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Approach to a new model of induction of stereoselectivity in the Nicholas reaction via a chiral 1-alkoxy-propargylium cation

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Abstract—A systematic study on the *syn–anti* diastereoselectivity of the Nicholas reaction between enantiopure propargyl acetal dicobalt–hexacarbonyl complexes, as precursors of chiral propargyl cobalt-hexacarbonyl cations, and several linear and cyclic silyl enol ethers is presented. A high yield up to 95% and high *syn–anti* diastereoselectivity (from 85:15 up to >99:1) is observed in the generation of the two new stereocenters. Moderate, but promising, *syn*(*R*,*R*)–*syn*(*S*,*S*), up to 70:30, is also observed in this preliminary work. This *syn*(*R*,*R*)–*syn*(*S*,*S*) diastereoselectivity formally would correspond to the enantioselectivity of the Nicholas reaction once the chiral auxiliary should be removed, in order to be recycled. This is the first approach to the induction of 'enantioselectivity' in the Nicholas C–C coupling based on cheap and commercially available enantiopure alcohols as chiral auxiliaries.

1. Introduction

The reaction between a propargyl cation stabilized as a dicobalt hexacarbonyl complex and a wide variety of nucleophiles is known as the Nicholas reaction. This reaction is very versatile and enables the introduction of different functional groups, especially by modification of the C–C triple bond, after demetallation. Thus, since its discovery by Nicholas and Pettit,[1] there have been many applications for this reaction,[2] varying either the cation or the nucleophile, and leading to the synthesis of complex biologically active compounds.[3]

There are precedents in the literature[2–4] on the Nicholas reaction, regarding to the *syn–anti* diastereoselectivity in the generation of two new stereocenters when the propargyl cation reacts with silyl enol ethers as nucleophiles. However, there are only a few studies about the induction of enantioselectivity in this reaction. In some of them,[5] a dissymmetric cluster $C_2Co_2(CO)_5L$ is generated by exchanging one CO ligand for another suitable ligand, L, normally a conveniently substituted phosphine or phosphite molecule. These seminal and meritorious models require, in some cases, preliminary resolutions of racemic starting propargyl alcohols and also separation of the mixture (normally 1:1) of diastereoisomers resulting from the ligand exchange. Nevertheless, a racemization and new resolution of the undesired stereoisomer could improve the process. Apart from this model, based on the design of a chiral cobalt cluster, there are other approaches found in the use of chiral

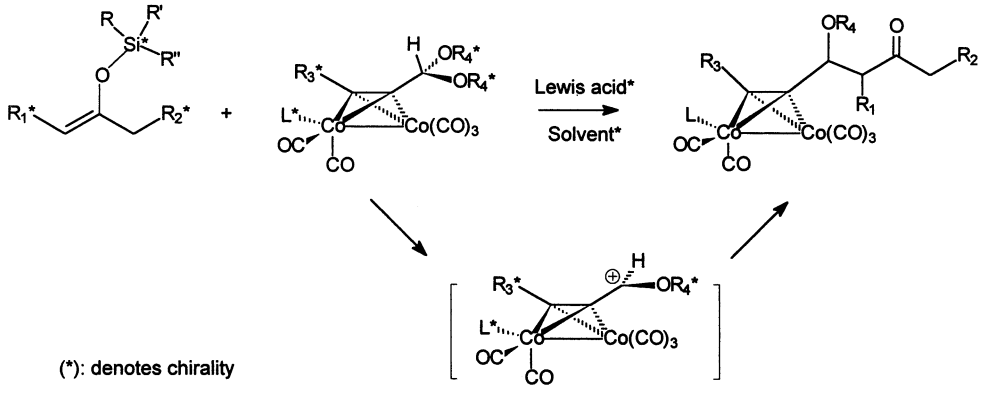

Figure 1. Different approaches to induce enantioselectivity in the Nicholas reaction.

Keywords: Nicholas reaction; *syn–anti* diastereoselectivity; enantioselectivity; cobalt complexes; enantiopure propargyl acetals.
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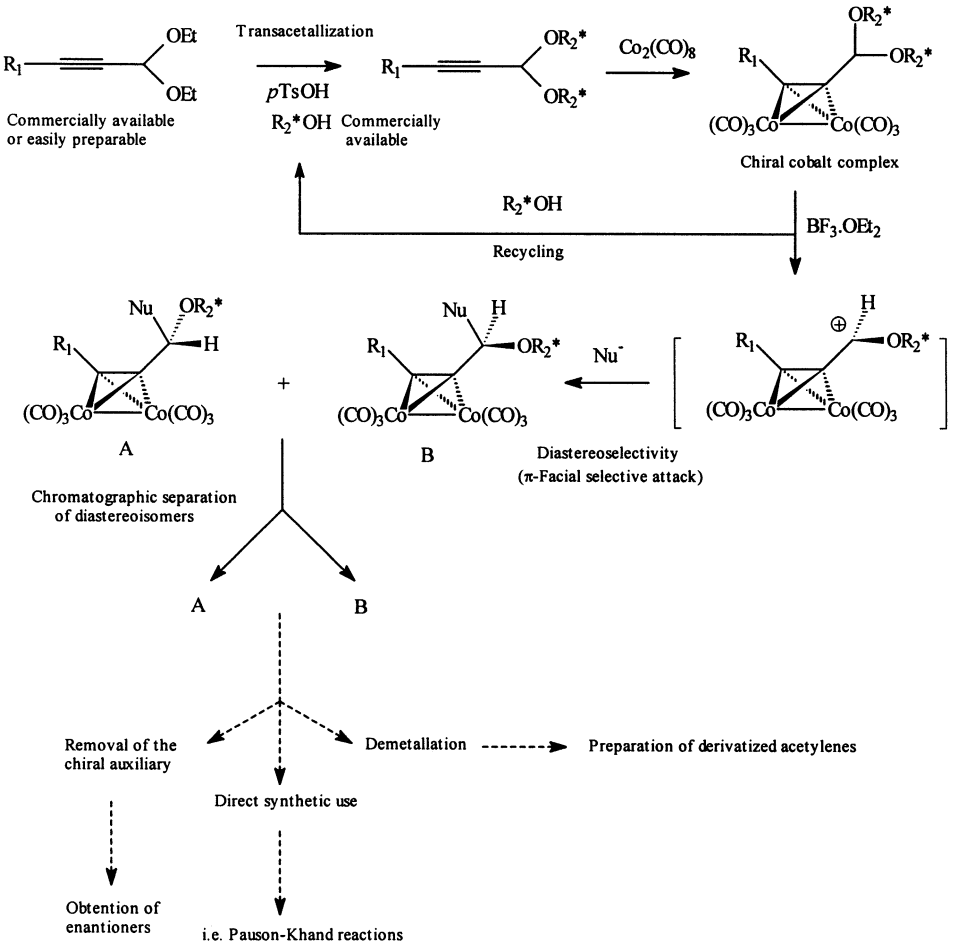


Figure 2. Representation of the approach to a new chirality induction model in the Nicholas reaction.

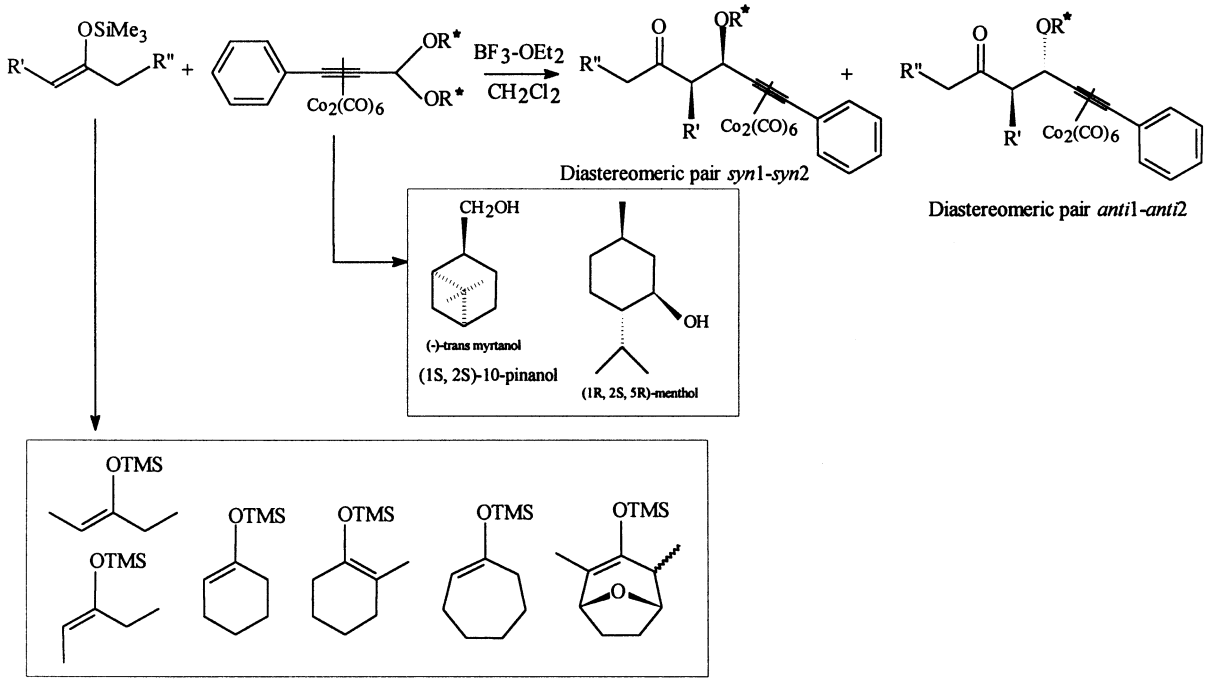
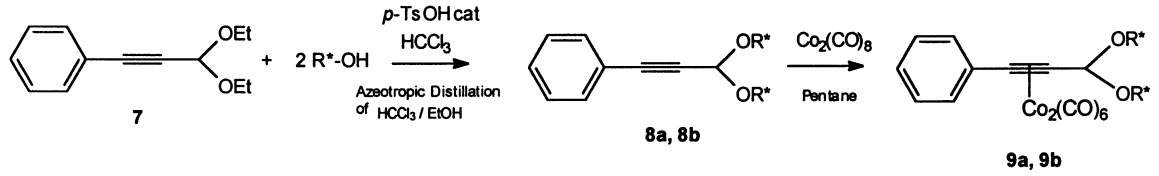
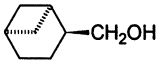
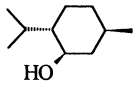


Figure 3. Silyl enol ethers and alkoxy substitution patterns of chiral propargyl acetals used in the Nicholas reaction.

Table 1. Preparation of the chiral propargyl acetals



R*–OH	*trans*-Acetallization		Metallation	
	Product	Yield (%)	Product	Yield (%)
 (-)-*trans*-Myrtanol	**8a**	66	**9a**	99
 (-)-Menthol	**8b**	65	**9b**	80

nucleophiles[6] (to be reacted with the propargyl cation), and also some authors induce dissymmetry in the Nicholas C–C coupling by using chiral propargyl precursors,[7] with the chiral moiety either as a substituent of the triple bond or as a chiral acetal function on the propargylic position.[8] The use of chiral Lewis acids and/or chiral solvents (with strong solvating properties) in the Nicholas reaction, to the best of our knowledge, have not been explored up to now.

All these approaches to induction of stereoselectivity in the Nicholas reaction are represented in Fig. 1.

With these precedents in mind, our target was the design of a general model for the improvement of *syn–anti* diastereoselectivity and for the approach to the induction of enantioselectivity in the Nicholas reaction by introduction of a chiral auxiliary at the site of the carbocation reactive center, instead of at the cobalt cluster. This approach is illustrated in Fig. 2.

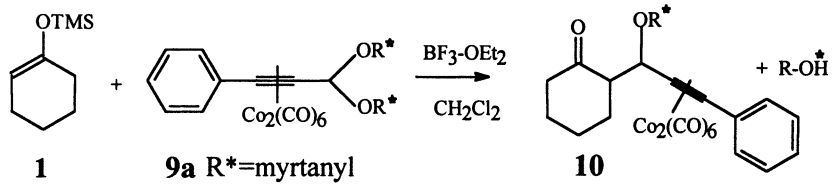
We prepared enantiopure propargyl acetals, as precursors of chiral propargyl dicobalt–hexacarbonyl cation complexes, starting from cheap and commercially available enantiopure alcohols (Fig. 3).

We report here a study on the introduction of chirality at the propargyl alkoxide level, using two different models:

(i) a model based on the propargyl acetal derived from (−)-*trans*-myrtanol, which places the closest asymmetric center of the chiral auxiliary three bonds away from the reactive center.
(ii) a second model based on the secondary alcohol (−)-menthol as the chiral auxiliary, which places the first stereo-differentiating asymmetric carbon, two bonds away from the cationic center.

For each model, we have evaluated the C–C coupling reaction with some prochiral enol silanes and thoroughly studied

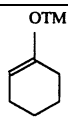
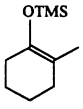
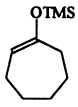
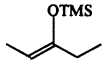
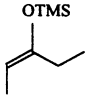
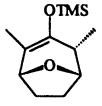
Table 2. Influence of the reaction conditions on the yield and stereoselectivity of the Nicholas reaction



Entry	Reaction conditions[a]				Results[b]	
	Cobalt complex (equiv.)	SEE[c] (equiv.)	$BF_3{\cdot}OEt_2$ (equiv.)	*T* (°C)	Yield (%)	Diastereoselectivity (*syn*/*anti*)
1	1	2	2	−78	50	85:15
2	1	2	1.5	−78	90	87:13
3	1	2	1.1	−78	95	85:15
4	1	1	2	−78	85	80:20
5	1	1	1	−78	0	–
6	1	1	1	0	41	85:15
7	1	1	1	rt	14[d]	78:22

[a] Reaction time until disappearance of the starting acetal cobalt complex, as observed by TLC (1–5 h). Dichloromethane was used as a solvent with a dilution of 17–140 mL/g of cobalt complex. 4 Å molecular-sieves powder was added to the reaction medium as a drying agent.
[b] Determined by 500 MHz ^{1}H NMR.
[c] Silyl enol ether.
[d] A high percent of complex decomposition products was observed at rt.

Table 3. Results of the alkylation reaction of enol silanes **1–6** with acetylenic acetal complex **9a**

Entry	SEE	Reaction conditions		Yield (%)	Product	Stereoselectivity[a]	
		T (°C)	*t* (h)			Diastereoselectivity (*syn*/*anti*)	Diastereoselectivity (*syn*-1/*syn*-2, *anti*-1/*anti*-2)[b]
1	 **1**	−78	4	95	**10**	85:15	Overlapped, 50:50
2	 **2**	−78	3.5	69	**11**	94:6	55:45, 50:50
3	 **3**	−78	3	95	**12**	72:28	60:40, 50:50
4	 **4**	−78	3	70	**13**	>99:1[c]	50:50, not detected
5	 **5**	−78	3	95	**13**	>99:1[c]	58:42, not detected
6	 **6**	−78 −23	4 3	0 0		–	–

[a] Determined by 500 MHz ^{1}H NMR.
[b] The *syn*-1/*syn*-2 or *anti*-1/*anti*-2 diastereoselectivities would correspond to the 'enantioselectivity' of the Nicholas reaction after the removal of the chiral auxiliary.
[c] Sensitivity limit of the 500 MHz NMR apparatus.

the corresponding alkylation products, both metallated and demetallated (Fig. 3).

2. Results and discussions

2.1. Preparation of silyl enol ethers

Enol silanes were prepared by following different reported procedures,[9–13] depending on the structure and stereochemistry of the desired product. The physical and spectroscopic properties of the prepared silyl enol ethers were identical to those reported in the literature.

2.2. Preparation of acetylenic acetals

The chiral propargyl acetals, **8a** and **8b** were prepared by transacetallization of the commercially available diethyl acetal of phenylpropargyl aldehyde, in the presence of catalytic amounts of anhydrous *p*-TsOH, with two equivalents of the corresponding enantiopure alcohol.[14] Dicobalthexacarbonyl complexes of these acetals were obtained, in high yield, by reaction of the appropriate acetylenic acetal with $Co_2(CO)_8$ in an inert solvent, at room temperature.[15] The yields in both steps of the synthetic pathway are quoted in Table 1.

2.3. Induction of stereoselectivity by using a model based on an enantiopure primary alcohol as a chiral auxiliary

First of all, a number of reaction parameters including temperature, stoichiometry and reaction time were explored to assess their effects on the yield and stereoselectivity of the Nicholas reaction. The parameters under evaluation and the results obtained from a selection of a high number of performed assays are presented in Table 2.

For a 1:1:1 stoichiometry, a decrease in the temperature was found to reduce the yield of C–C coupling, being null at −78°C (entry 5). When the Nicholas C–C coupling was carried out at room temperature (entry 7), the yield of alkylation products decreased because of decomposition of the starting acetal and formation of phenylpropionaldehyde. This decomposition under strict anhydrous conditions has also been previously observed by other authors.[16] Then, in order to enable a low working temperature (−78°C, favorable for stereo-controlled reactions) and to reach high conversions, in a reasonable period of time, it was necessary

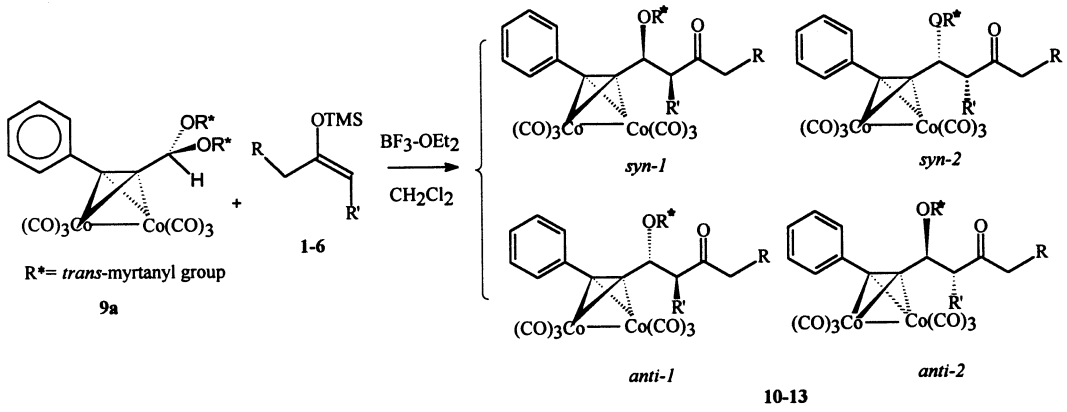


Figure 4. Four possible diastereoisomers are formed in the Nicholas reaction due to the generation of two stereocenters in the alkylation products.

to use excess of either $BF_3{\cdot}OEt_2$ or silyl enol ether (up to two equivalents. Entries 1–4). A relative excess of $BF_3{\cdot}OEt_2$ decreased the yield of C–C coupling due to the formation of phenylpropargylaldehyde (entries 1 and 4). Therefore, these results lead us to conclude that the treatment of a 1:2 mixture of cobalt complex and silyl enol ether, respectively, with 1.1 equiv. of Lewis acid give the alkylation products in good yield (95%) and high diastereoselectivity. None of the reaction parameters above evaluated considerably affected the stereochemical outcome of the reaction, obtaining an 85:15 average diastereomeric ratio (*syn*/*anti* ratio).

The Nicholas reaction of the chiral propargyl acetal cobalthexacarbonyl complex **9a** with silyl enol ethers of different nature (Fig. 3) was examined under the optimal conditions found in the previous experiments (see Table 2). The results obtained are presented in Table 3. In this case, as a result of generation of two new stereocenters, four diastereoisomers were observed by ^{1}H NMR (500 MHz): *syn*(*R*,*R*), *syn*(*S*,*S*), *anti*(*S*,*R*) and *anti*(*R*,*S*), (see Fig. 4).

From the results quoted in Table 3, it is possible to observe how the ring size in cyclic silyl enol ethers has an influence on the C–C coupling diastereoselectivity, probably due to the fact that the approach of reactants, in the transition state, is conditioned by the steric hindrance of the silyl enol ether moiety (see entries 1 and 3). Introduction of a methyl group at the reactive center in the nucleophilic silyl enol ether (entry 2), decreases the yield but increases the *syn*/*anti* diastereoselectivity (see entries 1 and 2), effects that could have also a stereo-electronic origin.

When a bulky and hindered silyl enol ether, having low conformational freedom, (entry 6) was used, no reaction was observed probably due to its difficulty to approach the electrophile (cobalt stabilized propargylium cation). The use of linear silyl enol ethers (entries 4 and 5) considerably raised the *syn*/*anti* diastereoselectivity (affording stereospecifically the *syn* diastereoisomer). These results could be interpreted on the basis of the smaller size of the linear carbon framework (maintaining the size and nature of the $OSiR_3$ group) of silyl enol ethers and their higher conformational freedom than the cyclic ones. This allows a better and less stereo-demanding approach of reactants and affords a better and less energetic matching in the transition state. These interpretations are discussed later based on modeling of the transition states that afford the different stereoisomers observed in the Nicholas reaction.

It is possible to distinguish the four diastereomeric products (the pair of *syn* diastereomers from the pair of *anti* diastereoisomers, Fig. 3) by 500 MHz ^{1}H- and 75 MHz ^{13}C NMR correlation studies, after a careful assignment of signals by 1D and 2D NMR experiments. This feature becomes even more marked in the alkylation products of cyclic trimethyl silyl enol ethers. ^{1}H NMR analysis of the reaction mixture allowed to conveniently determine the *syn*/*anti* ratio and, in most cases, the *syn*-1/*syn*-2 and *anti*-1/*anti*-2 ratios, by integration of the separated CH(OR*) diagnostic resonance peaks for each diastereomer, prior to their separation by column chromatography.

The stereochemical assignment was carried out on the basis of a comparative analysis of high field ^{1}H- and ^{13}C NMR data[17] (by correlation of both chemical shifts and values of coupling constants[18]) in conjunction with examination of molecular models and computational conformational analysis.[19] Once the minimum energy conformation was established for each configuration, the ^{1}H- and ^{13}C NMR correlations of chemical shifts confirmed the stereochemical assignment. This study was made for two alkylation products; one derived from a cyclic enol silane **1** and the other from the acyclic **4**. In all cases the CH(OR*) resonance signal for the major diastereomeric pair was deshielded relative to that of the minor. From the coupling constants between the hydrogens on the new C–C bond (formed in the Nicholas reaction), eight dihedral angles were deduced from the Karplus equation. Examination of models for these dihedral angles and computational analysis for both configurations *syn* and *anti* lead to a minimum energy conformation for each major and minor diastereomeric pair. The configuration that correlates the chemical shifts in the ^{1}H- and ^{13}C NMR spectra, for a given conformation of minimum energy, made possible the stereochemical assignment of the new stereocenters. All this extensive spectroscopic correlation study has been published elsewhere.[17]

2.4. Stereoselectivity induced by a chiral secondary alcohol auxiliary

Due to the conformational freedom of (−)-*trans*-myrtanol,

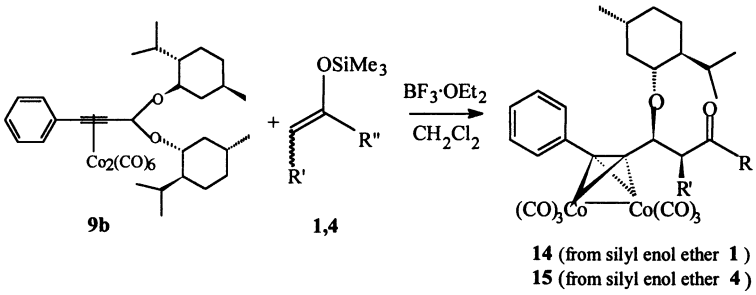


Figure 5. Nicholas C–C coupling between silyl enol ethers **1** and **4** and the enantiopure cobalt-complexed propargyl acetal **9b**, derived from (−)-*trans*-myrtanol.

natural (−)-menthol was chosen as an alternative (Fig. 5). In this new model, the C-1 stereogenic center of the chiral auxiliary is two bonds closer to the reactive cationic center than in the former model. The Nicholas reaction of the corresponding acetal (**9b**), with two silyl enol ethers (**1** cyclic and **4** acyclic), under the same stoichiometry and reaction conditions as in the primary model, proceeded with low yields of alkylation products. However, a promising 7:3 *syn*-1/*syn*-2 diastereoselectivity ratio for the major product was obtained when the nucleophile was the cyclic enol silane **1** (Table 4).

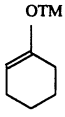
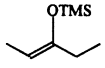
Therefore, in this case closer proximity of the first stereogenic center of the menthyloxy chiral auxiliary to the cationic center, together with the restriction of conformational rotation along the C1′–O and O–C1″ bonds (Fig. 6), enable the nucleophile to differentiate between both faces of the carbocation, better than in the former model.[19]

On the other hand, there is a certain decrease on the yield in the reaction of menthyl chiral acetals versus myrtanyl acetals. This fact could be probably due to the higher difficulty of the approach of reactants in the transition state, because of their greater bulkiness (this could be the explanation for the lower reactivity of cobalt-complex **9b** versus **9a**).

2.5. The origin of *syn/anti* diastereoselectivity

Once we had established the stereochemistry of the alkylation products we evaluated the stereo-electronic and orbital interactions between the reactant species in their approach to the transition state, in order to rationalize the

Table 4. Results of alkylation of enol silanes **1** and **4** by acetylenic acetal complex **9b**

Starting SEE	Reaction conditions				Product	Conversion (%)	Yield (%)	Diastereoselectivity	
	T (°C)	*t* (h)	Drying agent	Dilution (mL/g)				*syn*/*anti*	*syn*-1/*syn*-2, *anti*-1/*anti*-2
 **1**	−78	5	4 Å molecular sieves	50	**14**	84	40	75:25	70:30, 50:50
 **4**	−78	4.5	4 Å molecular sieves	50	**15**	85	74	85:15	60:40, 50:50

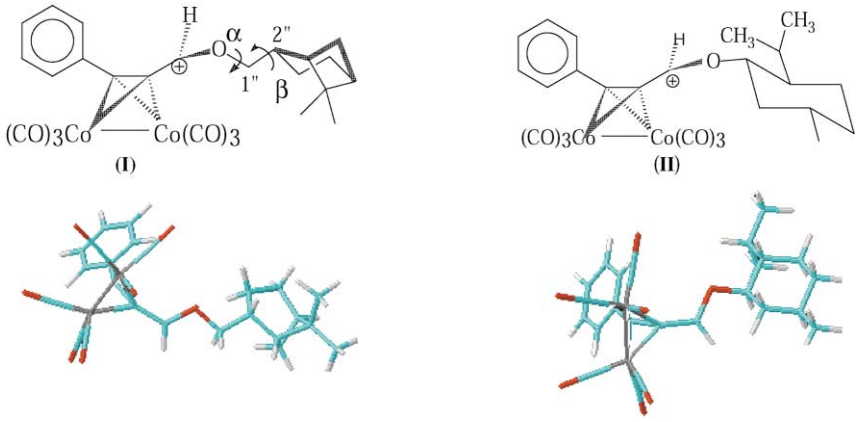


Figure 6. Optimized geometry of myrtanyl (I) and menthyl (II) 1-alkoxy-propargylium cations.[19]

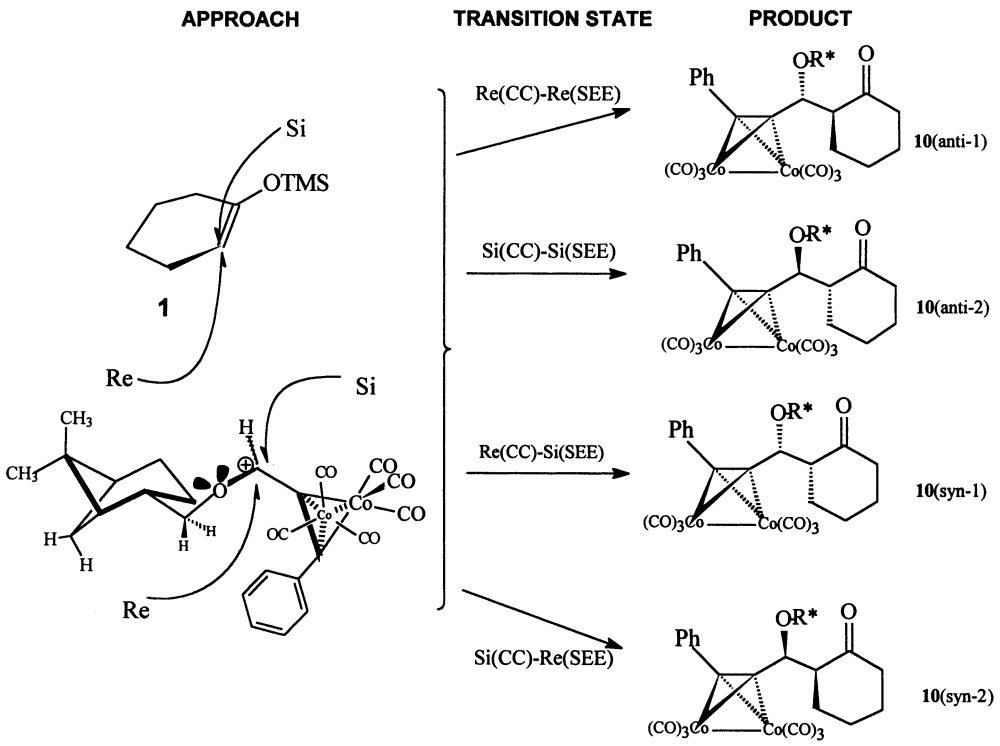


Figure 7. Possible approaches of silyl enol ether **1** to the cobalt stabilized propargylium cation, in the transition state leading to the formation of compound **10**.

stereochemical outcome of the Nicholas reaction, especially the diastereoselectivity in the formation of the two new stereogenic centers during the C–C coupling.

Modelling the transition states (TS) showed that interactions of the faces: *Re* (carbocation=CC) versus *Re* (silyl enol ether=SEE) and *Si*(CC)–*Si*(SEE) afforded the *anti* isomers, meanwhile the facial interactions *Re*(CC)–*Si*(SEE) and *Si*(CC)–*Re*(SEE) gave the *syn* diastereomers of compound **10** (See Fig. 7).

The *syn*/*anti* diastereoselectivity observed in the present work suggested that the TS approaches Si(CC)–Re(SEE) or Re(CC)–Si(SEE) were favored in the formation of **10**.

Today it is known that the chemical behavior of dicobalt–hexacarbonyl complexes of propargylium cations and the stereochemical outcome of the reactions in which they are involved are better explained by the consideration of resonance or canonical forms, where the cobalt atoms act as electron-donors assisting the electron-deficient carbon atom. These resonant forms allow the existence of a fluxional tautomerism[20] or equilibria among four valence or fluxional tautomers, which interconvert to each other by antarafacial and suprafacial migrations. This phenomenon has been extensively studied by Nicholas,[21a,b] Jaouen[21c–f] and Schreiber.[21g]

Due to the fluxional character of the cation there are four diastereomeric forms in equilibrium:[21g] two *syn* forms (having the phenyl and alkoxy OR* groups on the same side of the formal double bond of the cation, see Fig. 8) depending on which cobalt atom holds the positive charge; and two *anti* forms having the Ph and OR* groups on opposite sides of that formal double bond. According to this structural model, the two diastereomeric fluxional forms of the cation that show and confront the same face to the nucleophile (silyl enol ether), only differentiate in the relative positions (*syn*/*anti*) of their phenyl and alkoxide groups, in such a way that they exert different steric

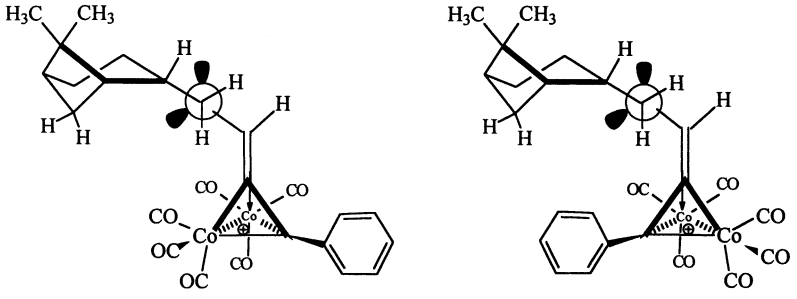


Figure 8. *syn*/*anti* Diastereomeric fluxional forms of the 1-myrtanyloxy-cobalthexacarbonyl-propargylium cation.

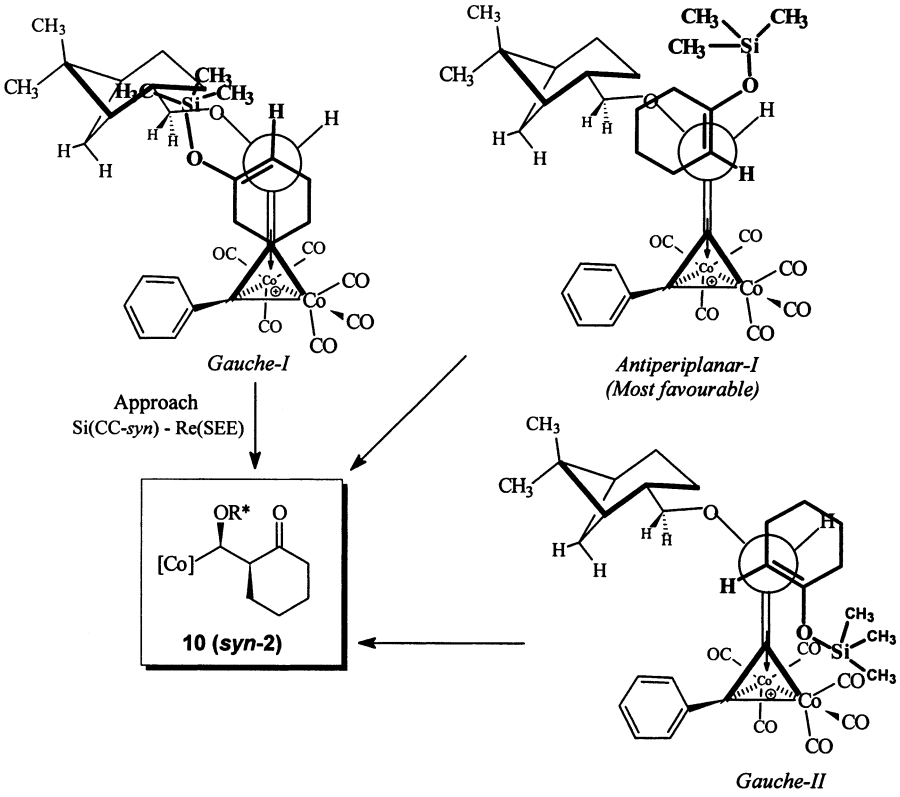


Figure 9. Approaches *Si*(CC-*syn*)–*Re*(SEE), considering *gauche* and antiperiplanar interactions, in the transition state for the formation of product **10** (*syn*-2).

hindrance and electronic and orbital effects on the attacking silyl enol ether, considering the same type of approach (*gauche* or antiperiplanar).

The myrtanyloxy group is a primary alkoxide and it could allocate its bulky bicycle far apart from the phenyl group, in the *anti* form of the cation, or far away from the cobalt-hexacarbonyl cluster in the *syn* form. So, it is possible to expect that the model of rationalization of the difference of stability of both forms should be similar to that observed by other authors.[15,21] In order to evaluate the influence of the fluxional equilibria of the carbocation in the transition state we studied all possible approaches of the *syn*/*anti* fluxional forms of the cation and the silyl enol ether. From this study we observed that the approach of the cation by one of its faces to both faces (*Si*, *Re*) of the silyl enol ether afforded the same alkylation products, independently of the *syn*/*anti* configuration of the fluxional cation. Also we observed that all approaches leading to the same alkylation product did not have the same feasibility because of the low matching possibilities of some of them due to stereo-electronic hindrance.

The facial stereoselectivity is mainly determined by four factors which control the matching of reactant species: the nature of the groups attached to the reactive center of the carbocation, the type of approach (*gauche* or antiperiplanar) of the π systems of both the silyl enol ether and the propargyl cation, the structure of the silyl enol ether (linear or cyclic) and finally the fluxional configuration of the cation (*syn*/*anti*). Concerning the first of these factors, it is possible to observe three groups attached to the reactive center of the cation, with different size and stereo-electronic nature, whose distribution around such reactive center condition the approach of the enol. These groups are: one hydrogen atom, a myrtanyloxy group and the organometallic cluster $C_2Co_2(CO)_6$, which interact with different intensity with both the carbon framework (linear or cyclic) and the bulky $OSiMe_3$ group of the enol ether. With regard to the second factor, according to Seebach,[22] in most cases the alkylation reactions of enolates by electrophiles, which result from a donor–acceptor π interaction, the stereochemical outcome of the reaction is better explained considering a *gauche* approach of the π systems due to stabilizing secondary orbital interactions. Based on this fact we proposed a model of *gauche* approach except for the case in which that approach should be untenable due to stereo-electronic reasons (destabilizing interactions of $OSiMe_3$ group with any of the steric demanding groups attached to the cation). In this particular case, we considered antiperiplanar models, with also a good overlapping of the p orbitals perpendicular to the π systems.

In the interpretation of the stereoselectivity in the Nicholas reaction of our substrates we considered a *syn* configuration for the cation, in accord with the studies of Schreiber.[21] Based on this assumption, we observed by modeling studies of the approach of the *syn*-carbocation by its *Si* face to the silyl enol ether, that the coupling by the *Re* face of the silyl enol ether was much more feasible, through an antiperiplanar-I interaction rather than either a *gauche*-I or a *gauche*-II interaction. This is due to the more favorable relative disposition of the four stereo-demanding groups (phenyl, $C_2Co_2(CO)_6$, $OSiMe_3$ and OR^*), which were far apart from each other, in the former case (see Figs. 9 and 10, and also Table 5).

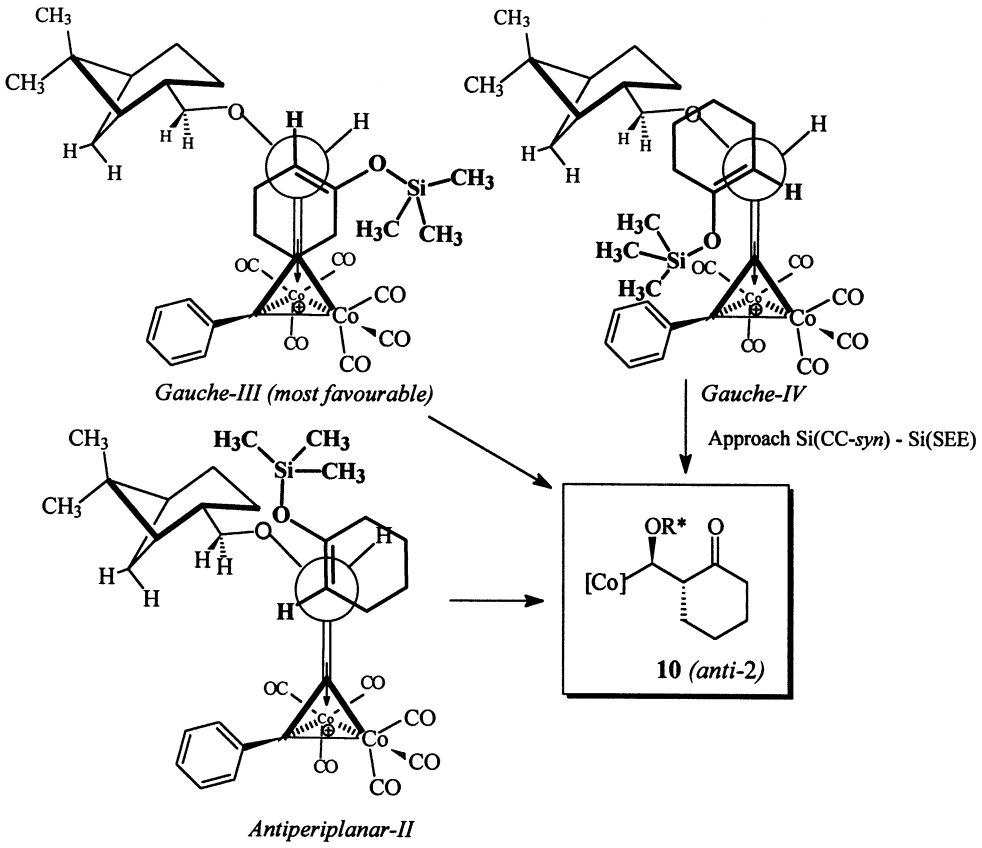


Figure 10. Approaches *Si*(CC-*syn*)–*Si*(SEE), considering *gauche* and antiperiplanar interactions, in the transition state for the formation of product **10** (*anti*-2).

A similar study of this approach by the other face of the silyl enol ether: *Si*(CC-*syn*)–*Si*(SEE), showed that the *gauche*-III TS was favored because of the interactions between the cyclohexene ring of the enol and the dicobalt cluster were in this case less unstabilizing than the interactions $OSiMe_3$–OR^* (antiperiplanar-II TS) or $OSiMe_3$–$C_2Co_2(CO)_6$ (*gauche*-IV TS), (see Fig. 10).

Models of the TS, which result from the approach of the *Re* face of the *syn*-cation to any of both faces of the enol allow to draw the same conclusions than before (See Table 5). The difference of energy between the antiperiplanar-I transition state (which affords the isomer **10**-*syn*2) and the *gauche*-III TS (leading to diastereoisomer **10**-*anti*2) could explain the *syn*/*anti* diastereoselectivity observed in the Nicholas reactions carried out in the present work.

2.6. The origin of *syn*1–*syn*2 diastereoselectivity

The moderate *syn*-1/*syn*-2 diastereoselectivity observed when the menthyloxy-propargyl cation was used could be interpreted as a result of the difference of energy of two antiperiplanar TS: *Re*(CC)–*Si*(SEE) versus *Si*(CC)–*Re*(SEE), which lead respectively to *syn*-1 and *syn*-2 diastereoisomers. In Fig. 11 we illustrate by means of arrows the main interactions, which should make the first TS less feasible and the *syn*1 isomer the minor one. Unfortunately, we did not be able to get pure crystalline samples from our reaction products, so we could not carry out X-ray diffraction analysis to confirm this model.

As mentioned elsewhere, the difference of *syn*1–*syn*2 diastereoselectivity between the models based on myrtanyloxy versus menthyloxy-cations, could be due to a closer proximity of the first stereogenic center of the menthyloxy chiral auxiliary to the cationic center, together with the restriction of conformational rotation along the C1′–O and O–C1″ bonds (Fig. 6). This enables the nucleophile to differentiate between both faces of the carbocation, better than in the former model. The difference of geometry,

Table 5. Interactions observed in the transition states leading to *syn*/*anti* diastereoisomers depending on the faces of the cation and silyl enol ether that confront to each other

Transition state	Interactions	Favored approach	Stereochemistry of alkylation product
Si(CC)–*Re*(SEE)	Cyclic ketone–OR^*<*cluster*-$OSiMe_3$<OR^*–$OSiMe_3$	Antiperiplanar-I	*syn*-2
Re(CC)–*Si*(SEE)		Antiperiplanar-I′	*syn*-1
Re(CC)–*Re*(SEE)	Cyclic ketone-cluster<*cluster*-$OSiMe_3$<OR^*–$OSiMe_3$	*gauche*-III′	*anti*-1
Si(CC)–*Si*(SEE)		*gauche*-III	*anti*-2

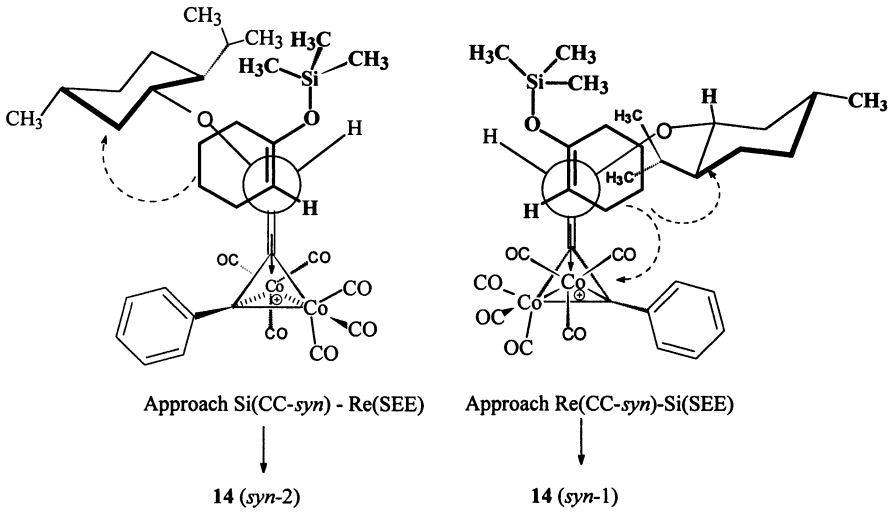


Figure 11. Transition states leading to *syn*-1 and *syn*-2 diastereoisomers of **14**.

hindrance and conformational freedom between both types of cations was clear from computational studies carried out on these species.[19] On the other hand, at this moment, the explanation of the lack of *anti*-1/*anti*-2 diastereoselectivity in both cation models is not clear.

3. Conclusions

The Nicholas reaction between silyl enol ethers and chiral propargyl acetals derived from enantiopure alcohols (myrtanol and menthol) proceeds with excellent *syn*/*anti* diastereoselectivity (from 7:3 up to >99:1). Furthermore, when a double restriction was introduced at the level of both the cation and the silyl enol ether, a *syn*-1/*syn*-2 diastereoselectivity 7:3 for the major product was obtained. Studies with new chiral propargyl acetals are currently in progress, in order to improve the *syn*-1/*syn*-2 or *anti*-1/*anti*-2 diastereoselectivity. Also studies to improve separation and demetallation of diastereoisomers, separation of chiral auxiliary from the alkylation products, by regioselective cleavage of ethers, and recycling of the chiral auxiliary are been conducted in our laboratory

4. Experimental

4.1. General methods

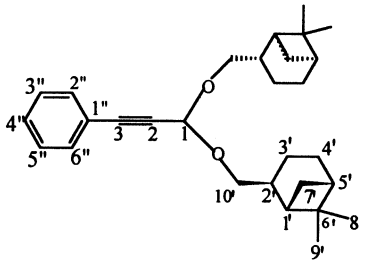
^{1}H NMR spectra were obtained at 300 or 500 MHz on Varian apparatuses. ^{13}C NMR was obtained at 75.4 MHz on a Varian Unity-300 plus spectrometer. Deuterated NMR solvents were dried over 4 Å molecular sieves, filtered through neutral alumina and stored and handled under nitrogen. NMR samples of cobalt complexes (10^{-2}–10^{-4} M in $CDCl_3$) were prepared on a vacuum line under prepurified nitrogen and filtered through a short pad of dry neutral alumina before use.

Analytical gas chromatography was carried out using a capillary column (cross linked Me–Ph silicone, 25 m× 0.2 mm×2.5 μm), in a HP-5890A GC apparatus. Two different programs of temperature have been used for GC analysis (A: 100°C, 1 min; 10°C min^{-1}; 290°C, 20 min and B: 50°C, 1 min; 10°C min^{-1}; 290°C, 20 min). Flash column chromatography was carried out with, oven-dried, E. Merck silica gel (230–400 mesh) and neutral alumina (100–125 mesh) under nitrogen pressure.

Glassware was washed in an alcoholic KOH bath and oven-dried at 120°C overnight, prior to use. Solvents were purified and dried by refluxing over drying agents for 1 h prior to distillation (CH_2Cl_2 and triethylamine from CaH_2; THF, diethyl ether and pentane from Na/benzophenone; acetone from anhydrous $MgSO_4$). 1,1-Diethoxy-3-phenyl-2-propyne (**7**), (−)-*trans*-myrtanol and (−)-menthol are commercially available. The silyl enol ether of cyclohexanone[9] (**1**), the (*Z*)-silyl enol ether of 3-pentanone (**4**) and of 2-methylcyclohexanone (**3**),[11] the (*E*)-silyl enol ether of 3-pentanone (**5**)[12] the silyl enol ether of cycloheptanone[10] (**2**) and 2,4-dimethyl-3-trimethylsilyloxy-8-oxabicyclo[3.2.1]oct-2-ene (**6**)[3a–d] were prepared according to the procedures described in the literature. The purity of all compounds showed to be >99% by ^{1}H NMR and GC. All the silyl enol ethers prepared and used as reactants were characterized, showing identical data as those previously reported in the literature.

4.2. Preparation of chiral acetylenic acetals RC≡CCH(OR*)$_2$

4.2.1. 3-Phenyl-1,1-bis[(1*S*,2*S*,5*S*)-10-pinane-10-oxy]-2-propyne, 8a

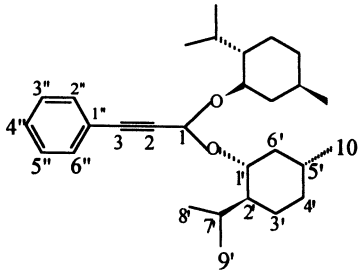


Under an atmosphere of nitrogen, diethyl acetal **7** (0.67 g,

3.3 mmol) and a catalytic amount (3%, w/w) of *p*-toluensulfonic acid (previously dried by azeotropic distillation with benzene) were placed in a 250 mL three-necked flask equipped with a 25 mL Dean–Stark apparatus. The system was purged with argon and chloroform (50 mL), previously dried over $CaCl_2$ and filtered through a short pad of dry neutral alumina, was added. Two equivalents of (−)-myrtanol (>99% ee, $[\alpha]_D^{20}=-28°$ (c=4, $CHCl_3$)) were added dropwise at 80–90°C under nitrogen with continuous stirring, removing the $HCCl_3$–EtOH azeotrop. The volume of chloroform in the reaction mixture was maintained constant by adding fresh solvent via syringe. The reaction was monitored by GC (program A) showing complete conversion of starting material after 5 h. Then, 4–5 drops of triethylamine were added to neutralize the acid media and the crude mixture was washed four times with saturated aqueous $NaHCO_3$ solution and water. The organic fraction was dried over anhydrous potassium carbonate, filtered and concentrated under vacuum at room temperature. The resulting crude oil was purified by distillation at 0.5 mmHg and 90–100°C, removing the unreacted diethylacetal **7** and the remaining free alcohol, affording 0.87 g (yield: 66%) of **8a** as a yellow oil.

IR (film, ν(cm^{-1})): 2915, 2234, 1600, 1461, 1445, 1100, 876–756. ^{1}H NMR (300 MHz, $CDCl_3$, δ(ppm)): 0.86 (6H, s, H8′), 1.22 (6H, s, H9′), 1.25–1.29 (2H, m, H3′ax), 1.63–1.67 (2H, m, H3′eq), 2.03–2.05 (2H, m, H7′eq), 1.32–1.36 (2H, m, H7′ax), 1.80–1.90 (8H, m, H1′, H5′, H4′), 2.30–2.34 (2H, m, H2′), 3.33–3–37 (2H, m, H10′A), 3.53–3.58 (2H, m, H10′B), 5.44 (1H, s, H1), 7.31–7.33 (3H, m, H3″, H4″, H5″), 7.45–7.49 (2H, m, H2″, H6″). ^{13}C NMR ($CDCl_3$, δ(ppm)): 18.54, 18.49 (C3′), 20.16 (C8′), 26.66 (C9′), 23.44 (C7′), 24.15 (C4′), 34.97 (C2′), 39.09 (C6′), 40.96 (C5′), 42.60, 42.56 (C1′), 69.35, 69.28 (C10′), 85.27, 84.50 (C2, C3), 92.35 (C1), 128.22 (C4″), 128.71 (C3″, C5″), 131.92 (C2″, C6″). MS (DIP–CI, NH_3, m/z (%)): 438 (8, M+18), 267 (100, M−RO), 130 (98, C_9H_6O). Anal. calcd for $C_{29}H_{40}O_2$: C, 82.81; H, 9.59. Found: C, 82.79; H 9.62%. GC (program A): R_t=20.8 min.

4.2.2. 3-Phenyl-1,1-bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-1-oxy]-2-propyne, 8b



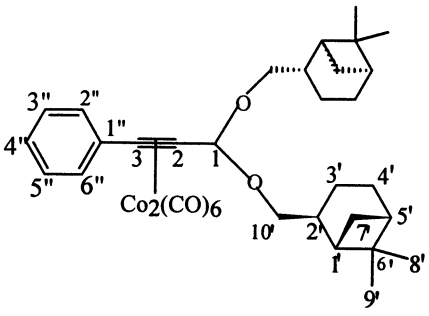
A procedure, similar to the one described earlier, was applied to the preparation of **8b**. An excess of (−)-menthol (>99% ee, $[\alpha]_D^{20}=-50°$ (c=10, EtOH)), (6:1 molar ratio) was used and a catalytic amount of *p*-toluensulfonic acid (previously dried by azeotropic distillation with benzene) was added. Complete reaction was observed after 3 h by GC. The reaction mixture was neutralized with the stoichiometric amount of Et_3N and passed through a short pad of dried neutral alumina to remove the formed salts. The excess of (−)-menthol was distilled off, under 3 mmHg at 100°C, affording 0.73 g (65% yield) of the colourless oily product **8b**.

IR (film,ν(cm^{-1})): 3058, 2950, 2233, 1700–2000, 1161, 1456, 690, 756. ^{1}H NMR (300 MHz, $CDCl_3$, δ(ppm)): 0.82 (3H, d, J=5.6 Hz, H8′), 0.79 (3H, d, J=5.6 Hz, H8′), 0.93, 0.89 (12H, d, not resolved, H9′, H10′), 0.98–1.02 (6H, m, 2H6′, 2H4′, 2H3′), 2.17–2.27 (3H, m, 2H6′, H7′), 1.63–1.67 (4H, m, 2H3′, 2H4′), 1.27–1.33 (4H, m, H5′, H2′), 3.65 (1H, td, $J_{1'2'}$=4 Hz, $J_{1'6'}$=10.2 Hz, H1′), 3.42 (2H, td, $J_{1'2'}$=4.4 Hz, $J_{1'6'}$=10.2 Hz, H1′), 5.33 (1H, s, H1), 7.29–7.31 (2H, m, H2″, H6″), 7.44–7.48 (3H, m, H3″, H4″, H5″). ^{13}C NMR ($CDCl_3$, δ(ppm)): 16.24, 16.07 (C8′), 21.19, 21.14 (C9′), 22.30 (C10′), 23.21, 23.01 (C3′), 25.35, 25.07 (C7′), 38.35 (C4′), 31.67, 31.60 (C5′), 42.37, 41.79 (C6′), 48.38, 48.12 (C2′), 77.80, 76.64 (C1′), 86.12, 84.88 (C2, C3), 91.78 (C1), 122.27 (C1″), 128.19 (C3″, C5″), 128.53 (C4″), 131.80 (C2″, C6″). MS (FAB(+), glycerol, m/z (%)): 269 (10, M−RO), 139 (100, R^+), 131 (85, C_9H_6O+1). MS (DIP–CI, NH_3, m/z (%)): 269 (100, M−RO), 287 (60, M−RO+18). Anal. calcd for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 82.05; H, 10.39%. GC (Program A): R_t=19.56 min.

4.3. Preparation of [RC≡CCH(OR*)$_2$]Co$_2$(CO)$_6$, 9. General procedure[3a–d]

In an efficient laboratory hood, dicobalt octacarbonyl (1 equiv.) was placed, under argon atmosphere, into a flask (previously flame-dried under vacuum and purged with argon). After weighting, the flask is fitted with a rubber septum and purged again with argon. Dry pentane (40 mL g^{-1} of acetal) was added at room temperature. Then, an equimolar amount of the acetal **8** was added, and the reaction mixture was stirred for 1.5 h. When the complexation reaction was complete, as observed by TLC, the dark red solution was filtered through a short pad of dry neutral alumina in a Schlenk flask. The transfer of the cobalt complex solution to the Schlenk flask was carried out under argon by cannula. Solvent was removed by rotary evaporation, (at room temperature!) resulting in a dark red oil, which was concentrated to dryness, under vacuum (1 mmHg) for 30 min, to remove traces of solvent. The yield fell, in all cases, within the range of 80–100%.

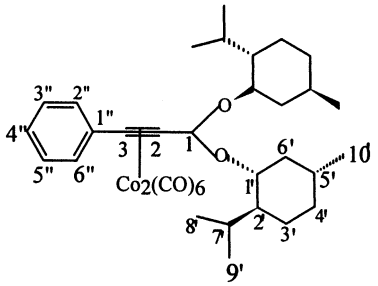
4.3.1. Hexacarbonyl-μ-η^4-{3-phenyl-1,1-bis[(1*S*,2*S*,5*S*)-pinane-10-oxy]-2-propyne}-dicobalt(Co–Co), 9a



Dark red oil, IR (film,ν(cm^{-1})): 3060, 2926, 2053, 1621, 1481–1443, 1102, 818, 758. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.82 (6H, s, H8′), 1.17, 1.19 (6H, s, H9′), 1.58–1.66 (2H, m, H3′), 1.30 (2H, m, H3′) 1.78–1.86 (8H, m,

H1′, H5′, H4′), 2.03–2.08 (2H, m, H7′), 1.32 (2H, m, H7′), 2.28–2.32 (2H, m, H2′), 3.45–3.50 (4H, m, H10′), 5.69 (1H, s, H1), 7.31–7.33 (3H, m, H3″, H4″, H5″), 7.57–7.61 (2H, m, H2″, H6″). ^{13}C NMR ($CDCl_3$, δ(ppm)): 18.45, 18.27 (C3′), 20.04 (C8′), 23.38, 23.33 (C7′), 24.14, 24.12 (C4′), 26.63, 26.58 (C9′), 35.33, 35.22 (C2′), 39.09, 39.05 (C6′), 40.93, 40.88 (C5′), 42.60, 42.55 (C1′), 72.00, 71.46 (C10′), 102.50 (C1), 128.56, 127.69 (C3″, C4″, C5″), 129.88 (C2″, C6″), 137.74 (C1″), 200 ($Co_2(CO)_6$). MS (DIP–CI, NH_3, *m/z* (%)): 553 (83, M−RO), 525 (8, M−RO−28), 172 (79, $C_{10}H_{17}$+35). Anal. calcd for $C_{35}H_{40}O_8Co_2$: C, 59.49; H, 5.71. Found: C, 59.53; H, 5.80%.

4.3.2. Hexacarbonyl-μ-η^4-{3-phenyl-1,1-bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl-1-oxy]-2-propyne}dicobalt(Co–Co), 9b



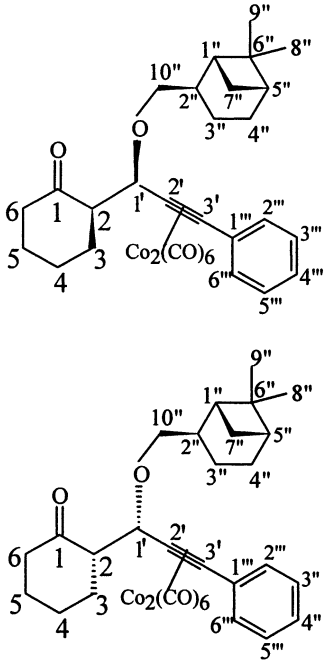
Dark red oil, IR (film, ν(cm^{-1})): 3060, 2958, 2024–2092, 1387, 1026, 691, 758. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.73 (3H, d, *J*=3.6 Hz, H8′), 0.76 (3H, d, *J*=3.3 Hz, H8′), 0.84 (3H, d, *J*=7.2 Hz, H10′ or H9′), 0.82 (3H, d, *J*=7.2 Hz, H10′ or H9′), 0.92 (3H, d, *J*=6.7 Hz, H9′ or H10′), 0.88 (3H, d, *J*=6.7 Hz, H9′ or H10′), 1.58–1.64 (4H, m, H3′ or H4′), 1.0–1.20 (4H, m, H3′ or H4′), 1.70 (4H, m, H2′, H5′), 2.47–2.51 (1H, m, H7′), 1.98–2.04 (1H, m, H7′), 2.35–2.45 (4H, m, H6′), 3.49 (1H, dt, $J_{1'2'}$=3.9 Hz, $J_{1'6'}$=10.8 Hz, H1′), 3.60 (1H, dt, $J_{1'2'}$=3.9 Hz, $J_{1'6'}$=10.8 Hz, H1′), 5.98 (1H, s, H1), 7.28–7.32 (3H, m, H3″, H4″, H5″), 7.53–7.58 (2H, m, H2″, H6″). ^{13}C NMR ($CDCl_3$, δ(ppm)): 200 (br., $Co_2(CO)_6$), 139 (C1″), 129.89 (C2″, C6″), 128.38, 127.34 (C3″, C4″, C5″), 77.96 and 77.24 (C1′), 49.62 and 48.52 (C2′), 42.96 and 41.85 (C6′), 34.25 (C4′), 32.01 and 31.38 (C5′), 25.13 and 24.79 (C7′), 22.90 (C3′), 22.27 and 22.08 (C10′), 21.07 and 21.30 (C9′), 15.97 and 16.29 (C8′). MS (FAB(+), glycerol, *m/z* (%)): 682 (5, M−CO), 654 (20, M−2CO), 598 (90, M−4CO), 570 (20, M−5CO), 542 (40, M−6CO), 555 (100, M−RO), 527 (60, M−RO–CO), 499 (10, M−RO–2CO), 471 (80, M−RO–3CO), 444 (20, M−RO–4CO). Anal. calcd for $C_{35}H_{44}O_8Co_2$: C, 59.16; H, 6.24. Found: C, 59.29; H, 6.11%.

4.4. Alkylation reactions of silyl enol ethers 1–6 with acetylenic acetal cobalt-complexes 9

A 1:2 molar ratio of the acetal complex **9** and the silyl enol ether (**1**–**6**), respectively, were dissolved in anhydrous dichloromethane (50 mL g^{-1} of complex). The solution was cooled to −78°C and one equivalent of $BF_3{\cdot}OEt_2$ was added by syringe under nitrogen and continuous stirring. The reaction mixture was maintained at this temperature under nitrogen until the starting material was completely transformed, as observed by TLC (SiO_2). Then, it was quenched with Et_3N (stoichiometric proportion with respect to the amount of added $BF_3{\cdot}OEt_2$) and washed successively with $NaHCO_3$ saturated aqueous solution (2×10 mL) at 0°C and brine (1×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness at room temperature, resulting in an oily dark-red crude mixture. Isolation of pure products was accomplished by flash column chromatography of the mixture on oven-dried silica gel with a short precolumn of dry neutral alumina. Mixtures of anhydrous pentane and diethyl ether of increasing polarity were used as eluents, separating the major diastereoisomeric alkylation products from the minor and from any elimination product and/or unchanged starting material. Yields of alkylation products and stereoselectivity are shown in Table 3 for the myrtanol model and in Table 4 for the menthol model.

The four expected diastereomeric alkylation products (*syn* and *anti* diastereomeric pairs) were distinguished by ^{1}H- and ^{13}C NMR owing to the introduction of the chiral auxiliary on the propargyl carbon. From the ^{1}H- and ^{13}C NMR, COSY and HETCOR spectra it was possible to assign the ^{1}H and ^{13}C chemical shifts of each *syn* and *anti* pair. However, the signals corresponding to the diastereoisomers of each pair: *syn*-1/*syn*-2 or *anti*-1/*anti*-2, were only differentiated in certain parts of the molecule, as it is shown, in italics, in the following data.

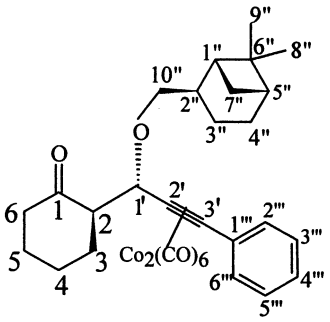
4.4.1. Hexacarbonyl-μ-η^4-2-{3-phenyl-1-[(1*S*,2*S*,5*S*)-pinane-10-oxy]-2-propyne-1-yl}-cyclohexan-1-one}-dicobalt(Co–Co), 10

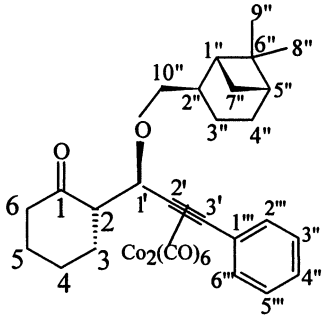


Diastereomeric pairs **10**-*syn* and **10**-*anti* were separated by flash column chromatography (54 g of dry silica gel, 2.87 g of reaction mixture, packing height=18 cm, column ϕ=2.5 cm), by elution with dry pentane/ether 8:2, under pressure of nitrogen.

***10**-(syn$_1$–syn$_2$)*: dark red oil, IR (film, ν(cm^{-1})): 3050, 2929, 2049–2089, 1713, 1603, 1443, 1383, 1368, 1095. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.79, (3H, s, H8″), *0.80* (3*H*, *s*,

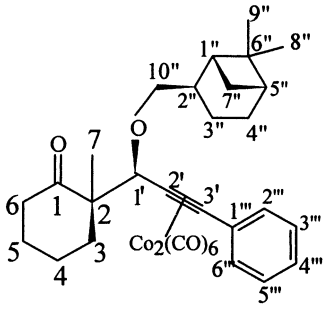
H8″), 1.15 (3H, s, H9″), *1.18* (3*H*, *s*, *H9″*), 1.60 (1H, m, H3″), 1.26 (1H, m, H3″), *1.46* (*1H*, *m*, *H3″*), *1.18* (*1H*, *m*, *H3″*), 1.7 (2H, m, H4″), 1.83 (1H, m, H5″), 1.98 (1H, m, H7″), 1.28 (1H, m, H7″), 1.75, (1H, m, H1″), *1.86* (*1H*, *m*, *H1″*), 2.20–2.25 (1H, m, H2″), 2.46–2.48 (1H, m, H6), 2.26 (1H, m, H6), 2.02 (1H, m, H5), 1.62 (1H, m, H5), 1.88 (1H, m, H4), 1.52 (1H, m, H4), 2.2 (1H, m, H3), 1.7 (1H, m, H3), *2.55–2.59* (*1H*, *m*, *H2*), 2.55–2.59 (1*H*, m, *H2*), 3.30–3.40 (1H, m, H10″), 3.40–3.48 (1H, m, H10″), *3.33–3.39* (*1H*, *m*, *H10″*), *3.44–3.51* (*1H*, *m*, *H10″*), 5.41 (1H, s, H1′), *5.42* (*1H*, *s*, *H1′*), 7.27–7.31 (3H, m, H3‴, H4‴, H5‴), 7.45–7.47 (2H, m, H2‴, H6‴). ^{13}C NMR ($CDCl_3$, δ(ppm)): 17.94 (C3″), *18.75* (*C3″*), 20.01 (C8″), 26.6 (C9″), *26.7* (*C9″*), 23.3 (C7″), *23.6* (*C7″*), 24.09 (C4″), *24.15* (*C4″*), 24.70 (C4), 27.24 (C5), 28.07 (C3), *28.18* (*C3*), 35.47 (C2″), *35.39* (*C2″*), 39.1 (C6″), 40.85 (C5″), *40.80* (*C5″*), 42.70 (C1″), *42.51* (*C1″*), 42.04 (C6), *42.01* (*C6*), 58.23 (C2), *58.33* (*C2*), 75.9 (C1′), *75.7* (*C1′*), 76.34 (C10″), *75.34* (*C10″*), 98 (C2′), 92 (C3′), 127.49 (C4‴), 129.51 (C1‴), 127.60–128.60 (C2‴, C3‴, C5‴, C6‴), 210.40 (C1), 199.44 ($Co_2(CO)_6$). MS (FAB(+), NBA, *m/z* (%)): 594 (28, M−2CO), 566 (25, M−3CO), 538 (100, M−4CO), 510 (70, M−5CO), 482 (98, M−6CO). Anal. calcd for $C_{31}H_{32}O_8Co_2$: C, 57.24; H, 4.96. Found: C, 57.30; H, 5.02%.

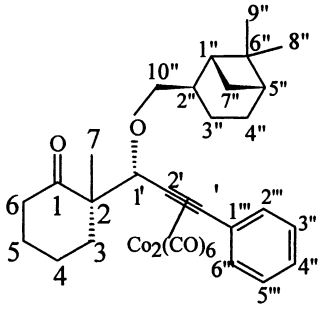




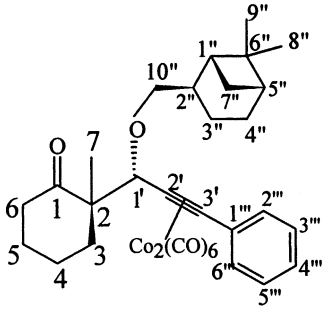
***10**-(anti$_1$–anti$_2$)*: dark red oil, IR (film,ν(cm^{-1})): 3045, 2930, 2050–2092, 1715, 1605, 1448, 1378, 1383, 1100. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): same chemical shifts as **10**-*syn* except for the following hydrogens: 2.70–2.74 (2H, m, H2), 1.4 (1H, m, H3), 1.9 (1H, m, H3), 2.98–3.02 (1H, m, H10″), 2.89–2.93 (1H, m, H10″), 5.07 (1H, d, *J*=7.0 Hz, H1′), *5.06* (*1H*, *d*, *J=7.5 Hz*, *H1′*). ^{13}C NMR ($CDCl_3$, δ(ppm)): same chemical shifts than **10**-*syn* except for the following carbons: 78.9 (C1′), *78.6* (*C1′*), 62.9 (C10″), *63.6* (*C10″*), 212.3 (C1). MS (FAB(+), NBA, *m/z* (%)): 594 (35, M−2CO), 566 (30, M−3CO), 538 (100, M−4CO), 510 (80, M−5CO), 482 (95, M−6CO). Anal. calcd for $C_{31}H_{32}O_8Co_2$: C, 57.24; H, 4.96. Found: C, 57.18; H, 4.98%.

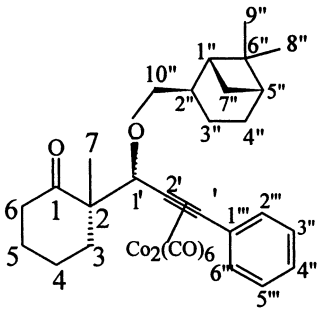
4.4.2. Hexacarbonyl-μ-η^4-{2-methyl-2-{3-phenyl-1-[(1*S*, 2*S*,5*S*)-pinane-10-oxy]-2-propyn-1-yl} cyclohexan-1-one}-dicobalt(Co–Co), 11. Diastereomeric pairs **11**-*syn* and **11**-*anti* were separated by flash column chromatography (17 g of dry silica gel, 89.4 mg of crude mixture, packing height=14 cm, column ϕ=2 cm), by elution with dry pentane/diethyl ether 9:1, under pressure of nitrogen.





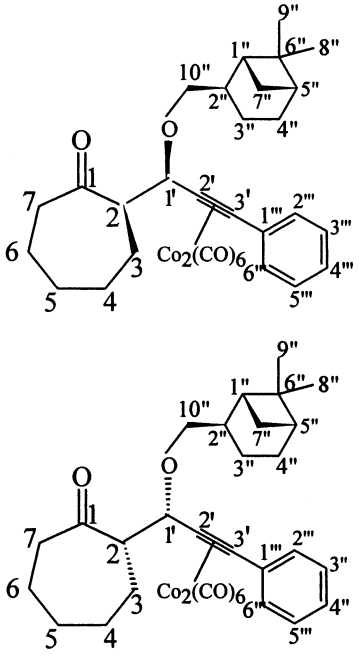
***11**-(syn$_1$–syn$_2$)*: dark red oil, IR (film,ν(cm^{-1})): 2929, 2020–2100, 1707, 1458. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.8 (3H, s, H8″), 1.25 (3H, s, H9″), 1.6 (3H, s, H7), 1.62 (1H, m, H3″), 1.30 (1H, m, H3″) 1.75 (2H, m, 4″), 1.82 (3H, m, H3″ and H5″), 1.28 (1H, m, H7″), 2.00 (1H, m, H7″), 1.80–2.00 (6H, m, H3, H4, H5), 2.23 (1H, m, H2″), 2.45–2.50 (2H, m H6), 3.57–3.61 (1H, m, H10″), 3.28–3.32 (1H, m, H10″), *3.65–3.69* (*1H*, *m*, *H10″*), *3.28–3.32* (*1H*, *m*, *H10″*), 5.09 (1H, s, H1′), *5.08* (*1H*, *s*, *H1′*), 7.2–7.4 (5H, m, H2‴, H3‴, H4‴, H5‴, H6‴). ^{13}C NMR ($CDCl_3$, δ(ppm)): 18.70 (C3″), 20.10 (C8″), 22.20 (C7), 26.70 (C10″), 23.60 (C7″), 24.13 (C4″), 35.40 (C2″), 40.80 (C5″), 42.90 (C1″), 76.50 (C10″), *78.00* (*C10″*), 84.00 (C1′), *83.73* (*C1′*), 127.1–128.2 (C3″, C4″, C5″), 129.9 (C2″, C6″), 199.5 ($Co_2(CO)_6$). MS (FAB(+), NBA): 608.3 (15, M−2CO), 580.3 (10, M−3CO), 552.3 (100, M−5CO), 524.4 (45, M−5CO), 496.4 (95, M−6CO). Anal. calcd for $C_{32}H_{34}O_8Co_2$: C, 58.91; H, 5.25. Found: C, 58.82; H, 5.30%.



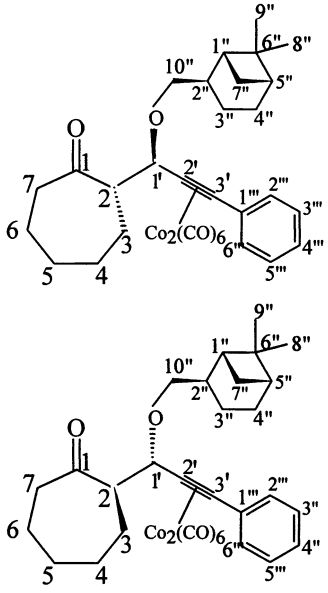


***11**-(anti$_1$–anti$_2$)*: dark red oil, IR (film, ν(cm^{-1})): 2931, 2020–2100, 1705, 1460. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): differing from **11**-*syn* in: 3.57–3.61 (1H, m, H10″), 3.33–3.37 (1H, m, H10″), *3.49–3.53* (*1H*, *m*, *H10″*), *3.33–3.37* (*1H*, *m*, *H10″*), 4.69 (1H, s, H1′), *4.66* (*1H*, *s*, *H1′*). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): differing from **11**-*syn* in the following signals 76.34 (C10″), *77.81* (*C10″*), 80.11 (C1′), *79.34* (*C1′*) 211.40 (C1). MS (FAB(+), NBA): 608 (20, M−2CO), 580 (8, M−3CO), 552 (100, M−4CO), 524 (52, M−5CO), 496 (90, M−6CO). Anal. calcd for $C_{32}H_{34}O_8Co_2$: C, 58.91; H, 5.25%. Found: C, 58.85; H, 5.11%.

4.4.3. Hexacarbonyl-μ-η^4-{2-{3-phenyl-1-[(1*S*,2*S*,5*S*)-pinane-10-oxy]-2-propyne-1-yl}-cycloheptan-1-one}-dicobalt(Co–Co), 12. Diastereomeric pairs **12**-*syn* and **12**-*anti* were separated by flash column chromatography (15 g of dry silica gel, 133 mg of reaction mixture, packing height=13 cm, column ϕ=2 cm), by elution with dry pentane/diethyl ether 9:1 and 8:2, respectively.

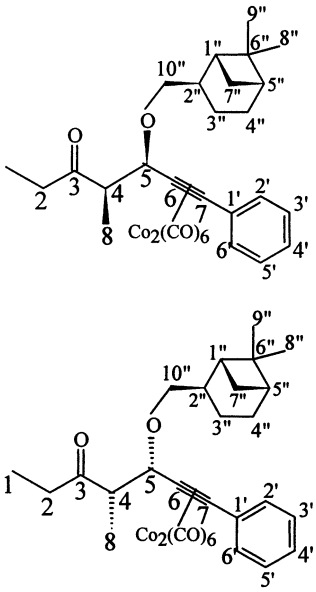


***12**-(syn$_1$/syn$_2$)*: dark red oil, IR (film, ν(cm^{-1})): 2930–2867, 2050–2090, 1704, 1443, 1074. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.79 (3H, s, H9″), 1.15 (3H, s, H8″), 1.20 (1H, m, H3″), 1.60 (1H, m, H3″), 1.70 (2H, m, H4″), 1.85 (2H, m, H5″, H1″), 1.25 (1H, m, H7″), 1.95 (1H, m, H7″), 1.8–2.00 (4H, m, H4,5), 1.85 (1H, m, H6), 1.50 (1H, m, H6), 2.18–2.22 (1H, m, H2″), 2.10 (1H, m, H3), 1.60 (1H, m, H3), 2.50–2.56 (2H, m, H7), 2.70–2.72 (1H, m, H2), 3.41–3.45 (1H, m, H10″), 3.23–3.27 (1H, m, H10″), *3.36–3.40* (*1H*, *m*, *H10″*), *3.23–3.27* (*1H*, *m*, *H10″*), 5.27 (1H, d, *J*=3.5 Hz, H1′), *5.26* (*1H*, *d*, *J=3.9 Hz*, *H1′*), 7.30–7.34 (3H, m, H3‴, H4‴, H5‴), 7.47–7.50 (2H, m, H2‴, H6‴). ^{13}C NMR ($CDCl_3$, δ(ppm)): 18.77 (C3″), *17.94* (*C3″*), 20.03 (C9″), 23.26 (C7″), 24.14 (C6), 24.30 (C4″), 25.26 (C3), 26.70 (C8″), 28.94 (C4), 29.69 (C5), 35.36 (C2″), 40.89 (C5″), 42.50 (C1″), 44.03 (C7), *43.94* (*C7*), 59.75 (C2), 76.56 (C10″), *75.50* (*C10″*), 80.90 (C1′), 123.66–127.62 (C3‴, C4‴, C5‴), 129.58 (C2‴, C6‴), 138.00 (C1‴), 199.00 ($Co_2(CO)_6$), 214.00 (C1). MS (FAB(+), NBA): 608 (15, M−2CO), 552 (73, M−4CO), 496 (100, M−6CO). Anal. calcd for $C_{32}H_{34}O_8Co_2$: C, 58.91; H, 5.25%. Found: C, 58.97; H, 5.12%.

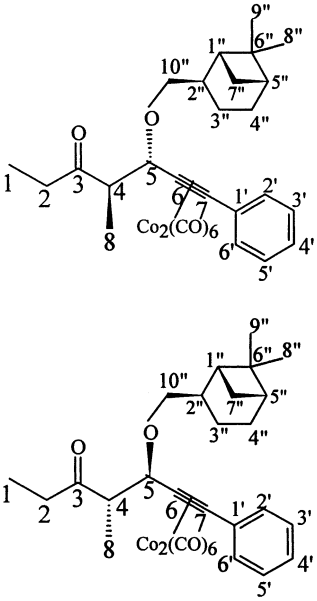


***12**-(anti$_1$/anti$_2$)*: dark red oil, IR (film, ν(cm^{-1})): 2930–2870, 2050–2090, 1706, 1445, 1080. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): differing from **12**-*syn* in the following signals: 1.16 (3H, s, H8″), *1.17* (*3H*, *s*, *H8″*), 2.87 (1H, m, H2), 3.56–3.60 (1H, m, H10″), 3.23–3.27 (1H, m, H10″), *3.50–3.54* (*1H*, *m*, *H10″*), *3.33–3.36* (*1H*, *m*, *H10″*), 5.05 (1H, d, *J*=5.5 Hz, H1′), *5.03* (*1H*, *d*, *J=5.5 Hz*, *H1′*). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): differing from **12**-*syn* in the following signals 75.83 (C10″), *76.12* (*C10″*), 79.6 (C1′), *80.2* (*C1′*), 212.67 (C1). MS (FAB(+), NBA): 608 (20, M−2CO), 552 (75, M−4CO), 496 (100, M−6CO). Anal. calcd for $C_{32}H_{34}O_8Co_2$: C, 58.91; H, 5.25%. Found: C, 58.79; H, 5.29%.

4.4.4. Hexacarbonyl-μ-η^4-{7-phenyl-4-methyl-5-[(1*S*,2*S*,5*S*)-pinane-10-oxy]-6-heptyn-3-one}-dicobalt(Co–Co), 13. Diastereomeric pairs **13**-*syn* and **13**-*anti* were separated by flash column chromatography (20 g of dry silica gel, 331 mg of reaction mixture, packing height=20 cm, column ϕ=1.5 cm), by elution with dry pentane/diethyl ether 9:1.

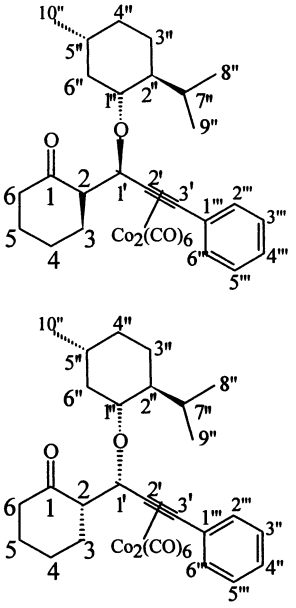


***13**-(syn$_1$–syn$_2$)*: dark red oil, IR (film,ν(cm^{-1})): 2929, 2050–2090, 1717, 1460, 1074, 693, 758. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.79 (3H, s, H8″), 0.95 (3H, t, *J*=6 Hz, H1), *0.94* (*3H*, *t*, *J=6 Hz*, *H1*), 1.19 (3H, s, H9″), *1.15* (*3H*, *s*, *H9″*), 1.23 (3H, d, *J*=6.9 Hz, H8), 1.52–1.56 (1H, m, H3″), 1.2 (1H, m, H3″) 1.73–1.77 (2H, m, H4″), 1.93–1.96 (1H, m, H7″), 1.24–1.26 (1H, m, H7″), 1.80–1.84 (2H, m, H5″, H1″), 2.14–2.18 (1H, m, H2″), 2.50 (1H, m, H2), 2.3 (1H, m, H2), 2.75 (1H, m, H4), 3.47 (1H, dd, *J*=8.5 Hz, H10″), 3.32 (1H, dd, *J*=7 Hz, H10″), 5.14 (1H, d, *J*=6.5 Hz, H5), *5.13* (*1H*, *d*, *J=6.9 Hz*, *H5*), 7.30–7.34 (3H, m, H3′, H4′, H5′), 7.41–7.43 (2H, m, H2′, H6′). ^{13}C NMR ($CDCl_3$, δ(ppm)): 7.47 (C1), 12.7 (C8), 18.69 (C3″), 19.97 (C8″), 26.6 (C9″), 23.56 (C7″), 24.14 (C4″), 35.1 (2″), 40.70 (C1″, C5″), 40.80 (C1″, C5″), 34.2 (C2), 54 (C4), 76.4 (C10″), *75.6* (*C10″*), 79.5 (C5), 92.35 (C2′, C3′), 97.6 (C2′, C3′), 127, 128 (C3′, C4′, C5′), 129 (C2′, C6′), 136.25 (C1′), 197.5 ($Co_2(CO)_6$), 212 (C3). MS (FAB(+), NBA): 610 (25, M−CO), 582 (30, M−2CO), 554 (70, M−3CO), 526 (60, M−4CO), 498 (75, M−5CO), 470 (100, M−6CO). Anal. calcd for $C_{30}H_{32}O_8Co_2$: C, 56.44; H, 5.05%. Found: C, 56.50; H, 4.98%.



***13**-(anti$_1$–anti$_2$)*: dark red oil, IR (film,ν(cm^{-1})): 2930, 2050–2090, 1715, 1465, 1075, 700, 756. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.78 (3H, s, H 8″), 0.88 (3H, d, *J*=6.9 Hz, H8), *0.89* (*3H*, *d*, *J=6.9 Hz*, *H8*), 1.07 (3H, t, *J*=5.5 Hz, H1), *1.06* (*3H*, *t*, *J=5.5 Hz*, *H1*), 1.18, 1.16 (3H, s, H9″), 1.42–1.46 (1H, m, H3″), 1.10 (1H, m, H3″), 1.73–1.77 (2H, m, H4″), 1.93–1.96 (1H, m, H7″), 1.24–1.26 (1H, m, H7″), 1.82 (2H, m, H1″, H5″), 2.22–2.26 (1H, m, H2″), 2.61 (1H, m, H2), 2.53 (1H, m, H2), 2.75 (1H, m, H4), 3.59 (1H, dd, *J*=8 Hz, H10″), (1H, dd, *J*=7 Hz, H10″), *3.51* (*1H*, *dd*, *J=8 Hz*, *H10″*), *3.21* (*1H*, *dd*, *J=4 Hz*, *H10″*), 4.80 (1H, d, *J*=9.5 Hz, H5), *4.79* (*1H*, *d*, *J=9.9 Hz*, *H5*), 7.30–7.33 (3H, m, H3′, H4′, H5′), 7.42–7.44 (2H, m, H2′, H6′). ^{13}C NMR (75.43 MHz,$CDCl_3$, δ(ppm)): same chemical shifts than **13**-*syn* except for the following carbons: 23.23 (C7″), 24.06 (C4″), 37.8 (C2), 82.8 (C5), 76.5 (C10″), 137.92 (C1′), 199.4 ($Co_2(CO)_6$), 213 (C3). MS (FAB(+), NBA): 610 (20, M−CO), 582 (38, M−2CO), 554 (60, M−3CO), 526 (75, M−4CO), 498 (83, M−5CO), 470 (100, M−6CO). Anal. calcd for $C_{30}H_{32}O_8Co_2$: C, 56.44; H, 5.05%. Found: C, 56.39; H, 5.11%.

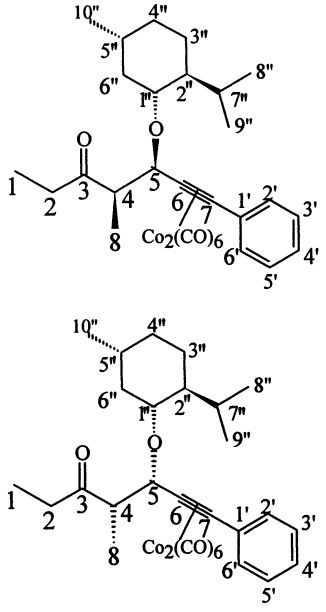
4.4.5. Hexacarbonyl-μ-η^4-{2-{1-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl-1-oxy]-3-phenyl-2-propyn-1-yl}-cyclohexan-1-one}-dicobalt(Co–Co), 14. Diastereomeric pair **14**-*syn* was purified by flash column chromatography (18 g of dry silica gel, 177 mg of reaction mixture, packing height=13 cm, column ϕ=2 cm), by elution with dry pentane/diethyl ether 9:1. Due to we worked on small scale, it was not possible the isolation of **14**-*anti*. However, the NMR correlation studies and the assignment of relative stereochemistry of both diastereomeric pairs was carried out on the crude mixture of the alkylation reaction, by 1D and 2D high field NMR experiments.



***14**-(syn$_1$–syn$_2$)*: dark red oil, IR (film,ν(cm^{-1})): 2960, 2024–2091, 1715, 1600, 1457, 1043, 692, 758. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.76 (3H, d, *J*=7 Hz, H8″), *0.69* (*3H*, *d*, *J=7 Hz*, *H8″*), 0.86 (3H, d, *J*=7 Hz, H9″), *0.82* (*3H*, *d*, *J=7 Hz*, *H9″*), 0.89 (3H, d, *J*=2.5 Hz, H10″), *0.88* (*3H*, *d*, *J=2.5 Hz*, *H10″*), 1.40–1.60 (6H, m, H2″, H3″, H4″, H5″), 2.28–2.32 (2H, m, H6″), *2.08–2.12* (*2H*, *m*,

H6″), 2.24–2.28 (1H, m, H7″), 2.47–2.52 (1H, m, H2), 2.20 (2H, m, H3), 1.80 (2H, m, H3), 1.60 (1H, m, H5), 2.00 (1H, m, H5), 2.20 (1H, m, H6), 2.40 (1H, m, H6), 3.38–3.41 (1H, m, H1″), *3.48–3.52* (*1H*, *m*, *H1″*), 5.85 (1H, d, *J*=3 Hz, H1′), *5.66* (*1H*, *d*, *J=3 Hz*, *H1′*), 7.28–7.32 (3H, m, H3‴, H4‴, H5‴), 7.46–7.50 (2H, m, H2‴, H6‴). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): 198.56 ($Co_2(CO)_6$), 211.3 (C1), 58.11 (C2), *58.23* (*C2*), 28.11 (C3), *28.21* (*C3*), 24.50 (C4), 27.18 (C5), 42.11 (C6), *42.15* (*C6*), 75.90 (C1′), *75.48* (*C1′*), 98.15 (C2′), 92.11 (C3′), 72.21 (C1″), *71.97* (*C1″*), 49.02 (C2″), *50.03* (*C2″*), 22.69 (C3″), *23.15* (*C3″*), 34.38 (C4″), 31.82 (C5″), *31.30* (*C5″*), 45.15 (C6″), 24.63 (C7″), 16.02 (C8″), 21.10 (C9″), 22.31 (C10″), 129.51 (C1‴), 128.60 (C2‴), 127.62 (C3‴), 127.49 (C4‴), 127.62 (C5‴), 128.60 (C6‴). MS (FAB(+), NBA): 624 (35, M−CO), 596 (50, M−2CO), 568 (45, M−3CO), 540 (70, M−4CO), 512 (83, M−5CO), 484 (100, M−6CO). Anal. calcd for $C_{31}H_{34}O_8Co_2$: C, 57.07; H, 5.25%. Found: C, 57.01; H, 5.32%.

4.4.6. Hexacarbonyl-μ-η^4-{4-methyl-5-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl-1-oxy]-7-phenyl-6-heptyn-3-one}-dicobalt(Co–Co), 15. Diastereomeric pair **15**-*syn* was purified by flash column chromatography (13 g of dry silica gel, 117 mg of reaction mixture, packing height=13 cm, column ϕ=2 cm), by elution with pentane/diethyl ether 99.5:0.5. Due to the small amount of **15**-*anti* formed in the reaction, it was not possible its isolation and physical characterization. However, the NMR correlation studies and the assignment of relative stereochemistry of both diastereomeric pairs were carried out on the crude mixture of the alkylation reaction, by 1D and 2D high field NMR experiments.

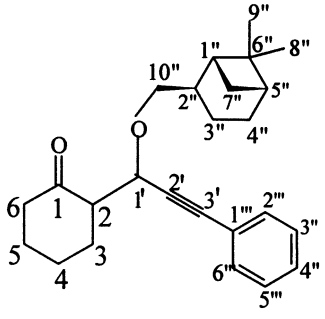


***15**-(syn$_1$–syn$_2$)*: dark red oil, IR (film, ν(cm^{-1})): 2930, 2029, 1715, 1443, 1093, 691, 760. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.76 (3H, d, *J*=7 Hz, H8″), *0.69* (*3H*, *d*, *J=7 Hz*, *H8″*), 0.86 (3H, d, *J*=7 Hz, H9″), *0.82* (*3H*, *d*, *J=7 Hz*, *H9″*), 0.89 (3H, d, *J*=2.5 Hz, H10″), *0.88* (*3H*, *d*, *J= 2.5 Hz*, *H10″*), 1.01 (3H, t, *J*=5 Hz, H1), *1.05* (*3H*, *t*, *J= 5 Hz*, *H1*), 1.23 (3H, d, *J*=7.5 Hz, H8), *1.24* (*3H*, *d*, *J= 7.5 Hz*, *H8*), 1.4–1.6 (6H, m, H2″, 3″, 4″, 5″), 2.28–2.32 (1H, m, H6″), *2.08–2.12* (*1H*, *m*, *H6″*), 1.15 (1H, m, H6″), *1.15* (*1H*, *m*, *H6″*), 2.24–2.28 (1H, m, H7″), 2.52–2.56 (2H, m, H2), 2.77–2.81 (1H, m, H4), *2.75–2.80* (*1H*, *m*, *H4*), 3.28–3.31 (1H, m, H1″), *3.21–3.24* (*1H*, *m*, *H1″*), 5.68 (1H, d, *J*=2.49 Hz, H5), *5.57* (*1H*, *d*, *J=2.9 Hz*, *H5*), 7.28–7.32 (3H, m, H3′, H4′, H5′), 7.47–7.49 (2H, m, H2′, H6′). ^{13}C NMR ($CDCl_3$, δ(ppm)): 7.84 (C1), 11.00 (C8), 15.98 (C8″), 21.10 (C9″), 22.20 (C10″), 22.70, 23.10 (C3″), 24.50 (C7″), 31.64 (C5″), *31.28* (*C5″*), 33.9 (C2), *34.04* (*C2*), 34.50 (C4″), *34.10* (*C4″*), 45.04 (C6″), 48.9 (C2″), *50.00* (*C2″*), 54.33 (C4), *54.51* (*C4*), 72.01 (C1″), *71.98* (*C1″*), 76.37 (C5), *76.41* (*C5*), 98 (C6), 112 (C7), 127.6–128.6 (C3′, C4′, C5′), 129.6 (C2′, C6′), 138 (C1′), 200 ($Co_2(CO)_6$), 212 (C3). MS (FAB(+), NBA): 612 (35, M−CO), 584 (40, M−2CO), 528 (60, M−4CO), 472 (100, M−6CO). Anal. calcd for $C_{30}H_{34}O_8Co_2$: C, 56.26; H, 5.35%. Found: C, 56.30; H, 4.28%.

4.5. General demetallation procedure

In a well-ventilated laboratory hood, the cobalt complex of the alkylation product (1 mmol), dissolved in dry acetone (50 mL per gram of complex) and dry triethylamine (0.3 mL per gram of complex) was placed in a round-bottomed flask, fitted with an efficient magnetic stirring bar and a gas outlet. To this solution, cerium ammonium nitrate (CAN) (3 mmol) was added (portionwise! and under vigorous stirring) at 0°C under a stream of nitrogen, to facilitate the elimination of CO and CO_2 formed during the oxidation process. The reaction was monitored by TLC or by IR (disappearance of st. peaks of CO ligands) and the mixture turned from dark red into orange after 1–3 h. Acetone was removed by a rotary evaporator and a 0.5 M aqueous solution of $NaHCO_3$ (50 mL) was added at room temperature and the mixture stirred until complete dissolution of the residual solid was observed. This aqueous solution was extracted with ether (8×25 mL). If interphases or emulsions were formed they were centrifuged in order to recover all the organic material. All organic extracts were combined together, washed with brine (2×25 mL), dried over anhydrous Na_2SO_4, percolated through a short pad of neutral alumina and finally concentrated to dryness under vacuum. Conversions in these reactions were always quantitative and yields fell within the range of 85–90%.

4.5.1. 2-{3-Phenyl-1-[(1*S*,2*S*,5*S*)-pinan-10-oxy]-2-propyn-1-yl}-cyclohexan-1-one, 16



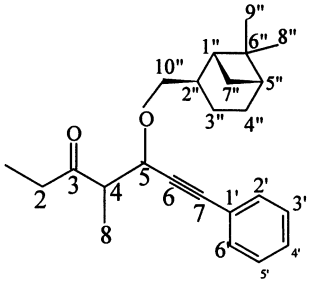
The crude product (123 mg), formed by demetallation of **10**, was submitted to flash column chromatography (15 g of silica gel (oven dried at 150°C), packing height=15 cm, column ϕ=2 cm) and eluting with dry hexane/ethyl acetate

85:15, pure samples of diastereomeric pairs **16**-*syn* and **16**-*anti* were isolated for their spectroscopic characterization.

***16**-(syn$_1$/syn$_2$)*: yellowish oil, IR (film,ν(cm^{-1})): 2929, 2200, 1715 (CO st), 1600–2000, 1419–1449, 1094, 691, 757. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.81 (3H, s, H8″), 1.17 (3H, s, H9″), 1.23–1.27 (1H, m, H3″), 1.55–1.59 (1H, m, H3″), 1.60 (1H, m, H4), 1.90 (1H, m, H4), 1.76–1.82 (2H, m, H4″), 1.89 (2H, m, H5″, H1″), 1.89 (1H, m, H7″), 2.02 (1H, m, H7″), 2.02 (1H, m, H5), 1.71 (1H, m, H5), 2.34 (1H, m, H3), 1.71 (1H, m, H3), 2.40 (1H, m, H6), 2.27 (1H, m, H6), 2.70–2.72 (1H, m, H2), 2.26–2.28 (1H, m, H2″), 3.57–3.61 (2H, m, H10″), 3.25–3.29 (2H, m, H10″), 4.69 (1H, d, *J*=6 Hz, H1′), *4.68* (*1H*, *d*, *J=6 Hz*, *H1′*), 7.26–7.28 (3H, m, H3‴, H4‴, H5‴), 7.38–742 (2H, m, H2‴, H6‴). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): 8.64 (C3″), 20.17 (C8″), 23.23 (C7″), 24.20 (C4″), 24.53 (C4), 26.66 (C9″), 27.74 (C5), 29.77 (C3), 34.93 (C2″), 38.20 (C6″), 40.98 (C5″), 42.61 (C1″), 42.08 (C6), 55.16 (C2), 69.03 (C1′), 73.69 (C10″), 128.20–129.10 (C3‴, C4‴, C5‴), 131.70 (C2‴, C6‴), 209.80 (C1). MS (CI, NH_3, *m/z* (%)): 382 (100, M+18). Anal. calcd for $C_{25}H_{32}O_2$: C, 82.37; H, 8.85%. Found: C, 82.41; H, 8.93%.

***16**-(anti$_1$/anti$_2$)*: yellowish oil, IR (film,ν(cm^{-1})): 2929, 2200, 1715 (CO st), 1600–2000, 1420–1449, 1096, 690, 758. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): same signals than in **16**-(*syn*$_1$/*syn*$_2$) except for: 2.60–2.64 (1H, m, H2), 4.65 (1H, d, *J*=6.3 Hz, H1′), *4.64* (*1H*, *d*, *J=6.6 Hz*, *H1′*), 3.55 (1H, m, H10″), 3.34, (1H, m, H10″), *3.55* (*1H*, *m*, *H10″*), *3.25* (*1H*, *m*, *H10″*). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): same signals than in **16**-(*syn*$_1$/*syn*$_2$) except for: 55.47 (C2), *55.57* (*C2*), 67.93 (C1′), *67.99* (*C1′*), 73.83 (C10″), *74.03* (*C10″*). MS (CI, NH_3, *m/z* (%)): 382 (100, M+18). Anal. calcd for $C_{25}H_{32}O_2$: C, 82.37; H, 8.85%. Found: C, 82.30; H, 8.80%.

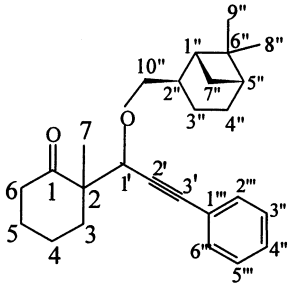
4.5.2. 5-[(1*S*,2*S*,5*S*)-Pinan-10-oxy]-7-phenyl-4-methyl-6-heptyn-3-one, 17. Diastereomeric pairs **17**-*syn* and **17**-*anti* (formed by demetallation of **13**) were separated and purified by flash column chromatography under pressure of nitrogen (13 g of silica gel, 120 mg of crude mixture, packing height=13 cm, column ϕ=2 cm), by elution with dry hexane/ethyl acetate 85:15.



***17**-(syn$_1$/syn$_2$)*: yellowish oil, IR (film,ν(cm^{-1})): 2927–2869, 2226, 1717 (CO st), 1460, 1086. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.85 (3H, s, H8″), 1.07 (3H, t, *J*=6.99 Hz, H1), 1.21 (3H, s, H9″), 1.26 (3H, d, *J*=0.99 Hz, H8), 1.61–1.64 (1H, m, H3″),1.25–1.27 (1H, m, H3″), 1.74–1.80 (2H, m, H4″), 1.34–1.36 (1H, m, H7″), 2.03–2.07 (1H, m, H7″), 1.85–1.88 (2H, m, H5″, H1″), 2.28–2.32 (1H, m, H2″), 2.58 (2H, dq, J_1=62 Hz, J_2=7.5 Hz, H2), 2.91–2.93 (1H, m, H4), 3.21–3.25 (1H, m, H10″), 3.59–3.61 (1H, m, H10″), 4.37 (1H, d, *J*=6.9 Hz, H5), *4.39* (*1H*, *d*, *J=6.9 Hz*, *H5*) 7.29–7.31 (3H, m, H3′, H4′, H5′), 7.39–7.41 (2H, m, H2′, H6′). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): 7.57 (C1), 12.75 (C8), *12.81* (*C8*), 18.83 (C3″), *18.45* (*C3″*), 20.18 (C8″), 23.62 (C7″), *23.55* (*C7″*), 24.19 (C4″), *24.17* (*C4″*), 35.01 (C2″), *34.98* (*C2″*), 35.76 (C2), *35.70* (*C2*), 39.40 (C6″), 40.90 (C5″), 42.70 (C1″), 51.25 (C4), *51.23* (*C4*), 71.33 (C5), 73.70 (C1″), 86.60–86.90 (C6, C7), 188.00 (C1′), 128.40–128.50 (C3′, C4′, C5′), 131.70 (C2′, C6′), 211.93 (C3). MS (CI, CH_4, *m/z* (%)): 353 (50, M+1), 267 (90, M−$C_5H_{10}O$), 199 (70, M−$C_{10}H_{17}O$), 137 (100, $C_{10}H_{16}^+$). Anal. calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15%. Found: C, 81.80; H, 9.32%. GC (conditions, type A): R_t=23.2 min.

***17**-(anti$_1$/anti$_2$)*: yellowish oil, IR (film,ν(cm^{-1})): 2929–2869, 2228, 1717 (CO st), 1458, 1087. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): same signal than in **17**-(*syn*$_1$/*syn*$_2$) except for: 1.14 (3H, d, *J*=6 Hz, H8), 2.24–2.26 (1H, m, H2″), 2.94 (1H, m, H4), 3.40–3.42 (1H, m, H1″), 3.11–3.13 (1H, m, H1″), 4.29 (1H, d, *J*=9.9 Hz, H5), *4.32* (*1H*, *d*, *J=9.9 Hz*, *H5*). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): same signal than in **17**-(*syn*$_1$/*syn*$_2$) except for: 13.80 (C8), 36.00 (C2), 50.30 (C4), 70.37 (C5), 73.10 (C1″). MS (CI, CH_4, *m/z* (%)): 353 (48, M+1), 267 (91, M−$C_5H_{10}O$), 199 (63, M−$C_{10}H_{17}O$), 137 (100, $C_{10}H_{16}^+$). Anal. calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15%. Found: C, 81.69; H, 9.23%. GC (conditions, type A): R_t=23.3 min.

4.5.3. 2-Methyl-2-{3-phenyl-1-[(1*S*,2*S*,5*S*)-pinan-10-oxy]-2-propyne-1-yl}-cyclohexan-1-one, 18



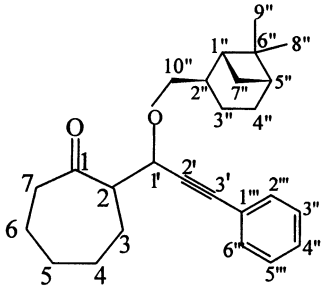
Diastereomeric pairs **18**-*syn* and **18**-*anti*, obtained by demetallation of **11**, were separated and purified by flash column chromatography under pressure of nitrogen (8 g of silica gel, 77 mg of crude mixture, packing height=25 cm, column ϕ=1.5 cm), by elution with dry pentane/ether 98:2.

***18**(syn$_1$/syn$_2$)*: yellowish oil, IR (film,ν(cm^{-1})): 2934, 2230, 1715 (CO st), 1491–1462, 1080, 691–756. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.82 (3H, s, H8″), 1.19 (3H, s, H9″), 1.23 (3H, s, H7), 1.60 (2H, m, H3″), 1.26 (2H, m, H3″), 1.72–1.76 (2H, m, H4″), 1.80–1.84 (2H, m, H5″, H1″), 2.00–2.04 (1H, m, H7″), 1.31–1.33 (1H, m, H7″), 2.16 (1H, m, H3), 1.64 (1H, m, H3), 1.84 (1H, m, H4), 1.64 (1H, m, H4), 1.93 (1H, m, H5), 1.80 (1H, m, H5), 2.24–2.26 (1H, m, H2″), 2.41–2.43 (2H, m, H6), 3.62–3.66 (1H, m, H10″), 3.17–3.19 (1H, m, H10″), 4.66 (1H, s, H1′), *4.70* (*1H*, *s*, *H1′*), 7.30–7.32 (3H, m, H3‴, H4‴, H5‴), 7.39–7.41 (2H, m, H2‴, H6‴). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): 18.46 (C3″), 19.00 (C7), 20.19 (C8″), 21.06 (C4), 23.60 (C7″), 24.19 (C4″), 26.70 (C9″),

27.43 (C5), *27.37* (*C5*), 34.90 (C2″), 36.06 (C3), 38.75 (C6), 40.93 (C5″), 42.77 (C1″), 53.64 (C2), 74.09 (C1′), 74.17 (C10″), 86, 87 (C2′, 3′), 122.90 (C1‴), 128.30 (C3‴, C4‴, C5‴), 131.70 (C2‴, C6‴), 213.00 (C1). MS (CI, NH_3, *m/z* (%)): 379 (50, M+1), 396 (100, M+18). $^+$). Anal. calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05%. Found: C, 82.52; H, 9.18%. GC (conditions, type A): R_t=27.7 min.

***18**-(anti$_1$/anti$_2$)*: yellowish oil, IR (film, ν(cm^{-1})): 2935, 2229, 1715 (CO st), 1490–1468, 1080, 690–755. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): same signals than in **18**-(*syn*$_1$/*syn*$_2$) except for: 3.58–3.61 (1H, m, H10″), 3.23–3.25 (1H, m, H10″), 4.58 (1H, s, H5), *4.59* (*1H*, *s*, *H5*). Anal. calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05%. Found: C, 82.31; H, 8.95%. MS (CI, NH_3, *m/z* (%)): 379 (43, M+1), 396 (100, M+18). GC (conditions, type A): R_t=26.9 min.

4.5.4. 2-{3-Phenyl-1-[(1*S*,2*S*,5*S*)-pinan-10-oxy]-2-propyn-1-yl}-cycloheptan-1-one, 19



Diastereomeric pairs **19**-*syn* and **19**-*anti*, obtained by demetallation of **12**, were separated and purified by flash column chromatography under pressure of nitrogen (7 g of silica gel, 107 mg of crude mixture, packing height=23 cm, column ϕ=1.5 cm), by elution with a 98:2 mixture of dry pentane/ether.

***19**-(syn$_1$/syn$_2$)*: yellowish oil, IR (film, ν(cm^{-1})): 2927, 2250, 1704 (CO st), 1491–1456, 1092, 691–756. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.84 (3H, s, H9″), 1.19 (3H, s, H8″), 1.52 (1H, m, H3″), 1.26 (1H, m, H3″), 1.78 (2H, m, H4″), 1.32 (1H, m, H7″), 2.02 (1H, m, H7″), 1.84 (1H, m, H5″ or H1″), 1.80 (1H, m, H5″ or H1″), 1.72 (1H, m, H3), 2.28 (1H, m, H3), 1.32 (1H, m, H4), 2.02 (1H, m, H4), 1.39 (1H, m, H5), 1.88 (1H, m, H5), 1.48 (1H, m, H6), 1.88 (1H, m, H6), 2.60 (1H, m, H7), 2.50 (1H, m, H7), 2.66–2.70 (1H, m, H2), 2.24–2.28 (1H, H2″), 3.54–3.58 (1H, m, H10″), 3.14–3.18 (1H, m, H10″), 4.57 (1H, d, *J*=5.5 Hz, H1′), 7.29–7.31 (3H, m, H3‴, H4‴, H5‴), 7.41–7.43 (2H, H2‴, H6‴). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): 18.92 (C3″), *18.48* (*C3″*), 20.21 (C9″), 23.70 (C7″), *23.63* (*C7″*), 24.19 (C4″), 24.74 (C6), 25.59 (C3), *25.67* (*C3*), 26.73 (C8″), 28.77 (C4), 30.09 (C5), *30.02* (*C5*), 34.90 (C2″), 39.29 (C6″), 40.93 (C5″), 42.75 (C1″), 44.38 (C7), *44.31* (*C7*), 57.85 (C2), 71.79 (C1′), *71.53* (*C1′*), 74.14 (C10″), *73.71* (*C10″*), 86.12, 87.45 (C2′, C3′), 122.70 (C4′), 128.27 (C3‴, C4‴, C5‴), 131.73 (C2‴, C6‴), 214.25 (C1). MS (CI, NH_3, *m/z* (%)): 396 (100, M+18), 379 (32, M+1). Anal. calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05%. Found: C, 82.40; H, 9.15%. GC (conditions, type A): R_t=18.7 min.

***19**-(anti$_1$/anti$_2$)*: yellowish oil, IR (film, ν(cm^{-1})): 2929, 2252, 1706 (CO st), 1490–1456, 1090, 691–756. ^{1}H NMR (500 MHz, $CDCl_3$, δ(ppm)): 0.83 (3H, s, H9″), 1.19 (3H, s, H8″), 1.30 (1H, m, H3″), 1.64 (1H, m, H3″), 1.78 (2H,m, H4″), 1.34 (1H, m, H7″), 1.90 (1H, m, H7″), 1.81–1.85 (2H, m, H5″, H1″), 1.78 (1H, m, H3), 2.24 (1H, m, H3), 1.46 (1H, m, H4), 2.15 (1H, m, H4), 1.46 (1H, m, H5), 1.94 (1H, m, H5), 1.60 (1H, m, H6), 1.90 (1H, m, H6), 2.53–2.55 (2H, m, H7), 2.93–2.96 (1H, m, H2), 2.23–2.25 (1H, H2″), 3.56–3.24 (1H, m, H10″), 3.23–3.25 (1H, m, H10″), 4.56 (1H, d, *J*=7.5 Hz, H1′), 7.29–7.31 (3H, m, H3‴, H4‴, H5‴), 7.41–7.43 (2H, H2‴, H6‴). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ(ppm)): 18.69 (C3″), *18.56* (*C3″*), 20.16 (C9″), 23.60 (C7″), 23.80 (C4″), 24.19 (C6), 25.36 (C3), 26.68 (C8″), 27.13 (C4), *27.28* (*C4*), 28.90 (C5), *28.78* (*C5*), 34.93 (C2″), 39.29 (C6″), 40.97 (C5″), 42.62 (C1″), 45.89 (C7), 56.52 (C2), *56.49* (*C2*), 71.03 (C1′), *70.99* (*C1′*), 73.97 (C10″), *73.96* (*C10″*), 87.11 (C2′, C3′), 122.80 (C4′), 128.27 (C3‴, C4‴, C5‴), 131.73 (C2‴, C6‴), 212.89 (C1). Anal. calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.38; H, 9.00%. MS (CI, NH_3, *m/z* (%)): 396 (100, M+18), 379 (28, M+1). GC (conditions, type A): R_t=18.9 min.

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