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The Nicholas Approach to Natural Product Hybrids**

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Abstract: The intermolecular Nicholas reaction of terpene-based scaffolds is an excellent access to natural product hybrid compounds. These intermolecular reactions have a low selectivity and are scarcely efficient for non-conjugated cations, but they are highly efficient to produce new terpene structures through an intramolecular reaction pathway. The use of cations derived from natural product derived $[Co_2(CO)_6]$–enyne complexes is, in contrast, a highly efficient regio- and stereoselective procedure to prepare very complex structures, incorporating diverse densely functionalized or labile moieties. Thus, β-pinene–diterpene–alkaloid or homohybrids can be accessed in totally stereo-, regio- and siteselective fashion. This approach efficiently discriminates between different propargylic positions by selecting the nature of the alcohol, being the enyne-derived cations the most reactive. The chimera **38** with a steroid–terpene–indole skeleton was prepared in this way.

Keywords: cobalt · hybrids · natural products · Nicholas reaction · synthesis

Introduction

The concept of natural product hybrids[1] is probably one of the last and maybe most fundamental breakthroughs in recent natural-product chemistry. A natural-product hybrid is a synthetic compound having two or more than two natural products derived fragments joined at least by one carbon–carbon bond. This idea like many others is inspired by Nature since many of the known natural products are built of fragments arising from different biosynthetic pathways.[2] Against the isolation of compounds which contain novel structures from natural sources, the synthesis of hybrid natural products warrants access to an almost inextinguishable variety of new structures and, most importantly, having structural diversity which is a leading idea in contemporaneous organic synthesis.[3] The underlying idea is that combination of diverse structural features from two or more functionally active substances into one new product may either enhance or alter the desired characteristic of individual components or lead to new types or properties.[1b] Perhaps, the naturally occurring alkaloid hybrid vincristine (**1**) is the best example[1a] to illustrate this point. This compound is a dimeric indole alkaloid having a vindoline and catharanthine moieties. Both monomeric compounds show no activity. However, vincristine is the drug of choice for lymphatic leukemia.[4] The quinone-mucocin[5] hybrid **2** bears a quinone moiety characteristic of ubiquinones replacing the butenolide moiety, which is characteristic of acetogenins isolated from *Annonaceae*. A final example is the estrone–talaromycin hybrid **3** derived from the joining of an steroid and the spirocyclic mycotoxin talaromycin (Figure 1).[6]

We have recently reported the diversity oriented synthesis of natural-product hybrids derived from (*R*)-(+)-sclareolide having a hispanane scaffold.[7] This route to new terpene derivatives introduces structural and stereochemical diversity through a single synthetic pathway. To expand the potential to produce new entities in the field of natural-product hybrids, the use of organometallic moieties as reagents has a double advantage: First, the possibility to effect otherwise impossible transformations and, second, the presence of the metal may also increase the structural diversity by producing bioorganometallic entities.[8] This approach will combine the two emerging fields of bioorganometallic chemistry and

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[**] For a preliminary communication of a part of this work see: E. Álvaro, M. C. de la Torre, M. A. Sierra, *Org. Lett.* **2003**, *5*, 2381–2384.

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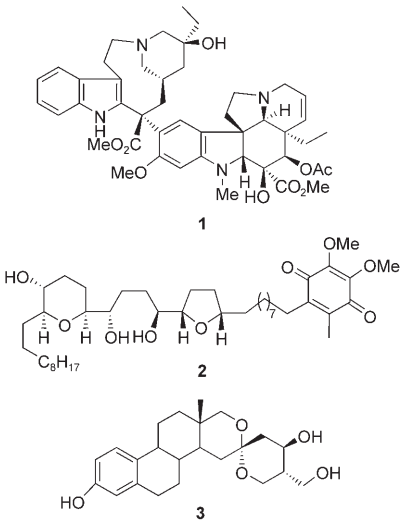
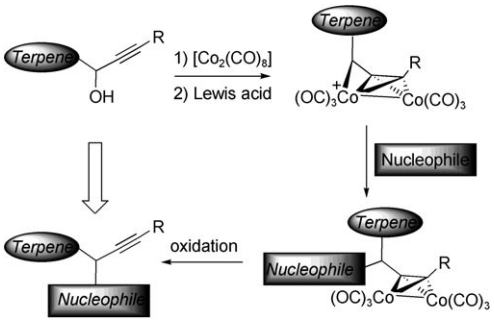


Figure 1. Examples of natural product hybrids isolated either from natural sources (**1**) or synthetic (**2** and **3**).

synthesis of natural-product hybrids. Furthermore, through a smart choice of the organometallic reagent it could be either maintained or eliminated at the end of the process. Co-complex stabilized α-carbocations meet these premises since the Nicholas reaction is a very efficient process to form C–C bonds from two different fragments, the required propargylic substrates are easy to made, and the Co complex is incorporated to the final products and may be choicely eliminated without altering the final products.[9] An additional attractive of this chemistry is the possibility of stressing well-established methodology by working in densely functionalized and sensitive systems, a problem that is today unsolved.[7]

Abstract in Spanish: *La reacción de Nicholas intermolecular de diversos derivados terpénicos es una ruta excelente para la preparación de productos naturales híbridos. Estas reacciones intermoleculares son poco selectivas y escasamente eficientes cuando se utilizan cationes no conjugados, pero son muy eficientes para producir nuevas estructuras terpénicas cuando la reacción es intramolecular. Los cationes derivados de complejos de productos naturales conteniendo un fragmento [$Co_2(CO)_6$]–enino son, por el contrario, excelentes reactivos para preparar compuestos estructuralmente muy complejos, incorporando fragmentos muy funcionalizados o lábiles, de forma totalmente regio- y estereoselectiva. Así, se pueden obtener híbridos de tipo diterpeno-β-pineno, -alcaloide u homohíbridos de forma estero-, regio- y locoselectiva. Esta aproximación discrimina de forma eficiente entre diferentes posiciones propargílicas si se selecciona la naturaleza del alcohol, siendo los cationes derivados de sistemas enínicos los más reactivos. La quimera **38** con un esqueleto de esteroide-teperno-indol se preparó siguiendo esta metodología.*

Scheme 1 depicts the general idea to be developed herein. Thus, a terpene derived propargylic alcohol will be complexed with [$Co_2(CO)_8$] and the cluster-stabilized α-cation, resulted from the acid treatment, will be reacted with an adequate nucleophile. The reaction product will be a bioorganometallic hybrid. Finally, if required, the Co moiety may be removed. Reported herein is the successful implementation of this approach to produce diverse terpene–terpene, terpene–alkaloid and, to stress the methodology, a steroid–terpene–alkaloid chimera. Furthermore, the requisites, scope and limitations of the Nicholas reaction in densely functionalized systems will be also discussed.

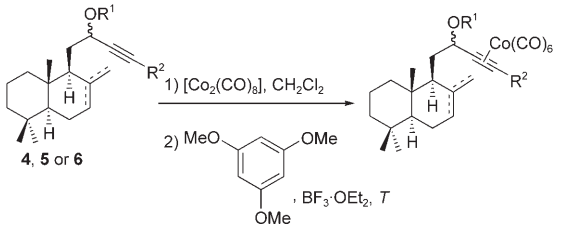


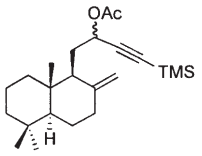
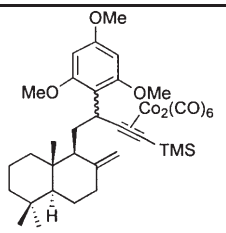
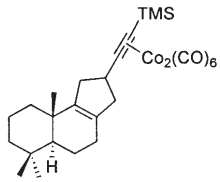
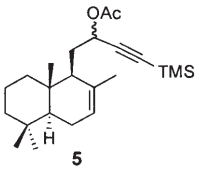
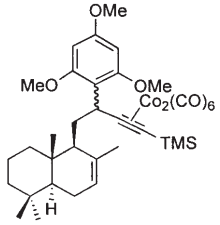
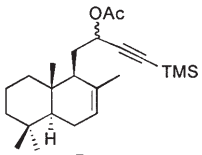
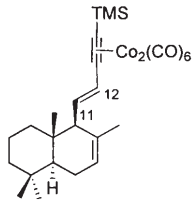
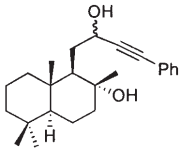
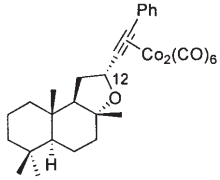
Scheme 1. Approach to natural product hybrids by intramolecular Nicholas reaction using terpene scaffolds.

Results and Discussion

Terpene substrates **4**, **5**, and **6** (Table 1) used in this work, were prepared by reaction of lithium trimethylsilyl acetylide or lithium phenyl acetylide with the appropriate aldehyde or lactol previously reported by us, followed by treatment of the resulting alcohols with Ac_2O/Pyr when required.[11,12] It soon became evident that compounds **4**, **5** and **6** were poor regents to build hybrids by using the intermolecular Nicholas reaction, even using strongly activated aromatic rings as nucleophiles. Thus, Co complexes of alkynes **4**, **5** and **6** were generated in situ with [$Co_2(CO)_8$] and reacted with either $BF_3{\cdot}Et_2O$ (compounds **4** and **5**) at 0 °C or HBF_4 at −20 °C (compound **6**) in the presence of 1,3,5-trimethoxybenzene (Table 1). Except for compound **5**, which formed the desired hybrid **7** in a respectable 85 % yield (Table 1, entry 2), compound **4** gave the anticipated product **8** together with tricyclic compound **9**, arising from the intramolecular capture of the carbocation by the exocyclic $\Delta^{8(17)}$ double bond (Table 1, entry 1). Furthermore, compounds **7** and **8** were obtained as mixtures of epimers at the newly formed stereogenic center (Table 1, entries 1 and 2). Intramolecular trapping of the carbocation derived from **6** also takes place yielding the tetrahydrofuran **10** exclusively (Table 1, entry 4).[13] Evidently, **9** and **10**, which are obtained as single stereoisomers, are the sole reaction products when the [$Co_2(CO)_6$]–alkyne complexes derived from substrates **4** and **6** were reacted with $BF_3{\cdot}Et_2O$ or HBF_4 in the absence of 1,3,5-trimethoxybenzene. A slight increase in yield (from 35 to 43 %) was ob-

Table 1. Nicholas reaction of **4**, **5** and **6** derived from (*R*)-(+)-sclareolide.



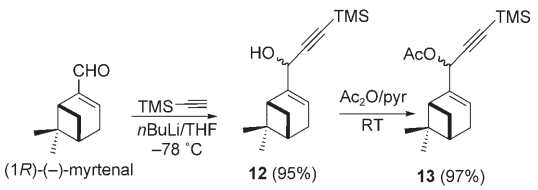
Entry	Substrate	Product	(Yield/%)[a]
1[b]	 **4**		**8**[f] (40)
			**9**[e,f] (35)
2[b]	 **5**		**7**[f] (85)
3[c]	 **5**		**11** (82)
4[d]	 **6**		**10** (83)

[a] Yields are given on pure compounds [b] $BF_3{\cdot}OEt_2$, at 0 °C. [c] $BF_3{\cdot}OEt_2$, at 0 °C, absence of nucleophile. [d] HBF_4, at −20 °C. The same reaction product is obtained in the presence or absence of nucleophile. [e] Compound **9** was obtained as the sole reaction product in absence of nucleophile. [f] For the alkyne liberation from **7**, **8** and **9** see Supporting Information.

served in the case of **9**.[14] The stereochemistry at carbon C-12[15] of tricyclic derivative **10** was ascertained on the basis of NOE measurements. Irradiation of H-12 (δ_H 5.39) caused an increase in the intensity of the signal corresponding to the β-axially oriented C-17 Me-group at 1.25 ppm. Therefore proton H-12 and C-17 methyl are located on the same side of the plane defined by the tetrahydrofuran ring. The stereochemistry of carbon C-12 for **9** could not be established, since unambiguous assignment of protons H-11 and H-17 was not possible. The intramolecular capture of the stabilized carbocation derived from **5**, having a Δ^7 double bond, did not occur; dienyne **11** was obtained instead (Table 1, entry 3).[16] The *trans*-stereochemistry of **11** at the new double bond was assigned on the basis of the value of the coupling constant (J = 14.8 Hz) between protons H-11 and H-12.

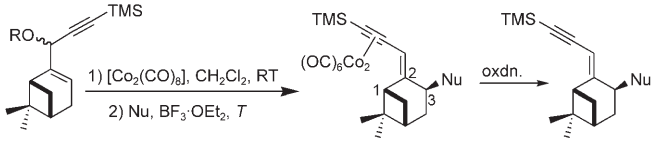
Alkynes **12** and **13**, derived from (1*R*)-(−)-myrtenal, by addition of lithium trimethylsilyl acetylide and subsequent acetylation (Scheme 2), were investigated next as scaffolds to construct terpene derived hybrids. In situ preparation of the corresponding $[Co_2(CO)_6]$–alkyne complexes was achieved as described above and subsequently reacted with 1,3,5-trimethoxybenzene in the presence of $BF_3{\cdot}Et_2O$ (Table 2). Gratifyingly, compound **14** was obtained in nearly quantitative yield (93 %) and as a single stereoisomer. This was a general reaction for activated aromatic rings such as furan or *N*-methylindole, which formed a single stereoisomer of compounds **15** and **16** in 99 and 93 % yields, respectively (Table 2).

Compounds **14**–**16** were derived from the addition of the nucleophile to carbon C-3 of the β-pinene framework. This fact was established unambiguously by extensive NMR spectroscopy of the hybrids **17**, **18** and **19** obtained by oxidation of the corresponding cobalt complexes either with cerium(IV)



Scheme 2. Synthesis of derivatives **12** and **13** from (1*R*)-(−)-myrtenal.

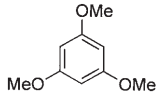
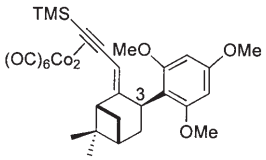
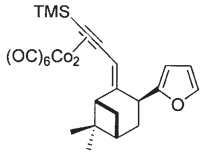
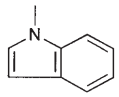
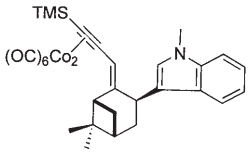
Table 2. Nicholas Reaction of **12** and **13** derived from (1*R*)-(−)-myrtenal.



12: R = H
13: R = Ac

14, **15** and **16**

17, **18** and **19**

Entry	Nucleophile	*T* [°C]	Product	(Yield/%)[a]	Alkynes (Yield/%)[a]
1		0		**14**[b] (93)	**17** (94)
2		−20		**15**[c] (99)	**18** (77)
3		−78		**16** (93)	**19** (59)

[a] Yields are given for pure compounds. [b] Compound **13** was used as starting material. [c] Alcohol **12** was used starting material.

v)ammonium nitrate (CAN)[17] or I_2.[18] In all cases, a gHMBC cross peak is observed between H-3 of the β-pinene fragment (**17**: δ_H 4.59) and the carbon of the nucleophile attached to the terpene (**17**: δ_C 113.8). Therefore, the formation of derivatives **14**–**16** occurred with allylic rearrangement, from an α- to a β-pinene derivative. Although α- to β-pinene isomerizations are known[19] these reactions are less efficient than the one described here.

The stereochemistry of compound **17**, and hence of hybrids **18** and **19** derived from (1*R*)-(−)-myrtenal, at carbon C-3 and at the exocyclic double bond was established by NOE experiments (Figure 2). Selective irradiation of H-3 at

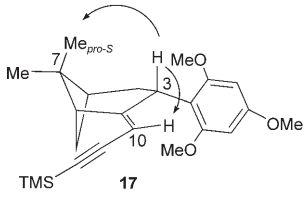


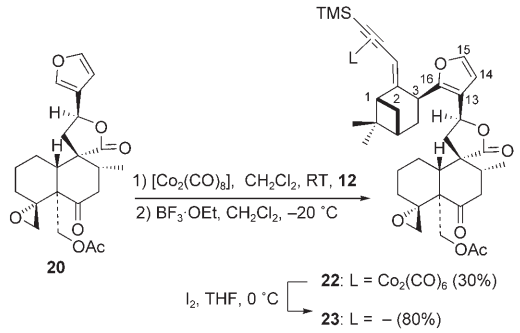
Figure 2. Main NOE increments observed for hybrid **17**.

δ_H 4.59 caused a strong NOE signal corresponding to the pro-*S* methyl group at carbon C-7. Therefore proton H-3 and carbon C-7 must have a *syn* relationship. Additionally, irradiation of the olefinic proton H-7 (δ_H 4.83) caused a positive NOE increment of the signal assigned to proton H-3, establishing an *E* stereochemistry for the $\Delta^{2(10)}$ double bond (Figure 2, see also preliminary communication).

The bias of cations derived from 1-[(alkynyl)dicobalt hexacarbonyl]allyl to form exclusively (*E*)-1,3-enynes was reported by Nicholas.[20] The origin of this bias was attributed to the considerable steric hindrance of the $[Co_2(CO)_6]$ moiety and not to any hypothetical stabilizing conjugative interaction between the C=C double bond and the alkyne complex. In our case there is a clear preference to place the bulky Co_2–alkyne complex away from the incoming nucleophile to minimize the steric repulsion.[21] This may be the origin of the exclusive *E* stereochemistry observed in products **14**–**16** and in all related compounds throughout this work (see below). The stereochemical outcome of the addition of aromatic nucleophiles to carbon C-3 of (1*R*)-(−)-myrtenal derived alkynes may be due to the steric hindrance exerted by the geminal dimethyl group at carbon C-7, which drives the addition of the nucleophile by the face opposite to the bulky dimethyl group.

After the ability of (1*R*)-(−)-myrtenal derived alkynes **12** and **13** to react with activated aromatic rings was established, this reaction was used for the preparation of terpene hybrids derived from densely functionalized and labile natural products. The selective manipulation of densely functionalized compounds is, as stated above, an unsolved problem.[7] We chose the neoclerodane diterpene 19-acetylgnaphalin (**20**)[22] and (−)-reserpine (**21**).[23] 19-Acetylgnaphalin (**20**) is extremely prone to rearrange in acid or basic media[24] due to its functional arrangement but it has, in principle, a single reactive site towards the carbocation formed from (1*R*)-(−)-myrtenal derived alkyne, namely the furan ring. (−)-Reserpine (**21**) was selected to investigate the potential of this methodology to selective react in a complex system having, in principle, two reactive sites, the indole and the benzene ring. Furthermore, the success of these reactions would demonstrate the usefulness of this approach to prepare sophisticated terpene–terpene and terpene–alkaloid hybrids.

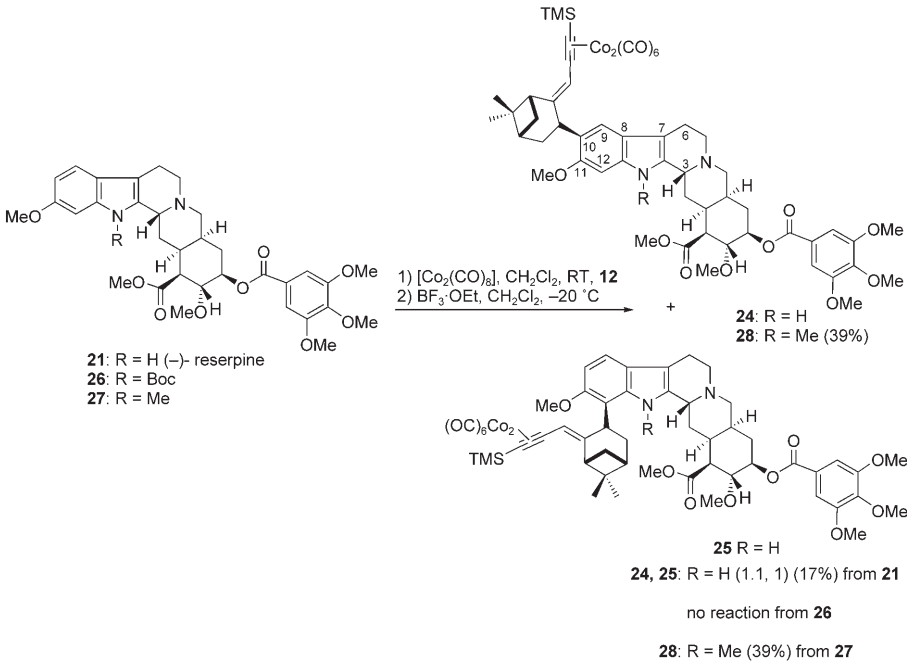
The Nicholas reaction of the dicobalt complex prepared from alcohol **12** and 19-acetylgnaphalin (**20**) in the presence of $BF_3{\cdot}Et_2O$ gave a single reaction product in 30% yield (90% based on recovered 19-acetylgnaphalin) (Scheme 3). Neither decomposition nor rearranged derivatives from 19-acetylgnaphalin were obtained, in spite of the acid sensitivi-



Scheme 3. Nicholas reaction of the sensible diterpene 19-acetylgnaphalin **20** and alcohol **12**.

ty of this compound. The structure of the reaction product was established as **22** on spectroscopic grounds of the Co-free compound **23**. Treatment of **22** with I_2 liberates the alkyne moiety producing the terpene-based hybrid **23** in 80% yield. The signals for the two terpenic fragments were easily recognized in the ^{1}H and the ^{13}C NMR spectra. The pattern for the β-pinene fragment was identical to the hybrids described above. Accordingly, the addition of the furanic nucleophile had taken place at carbon C-3, and following the same stereochemical course. With respect to the neoclerodane part, the ^{1}H NMR spectrum of **23** was almost identical to 19-acetylgnaphalin (**20**) except for the signals corresponding to the furanic moiety. Thus, hybrid **23** showed signals for only two furanic protons instead of the three of 19-acetylgnaphalin. The signal at 6.29 ppm corresponds to the β-furanic proton H-14, while the signal at 7.29 ppm must be attributed to one α-furan proton at C-15 or C-16 positions. Since both signals are coupled each other with a *J* value of 1.8 Hz, the signal at 7.29 ppm must be assigned to proton H-15. This observation was substantiated by the gHMBC spectrum. In particular, correlation between proton H-3 of the β-pinene part (δ_H 3.90) and the quaternary carbon C-16 of the neoclerodane fragment (δ_C 158.6) clearly establishes that the Nicholas reaction has proceeded exclusively through carbon C-16, yielding a dicobalt C-3, C16–β-pinene-neoclerodane hybrid **23**. It is worth noting that the reaction between the Co complex derived from **12** and 19-acetylgnaphalin is not only totally stereoselective but also totally regioselective (the site-selectivity is ensured by the absence of additional nucleophile groups).

Once the compatibility of our approach to prepare terpene hybrids with sensitive natural products was proven, the reaction of the Co complex derived from **12** with reserpine **21** as nucleophile was next pursued. The reaction of the cobalt complex derived from **12** and a slight excess of reserpine, in the presence of BF_3·Et_2O at −20 °C, formed a mixture (1.1:1) of two inseparable regioisomers identified as **24** and **25**, in low yield (17% combined) (Scheme 4). Iterative chromatography allowed the isolation[25] of a small amount of both hybrids **24** and **25** for which ^{1}H NMR spectra could be obtained. In both cases, signals for unchanged 3,4,5-trimethoxybenzoate ester were observed, while signals due the indole moiety accounted for only two protons. Therefore, site-selectivity towards the indole aromatic ring could be achieved but without regioselectivity and in low yields. Since the free indole nitrogen may be, in principle, interfering with the reaction, the N-Boc derivative of reserpine **26** was prepared and treated with the complex derived from **12**. No products derived from electrophilic aromatic substitution were observed. Clearly, the decrease in the electronic density of the indole aromatic ring caused by the carbamate group totally inhibits the reaction.



Scheme 4. Nicholas reaction of reserpine **21**, *N*-Boc and *N*-methylreserpine, **26** and **27** with alcohol **12**.

The reaction of *N*-methylreserpine **27** was investigated next. In this case, a clean reaction resulted under the usual conditions from which compound **28** was isolated in a 39% yield. No traces of other regioisomers were observed (Scheme 4). Unreacted reserpine was the only product present in the mixture. Clearly, the methyl group not only avoids the interference of the indole nitrogen group in the reaction but also produces a steric hindrance that precludes

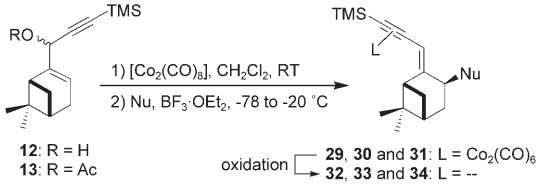
the addition of the Co complex estabilized carbocation to C-12 carbon of the reserpine.[26]

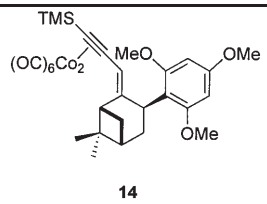
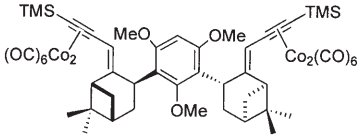
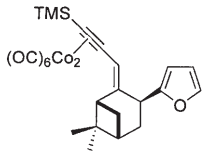
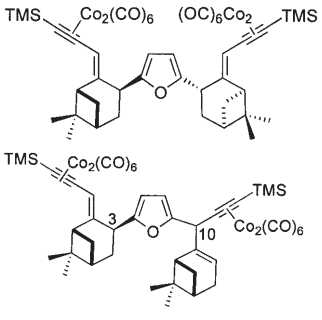
The structure of **28** was unambiguously established based on the spectroscopic investigations. The ^{1}H NMR spectrum showed the pattern of signals for a β-pinene fragment, identical to the above described Nicholas educts, establishing the incorporation of reserpine to carbon C-3 of the terpenic fragment by the opposite face to the geminal dimethyl group. The regiochemistry at the reserpine part was evidenced by the presence of a signal singlet at δ_H 7.11 corresponding to proton H-9 of the indole fragment, instead of the signal doublet at δ_H 7.32 (J = 7.2 Hz) observed for the unsubstituted *N*-methylreserpine **27**. Therefore, the Nicholas reaction between the Co complex from **12** and *N*-methylreserpine proceeds with complete regio- and stereoselectivity yielding hybrid **28**.

Cobalt–β-pinene hybrids **14** and **15** are perfect precursors for using as nucleophiles on a second Nicholas reaction. Access to a new class of compounds having two β-pinene units tethered by an aromatic or heteroaromatic spacer was achieved by treating cobalt complex from **12** and **13** with hybrids **14** and **15** under the usual conditions. Thus, compound **29** was obtained as a single diastereomer from **14**, while regioisomeric compounds **30** and **31** were obtained when the furan derivative **15** was used as nucleophile (Table 3). Oxidation of the cobalt moiety of hybrids **29**–**31** yielded alkynes **32**–**34**, respectively. Mass spectrometric analysis of alkynes **32** and **33** accounts for the incorporation of a second β-pinene fragment. Additionally, as expected for a molecule having a C_2 symmetry axis, the ^{1}H NMR for both hybrids showed a single group of signals, due to the terpenic part, identical to hybrids **14** and **15**, and only one signal singlet for one aromatic proton, at δ 6.25 ppm in the case of **32**, and for two β furanic protons at 5.84 ppm in the case of **33**. On the contrary, alkyne **34** showed ^{1}H and ^{13}C NMR signals for one β-pinene fragment, originating from nucleophile **15**, and for one α-pinene fragment due to the Co complex from **12** (Table 3). In addition, long-range gHMBC cross peaks between proton H-3 of the β-pinene part (δ_H 3.74) with one quaternary α furan carbon at δ_C 158.9, and between proton H-7 of the α-pinene part (δ_H 4.31) with the remaining α-furanic carbon at δ_C 150.9, established unambiguously the regiochemistry of the reaction. Therefore, the Nicholas reaction of the Co-stabilized carbocation derived from **12** with the β-pinene–furane hybrid **15** as nucleophile has proceeded in part at the exocyclic carbon C-7 producing compound **31**. It is worthy to note that compound **31** was obtained as a single diastereoisomer albeit in this case the second Nicholas reaction took place at carbon C-10, the exocyclic position of the intermediate carbocation, without allylic rearrangement (Table 3).

The synthesis of homohybrids **29** and **30** demonstrates that sequential Nicholas reactions can be effected to increase the complexity of the products in a controlled manner. Two remaining questions were finally addressed: the reactivity of tertiary cobalt stabilized carbocations and the control of the regioselectivity of the reaction. First, the $[Co_2(CO)_6]$-derivative **35** was prepared in situ by treating mestranol with $[Co_2(CO)_8]$ and reacted with *N*-methylindole, in the presence of $BF_3{\cdot}Et_2O$ at −78 °C. The steroid–indole hybrid **36** was obtained in 16% isolated yield. Structure **36** is in agreement with its spectroscopic data. In particular, the ^{13}C NMR showed signals attributable to the steroid part, almost identical to the mestranol–Co complex **35**, except for the signals corresponding to carbons C-12 and C-14 that appeared shifted at lower field ($\Delta\delta_{C\text{-}12}$ = +3.9 and $\Delta\delta_{C\text{-}14}$ = +7.3). This displacement should be a consequence of the lack of the tertiary hydroxyl group at C-17, which on **35** exerted a shielding γ-*gauche* effect on the aforementioned

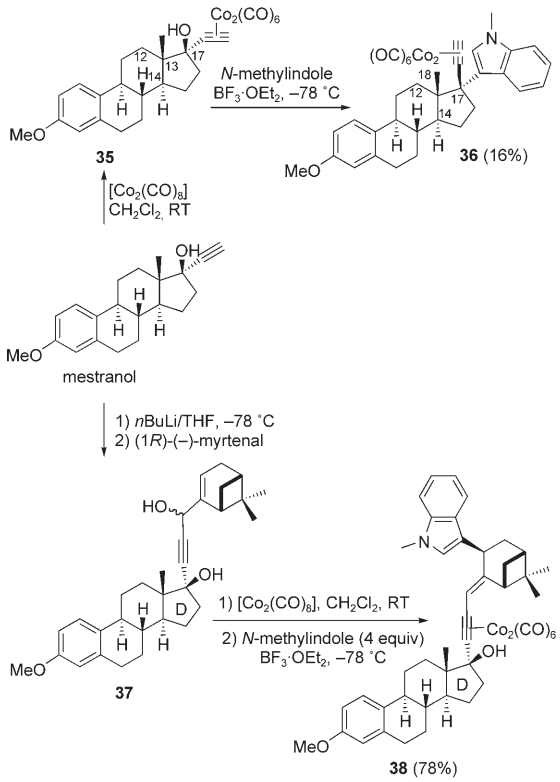
Table 3. Nicholas reaction of **12** and **13** with hybrids **14** and **15**.



Entry	Nucleophile	Product	(Yield/%)[a]	Alkynes[e]
1	 **14**		**29**[b] (72)	**32** (47)
2[c,d]	 **15**		**30** **31**	**33** (36) **34** (40)

[a] Yields are given for pure compounds. [b] Using **13** as starting material. [c] Using alcohol **12** as starting material. [d] Global yield 53%, **30**/**31** 1:2. [e] Procedures for the oxidation of the cobalt complexes are given in the Experimental Section and in the Supporting Information.

carbon atoms. Additionally, the gHMBC cross peak between proton H-2 of the indol fragment at δ 5.70 ppm and carbon C-17 of the esteroid at 43.8 ppm establishes that mestranol and indole parts are joined through carbons C-17 and C-3, respectively. Regarding the stereochemistry at the quaternary center C-17, irradiation of the β-axially oriented methyl group C-18 at δ 1.04 ppm caused an increment in the intensity of the signal corresponding to the propargylic proton of the Co complex at δ 6.14 ppm. Consequently, the addition of the indole has taken place by the α-face, placing the Co complex and methyl C-18 at the same side of the plane defined by the ring D of the steroid (Scheme 5).



Scheme 5. Synthesis of mestranol–indol hybrid **36** and mestranol–myrtenal–indol quimera **38**.

Compared with the reactivity of the secondary propargyl alcohols derived from (1*R*)-(−)-myrtenal **12** and **13**, the reactivity of complex **35** is considerably decreased. This fact was used to discriminate between two propargylic alcohols in a complex substrate. Thus, diol **37** was prepared by addition of the dianion derived from mestranol to (1*R*)-(−)-myrtenal. The corresponding $[Co_2(CO)_6]$ complex was subsequently reacted with one equivalent of *N*-methylindole in the presence of $BF_3{\cdot}Et_2O$ at −78 °C. Chimera **38** having steroid, terpene and indole fragments was obtained as a single regio- and stereoisomer although in low yield (14%). However, by increasing the amount of *N*-methylindole to four equivalents, compound **38** was obtained in 78% isolated yield (Scheme 5). NMR analysis indicated that only one molecule of indole has been incorporated to the complex derived from **37**. The location of the *N*-methylindole must be at the (1*R*)-(−)-myrtenal C-3 carbon, since characteristic signals for a β-pinene arrangement are distinguished in the ^1H and ^{13}C NMR spectra. These similarities also established an identical stereochemical reaction course to the Nicholas reactions described above for (1*R*)-(−)-myrtenal derived cobalt complexes **12** and **13**.

These reactions clearly demonstrate that the selective functionalization of complex substrates can be achieved by using the different reactivity of conjugated Co-complex stabilized cations (the more reactive) and non-conjugated tertiary carbocations.

In conclusion, the intermolecular Nicholas reaction of terpene-based scaffolds provides an excellent access to natural product hybrid compounds. These reactions are low selective and efficient for non-conjugated cations, but become highly efficient to produce new terpene structures in an intramolecular way. The use of cations derived from natural product $[Co_2(CO)_6]$–enyne complexes is, in contrast, a highly efficient regio- and stereoselective procedure to prepare very complex structures, incorporating diverse densely functionalized or labile moieties. Thus, β-pinene–diterpene, –alkaloid or homohybrids can be accessed in totally stereoselective an, except for homodimer **31**, regio- and siteselective fashion. Finally, it is possible to discriminate between different propargylic positions by selecting the nature of the alcohol, being the enyne-derived cations the most reactive. The chimera **38** having a steroid–terpene–indole skeleton was prepared in this way. Further work to stress this methodology to prepare even more sophisticated structures (chimeras) is in progress in our laboratories.

Experimental Section

General methods: Unless noted otherwise, all reactions were carried out under an argon atmosphere using standard Schlenk techniques. All glassware was oven dried for approximately 1 h prior to use. THF and Et_2O were distilled from Na/benzophenone under argon. CH_2Cl_2 was distilled from CaH_2. Other solvents were HPLC grade and were used without further purification. All reagents were obtained from commercial sources and used without further purification, unless noted otherwise. $BF_3{\cdot}OEt_2$ was distilled from CaH_2 under vacuum prior to use. Furan was distilled prior to use. Silica gel 60 F_{254} plates were used for TLC analysis. Flash column chromatography was performed using silica-gel (Merck, No 9385, 230–400 mesh). ^1H and ^{13}C NMR spectra were recorded at 200, 300, 400 or 500 MHz (^1H) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, δ 7.25 and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Mass spectra were recorded using the electronic impact technique with an ionization energy of 70 eV or using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes. IR spectra were obtained on a Perkin-Elmer 681 spectrophotometer. Optical rotations were measured on a 241 MC polarimeter using a sodium lamp. Melting points were determined on a Koffler block and are uncorrected. Elemental analyses were made with a Carlo Erba EA 178 apparatus. The following procedures are representative for the methodologies used through this paper. Full experimental

procedures and data for all the compounds obtained in this work are given as the Supporting Information.

Hybrid 28 from 12 and *N*-methylreserpine (27): $[Co_2(CO)_8]$ (72 mg, 0.17 mmol) was added to a solution of **12** (37 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1 h, cooled to −20 °C and then treated dropwise with $BF_3{\cdot}OEt_2$ (38 mL, 0.30 mmol). After 5 min of stirring, a CH_2Cl_2 solution of *N*-methylreserpine (95 mg, 0.15 mmol in 1 mL CH_2Cl_2) was added via cannula. The mixture was kept at −20 °C for 20 h. After quenching with saturated aqueous $NaHCO_3$, the cooling bath was removed and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes/AcOEt 3:2) to give **28** as a dark green oil (67 mg, 39 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 2H), 7.11 (s, 1H), 6.71 (s, 1H), 6.22 (brs, 1H), 5.05 (m, 1H), 4.44 (brs, 1H), 4.28 (d, J = 9.2 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 7H), 3.73 (s, 3H), 3.62 (s, 3H), 3.54 (t, J = 5.5 Hz, 1H), 3.50 (s, 3H), 3.13–2.99 (m, 3H), 2.71 (dd, J = 11.4, 4.8 Hz, 1H), 2.61 (t, J = 11.5 Hz, 1H), 2.43–2.28 (m, 5H), 2.15 (m, 1H), 2.02 (m, 3H), 1.68 (d, J = 14.3 Hz, 1H), 1.61 (d, J = 9.9 Hz, 1H), 1.36 (s, 3H), 0.25 (m, 2H), 0.94 (s, 3H), 0.37 (s, 9H); ^{13}C NMR (70 MHz, $CDCl_3$): δ = 200.6 (6C), 172.6 (C), 165.4 (C), 154.3 (C), 153.0 (3C), 142.2 (C), 136.1 (C), 131.4 (C), 125.4 (C), 122.9 (CH), 119.9 (C), 78.8 (C), 76.7 (2CH), 70.2 (C), 91.2 (CH), 80.1 (C), 77.9 (CH), 77.7 (CH), 60.9 (CH_3), 60.8 (CH_3), 56.2 (2CH_3), 55.7 (CH_3), 55.4 (CH), 51.8 (CH), 51.6 (CH_3, CH_2), 49.4 (CH_2), 47.7 (CH), 42.1 (CH), 41.0 (C), 34.7 (CH_2), 33.8 (CH), 32.1 (CH_3), 30.2 (CH_2), 29.7 (CH_2), 25.7 (CH_3), 25.2 (CH_2), 21.7 (CH_3), 17.1 (CH_2), 1.1 (3CH_3); IR (KBr): ν_{max} = 2081, 2043, 2014 cm^{-1}; elemental analysis calcd (%) for $C_{55}H_{64}N_2O_{15}SiCo_2$: C 57.99, H 5.66; found: C 57.54, H 5.43.

Compounds 30 and 31: $[Co_2(CO)_8]$ (549 mg, 1.33 mmol) was added to a solution of **12** (300 mg, 1.33 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 1 h, cooled to −78 °C, and treated with **15** (707 mg, 1.22 mmol) and $BF_3{\cdot}OEt_2$ (0.31 mL, 2.42 mmol in 7 mL CH_2Cl_2). The temperature was allowed to warm from −78 to −20 °C, and kept at −20 °C for 3.5 h. Then, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and warmed to room temperature with stirring. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes) to give **30–31** (1:2 mixture of regioisomers) as a dark brown oil (706 mg, 53 %). **30–31** could be obtained separated.

Data for **30** (minor isomer): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.28 (d, J = 1.6 Hz, 2H), 5.82 (s, 2H), 3.83 (brd, J = 8.4 Hz, 2H), 3.37 (t, J = 5.9 Hz, 2H), 2.42–2.31 (m, 4H), 2.12–2.04 (m, 4H), 1.54–1.41 (d, J = 7.1 Hz, 2H), 1.34 (s, 6H), 0.84 (s, 6H), 0.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4 (12C), 158.9 (2C), 149.5 (2C), 122.7 (2CH), 75.6 (2CH), 99.2 (2C), 80.0 (2C), 46.8 (2CH), 40.9 (2CH), 40.7 (2C7), 35.6 (2CH), 30.9 (2CH_2), 27.8 (2CH_2), 25.8 (2CH_3), 21.8 (2CH_3), 1.0 (6CH_3); IR (KBr): ν_{max} = 2955, 2916, 2083, 2044, 2003, 1619, 1574, 1249, 838 cm^{-1}.

Data for **31** (major isomer): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.25 (s, 1H), 5.96 (d, J = 2.9 Hz, 1H), 5.79 (d, J = 2.9 Hz, 1H), 5.53 (s, 1H), 4.77 (s, 1H), 3.81 (d, J = 9.2 Hz, 1H), 3.39 (t, J = 6.0 Hz, 1H), 2.57–2.25 (m, 7H), 2.11–2.04 (m, 2H), 1.55 (m, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.23–1.19 (m, 1H), 0.83 (s, 3H), 0.62 (s, 3H), 0.32 (s, 9H), 0.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.8 (12C), 160.5 (C), 154.1 (C),149.7 (C), 146.8 (C), 123.7 (CH), 120.7 (CH), 111.5 (C), 77.6 (CH), 76.2 (CH), 99.2 (C), 80.5 (C), 79.3 (C), 53.4 (CH), 47.0 (CH), 45.0 (CH), 41.6 (CH), 41.4 (C), 40.6 (CH), 38.8 (C), 36.2 (CH), 32.7 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 27.9 (CH_2), 26.7 (CH_3), 26.1 (CH_3), 22.2 (CH_3), 21.0 (CH_3), 1.6 (6CH_3); IR (KBr): ν_{max} = 2917, 2084, 2044, 2013, 1625, 1598, 1249, 839 cm^{-1}.

Compound 37: A solution of mestranol (157 mg, 0.51 mmol) in THF (7 mL) at −78 °C was treated dropwise with a solution of *n*BuLi (0.8 mL, 1.1 mmol, 1.4 M solution). The mixture was stirred for 30 min, and then (1*R*)-(−)-myrtenal (0.12 mL, 0.77 mmol) was added dropwise via cannula. The reaction was stirred for 4 h from −78 °C to RT. Subsequently, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the cooling bath was removed. The mixture was extracted with Et_2O (2×), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Silica gel chromatography (hexanes/AcOEt 20:1 → 9:1) of the crude product provided **37** (mixture of diastereoisomers) as a clear oil (119 mg, 51 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.7 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H),5.63 (brs, 1H), 4.83 (brs, 1H), 3.77 (s, 3H), 2.84 (m, 2H), 2.46–1.32 (m, 18H), 1.30, 1.29 (s, 3H), 1.20, 1.17 (d, J = 7.8 Hz in both cases, 1H), 0.86 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4 (C), 146.6, 145.5 (C), 137.9 (C), 132.5 (C), 126.3 (CH), 119.9, 119.4 (CH), 113.7 (CH), 111.4 (CH), 89.1, 88.8 (C), 84.9, 84.8 (C), 79.9, 79.8 (C), 65.3, 64.9 (CH), 55.2 (CH_3), 49.4 (CH), 47.2, 47.1 (C), 43.5 (CH), 42.7, 42.6 (CH), 40.7, 40.6 (CH), 39.4 (CH), 39.0, 38.8 (CH_2), 37.9, 37.8 (C), 33.0, 32.9 (CH_2), 31.9, 31.8 (CH_2), 31.0 (CH_2), 29.8 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 22.8 (CH_2), 21.2, 21.1 (CH_3), 12.7 (CH_3); IR (film): ν_{max} = 3434, 2932, 2202, 167, 1500, 1255, 744 cm^{-1}; MS (EI): *m*/*z* (%): 460 (19) [M^+], 442 (15) [M^+-H_2O], 427 (13) [$M^+-H_2O-CH_3$], 399 (9), 335 (7), 37 (14), 284 (24), 242 (46), 227 (70), 174 (67), 147 (58), 91 (28); elemental analysis calcd (%) for $C_{31}H_{40}O_3$: C 80.83, H 8.75; found: C 80.94, H 8.67.

Chimera 38 from 37 and *N*-methylindole: $[Co_2(CO)_8]$ (96 mg, 0.23 mmol) was added to a solution of **37** (97 mg, 0.21 mmol) in CH_2Cl_2 (5.5 mL). The mixture was stirred at room temperature for 1 h, cooled to −78 °C, and treated with *N*-methylindole (17 mg, 0.84 mmol in 2 mL CH_2Cl_2) and $BF_3{\cdot}OEt_2$ (59 mL, 0.46 mmol) for 45 min at −78 °C. Then, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and warmed to room temperature with stirring. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes/AcOEt 50:1 → 25:1) to provide **38** (181 mg, 78 %) as dark green oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, J = 7.8 Hz, 1H), 7.21–7.05 (m, 4H), 6.72 (d, J = 2.4 Hz, 1H), 6.70 (s, 1H), 6.60 (m, 2H), 4.21 (brd, J = 8.8 Hz, 1H), 3.85 (t, J = 5.4 Hz, 1H), 3.79 (s, 3H), 3.41 (s, 3H), 2.78–2.48 (m, 4H), 2.25–2.03 (m, 5H), 1.77–1.25 (m, 7H), 1.39 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.86 (m, 1H); ^{13}C NMR (70 MHz, $CDCl_3$): δ = 200.5 (6C), 158.1 (C), 157.5 (C), 137.9 (C), 137.0 (C), 132.6 (C), 126.7 (C), 126.3 (CH), 126.2 (CH), 123.4 (C), 121.5 (CH), 120.1 (CH), 119.3 (CH), 118.6 (CH), 113.7 (CH), 111.2 (CH), 79.4 (CH), 78.3 (C), 87.1 (C), 87.0 (C), 55.2 (CH_3), 49.3 (CH), 49.1 (C), 46.0 (CH), 43.0 (CH_2), 42.4 (CH), 41.7 (CH), 40.5 (C), 39.3 (CH), 34.3 (CH_2), 34.2 (CH), 33.0 (CH_2), 32.2 (CH_3), 29.5 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 25.7 (CH_3), 23.7 (CH_2), 22.0 (CH_3), 15.9 (CH_3); IR (KBr): ν_{max} = 3435, 2931, 2082, 2044, 2017, 1611, 1500, 1465, 1372, 1255, 736 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{47}NO_8Co_2$: C 64.26, H 5.51; found: C 64.43, H 5.37.

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