n-C_6H_{13}) and **18b** (n = 1, R^1 = n-C_5H_{11}).

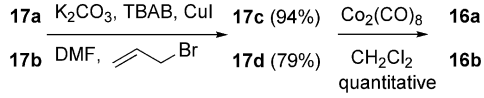
Our first aim, therefore, was the preparation of enantiomerically enriched alcohols **18a** (n = 0, R^1 = n-C_6H_{13}) and **18b** (n = 1, R^1 = n-C_5H_{11}). The synthesis of **18a** began with commercially available heptaldehyde, which was subjected to a two-carbon homologation by means of a Horner–Emmons reaction with the sodium salt of trimethyl phosphonoacetate in benzene, affording the α,β-unsaturated ester (E/Z > 20:1), which was reduced to allylic alcohol **20** (Scheme 5). With **20** in hand, we performed a Katsuki–Sharpless asymmetric epoxidation using (+)-diethyl tartrate as chiral auxiliary to afford 2,3-epoxy alcohol **21**.[23] Epoxy alcohol **21** was directly converted into vinyl carbinol **18a**[24] with an enantiomeric excess (*ee*) of 89%[25] by treatment with bis(cyclopentadienyl)titanium(III) chloride.[26] In order to obtain homoallylic alcohol **18b**, the catalytic asymmetric allylation protocol developed by Keck et al. was applied.[27] Desired homoallylic alcohol **18b** was formed in good yield with 91%*ee* upon consecutive addition of hexanal and allyltributylstannane to a solution of a catalyst formed in situ from Ti(O*i*Pr)$_4$ and (*R*)-BINOL (1:2 ratio) in the presence of 4 Å molecular sieves (MS).

Initial attempts to obtain **17** with the use of (*S*)-non-1-en-3-ol (**18a**) as the incoming alcohol over the cobalt complex of racemic oct-7-en-4-yn-3-ol (**19a**, R^2 = C_2H_5, R^3 = $CH_2CH{=}CH_2$)[28] were fruitless yielding a complex mixture, presumably by internal participation of the double bond of the enyne substrate. Trying to overcome this difficulty, we turned our attention to the cobalt complex of commercially available racemic 1-pentyn-3-ol (**19b**, R^2 = C_2H_5, R^3 = H), relegating the allylation process to a later stage in the synthesis. In order to obtain the α,α′-disubstituted linear ethers, the optimized conditions for the interNR were applied to cobalt complex **19b** and allylic alcohol **18a**, but a moderate yield was achieved. Fortunately, by decreasing the reaction concentration to 0.2 M by using 2 equivalents of Lewis acid and slow addition of the secondary alcohol we were able to obtain branched ether **17a** (n = 0, R^1 = n-C_6H_{13}, R^2 = C_2H_5, R^3 = H) in good yield (Scheme 6). Alternatively, the construction of ether **17b** (n = 1, R^1 = n-C_5H_{11}, R^2 = C_2H_5, R^3 = H) was performed with the use of **18b** as the nucleophilic alcohol and **19b** as the cobalt complex and by applying the optimized conditions for the interNR described in Table 1 (Scheme 6).



Scheme 6. Direct preparation of linear ethers having the linkage between two stereogenic secondary carbon atoms.

Although at this point of the synthesis it was very difficult to ensure the stereoselection of the newly created stereocenter in compounds **17a** and **17b**, more elaborated fragments in the synthesis (vide infra) showed us a ratio of approximately 1:1.7 for **17a** and 1:1.1 for **17b** of both diastereoisomers in favor of the α,α′-*anti*-isomers. With ethers **17a** and **17b** in hand, the preparation of the necessary dienes for the RCM step required only a simple alkylation. To this end, copper-catalyzed homologation of **17a** and **17b** with allyl bromide provided dienyl derivatives **17c** and **17d** in excellent yield. Because cyclization to form a medium-sized ring is impractical with a free alkyne as part of the ring, the cobalt metallic core in **17c** and **17d** is crucial for the ring closure. Thus, **17c** and **17d** were treated with $Co_2(CO)_8$ to obtain cobalt complexes **16a** (n = 0, R^1 = n-C_6H_{13}, R^2 = C_2H_5, R^3 = $CH_2CH{=}CH_2$) and **16b** (n = 1, R^1 = n-C_5H_{11}, R^2 = C_2H_5, R^3 = $CH_2CH{=}CH_2$) in quantitative yields (Scheme 7).

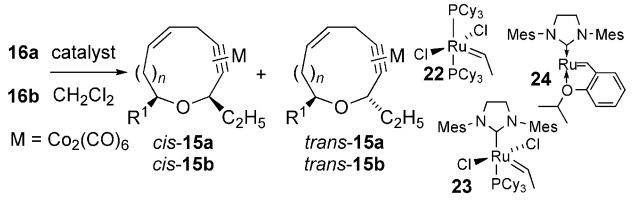


Scheme 7. Preparation of the $Co_2(CO)_6$ linear ethers for RCM.

Three 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;[14] second, the bending[12,13] in the acetylenic system when forming the cobalt complex could overcome the unfavorable entropic and enthalpic factors involved in the formation of the eight- and nine-membered rings[15] (the final ring has an endocyclic triple bond); third, the $Co_2(CO)_6$–alkyne in the *endo* position can be used as a stereochemical control agent for a critical isomerization process in the final cyclic product.

Our first attempts to perform the cyclization reaction with the use of first-generation Grubbs' catalyst (**22**) led to poor conversions and yields of the corresponding cyclic ethers (Table 3, Entry 1). When the temperature was raised, the yield was slightly improved (Table 3, Entry 2). Then, we decided to explore the cyclization step using second-generation Grubbs' catalyst (**23**), but unfortunately, at room temperature starting material **16a** was fully recover (Table 3, Entry 3). Satisfactorily, when second-generation Grubbs' catalyst (**23**) was used under reflux and diluted conditions (0.001 M) in dichloromethane, an 83% yield of **15a** was obtained (Table 3, Entry 4). The use of Hoveyda's catalyst (**24**) was unfruitful, even after a long reaction time (Table 3, Entry 5). The same conditions applied to obtain **15a** were used to obtain $Co_2(CO)_6$–cycloalkyne ether **15b** in excellent yield (Table 3, Entry 6).

Table 3. RCM of $Co_2(CO)_6$ linear ethers **16a** and **16b**.

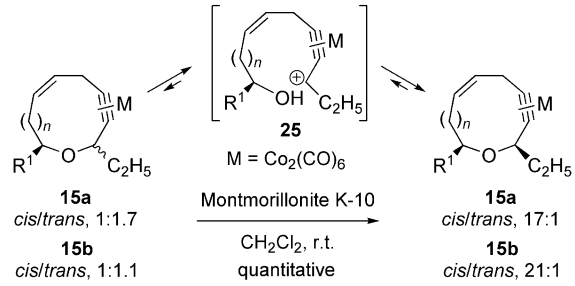


Entry	Substrate	Catalyst [mol-%]	Conc. [mM]	*T* [°C]	*t* [h]	Yield[a] [%]	*cis*/*trans*
1	**16a**	**22** (10)	5	25	5	18	1:1.7
2	**16a**	**22** (30)	1	35	2	45	1:1.7
3	**16a**	**23** (30)	1	25	48	–[b]	–
4	**16a**	**23** (30)	1	35	2	83	1:1.7
5	**16a**	**24** (30)	1	35	24	–[b]	–
6	**16b**	**23** (30)	1	35	2	93	1:1.1

[a] Isolated yields after flash chromatography. [b] Starting material was fully recovered.

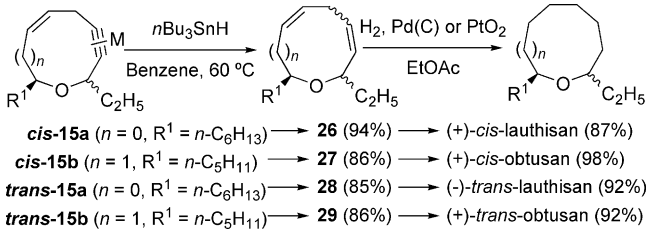
Interestingly, at this point of the synthesis both diastereoisomers of **15a** and **15b** were separated very easily by silicagel column chromatography. NOE studies of both isomers allowed the assignment of the relative stereochemistry.[29]

As aforementioned, separation of both diastereoisomers was very simple at this step. However, considering that the major isomers isolated were *trans*-**15a** and *trans*-**15b**, we pondered the possibility of performing an isomerization to the *cis* isomer by considering that such stereoisomers are usually thermodynamically more stable. Disappointingly, treatment of a *cis*/*trans* mixture of **15a** under various acidic conditions (including $BF_3{\cdot}OEt_2$, CF_3COOH, and TsOH) resulted in either decomposition or complete recovery of the starting mixture.[30] Fortunately, 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 cation intermediate **25** (Scheme 8).[31] The original mixture evolved quantitatively to a nice *cis*/*trans* ratio of 17:1 for eight-membered ring **15a** and a *cis*/*trans* ratio of 21:1 for nine-membered ring **15b**.



Scheme 8. Isomerization of 2,8- and 2,9-dialkyl $Co_2(CO)_6$–cycloalkynic ethers promoted by montmorillonite K-10.

The last steps required to complete the synthesis of the targets (+)-*cis*-lauthisan and (+)-*cis*-obtusan were the cleavage of the cobalt complex and reduction to the final oxacycle (Scheme 9). The reductive decomplexation reported by Isobe et al. produced cyclodienes **26** (n = 0, R^1 = n-C_6H_{13}) and **27** (n = 1, R^1 = n-C_5H_{11}) very efficiently, although as inseparable mixtures of stereoisomers in the newly created double bond.[16a,16b] However, the hydrogenation under standard conditions of **26** and **27** provided cleanly (+)-*cis*-lauthisan $[a]_D^{25}$ = +4.1 (c = 0.9, $CHCl_3$)[21k] and (+)-*cis*-obtusan $[a]_D^{25}$ = +3.9 (c = 2.1, $CHCl_3$), respectively.



Scheme 9. Reductive cleavage of $Co_2(CO)_6$–cycloalkynic ethers and hydrogenation.

Finally, in order to obtain the *trans* isomers of lauthisan and obtusan, we applied the same sequence of reactions shown above (Scheme 9) to *trans*-**15a** and *trans*-**15b**, previously available from the column chromatography purification of the RCM reactions.[32] Accordingly, *trans*-(–)-lauthi-

san {$[\alpha]_D^{25}$ = –8.3 (c = 0.9, $CHCl_3$)} and (+)-*trans*-obtusan {$[\alpha]_D^{25}$ = +6.3 (c = 1.4, $CHCl_3$)} were obtained in excellent yields.

Conclusions

In summary, we described a new and efficient method to prepare branched linear ethers having two secondary carbon atoms vicinal to the oxygen atom through an intermolecular Nicholas reaction (interNR). The methodology is practical, simple to use, and compatible with a wide range of functional groups. A tandem interNR, RCM, and isomerization of $Co_2(CO)_6$–cycloalkyne ether complexes catalyzed by montmorillonite K-10 are the basis for the stereocontrolled synthesis of *cis* isomers of saturated and unsaturated eight- and nine-membered 2,8-dialkyl and 2,9-dialkyl cyclic ethers, respectively. All these procedures were exemplified in the stereoselective synthesis of (+)-*cis*-lauthisan and (+)-*cis*-obtusan and also in the synthesis of their *trans* isomers. Current efforts are focused on the expansion of this strategy to the synthesis of natural products containing medium-ring ethers in their structures.

Experimental Section

General: ^1H NMR spectra were recorded at 500, 400, or 300 MHz, and ^{13}C NMR spectra were recorded at 75 or 100 MHz; chemical shifts are reported relative to internal Me_4Si. IR spectra were recorded as films on NaCl. Column chromatography was performed on silica gel, 60 Å and 0.2–0.5 mm. Compounds were visualized by use of UV light, 2.5% phosphomolybdic acid in ethanol, or vanillin with acetic and sulfuric acid in ethanol with heating. All solvents were purified by standard techniques. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

General Procedure for the Preparation of Cobalt-Complexed Propargyl Alcohols: Solid $Co_2(CO)_8$ (376 mg, 1.1 mmol) was added to a solution of the corresponding alkyne (1 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The dark solution was stirred at room temperature until TLC showed the formation of the complex to be completed (ca. 2 h). The solvent of the resulting reaction mixture was then removed under vacuum, and the residue was used without further purification.

Preparation of (Oct-1-yn-3-yloxy)cyclohexane (2) as a Representative Example for the Preparation of α,α′-Disubstituted Linear Ethers: To a cooled mixture of $Co_2(CO)_6$–1-octyn-3-ol (412 mg, 1 mmol) and cyclohexanol (533 μL, 5 mmol) in dry CH_2Cl_2 (2 mL, 0.5 M) was added $BF_3{\cdot}OEt_2$ (317 μL, 2.5 mmol) under a nitrogen atmosphere at 0 °C. After the addition, the reaction mixture was stirred for 1 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 to yield the crude cobalt complex as an oil, which was used without further purification. Such cobalt complex was dissolved in reagent-grade acetone (10 mL) under a nitrogen atmosphere at 0 °C. Ceric ammonium nitrate (2.2 g, 4 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (ca. 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 with Et_2O (2×). The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography to yield **2** (171 mg, 82% yield) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m, 3 H), 1.22–1.35 (m, 8 H), 1.44 (m, 4 H), 1.67–1.73 (m, 4 H), 1.89 (m, 2 H), 2.35 (d, J = 2.1 Hz, 1 H), 3.55 (m, 1 H), 4.12 (ddd, J = 2.2, 6.6, 6.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (q), 22.3 (t), 23.8 (t), 23.9 (t), 24.8 (t), 25.6 (t), 31.0 (t), 31.2 (t), 33.1 (t), 35.9 (t), 65.9 (d), 72.1 (s), 75.3 (d), 84.1 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3310, 2931, 2857, 1453, 1085 cm^{-1}. $C_{14}H_{24}O$ (208.3): calcd. C 80.71, H 11.61; found C 80.51, H 12.19.

3-(Oct-1-yn-3-yloxy)oct-1-yne (4): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to the cobalt complex of 1-octyn-3-ol (412 mg, 1 mmol) and 1-octyn-3-ol (729 μL, 5 mmol), yielding a 1.5:1.0 mixture of diastereoisomers **4** (241 mg, 97% yield) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (dd, J = 6.6, 6.6 Hz, 15 H), 1.31 (m, 20 H), 1.45 (m, 10 H), 1.63–1.82 (m, 10 H), 2.39 (d, J = 1.9 Hz, 3 H), 2.44 (d, J = 2.0 Hz, 2 H), 4.27 (ddd, J = 6.5, 6.5, 2.0 Hz, 2 H), 4.40 (ddd, J = 6.5, 6.5, 1.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (q), 22.3 (t), 24.4 (t), 24.5 (t), 31.2 (t), 34.9 (t), 35.3 (t), 62.1 (s), 66.8 (t), 67.6 (t), 73.2 (s), 73.3 (s), 82.6 (s), 82.9 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3310, 2930, 2861, 1076 cm^{-1}. $C_{16}H_{26}O$ (234.4): calcd. C 81.99, H 11.18; found C 81.97, H 11.41.

3-(Hept-1-en-3-yloxy)oct-1-yne (5): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to the cobalt complex of 1-octyn-3-ol (412 mg, 1 mmol) and hept-1-en-3-ol (679 μL, 5 mmol), yielding a 2.1:1.0 mixture of diastereoisomers **5** (178 mg, 80% yield) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 18.6 H), 1.10–1.73 (m, 43.4 H), 2.35 (d, J = 1.7 Hz, 2.1 H), 2.37 (d, J = 1.7 Hz, 1 H), 3.86–3.92 (m, 2 H), 3.97–4.11 (m, 4.2 H), 5.13–5.24 (m, 6.2 H), 5.54–5.66 (m, 2.1 H), 5.79–5.85 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (q), 13.8 (q), 22.0 (t), 22.4 (t), 27.3 (t), 29.4 (t), 31.0 (t), 31.7 (t), 34.9 (t), 68.7 (t), 70.4 (s), 80.2 (d), 116.1 (t), 116.2 (t), 126.3 (d), 134.1 (d), 139.2 (d), 139.6 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3310, 2957, 2862, 1466, 1072, 926 cm^{-1}. $C_{15}H_{26}O$ (222.4): calcd. C 81.02, H 11.79; found C 81.06, H 11.57.

3-(Hepta-1,6-dien-4-yloxy)oct-1-yne (6): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to the cobalt complex of 1-octyn-3-ol (412 mg, 1 mmol) and hepta-1,6-dien-4-ol (649 μL, 5 mmol), yielding **6** (163 mg, 79% yield) as an oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (m, 3 H), 1.29 (dd, J = 3.5, 3.5 Hz, 4 H), 1.43 (m, 2 H), 1.66 (m, 2 H), 2.26–2.37 (m, 4 H), 2.37 (d, J = 0.5 Hz, 1 H), 3.71 (dd, J = 5.8, 11.7 Hz, 1 H), 4.13 (ddd, J = 1.7, 6.5, 6.5 Hz, 1 H), 5.05 (m, 4 H), 5.82 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (q), 22.3 (t), 24.7 (t), 31.3 (t), 35.8 (t), 37.2 (t), 38.6 (t), 67.5 (d), 72.7 (d), 77.2 (d), 83.7 (s), 116.5 (t), 117.0 (t), 134.3 (d), 134.8 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3309, 2928, 2859, 1083, 913 cm^{-1}LRMS (EI): m/z (%) = 219 (49) $[M - H]^+$, 111 (7) $[M - C_8H_{13}]^+$, 57 (100). HRMS (EI): calcd. for $C_{15}H_{23}O$ $[M - H]^+$ 219.1741; found 219.1749.

3-[(*S*)-Octan-2-yloxy]oct-1-yne (7): The general procedure for the preparation of α,α′-disubstituted linear ethers above was applied to the cobalt complex of 1-octyn-3-ol (412 mg, 1 mmol) and (*S*)-octan-2-ol (792 μL, 5 mmol), yielding a 1.2:1.0 mixture of diastereoisomers **7** (143 mg, 60% yield) as an oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.90 (m, 13.2 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.20 (d, J = 6.1 Hz, 3.6 H), 1.27–1.46 (m, 30.8 H), 1.69 (m, 8.8 H), 2.33 (d, J = 2.1 Hz, 1 H), 2.36 (d, J = 2.0 Hz, 1.2 H), 3.66 (m, 2.2 H), 4.05 (m, 2.2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (q),

13.8 (q), 18.8 (q), 20.6 (q), 22.3 (t), 24.7 (t), 24.9 (t), 25.3 (t), 29.1 (t), 29.2 (t), 31.3 (t), 31.6 (t), 35.7 (t), 35.8 (t), 35.9 (t), 37.1 (t), 66.3 (d), 67.4 (d), 72.2 (s), 72.9 (d), 74.5 (d), 84.3 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3311, 2928, 2858, 1118 cm^{-1}. $C_{16}H_{30}O$ (238.4): calcd. C 80.61, H 12.68; found C 80.60, H 12.63.

(2*R*)-Ethyl 2-(Oct-1-yn-3-yloxy)propanoate (8): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to the cobalt complex of 1-octyn-3-ol (412 mg, 1 mmol) and (+)-(*R*)-ethyl lactate (568 μL, 5 mmol), yielding a 1.9:1.0 mixture of diastereoisomers **8** (138 mg, 61% yield) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (m, 8.7 H), 1.26–1.33 (m, 17.4 H), 1.40–1.51 (m, 11.6 H), 1.58 (m, 5.8 H), 1.75 (m, 5.8 H), 2.41 (d, *J* = 2.0 Hz, 2.9 H), 4.20 (m, 8.7 H), 4.37 (ddd, *J* = 6.9, 13.8, 13.8 Hz, 2.9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (q), 14.0 (q), 18.7 (q), 22.3 (t), 24.5 (t), 31.2 (t), 35.5 (t), 60.5 (t), 68.5 (d), 71.8 (d), 73.6 (d), 82.4 (s), 173.0 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3309, 3291, 3274, 2956, 2871, 1747, 1126 cm^{-1}. $C_{13}H_{22}O_3$ (226.3): calcd. C 68.99, H 9.80; found C 68.67, H 9.23.

3-(Oct-1-yn-3-yloxy)cyclohex-1-ene (9): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to the cobalt complex of 1-octyn-3-ol (412 mg, 1 mmol) and 2-cyclohexen-1-ol (491 μL, 5 mmol), yielding a 1.0:1.0 mixture of diastereoisomers **9** (190 mg, 92% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (dd, *J* = 5.3, 6.5 Hz, 6 H), 1.2–2.02 (m, 28 H), 2.38 (dd, *J* = 0.5, 1.3 Hz, 2 H), 4.16 (m, 4 H), 5.75 (m, 2 H), 5.87 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (q), 18.8 (t), 19.0 (t), 22.3 (t), 24.7 (t), 24.8 (t), 24.9 (t), 25.0 (t), 27.4 (t), 29.4 (t), 31.2 (t), 35.9 (t), 36.0 (t), 66.5 (d), 66.9 (d), 70.4 (d), 71.0 (d), 72.5 (s), 126.8 (d), 128.1 (d), 130.6 (d), 131.0 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3308, 2933, 1716, 1075 cm^{-1}. LRMS (EI): *m*/*z* (%) = 206 (0.84) $[M]^+$, 98 (32), 81 (100). HRMS (EI): calcd. for $C_{14}H_{22}O$ $[M]^+$ 206.1671; found 206.1675.

4-(Oct-1-yn-3-yloxy)cyclohex-1-ene (10): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to $Co_2(CO)_6$–1-octyn-3-ol (412 mg, 1 mmol) and 3-cyclohexen-1-ol (491 μL, 5 mmol), yielding a 1.0:1.0 mixture of diastereoisomers **10** (196 mg, 95% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (dd, *J* = 6.6, 6.9 Hz, 6 H), 1.25–1.75 (m, 20 H), 2.12 (m, 8 H), 2.34 (dd, *J* = 2.0, 3.1 Hz, 1 H), 2.37 (dd, *J* = 2.0, 3.1 Hz, 1 H), 3.70 (m, 1 H), 3.85 (m, 1 H) 4.05 (m, 1 H), 4.15 (ddd, *J* = 2.0, 6.7, 11.8 Hz, 1 H), 5.60 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (q), 22.3 (t), 22.7 (t), 23.7 (t), 24.1 (t), 24.7 (t), 24.8 (t), 25.2 (t), 26.8 (t), 28.8 (t), 29.4 (t), 30.1 (t), 30.7 (t), 31.2 (t), 32.3 (t), 32.5 (t), 35.9 (t), 66.4 (d), 72.0 (s), 72.3 (d), 72.3 (d), 72.4 (d), 72.5 (d), 123.7 (d), 124.4 (d), 126.3 (d), 126.9 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3310, 2924, 2857, 1466, 1088 cm^{-1}. LRMS (EI): *m*/*z* (%) = 207 (1.5) $[M + H]^+$, 111 (41), 98 (49), 67 (100). HRMS (EI): calcd. for $C_{14}H_{23}O$ $[M + H]^+$ 207.1749; found 207.1750.

(3*R*)-4,4-Dimethyl-3-(oct-1-yn-3-yloxy)dihydrofuran-2(3*H*)-one (11): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to $Co_2(CO)_6$–1-octyn-3-ol (412 mg, 1 mmol) and (*R*)-(–)-pantolactone (651 mg, 5 mmol), yielding a 1.4:1.0 mixture of diastereoisomers **11** (167 mg, 70% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (dd, *J* = 6.6, 6.6 Hz, 7.2 H), 1.07 (s, 7.2 H), 1.18 (s, 7.2 H), 1.29–1.33 (m, 9.6 H), 1.43 (m, 4.8 H), 1.65–1.98 (m, 4.8 H), 2.40 (d, *J* = 2.0 Hz, 1 H), 2.49 (d, *J* = 2.0 Hz, 1.4 H), 3.89 (m, 4.8 H), 4.07 (s, 1 H), 4.16 (s, 1.4 H), 4.33 (ddd, *J* = 2.0, 4.8, 4.8 Hz, 2.4 H) 4.67 (m, 2.4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (q), 19.1 (q), 22.2 (t), 22.6 (q), 24.3 (t), 31.2 (t), 35.1 (t), 39.9 (s), 68.9 (d), 73.9 (d), 76.2 (t), 78.6 (d), 82.2 (s), 175.3 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3309, 2958, 2928, 2857, 1791, 1117 cm^{-1}. LRMS (EI): *m*/*z* (%) = 223 (100) $[M - CH_3]^+$, 99 (54). HRMS (EI): calcd. for $C_{14}H_{22}O_3$ $[M - CH_3]^+$ 223.1334; found 223.1341.

3-(1-Bromopropan-2-yloxy)oct-1-yne (12): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to $Co_2(CO)_6$–1-octyn-3-ol (412 mg, 1 mmol) and 1-bromo-2-propanol (454 μL, 5 mmol), yielding a 1.2:1.0 mixture of diastereoisomers **12** (173 mg, 70% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (m, 6.6 H), 1.24–1.44 (m, 15.4 H), 1.44–1.46 (m, 4.4 H), 1.65–1.74 (m, 4.4 H), 2.39 (dd, *J* = 2.5, 3 Hz, 2.2 H), 3.29–3.36 (m, 3.2 H), 3.48–3.51 (m, 1 H), 3.94 (m, 2.2 H), 4.12 (dd, *J* = 2.5, 18.5 Hz, 1 H), 4.16 (dd, *J* = 2.5, 8.5 Hz, 1.2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (q), 18.5 (q), 20.4 (q), 22.9 (t), 25.2 (t), 25.3 (t), 31.8 (t), 31.8 (t), 36.8 (t), 36.8 (t), 37.2 (t), 68.2 (d), 68.7 (d) 73.4 (d), 73.6 (d), 83.6 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3308, 2932, 2861, 654 cm^{-1}. LRMS (EI): *m*/*z* (%) = 167 (1.2) $[M - Br]^+$, 105 (100), 77 (42). HRMS (EI): calcd. for $C_{11}H_{19}O$ $[M - Br]^+$ 167.1436; found 167.1431.

3-(1-Chloropropan-2-yloxy)oct-1-yne (13): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to $Co_2(CO)_6$–1-octyn-3-ol (412 mg, 1 mmol) and 1-chloro-2-propanol (425 μL, 5 mmol), yielding a 1.0:1.0 mixture of diastereoisomers **13** (174 mg, 86% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (m, 6 H), 1.21–1.43 (m, 14 H), 1.44–1.49 (m, 4 H), 1.51–1.73 (m, 4 H), 2.40 (dd, *J* = 1, 2.5 Hz, 2 H), 3.41–3.48 (m, 3 H), 3.6 (m, 1 H), 3.95 (m, 2 H), 4.11 (m, 1 H), 4.17 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (q), 117.7 (q), 19.5 (q), 22.9 (t), 25.2 (t), 31.8 (t), 36.3 (t), 36.3 (t), 47.7 (t), 48.4 (t), 68.1 (d), 68.9 (d), 73.7 (d), 73.8 (d), 73.9 (d), 74.0 (d), 83.5 (s), 83.8 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3303, 2957, 2932, 667 cm^{-1}. $C_{11}H_{19}ClO$ (202.7): calcd. C 65.17, H 9.45; found C 65.21, H 9.33.

3-*tert*-Butoxyoct-1-yne (14): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to $Co_2(CO)_6$–1-octyn-3-ol (412 mg, 1 mmol) and *tert*-butyl alcohol (478 μL, 5 mmol), yielding **14** (69 mg, 38% yield) as a oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (m, 3 H), 1.25–1.44 (m, 15 H), 1.61–1.67 (m, 2 H), 2.33 (s, 1 H), 4.08 (d, *J* = 13.3, 6.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (q), 22.9 (t), 25.4 (t), 28.6 (d), 31.9 (t), 37.9 (t), 62.1 (d), 87.0 (s) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2956, 2928, 1596 cm^{-1}. LRMS (EI): *m*/*z* (%) = 125 (1.6) $[M - t\text{Bu}]^+$, 121 (32), 109 (4), 91 (40). HRMS (EI): calcd. for $C_{12}H_{23}O$ $[M + H]^+$ 183.1749; found 183.1757.

(*S*)-3-[(*R* and *S*)-Pent-1-yn-3-yloxy]non-1-ene (17a): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to 1-pentyn-3-ol on (0.5 g, 5.9 mmol). The reaction mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ was added (1.5 mL, 11.9 mmol). Then, allylic alcohol **18a** was dissolved in dry CH_2Cl_2 (5 mL) and added to the reaction mixture with a syringe pump (0.1 mL min^{-1}). 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 layer was dried ($MgSO_4$), filtered, and concentrated to yield the crude cobalt complex as an oil, which was used without further purification. The cobalt complex previously obtained was dissolved in reagent-grade acetone (30 mL) under a nitrogen atmosphere at 0 °C. Ceric ammonium nitrate (13.0 g, 23.8 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 with Et_2O (2×). The combined organic extracts were

dried, filtered, concentrated, and subjected to silica-gel flash chromatography, yielding a 1.7:1.0 mixture of diastereoisomers **17a** (780 mg, 63% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (dd, J = 6.1, 6.8 Hz, 7.5 H), 0.99 (m, 7.5 H), 1.27–1.47 (m, 23 H), 1.58–1.75 (m, 7 H), 2.33 (d, J = 1.96 Hz, 1.5 H), 2.36 (d, J = 2.1 Hz, 1 H), 4.00 (m, 5 H), 5.18 (m, 5 H), 5.57 (ddd, J = 2.0, 8.1, 17.7 Hz, 1.5 H), 5.79 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.3 (q), 9.5 (q), 14.0 (q), 22.6 (t), 25.1 (t), 25.2 (t), 28.5 (t), 28.9 (t), 29.1 (t), 29.2 (t), 31.8 (t), 34.8 (t), 35.5 (t), 67.2 (d), 68.5 (d), 72.7 (d), 72.7 (d), 78.7 (d), 80.0 (d), 83.5 (s), 83.8 (s), 115.9 (t), 117.3 (t), 138.7 (d), 139.4 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3311, 2930, 2858, 1458, 1102 cm^{-1}. $C_{14}H_{24}O$ (208.3): calcd. C 80.71, H 11.61; found C 80.92, H 11.75.

(*S*)-4-[(*R* and *S*)-Pent-1-yn-3-yloxy]non-1-ene (17b): The general procedure for the preparation of α,α′-disubstituted linear ethers described above was applied to $Co_2(CO)_6$–1-octyn-3-ol (0.5 g, 5.9 mmol) and (*S*)-non-1-en-4-ol (**18b**; 4.2 g, 29.5 mmol), yielding a 1.1:1.0 mixture of diastereoisomers **17b** (799 mg, 65% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (m, 6 H), 0.98 (ddd, J = 2.4, 7.2, 7.2 Hz, 6 H), 1.24–1.73 (m, 20 H), 1.58 (s, 1 H), 2.22–2.36 (m, 4 H), 3.57 (m, 2 H), 4.02 (m, 2 H), 5.04 (m, 4 H), 5.82 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0 (q), 10.0 (q), 14.4 (q), 14.4 (q), 22.9 (t), 25.0 (t), 25.5 (t), 29.6 (t), 29.6 (t), 32.3 (t), 32.4 (t), 33.5 (t), 34.7 (t), 38.3 (t), 39.4 (t), 68.9 (d), 69.5 (d), 73.1 (d), 73.2 (d), 77.1 (d), 78.1 (d), 84.3 (s), 84.4 (s), 116.8 (t), 117.3 (t), 135.2 (d), 135.7 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 3295, 2927, 2854, 1158 cm^{-1}.

Preparation of (*S*)-3-[(*R* and *S*)-Oct-7-en-4-yn-3-yloxy]non-1-ene (17c) as a Representative Example for the Alkylation of Terminal Alkynes with Allyl Bromide: To a stirred solution of terminal alkyne **17a** (0.7 g, 3.4 mmol) in dry DMF (1.1 mL) was added K_2CO_3 (650 mg, 4.7 mmol) and copper(I) iodine (32 mg, 0.16 mmol) sequentially under an atmosphere of nitrogen at room temperature After 10 min, allyl bromide (378 μL, 4.4 mmol) was added. The reaction mixture was stirred for 40 h. Then, it was poured into H_2O and extracted with diethyl ether. The combined organic phase was washed with brine, dried, and concentrated. The crude obtained was purified by flash chromatography, yielding **17c** (785 mg, 94% yield) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (dd, J = 6.0, 6.8 Hz, 10 H), 1.27 (m, 16 H), 1.64 (m, 5 H), 2.98 (ddd, J = 1.2, 3.2, 5.1 Hz, 3 H), 4.02 (m, 3 H), 5.11 (m, 6 H), 5.60 (m, 1 H), 5.80 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.5 (q), 9.7 (q), 14.0 (q), 22.6 (t), 22.6 (t), 23.0 (t), 25.1 (t), 25.3 (t), 28.8 (t), 29.1 (t), 29.2 (t), 31.8 (t), 34.8 (t), 35.5 (t), 62.3 (s), 67.7 (d), 69.0 (d), 78.4 (d), 79.5 (d), 81.5 (d), 81.6 (s), 82.2 (s), 82.5 (s), 115.6 (t), 115.8 (t), 115.8 (t), 116.9 (t), 132.5 (d), 132.6 (d), 139.0 (d), 139.7 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2931, 2858, 1729, 1060 cm^{-1}. LRMS (EI): m/z (%) = 163 (24) [M – C_6H_{13}]$^+$, 125 (35), 107 (100). HRMS (EI): calcd. for $C_{16}H_{25}O$ [M – CH_3]$^+$ 233.1905; found 233.1907.

(*S*)-4-[(*R* and *S*)-Oct-7-en-4-yn-3-yloxy]non-1-ene (17d): The general procedure for the alkylation of terminal alkynes with allyl bromide described above was applied to **17b** (0.7 g, 3.4 mmol), yielding **17d** (667 mg, 79% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (dd, J = 6.5, 9 Hz, 6 H), 0.92 (ddd, J = 3, 9, 9 Hz, 6 H), 1.18–2.18 (m, 20 H), 2.98 (dd, J = 2.5, 2.5 Hz, 4 H), 3.52 (m, 2 H), 3.99 (m, 2 H), 4.93–5.04 (m, 6 H), 5.24 (ddd, J = 1.5, 1.5, 21 Hz, 2 H), 5.73 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1 (q), 10.2 (q), 14.3 (q), 14.4 (q), 22.9 (t), 23.0 (t), 23.4 (t), 23.4 (t), 25.1 (t), 25.6 (t), 29.9 (t), 29.9 (t), 32.3 (t), 32.4 (t), 33.6 (t), 34.8 (t), 38.4 (t), 39.6 (t), 69.4 (d), 69.9 (d), 76.8 (d), 77.8 (d), 81.8 (s), 81.9 (s), 82.9 (s), 82.9 (s), 116.2 (t), 116.5 (t), 117.1 (t), 132.9 (d), 135.3 (d), 135.9 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2934, 2862, 1604, 1126 cm^{-1}. LRMS (EI): m/z (%) = 167 (9) [M – 2C_3H_5 + H]$^+$, 109 (3), 83 (30). HRMS (EI): calcd. for $C_{11}H_{19}O$ [M – 2C_3H_5+H]$^+$ 167.1436; found 167.1437.

Preparation of Dicobalt Hexacarbonyl Complex of (*S*)-3-[(*R* and *S*)-Oct-7-en-4-yn-3-yloxy]non-1-ene (16a): The general procedure for the preparation of cobalt-complexed propargyl alcohols described above was applied to **17c** (700 mg, 2.8 mmol), yielding **16a** (1.51 g, quantitative) as a dark-red oil.

Preparation of Dicobalt Hexacarbonyl Complex of (*S*)-4-[(*R* and *S*)-Oct-7-en-4-yn-3-yloxy]non-1-ene (16b): The general procedure for the preparation of cobalt-complexed propargyl alcohols described above was applied to **17d** (600 mg, 2.4 mmol), yielding **16b** (1.29 g, quantitative) as a dark-red oil.

Dicobalt Hexacarbonyl Complexes of (2*R* and 2*S*,8*S*)-2-Ethyl-8-hexyl-3,4-didehydro-5,8-dihydro-2*H*-oxocine (*cis*-15a and *trans*-15a): To a stirred solution of cobalt complexes **16a** (250 mg, 0.47 mmol) in dry CH_2Cl_2 (470 mL, 0.001 M) was added the 2nd generation Grubbs catalyst (120 mg, 0.14 mmol, 30 mol-%). The reaction was warmed at 35 °C and kept at such a temperature until TLC showed complete conversion. Then, the solvent was evaporated, and the residue was purified by column chromatography yielding *cis*-**15a** (73 mg, 31% yield) and *trans*-**15a** (124 mg, 52% yield). Data for *cis*-**15a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.6 Hz, 3 H), 1.18 (dd, J = 7.3, 7.3 Hz, 3 H), 1.30–1.90 (m, 12 H), 3.45 (dd, J = 7.9, 15.6 Hz, 1 H), 3.71 (m, 1 H), 4.11 (dd, J = 4.6, 8.3 Hz, 1 H), 4.53 (dd, J = 2.2, 9.7 Hz, 1 H), 5.55 (dd, J = 9.0, 10.0 Hz, 1 H), 6.08 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (q), 13.8 (q), 22.3 (t), 25.0 (t), 29.0 (t), 30.6 (t), 31.5 (t), 31.9 (t), 36.2 (t), 75.4 (d), 83.8 (d), 99.5 (s), 101.4 (s), 131.6 (d), 136.3 (d) ppm. Data for *trans*-**15a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (m, 6 H), 0.90–1.85 (m, 12 H), 3.50 (dd, J = 7.2, 17.4 Hz, 1 H), 3.80 (m, 1 H), 4.15 (m, 1 H), 4.45 (dd, J = 2.9, 9.0 Hz, 1 H), 5.55 (dd, J = 9.8, 9.8 Hz, 1 H), 6.18 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (q), 13.8 (q), 22.3 (t), 25.0 (t), 29.0 (t), 30.6 (t), 31.5 (t), 31.9 (t), 36.2 (t), 75.4 (d), 83.8 (d), 101.4 (s), 131.5 (d), 136.3 (d) ppm.

Dicobalt Hexacarbonyl Complexes of (2*R* and 2*S*,9*S*)-2-Ethyl-9-pentyl-3,4-didehydro-2,5,8,9-tetrahydrooxonine (*cis*-15b and *trans*-15b): The same procedure used above to obtain compounds **15a** was applied to **16a** (250 mg, 0.47 mmol), yielding *cis*-**15b** (105 mg, 44% yield) and *trans*-**15b** (116 mg, 49% yield). Data for *cis*-**15b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 3 H), 1.14 (dd, J = 7.6, 7.6 Hz, 3 H), 1.33–1.80 (m, 10 H), 1.93 (m, 1 H), 2.09 (m, 1 H), 2.73 (dd, J = 3.2, 11.2 Hz, 1 H), 3.41 (dd, J = 7.6, 14.8 Hz, 1 H), 3.78 (dd, J = 6.4, 15.2 Hz, 1 H), 3.91 (m, 1 H), 4.56 (dd, J = 3.4, 9.2 Hz, 1 H), 5.68 (m, 1 H), 5.94 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (q), 14.4 (q), 22.9 (t), 26.5 (t), 31.7 (t), 32.3 (t), 32.3 (t), 32.7 (t), 35.1 (t), 80.1 (d), 82.6 (d), 99.6 (s), 102.1 (s), 129.7 (d), 130.2 (d) ppm. Data for *trans*-**15b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 3 H), 1.14 (m, 3 H), 1.37–1.78 (m, 10 H), 1.90 (m, 1 H), 2.07 (m, 1 H), 2.88 (m, 1 H), 3.50 (dd, J = 8, 15 Hz, 1 H), 3.74 (m, 2 H), 4.28 (dd, J = 2.8, 10.4 Hz, 1 H), 5.76 (m, 1 H), 5.94 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (q), 14.4 (q), 22.9 (t), 27.2 (t), 31.9 (t), 32.3 (t), 32.4 (t), 32.8 (t), 34.7 (t), 71.5 (d), 79.5 (d), 100.0 (s), 102.5 (s), 129.3 (d), 133.1 (d) ppm.

Isomerization of 2,8-Dialkyl $Co_2(CO)_6$–Cycloalkynic Ethers by Montmorillonite K-10: To a solution of $Co_2(CO)_6$ complexes *cis*-**15a** and *trans*-**15a** (1:1.7, 197 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) was added Montmorillonite K-10 (591 mg), and the mixture was stirred overnight at room temperature Then, the mixture was fil-

tered and concentrated, and the residue was purified by flash column chromatography, yielding *cis*-**15a** (186 mg) and *trans*-**15a** (11 mg).

Isomerization of 2,9-Dialkyl $Co_2(CO)_6$–Cycloalkynic Ethers by Montmorillonite K-10: The same procedure used above to the isomerization of 2,8-dialkyl $Co_2(CO)_6$–cycloalkynic ethers by Montmorillonite K-10 was applied to $Co_2(CO)_6$ complexes *cis*-**15b** and *trans*-**15b** (1:1.1, 47 mg, 0.09 mmol), yielding *cis*-**15b** (43 mg) and *trans*-**15b** (2 mg).

(+)-*cis*-Lauthisan: To the solution of $Co_2(CO)_6$ complex *cis*-**15a** (150 mg, 0.3 mmol) in benzene (30 mL) was added nBu$_3$SnH (0.97 mL, 3.6 mmol). After stirring for 2 h at 60 °C, the reaction mixture was concentrated under reduced pressure. The remaining residue was chromatographed on a silica-gel column to provide endocyclic diene **26** (62.6 mg, 94% yield) as an inseparable mixture of *trans* and *cis* isomers in the newly created double bond. To a stirred solution of **26** (50 mg, 0.22 mmol) in dry ethyl acetate (2.3 mL) was added 10% Pd(C) (12 mg, 0.011 mmol) at room temperature under an H_2 atmosphere (1 atm). The reaction mixture was stirred for 16 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 phase was concentrated, and the crude obtained was purified by flash chromatography to yield (+)-*cis*-lauthisan (43 mg, 87% yield). $[\alpha]_D^{25}$ = +4.1 (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 6 H), 1.27–1.76 (m, 22 H), 3.33 (m, 1 H), 3.41 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.6 (q), 13.85 (q), 22.3 (t), 23.8 (t), 26.0 (t), 26.8 (t), 29.2 (t), 29.5 (t), 31.6 (t), 33.1 (t), 33.4 (t), 36.8 (t), 79.4 (d), 80.8 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2926, 2856, 1457, 1089 cm^{-1}. $C_{15}H_{30}O$ (226.4): calcd. C 79.58, H 13.36; found C 79.57, H 13.77.

(+)-*cis*-Obtusan: The same procedure used above to obtain (+)-*cis*-lauthisan was applied to *cis*-**15b** (69 mg, 2.3 mmol), yielding in the first step endocyclic diene **29** (26 mg, 86% yield) as an inseparable mixture of *trans* and *cis* isomers in the newly created double bond, and in the second step (+)-*cis*-obtusan (26 mg, 98% yield). $[\alpha]_D^{25}$ = +3.9 (c = 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (m, 6 H), 1.29–1.79 (m, 22 H), 3.33 (m, 1 H), 3.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6 (q), 14.0 (q), 22.6 (t), 22.7 (t), 22.8 (t), 25.8 (t), 26.5 (t), 26.6 (t), 28.9 (t), 32.0 (t), 32.1 (t), 32.3 (t), 36.3 (t), 79.6 (d), 81.0 (d); 2927, 2856, 1458, 1090 ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2926, 2858, 1462, 1088 cm^{-1}. $C_{15}H_{30}O$ (226.4): calcd. C 79.58, H 13.36; found C 79.79, H 13.07.

(–)-*trans*-Lauthisan: The same procedure used above to obtain (+)-*cis*-lauthisan was applied to *trans*-**15a** (80 mg, 0.16 mmol), yielding in the first step endocyclic diene **28** (30 mg, 85% yield) as an inseparable mixture of *trans* and *cis* isomers in the newly created double bond, and in the second step (–)-*trans*-lauthisan (28 mg, 92% yield). $[\alpha]_D^{25}$ = –8.3 (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 6 H), 1.13–1.64 (m, 22 H), 3.52 (m, 1 H), 3.60 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4 (q), 13.9 (q), 22.4 (t), 25.6 (t), 25.8 (t), 25.9 (t), 26.4 (t), 29.3 (t), 29.3 (t), 31.6 (t), 31.9 (t), 32.3 (t), 36.5 (t), 74.1 (d), 75.1 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2925, 2849, 1456, 1089 cm^{-1}. $C_{15}H_{30}O$ (226.4): calcd. C 79.58, H 13.36; found C 79.56, H 13.64.

(+)-*trans*-Obtusan: The same procedure used above to obtain (+)-*cis*-lauthisan was applied to *trans*-**15b** (45 mg, 0.09 mmol), yielding in the first step endocyclic diene **29** (17 mg, 86% yield) as an inseparable mixture of *trans* and *cis* isomers in the newly created double bond, and in the second step (+)-*trans*-obtusan (17 mg, 92% yield). $[\alpha]_D^{25}$ = +6.3 (c = 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m, 6 H), 1.28–1.72 (m, 22 H), 3.53 (m, 1 H), 3.62 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 (q), 14.0 (q), 22.6 (t), 25.1 (t), 25.2 (t), 25.9 (t), 26.1 (t), 26.2 (t), 29.1 (t), 31.5 (t), 31.9 (t), 32.1 (t), 36.3 (t), 75.3 (d), 76.2 (d) ppm. IR (film, NaCl plates): $\tilde{\nu}$ = 2956, 2926, 1462, 1087 cm^{-1}. $C_{15}H_{30}O$ (226.4): calcd. C 79.58, H 13.36; found C 79.77, H 13.28.

Supporting Information (see footnote on the first page of this article): Experimental details, spectroscopic characterization, and ^{1}H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

This research was supported by Ministerio de Educación y Ciencia of Spain cofinanced by the European Regional Development Fund (CTQ2005-09074-C02-01 and CTQ2005-09074-C02-02) and the Canary Islands Government. N. O. thanks the Canary Islands Government for a predoctoral fellowship.

[1] a) R. E. Moore in *Marine Natural Products* (Eds.: P. J. Scheuer), Academic Press, New York, **1978**, vol. 1, pp. 43–121; b) K. L. Erickson in *Marine Natural Products* (Eds.: P. J. Scheuer), Academic Press, New York, **1983**, vol. V, pp. 131–257; c) T. Yasumoto, M. Murata, *Chem. Rev.* **1993**, *93*, 1897–1909; d) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–48, and preceding issues.

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

[3] For representative examples, see: a) M. Hirama, T. Oishi, H. Uehara, M. Inoue, M. Maruyama, H. Oguri, M. Satake, *Science* **2001**, *294*, 1904–1907; b) M. T. Crimmins, J. She, *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791; c) J. S. Clark, M. C. Kimber, J. Robertson, C. S. P. McErlean, C. Wilson, *Angew. Chem. Int. Ed.* **2005**, *44*, 6157–6162; d) K. Sato, M. Sasaki, *Angew. Chem. Int. Ed.* **2007**, *46*, 2518–2522.

[4] S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440.

[5] a) M. T. Crimmins, A. L. Choy, *J. Org. Chem.* **1997**, *62*, 7548–7549; b) M. T. Crimmins, A. L. Choy, *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660; c) M. T. Crimmins, K. A. Emmitte, *Org. Lett.* **1999**, *1*, 2029–2032; d) M. T. Crimmins, E. A. Tabet, *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476; e) M. T. Crimmins, K. A. Emmitte, J. D. Katz, *Org. Lett.* **2000**, *2*, 2165–2167; f) M. T. Crimmins, K. A. Emmitte, *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534; g) M. T. Crimmins, K. A. Emmitte, A. L. Choy, *Tetrahedron* **2002**, *58*, 1817–1834; h) M. T. Crimmins, A. C. DeBaillie, *Org. Lett.* **2003**, *5*, 3009–3011; i) M. T. Crimmins, M. T. Powell, *J. Am. Chem. Soc.* **2003**, *125*, 7592–7595; j) J. S. Clark, R. P. Freeman, M. Cacho, A. W. Thomas, S. Swallow, C. Wilson, *Tetrahedron Lett.* **2004**, *45*, 8639–8642; k) M. T. Crimmins, H. B. Brown, *J. Am. Chem. Soc.* **2004**, *126*, 10264–10266.

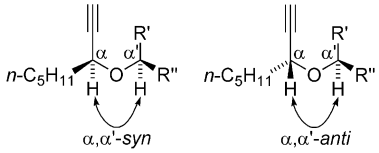
[6] a) H. J. Rhee, H. Y. Beom, H.-D. Kim, *Tetrahedron Lett.* **2004**, *45*, 8019–8022; b) H. Lee, H. Kim, T. Yoon, B. Kim, S. Kim, H. Kim, D. Kim, *J. Org. Chem.* **2005**, *70*, 8723–8729; c) J. Park, B. Kim, H. Kim, S. Kim, D. Kim, *Angew. Chem. Int. Ed.* **2007**, *46*, 4726–4728.

[7] I. Kadota, H. Uyehara, Y. Yamamoto, *Tetrahedron* **2004**, *60*, 7361–7365.

[8] a) K. Fujiwara, S.-I. Souma, H. Mishima, A. Murai, *Synlett* **2002**, 1493–1495; b) K. Fujiwara, A. Yoshimoto, S.-I. Souma, H. Mishima, A. Murai, H. Kawai, T. Suzuki, *Tetrahedron Lett.* **2005**, *46*, 6819–6822.

[9] J. M. Palazón, V. S. Martín, *Tetrahedron Lett.* **1995**, *36*, 3549–3552.

[10] For the synthesis of cyclic ethers by intramolecular Nicholas reactions, see: a) C. Mukai, S. Yamaguchi, Y. Sugimoto, N. Miyakoshi, E. Kasamatsu, M. Hanaoka, *J. Org. Chem.* **2000**, *65*, 6761–6765, and references cited therein; b) F. R. P. Crisóstomo, T. Martín, V. S. Martín, *Org. Lett.* **2004**, *66*, 565–568; c) A. Mamajima, M. Isobe, *Org. Lett.* **2006**, *8*, 1205–1208, and references therein.
[11] J. M. Betancort, T. Martín, J. M. Palazón, V. S. Martín, *J. Org. Chem.* **2003**, *68*, 3216–3224.
[12] For RCM with cobalt–alkyne complexes, see: a) J. R. Green, *Synlett* **2001**, 353–356; b) J. A. Burlison, J. M. Gray, D. G. J. Young, *Tetrahedron Lett.* **2001**, *42*, 5363–5365; c) D. G. J. Young, J. A. Burlison, U. Peters, *J. Org. Chem.* **2003**, *68*, 3494–3497; d) M. Rosillo, L. Casarrubios, G. Domínguez, J. Pérez-Castells, *Org. Biomol. Chem.* **2003**, *1*, 1450–1451; e) Z.-Q. Yang, X. Geng, D. Solit, C. A. Pratilas, N. Rosen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 7881–7889.
[13] G. G. Melikyan, S. Bright, T. Monroe, K. I. Hardcastle, J. Ciurash, *Angew. Chem. Int. Ed.* **1998**, *37*, 163–164.
[14] For representative examples of enyne metathesis, see: S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382.
[15] a) S. J. Miller, S. H. Kim, Z.-R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109; b) S. J. Miller, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 5855–5856; c) A. Furstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746–8749; d) S. F. Martin, H.-J. Chen, A. K. Courtney, Y. Liao, M. Patzel, M. N. Ramser, A. A. Wagman, *Tetrahedron* **1996**, *52*, 7251–7264; e) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 123–126; f) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 127–130; g) M. Delgado, J. D. Martin, *Tetrahedron Lett.* **1997**, *38*, 6299–6300; h) R. J. Linderman, J. Siedlecki, S. A. O'Neill, H. Sun, *J. Am. Chem. Soc.* **1997**, *119*, 6919–6920.
[16] a) S. Hosokawa, M. Isobe, *Tetrahedron Lett.* **1998**, *39*, 2609–2612; b) S. Shibuya, M. Isobe, *Tetrahedron* **1998**, *54*, 6677–6698; c) K. Kira, A. Hamajima, M. Isobe, *Tetrahedron* **2002**, *58*, 1875–1888; d) K. Kira, H. Tanda, A. Hamajima, T. Baba, S. Takai, M. Isobe, *Tetrahedron* **2002**, *58*, 6485–6492.
[17] For a preliminary communication, see: N. Ortega, T. Martín, V. S. Martín, *Org. Lett.* **2006**, *5*, 871–873.
[18] D. D. Díaz, V. S. Martín, *Tetrahedron Lett.* **2000**, *41*, 9993–9996.
[19] 1-Bromo- and 1-chloro-2-propanol are commercially available as a mixture of secondary and primary alcohols in a 70:30 ratio. However, purification of the secondary alcohol was possible by simple partial esterification reaction with benzoyl chloride at 0 °C.
[20] Diastereoisomers *anti* and *syn* of the α,α′-disubstituted linear ethers are defined as described in the figure below:



[21] For previously reported syntheses of lauthisan, see: a) R. W. Carling, A. B. Holmes, *J. Chem. Soc., Chem. Commun.* **1986**, 565–567; b) H. Kotsuki, Y. Ushio, I. Kadota, M. Ochi, *J. Org. Chem.* **1989**, *54*, 5153–5161; c) K. Tsushima, A. Murai, *Chem. Lett.* **1990**, 761–764; d) K. C. Nicolaou, D. G. McGarry, P. K. Somers, B. H. Kim, W. W. Ogilvie, G. Yiannikouros, C. V. C. Prasad, C. A. Veale, R. R. Hark, *J. Am. Chem. Soc.* **1990**, *112*, 6263–6276; e) L. A. Paquette, T. J. Sweeney, *J. Org. Chem.* **1990**, *55*, 1703–1704; f) J. U. Udding, J. P. M. Giesselink, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1994**, *59*, 6671–6682; g) H. Kim, C. Ziani-Cherif, J. Oh, J. K. Cha, *J. Org. Chem.* **1995**, *60*, 792–793; h) Y.-G. Suh, B.-A. Koo, E.-N. Kim, N.-S. Choi, *Tetrahedron Lett.* **1995**, *36*, 2089–2092; i) M. J. Coster, J. J. De Voss, *Org. Lett.* **2002**, *4*, 3047–3050; j) see ref.[6a]; k) M. C. Carreño, R. Des Mazery, A. Urbano, F. Colobert, G. Solladie, *Org. Lett.* **2005**, *7*, 2039–2042; l) see ref.[17]; m) N. Miyakoshi, Y. Ohgaki, K. Masui, C. Mukai, *Heterocycles* **2007**, *74*, 185–189.
[22] For previously reported syntheses of obtusan, see: a) R. W. Carling, N. R. Curtis, A. B. Holmes, *Tetrahedron Lett.* **1989**, *30*, 6081–6084; b) R. W. Carling, J. S. Clark, A. B. Holmes, *J. Chem. Soc. Perkin Trans. 1* **1992**, *83*–94; c) M. C. Elliott, C. J. Moody, *Synlett* **1993**, 909–910; d) D. S. Brown, M. C. Elliott, C. J. Moody, T. J. Mowlem, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1137–1144.
[23] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) T. Katsuki, V. S. Martín, *Organic Reactions* (Eds.: L. A. Paquette), John Wiley & Sons, New York, New York, **1996**, vol. 48, pp. 1–299.
[24] The synthesis of **18a** with higher enantiomeric purity could be achieved by kinetic resolution of racemic allylic alcohol (±)-**18a** by using (–)-DET, see: V. S. Martín, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.
[25] The enantiomeric excess was determined by Mosher's ester. See the Supporting Information
[26] J. S. Yadav, T. Shekharam, V. R. Gadgil, *J. Chem. Soc., Chem. Commun.* **1990**, 843.
[27] G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
[28] For the preparation of oct-7-en-4-yn-3-ol (**19a**), see ref.[17]
[29] See the Supporting Information
[30] For acid-induced isomerization in fused medium-sized $Co_2(CO)_6$–cycloalkyne ethers, see: a) T.-Z. Liu, J.-M. Li, M. Isobe, *Tetrahedron* **2000**, *56*, 10209–10219; b) see ref.[11]
[31] F. R. P. Crisóstomo, R. Carrillo, T. Martín, V. S. Martín, *Tetrahedron Lett.* **2005**, *46*, 2829–2832.
[32] The hydrogenation of the *cis* compounds was performed with Pd(C) as catalyst. Although the use of Pd(C) for the *trans* isomers produced decomposition of the starting material, the hydrogenation was successfully performed with the use of PtO_2 as catalyst.

Received: October 29, 2008
Published Online: December 12, 2008

