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[1,3]-Transfer of Chirality during the Nicholas Reaction in γ-Benzyloxy Propargylic Alcohols

David D. Díaz, Miguel A. Ramírez, and Víctor S. Martín*[a]

Abstract: A highly regio- and stereoselective intramolecular [1,5]-hydrogen-transfer process is described. Treatment of γ-benzyl-protected $Co_2(CO)_6$-α,γ-acetylenic diols with $BF_3{\cdot}OEt_2$ provides bis-homopropargylic alcohols. The reaction occurs within seconds, tolerates a wide range of functionalities, and provides good yields. When the ether group is located at a stereochemically defined carbon atom, the rearrangement occurs with high stereoselectivity, transferring the chirality of the carbinol center to the newly created stereocenter. The cleavage of the benzyloxy group is totally regioselective when additional benzyl ethers are present. The scope and limitations of this novel process in densely substituted substrates are evaluated, and possible competitive reactions and/or stereochemical influences are also described. A mechanism based on a highly ordered chair-like transition state substantiated by a theoretical study is also included.

Keywords: asymmetric synthesis · cobalt · natural products · Nicholas reaction · propargylic alcohols

Introduction

The synthesis of complex molecules requires powerful methodologies to solve specific structural problems.[1] Key steps capable of generating defined molecular constitutions and stereochemistries are critical to accomplish these usually formidable tasks.[2] Stereocontrol originating from remote chiral centers during the construction of polysubstituted acyclic systems remains a central theme in the total synthesis of complex natural products.[1] One possible approach to this problem is based on chirality transfer[3] mediated by highly stereocontrolled rearrangement reactions, which requires a highly ordered transition state. In this context, special attention has been directed towards [3,3]-sigmatropic rearrangements (Claisen and Cope reactions), which have become some of the most commonly used and powerful methods for stereoselective carbon–carbon bond formation, and are supported by numerous reports concerning intramolecular chirality transfer using chiral substrates.[4] In this regard, the [2,3]-Wittig rearrangement of ethers has also come under close scrutiny as a carbon–carbon bond-forming reaction of potential application to the stereodirected synthesis of acyclic alcohols.[5] Chirality transfer during [2,3]-sila-Wittig rearrangements allows the stereoselective formation of Si–C bonds.[6] In the literature, very efficient chirality transfers in acyclic systems have also been achieved from chiral heteroatoms to carbon derivatives,[7] and in chiral metal complexes,[8] palladium(0)-promoted intra- and intermolecular allylation reactions,[9] and [3,3]-sigmatropic rearrangements of allylic acetates catalyzed by palladium(II).[10] In addition, intramolecular hydrogen transfer is the key step in stereoselective processes such as the reduction of β-hydroxy ketones,[11] the aldol-Tishchenko reaction,[12] and some intramolecular ionic hydrogenations.[13]

In the present work, we disclose full details of our results concerning complete chirality transfer in stereoselective intramolecular propargylic reduction in γ-benzyl-protected $Co_2(CO)_6$-α,γ-acetylenic diols, in which the chirality was introduced by way of an enantioselective Katsuki–Sharpless epoxidation.[14] The present study also demonstrates that the chiral integrity of the starting asymmetric center is preserved during the hydrogen transfer from the benzylic position. In particular, the methodology offers a mild, general solution to the problem of controlling the stereochemistry in an alkyl group introduced in a hydrocarbon chain. Beyond our efforts to delineate the scope and limitations of this process, we also report herein on the results of a theoretical study that provides substantiation of a proposed mechanism.

[a] Dr. D. D. Díaz, Prof. M. A. Ramírez, Prof. V. S. Martín
Instituto Universitario de Bio-Orgánica "Antonio González"
Universidad de La Laguna
C/Astrofísico Francisco Sánchez, 2, 38206 La Laguna, Tenerife (Spain)
Fax: (+34) 922-318-571
E-mail: vmartin@ull.es

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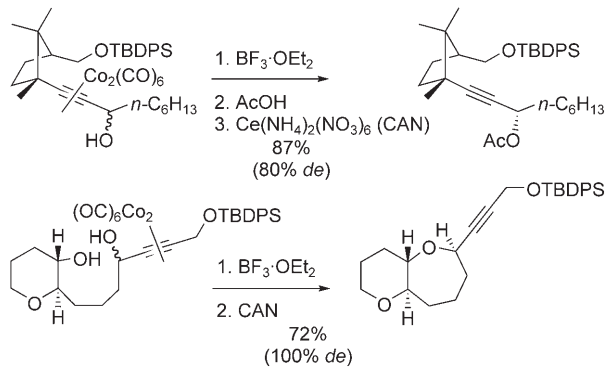
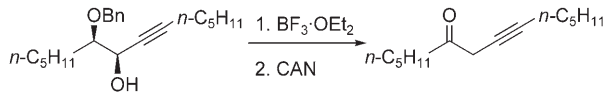
Results and Discussion

Antecedents: We have previously reported on novel stereoselective procedures for obtaining enantiomerically enriched products based on the Nicholas reaction that involve trapping of the carbocation generated by acid treatment of a chiral $Co_2(CO)_6$-complexed secondary propargylic alcohol with nucleophiles (Scheme 1). In both the intra- and intermolecular methodologies, the stereochemistry at the newly created stereocenter can be controlled by the existing substituents on the linear precursors.[15]



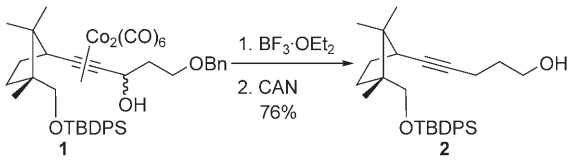
Scheme 1. Influence of existing stereocenters in the formation of C–O bonds using the Nicholas reaction. TBDPS = *tert*-butyldiphenylsilyl, CAN = cerium ammonium nitrate.

To study the behavior of this reaction in the presence of additional functional groups, we turned our attention to the influence of additional protected hydroxy groups at the linear propargylic alcohol. However, these studies yielded some unexpected results. For instance, α,β-acetylenic diol derivatives afforded the very unstable homopropargylic ketones under the Nicholas reaction conditions (Scheme 2).[16]



Scheme 2. Synthesis of homopropargylic ketones from β-benzyloxy propargylic alcohols.

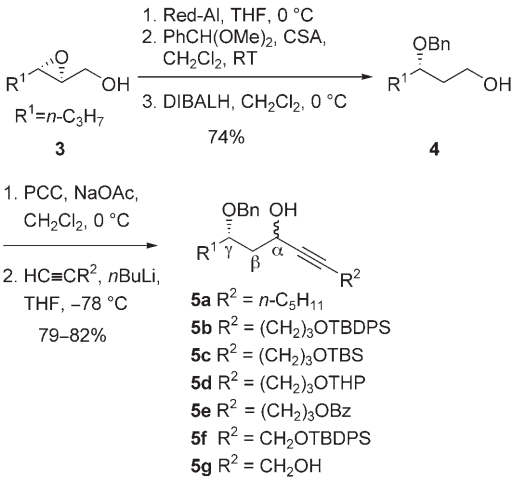
When we tried to extend our study, locating the benzyloxy group at the γ-position, we found an unprecedented participation of this group that causes reduction at the propargylic position. Thus, when the diastereomeric mixture **1** was submitted to the standard acidic conditions, the unprotected bis-homopropargylic alcohol **2** was obtained in good yields (Scheme 3).[17] It should be mentioned that the presence of the benzyl group[18] is essential for achieving the reported transformation since when the terminal hydroxy group was either unprotected or protected as a silyl ether (TBDPS or *tert*-butyldimethylsilyl (TBDMS)), the reduction did not occur.



Scheme 3. Propargylic reduction in γ-benzyloxy propargylic alcohols.

This new process may be formally considered as an alternative to standard acetylene coupling, avoiding elimination reactions and taking advantage of the high reactivity of acetylide anions towards carbonyl compounds.

Synthesis of simple γ-benzyloxy propargylic alcohols and preliminary results: To study the generality of this new process, we decided to synthesize a series of γ-benzyloxy propargylic alcohols, having characterized the stereochemistry at the ether position. A general methodology starting from enantiomerically enriched 2,3-epoxy alcohols **3** obtained by Katsuki–Sharpless epoxidation was developed (Scheme 4).

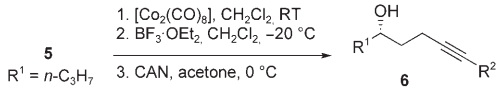


Scheme 4. General preparation of simple γ-benzyloxy propargylic alcohols. CSA = 10-camphorsulfonic acid, DIBALH = diisobutylaluminum hydride, PCC = pyridinium chlorochromate.

Regioselective opening of **3**[19] using Red-Al provided the corresponding 1,3-diols,[20] which were protected as benzylidene derivatives and further reduced with DIBALH to yield the mono-protected diols **4**.[21] Oxidation to the aldehyde and treatment with the appropriate lithium acetylide provided diastereomeric mixtures of propargylic alcohols **5**.

When the $Co_2(CO)_6$ complex of **5** was submitted to the usual acidic conditions of the Nicholas reaction ($BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C), the reduction at the propargylic position with concomitant benzyl cleavage occurred almost instantly yielding, after cleavage of the complex, the stereochemically defined bis-homopropargylic alcohol **6** (Table 1). If a THP ether was present (Table 1, entry 4), the isolated product showed that such a protecting group had been cleaved. The

Table 1. Representative examples of propargylic reduction in γ-benzyl-protected $Co_2(CO)_6$-α,γ-acetylenic diols under Lewis acid treatment.

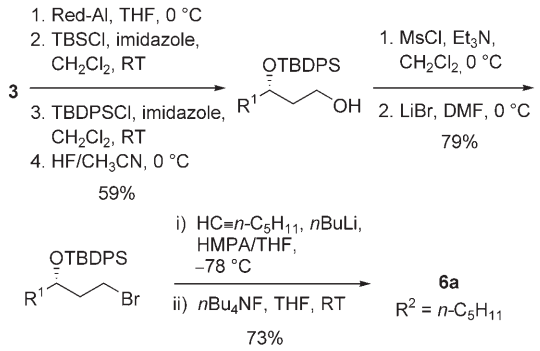


Entry	5	Yield [%][a]
1	**5a** $R^2 = n\text{-}C_5H_{11}$	65 (70)
2	**5b** $R^2 = (CH_2)_3OTBDPS$	69 (78)
3	**5c** $R^2 = (CH_2)_3OTBS$	68 (75)
4	**5d** $R^2 = (CH_2)_3OTHP$	40 (46)[b]
5	**5e** $R^2 = (CH_2)_3OBz$	77 (80)
6	**5f** $R^2 = CH_2OTBDPS$	69 (77)
7	**5g** $R^2 = (CH_2)_3OH$	46 (51)

[a] Figures in parentheses denote the yield from the corresponding $Co_2(CO)_6$–alkyne complex. [b] The product was isolated as a free diol (**6g**).

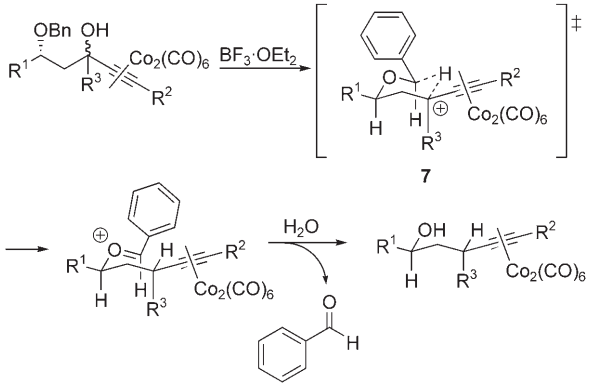
procedure was also found to work in the presence of additional free hydroxy groups (Table 1, entry 7), albeit in moderate yields. When the hydroxy groups were protected as silyl ethers (TBDPS or TBDMS) (Table 1, entries 2, 3, and 6) or as an ester (Table 1, entry 5), satisfactory yields were obtained regardless of the position of the protected hydroxy group relative to the triple bond. In all cases, the $Co_2(CO)_6$-bis-homopropargylic alcohols were satisfactorily decomplexed from the metal in the standard manner.

A very interesting feature of this process is that the rearrangement occurred with complete integrity of the stereogenic center at the secondary position at which the benzyloxy group was located. To probe this fact, **6a** ($R^2 = n\text{-}C_5H_{11}$) was prepared by an alternative process using standard conditions based on nucleophilic substitution (Scheme 5); the specific rotation of the product thus obtained, $[\alpha]_D^{25} = +5.26$ ($c = 2.3$ in $CHCl_3$), was found to be essentially the same as that of the product obtained by the propargylic reduction (Table 1, entry 1), $[\alpha]_D^{25} = +5.28$ ($c = 2.3$ in $CHCl_3$).



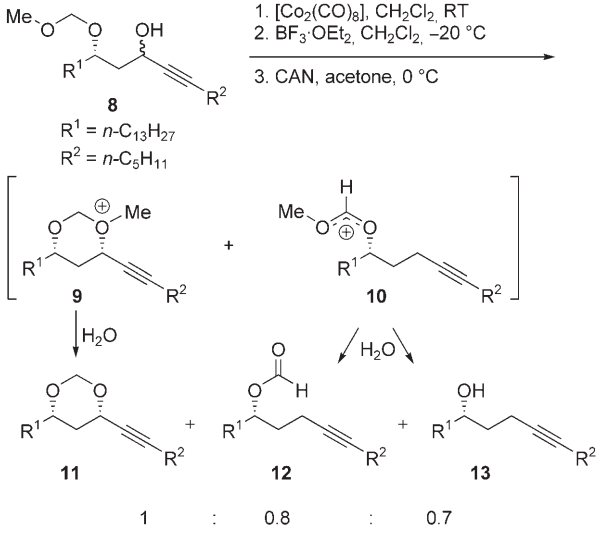
Scheme 5. Preparation of stereochemically defined bis-homopropargylic alcohols from 2,3-epoxy alcohols following a classical route. HMPA = hexamethylphosphoramide.

As mentioned above, the presence of the benzyl protecting group at the γ-position is essential to achieve the reduction at the propargylic position. Our hypothesis to explain such a process is based on a hydrogen transfer from the benzylic methylene unit to the propargylic cation through a chair-like transition state, followed by attack of water on the benzylic oxonium ion, liberating benzaldehyde and the reduced bis-homopropargylic alcohol (Scheme 6).[22]



Scheme 6. Mechanistic proposal for propargylic reduction in γ-benzyloxy propargylic alcohols.

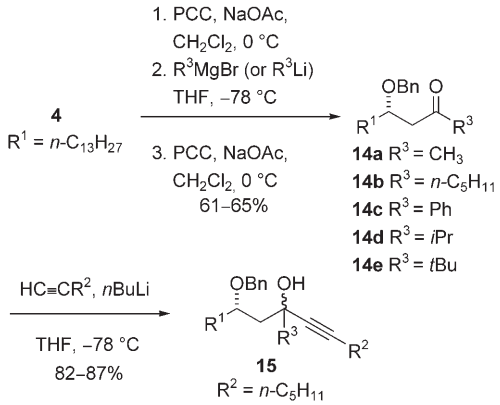
To obtain additional evidence about this plausible mechanism based on the highly ordered transition state **7**, we protected the γ-hydroxy group as a MOM ether, assuming that the methylene unit in this group may have similar properties to those of the benzyl group in terms of hydride transfer ability. However, when the diastereoisomeric mixture **8**[23] was submitted to the above-mentioned conditions, a 1:0.8:0.7 mixture of **11**, **12**, and **13** was obtained in 85% overall yield (Scheme 7). The expected bis-homopropargylic alcohol **13** was contaminated with the acetal **11** and the formate ester **12** resulting from attack of water on the cations **9**



Scheme 7. Propargylic reduction in γ-MOM-protected α,γ-acetylenic diols.

and **10**, respectively. Although the reaction was observed to behave differently with this protecting group, the idea of a six-membered transition state is reinforced.

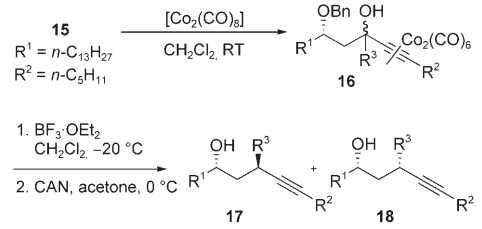
Stereochemical course of the [1,5]-hydrogen rearrangement in the acidic treatment of γ-benzyloxy $Co_2(CO)_6$-propargylic alcohols. Stereoselective synthesis of 2,4-disubstituted γ-lactones: Considering the mechanistic hypothesis outlined in Scheme 6, we wondered whether the hydrogen rearrangement could occur in a stereoselective manner. We anticipated that if the reaction implies a highly ordered transition state, the newly created stereocenter at the propargylic cation could be controlled by two major factors: the configuration of the benzyl-protected carbinol and the conformation of the cationic receptor. To probe this assumption, a series of new compounds containing tertiary propargylic alcohol functions and having a well-defined stereochemistry at the benzyloxy position was prepared (Scheme 8). Oxidation of the primary alcohol **4** to the corresponding aldehyde, nucleophilic addition of the appropriate Grignard or lithium reagent, and subsequent oxidation of the secondary alcohol provided the ketones **14**. These ketones were reacted with the lithium acetylide of 1-heptyne to yield the diastereomeric tertiary alcohols **15**. It should be pointed out that such carbinols were prepared despite the bulkiness of the R^3 group relative to the $Co_2(CO)_6$-acetylenic complex.



Scheme 8. Preparation of γ-benzyloxy tertiary propargylic alcohols.

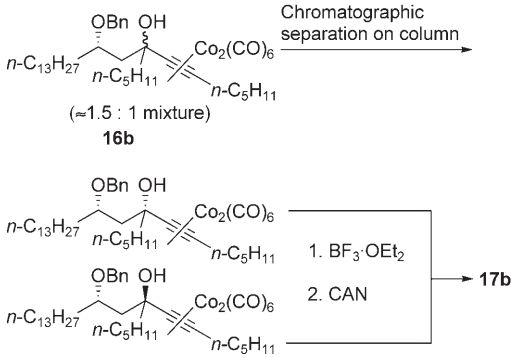
The $Co_2(CO)_6$-alkyne complexes **16** were smoothly prepared in the standard manner. To our satisfaction, we found that under the usual acidic conditions ($BF_3{\cdot}OEt_2$) such complexes provided, after demetalation, the desired *sec*-alkyl bis-homopropargylic alcohols **17** and **18** (Table 2).[24] As can be observed, the most interesting feature of this new transformation is that, except in those cases where R^3 is very bulky, such as the *tert*-butyl group (Table 2, entry 5), the reaction proceeded to yield exclusively one diastereoisomer.[25] In fact, these experimental results reinforce the idea of a chair-like transition state in which the bulkiest group becomes located at a pseudo-equatorial position (Scheme 6). Thus, *the obtained products are indicative of a new reaction in which complete chirality has been transmitted from the γ-position to the propargylic center*. In addition, the stereochemical course of the reaction proved insensitive to the absolute configuration of the propargylic alcohol since independent experiments with both diastereomers yielded the same final reduced product (Scheme 9).

Table 2. Diastereoselective propargylic reduction in γ-benzyloxy tertiary $Co_2(CO)_6$-propargylic alcohols.



Entry	**15**	**17:18**	Yield [%][a]
1	**15a** $R^3 = CH_3$	100:1[b]	79 (89)
2	**15b** $R^3 = n\text{-}C_5H_{11}$	100:1[b]	82 (86)
3	**15c** R^3 = Ph	100:1[b]	84 (87)
4	**15d** $R^3 = i$Pr	30:1	72 (81)
5	**15e** $R^3 = t$Bu	1:1	70 (79)

[a] Overall yield from **15** (in parentheses the yield from **16**). [b] Within the NMR detection limits, **18** was not detected.



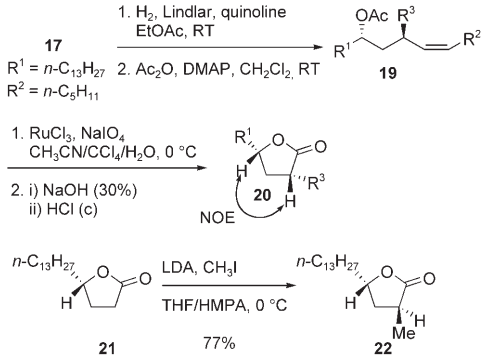
Scheme 9. Comparative experiment using both diastereoisomers at the propargylic position.

We also proved that without the formation of the $Co_2(CO)_6$ complex the transfer did not occur. Neither microwave nor acid treatment of **15c** (R^3 = Ph) under various conditions yielded any reduced product. In most cases, the material remained unaffected or small amounts of elimination products were detected.

To determine the stereochemistry at the newly created stereocenter, we pondered the idea of transforming products **17** into the corresponding α,γ-disubstituted γ-lactones. If successfully accomplished, this would achieve two goals simultaneously: to establish the relative stereochemistry of the reduced acetylenic compound and the development of a new and powerful synthetic method for the construction of a commonly encountered structural unit in many bioactive compounds. Thus, consecutively, **17a–d** were hydrogenated

under Lindlar's conditions and acetylated to afford the (*Z*)-acetate **19**. RuO_4 cleavage of the double bond, basic hydrolysis of the ester, and lactonization under acidic conditions provided the corresponding γ-lactones **20** (Table 3).[26] This

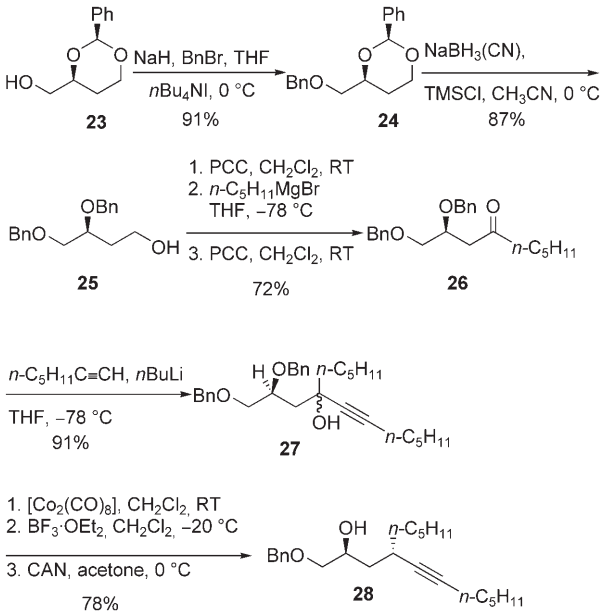
Table 3. Stereoselective synthesis of *cis*-α,γ-butyrolactones.



Entry	**17**	**19** Yield [%]	**20** Yield [%]
1	**17a** $R^3 = CH_3$	88	72
2	**17b** $R^3 = n\text{-}C_5H_{11}$	85	71
3	**17c** $R^3 = i$Pr	85	63
4	**17d** R^3 = Ph	87	64

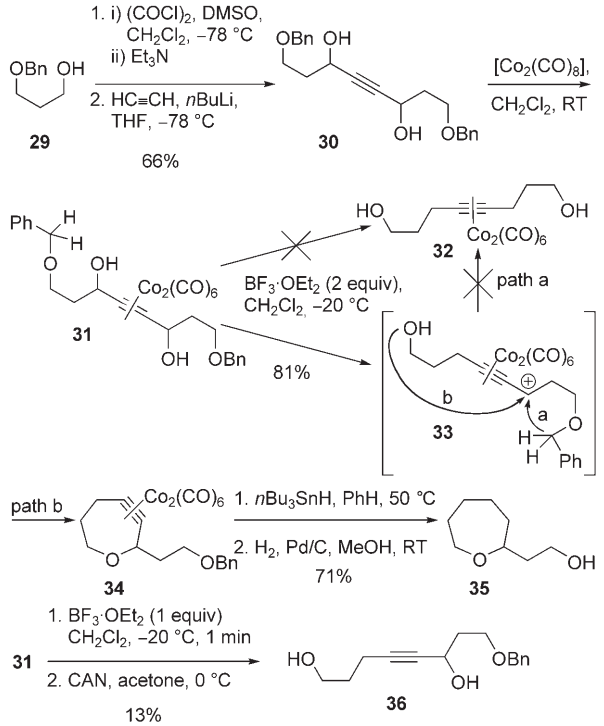
method was successful, except when R^3 was a phenyl group. In this case, the double bond fragmentation was performed by way of the *cis*-diol (OsO_4, NMO) and further oxidative cleavage ($KMnO_4$, K_2CO_3, $NaIO_4$). Although the relative stereochemistry was established by NOE studies, we prepared the alternative *trans*-lactone **22** from **21** to avoid any misinterpretation arising from conformational fluctuation of the five-membered ring.[27] Alkylation of **21** under the usual basic conditions provided the expected *trans*-lactone **22** as the major product.[28] Comparative NOE studies permitted us to establish unambiguously that the γ-butyrolactones obtained from the reduced acetylene have the *cis* relative stereochemistry.

Regioselectivity and influence of additional substituents attached to the linear chain: Another very important synthetic feature of the described process is the complete regioselectivity of the reaction. *Only benzyl ethers located in the γ-position relative to the triple bond undergo the hydrogen transfer*. Such behavior could be easily demonstrated using the di-*O*-benzyl derivative **25**, which was synthesized from the known alcohol **23**, in turn obtained from commercially available (*S*)-malic acid (Scheme 10).[29] The ether **24** was regioselectively reduced with a mixture of $NaBH_3(CN)$/TMSCl to afford **25**; these conditions were used since the standard benzylidene reduction using DIBALH led to the benzyl ether being located at the primary position. The use of a sequence similar to that described above led to the diastereomeric mixture of tertiary carbinols **27**. Finally, application of the usual protocol for performing the hydrogen transfer led to **28** as the only isolated product, with remarkable double regio- and stereoselectivity.



Scheme 10. Regioselective transfer of hydrogen in γ,δ-dibenzyloxy propargylic alcohols.

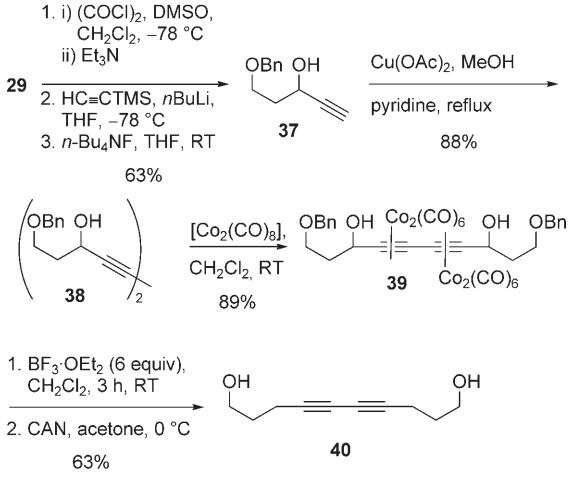
To explore the full potential of the described reaction, we speculated about the possibility of a double hydrogen transfer in the same molecule. Our first attempt was applied to the symmetrical $Co_2(CO)_6$-dipropargylic alcohol **31**, offering two sets of the necessary functional groups in the same substrate. This compound was easily synthesized from the monobenzyl ether of propanediol **29** (Scheme 11). When two



Scheme 11. Competitive reactions in symmetrical dibenzyloxy propargylic alcohols.

equivalents of Lewis acid were added, the complexed oxepane **34** was the only product obtained and no traces of the expected compound **32** were found. To characterize the seven-membered ring, the cobalt complex was submitted to the methodology developed by Isobe et al.[30] and further catalytic hydrogenation. As indicated in Scheme 11, **34** was formed by two consecutive processes: a hydrogen transfer leading to **33** and an intramolecular Nicholas cyclization leading to the corresponding cyclic ether (path b).[15] Further reduction of **34** and subsequent hydrogenation yielded compound **35**, which unequivocally supports the previous formation of **34**. Evidence for this two-stage mechanism was obtained by treatment of **31** with just one equivalent of $BF_3{\cdot}OEt_2$ during a very short reaction time (ca. 1 min), which led to a small amount of the mono-reduced alcohol **36**.

In an attempt to avoid the cyclization product, we subjected the dibenzyl ether of 4,6-decadiyne-1,3,8,10-tetraol **38** to our synthetic protocol, considering that the presence of the two consecutive triple bonds should strongly disfavor nine-membered ring formation. Compound **38** was synthesized by Eglinton coupling of the propargylic alcohol **37**, which was easily obtained from the benzyl ether of propanediol **29** (Scheme 12). Gratifyingly, when the corresponding di-$Co_2(CO)_6$ complex **39** was submitted to the usual acidic conditions, the expected reduced product **40** was obtained. However, it should be pointed out that room temperature and longer reaction times were necessary to accomplish the entire process.



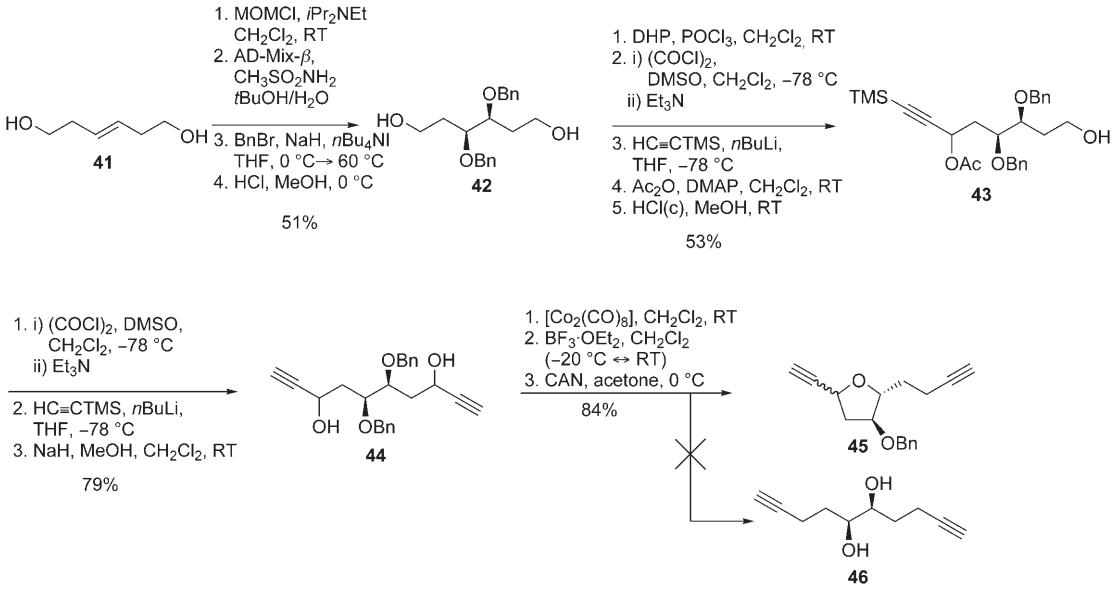
Scheme 12. Effective double hydrogen transfer.

In the above, we have described two processes in which the double transfer is designed to take place from the "outer" to the "inner" part of the molecules. Considering the simplicity of the synthesis of the vicinal diol, we contemplated a symmetrical molecule having two benzyl-protected alcohols as the central structural core and the necessary propargylic alcohol functions located in suitable positions. With this idea in mind, we synthesized the diol **44**, which is suitably predisposed to probe the double transfer concept from the inner to the outer part of a molecule. The known (*E*)-3-hexene-1,6-diol (**41**)[31] was consecutively di-protected as the MOM ether, enantioselectively dihydroxylated, dibenzylated, and submitted to MOM cleavage to afford the diol **42**. After unsuccessful attempts to simultaneously oxidize both alcohol functions to the corresponding aldehydes, homologation at both sides was performed in a stepwise manner. Thus, after monoprotection as the THP derivative, a sequence consisting of Swern oxidation, lithium acetylide addition, acetylation, and removal of the THP ether provided **43**. This primary alcohol was similarly homologated following a parallel series of reactions to provide, after removal of the acetate, the desired dipropargylic diol **44**. When this diacetylenic diol was complexed with $[Co_2(CO)_8]$ and submitted to various conditions, varying the temperature from −20 °C to ambient, instead of the expected diol **46** resulting from the double transfer reaction, an approximately 1:1 diastereoisomeric mixture of tetrahydrofuran **45** was isolated. This example shows the high propensity for cyclization as opposed to hydrogen transfer in those systems in which the two competing reactions are possible (Scheme 13).[32]

Once the possible competition between the newly described hydrogen transfer and intramolecular cyclization had been studied, we pondered the influence of additional substituents located on the linear chain on both the stereochemistry and the viability of the reaction itself. Especially important for us was to study highly oxygenated systems, mainly in view of their wide distribution in biological systems and the fact that under the reaction conditions we previously observed a competing elimination in α,β-dioxygenated acetylenes leading to homopropargylic ketones.[16] To carry out our studies, we needed a molecular model of type **47** having the necessary γ-benzyloxy group, the propargylic alcohol function, and an additional β-substituent (alkyl or alkoxy group) (Figure 1).[33]

Thus, we decided to prepare both stereoisomers with an additional benzyloxy group located at the β-position. Previously prepared benzoate diol **48**[34] was transformed into the corresponding benzyloxy derivative **49**. Mono-protection of the primary hydroxy group permitted the formation of the additional benzyl ether at the C-2 carbon by simple Williamson-type alkylation followed by THP cleavage. Subjecting **50** to a similar protocol as that previously used to build a propargylic system afforded **51**. Finally, the sequence used to induce the hydrogen transfer led to the expected product **52**, although the reaction was sluggish and the yield was slightly lower than in the absence of the β-substituent (Scheme 14 and Table 4).

To study the stereochemical influence of the β-substituent, we prepared the corresponding *syn*-β,γ-dibenzyloxy isomer **53** (Scheme 15). (*E*)-2-Hexen-1-ol was protected as the corresponding THP ether, submitted to Sharpless asymmetric dihydroxylation, and the resulting diol protected as the corresponding dibenzyl ether to afford, after acid THP cleavage, **53**. Application of the sequence used above to construct



Scheme 13. Ring formation versus hydrogen transfer. MOM = methoxymethyl, DHP = 3,4-dihydro-2*H*-pyran, DMAP = 4-diaminopyridine.

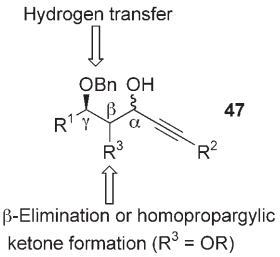
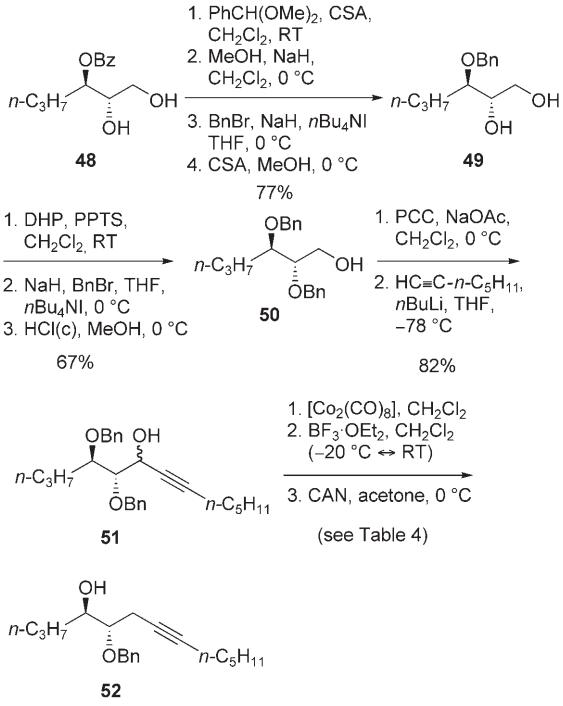


Figure 1. Substrates with possible competition affecting the hydrogen transfer.

the propargylic system afforded **54**. Surprisingly, all attempts to obtain **55** by the hydrogen transfer were completely fruitless. This result indicates the importance of the substituent at the β-position, including with regard to stereochemical considerations. In the light of these results, we prepared a library of different substrates of type **47**, considering different oxygenated substituents, such as methoxy and hydroxy groups, as well as an alkyl group (methyl).

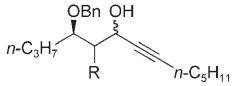
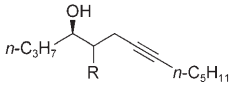
For the synthesis of β-methoxy-containing substrates, the diol **49** was mono-THP protected, methylated at the secondary carbinol, and then subjected to THP cleavage to afford the *anti*-alcohol **56** (Scheme 16). Alternatively, **49** was fully mesylated, treated with potassium acetate, and the acetate groups were hydrolyzed to afford the *syn*-isomer **58**.[35] When **58** was submitted to a similar sequence as that applied to **49**, the corresponding methoxy derivative **59** was obtained. In the same manner as used to prepare the β-hydroxy-containing derivatives, we performed a similar sequence to introduce a *p*-methoxybenzyl group at the C-2 position, with the understanding that such a protecting group could be easily removed under oxidative conditions. Thus, a simple variation of the sequence, using *p*-methoxybenzyl chloride instead of methyl iodide, provided the PMB-protected alcohols **57** and **60** in a straightforward manner.

For the synthesis of the prototype **47** having a methyl group as a β-substituent, we performed the sequence outlined in Scheme 17. The diol **49** was oxidatively cleaved and the resulting aldehyde was subjected to Horner–Wadsworth–Emmons[36] conditions to afford the (*E*)-unsaturated ester **61**. Reduction of **61** with *in situ* generated alane provided the allylic alcohol **62**, which was successfully submitted to Katsuki–Sharpless asymmetric epoxidation using both enantiomers of diethyl tartrate. The resulting epoxides **63** and **65** were regioselectively opened at C-3 with $AlMe_3$, leading to the diols **64** and **66** as the major regioisomers.



Scheme 14. Hydrogen transfer in *anti*-β,γ-dibenzyloxy propargylic alcohols. PPTS = pyridinium 4-toluenesulfonate.

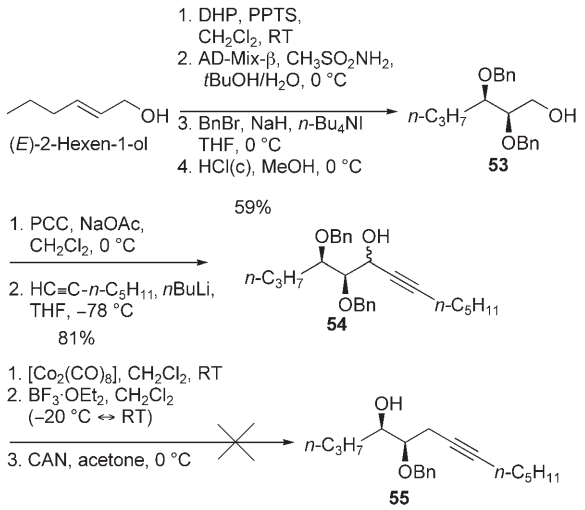
Table 4. Influence of the substitution at the β-carbon on the hydrogen-transfer process.

Entry		T [°C]	Time[a]	 (Yield [%][b])
1	**5a** (R = H)	−20	5 min	**61** (81)
2	**5a** (R = H)	0	1 min	**61** (79)
3	**5a** (R = H)	RT	1 min	**61** (83)
4	**51** (R = OBn) (*S*)	−20	20 h	**52** (59)
5	**51** (R = OBn) (*S*)	0	9 h	**52** (62)
6	**51** (R = OBn) (*S*)	RT	3.5 h	**52** (73)
7	**54** (R = OBn) (*R*)	−20	44 h	–
8	**54** (R = OBn) (*R*)	0	23 h	–
9	**54** (R = OBn) (*R*)	RT	13 h	–
10	**67** (R = OMe) (*S*)	−20	24 h	**73** (43)
11	**67** (R = OMe) (*S*)	0	1 h	**73** (55)
12	**67** (R = OMe) (*S*)	RT	2 min	**73** (72)
13	**68** (R = OMe) (*R*)	−20	22 h	**74** (35)
14	**68** (R = OMe) (*R*)	0	5 h	**74** (62)
15	**68** (R = OMe) (*R*)	RT	40 min	**74** (69)
16	**69** (R = OH) (*S*)	−20	30 h	**75** (6)
17	**69** (R = OH) (*S*)	0	18 h	**75** (32)
18	**69** (R = OH) (*S*)	RT	45 min	**75** (41)
19	**70** (R = OH) (*R*)	−20	32 h	**76** (38)
20	**70** (R = OH) (*R*)	0	14 h	**76** (47)
21	**70** (R = OH) (*R*)	RT	30 min	**76** (65)
22	**71** (R = Me) (*S*)	−20	70 min	**77** (73)
23	**71** (R = Me) (*S*)	0	15 min	**77** (79)
24	**71** (R = Me) (*S*)	RT	4 min	**77** (82)
25	**72** (R = Me) (*R*)	−20	35 h	**78** (41)
26	**72** (R = Me) (*R*)	0	23 h	**78** (57)
27	**72** (R = Me) (*R*)	RT	75 min	**78** (68)

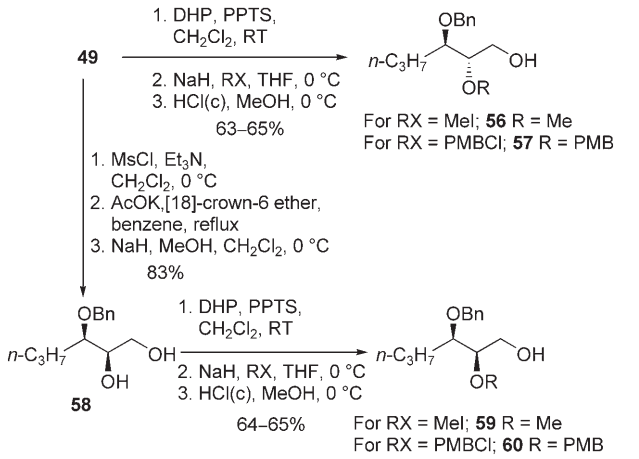
[a] Times refer to the hydrogen transfer over the corresponding $Co_2(CO)_6$-acetylenic complex until TLC shows complete conversion. [b] Overall yield from propargylic alcohols.

cleaved by oxidative treatment with CAN, giving the desired propargylic alcohols **69** and **70**.

Table 4 outlines the results obtained (**61**, **52**, **73**–**78**) when the above propargylic alcohols were submitted to the whole sequence used to induce the hydrogen transfer. In general, the substitution at the β-carbon atom decreases the rates and yields of the hydrogen transfer, which are better when the substituents at the β- and γ-carbon atoms are in an *anti* configuration.[33] Only with a hydroxy group as the β-substituent did the *syn*-isomer yield a faster reaction (Table 4, entries 16–21). The β-alkyl derivatives were found to be more convenient substrates for hydrogen transfer than the β-alkoxy analogues, presumably because of an interaction between the β-oxygenated center and the propargylic cation in the latter. Neither β-elimination products nor homopropargylic ketones were observed at 0 °C or below, with minuscule amounts of these side products only being detected in certain cases when the reaction was carried out at room temperature. A dramatic result was observed for the *syn*-(*R*)-β-benzyloxy derivative **54**: after long periods of time, only an irresolvable mixture of products of low polarity was obtained, along with remaining starting material (Table 4, entries 7–9).

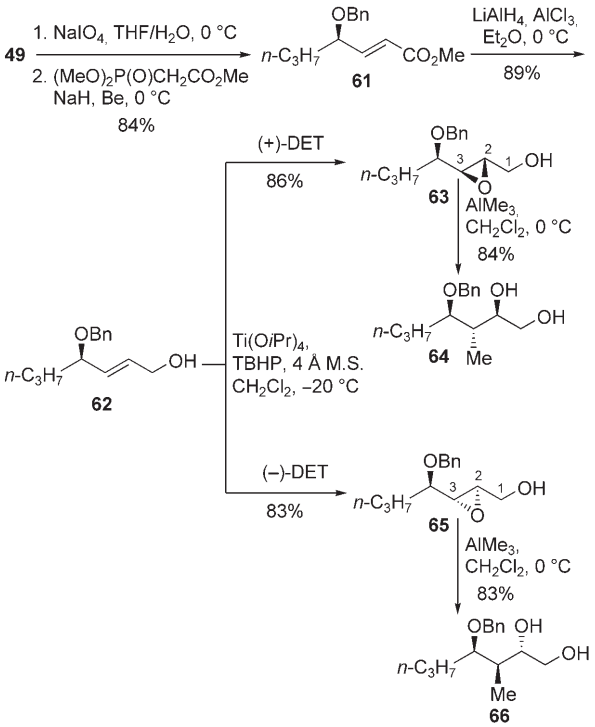


Scheme 15. Failed attempt at hydrogen transfer in *syn*-β,γ-dibenzyloxy propargylic alcohols.

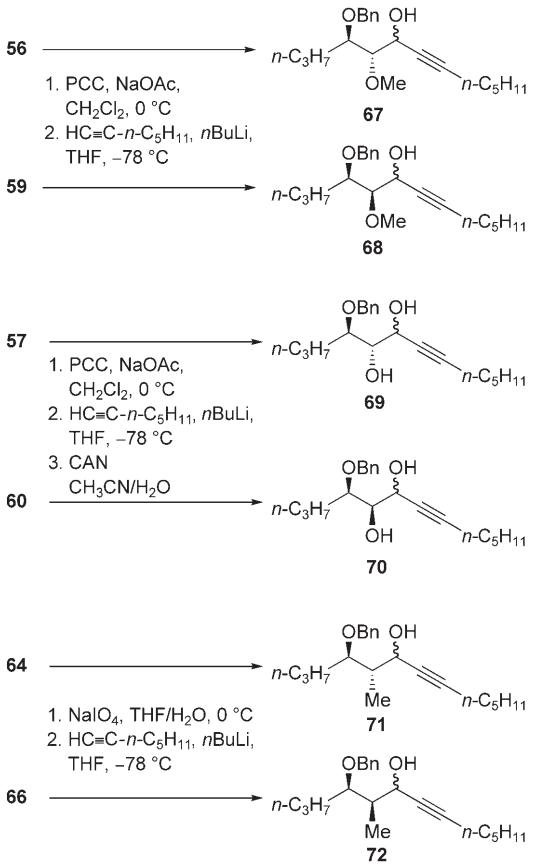


Scheme 16. Stereocontrolled synthesis of 2-alkoxy-3-benzyloxy-1-alkanols.

With alcohols **56**, **57**, **59**, **60**, **64**, and **66** in hand, we incorporated the propargylic unit by oxidation or diol cleavage to give the corresponding aldehyde followed by addition of the appropriate lithium acetylide (Scheme 18). Finally, to obtain the derivatives having a free hydroxy group, the PMB ether functions in the products from **57** and **60** were efficiently

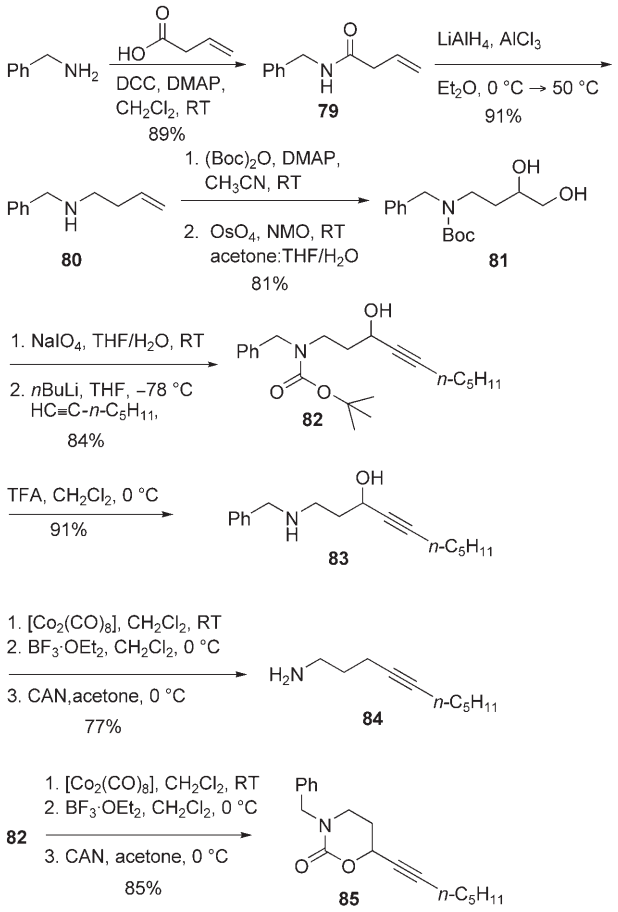


Scheme 17. Stereocontrolled synthesis of 3-methyl-4-benzyloxy-1,2-diols.



Scheme 18. Synthesis of γ-benzyloxy β-substituted propargylic alcohols **47** (R^3 = Me, OMe).

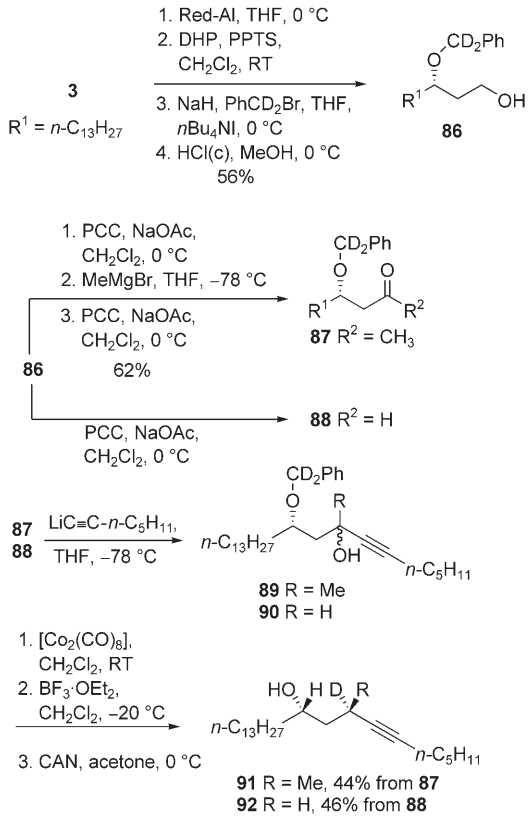
[1,5]-Hydrogen transfer in γ-benzylamine propargylic alcohols: With an eye toward the application of this methodology to the synthesis of natural products, we decided to assess whether the hydrogen transfer could be extended to the corresponding γ-nitrogenated systems. To probe this idea, the γ-benzylamino derivative **83** (Scheme 19) was conveniently synthesized starting from benzylamine. DCC-coupling with vinylacetic acid provided the corresponding amide **79**, which was reduced with alane to the secondary amine **80**. Boc-protection of the nitrogen center, dihydroxylation of the terminal alkene, oxidative cleavage of the vicinal diol, and finally coupling with the appropriate lithium acetylide yielded the propargylic alcohol **82**. Acidic cleavage of the Boc group provided the desired propargylic alcohol **83**, which was submitted to the protocol for inducing the hydrogen transfer. Satisfyingly, the bis-homopropargylic amine **84** was formed, demonstrating the feasibility of application of the described methodology to nitrogenated systems. It is noteworthy that when the *N*-Boc-protected alcohol **82** was submitted to the same conditions as **84** to perform the hydrogen transfer, the cyclized product **85** was exclusively ob-



Scheme 19. Propargylic reduction in $Co_2(CO)_6$-γ-benzylamino propargylic alcohols. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

tained in very good yield as a result of intramolecular attack of the Boc oxygen at the propargylic position.

Mechanistic considerations: Isotope effect in the hydrogen transfer: To obtain additional mechanistic evidence, we decided to perform an isotopic substitution at the benzylic position, looking for evidence of an isotope effect during the transfer. Thus, the necessary deuterated propargylic alcohols **89** and **90** (Scheme 20) were prepared in the same manner

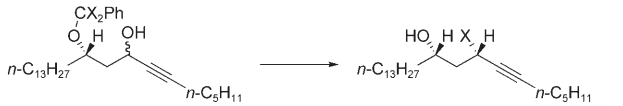


Scheme 20. Stereoselective synthesis of deuterium-labeled methines and methylenes.

as used to prepare the protonated analogues (Scheme 4 and Scheme 8) but using α,α-[D_2]benzyl bromide. Application of the procedure for inducing the transfer to substrates **89** and **90** cleanly afforded the compounds **91** and **92**, demonstrating the applicability of this methodology to the stereoselective synthesis of deuterium-labeled methines and methylenes.

In spite of the high rate of the transfer at −20 °C, when the reaction was carried out at −40 °C an isotope effect was observed when the benzylic hydrogen atoms were replaced with deuterium atoms (Table 5). This supports the rupture of such a bond during the transition state. Thus, after a reaction time of 15 min at −40 °C, the deuterated benzyl ether (entry 2) provided only 20% conversion, while the reaction using the protium derivative afforded 41% conversion in only 5 min. Although this is only a qualitative study, the evidence strongly supports the assumption that the breaking of a C–H(D) bond is involved in the process during the transition state.

Table 5. Isotopic effect in the hydrogen transfer.



Entry	X	T [°C]	Time [min]	Conversion [%]	Yield [%]
1	H	−40	5	41	93
2	D	−40	15	20	92
3	H	−30	3	82	92
4	D	−30	6	79	92
5	H	−20	1	91	93
6	D	−20	1	90	93

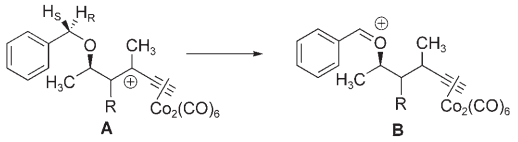
Calculations: The structural complexity involved in the reported hydrogen transfer warrants an initial theoretical model based on a semiempirical treatment. PM3(tm) was the chosen Hamiltonian as it is the only one existing to date that possesses the necessary parameterization of the cobalt atom. This Hamiltonian was used to optimize geometries for the transformation of several α,β-substituted γ-benzyloxy propargylic cations complexed with [$Co_2(CO)_8$] into the corresponding reduced entities. To facilitate the calculations, 1-hexyne was used as a base structure on which the different substituents were located. We studied hypothetical transformations involving hydrogen transfer from both benzylic hydrogen atoms to both prochiral faces of the carbocation. The most relevant energetic and structural features concerning the stationary points are summarized in Table 6.

A model based on the results presented in Table 6 predicts endothermic processes with relatively large activation energies (between 23.5 and 39.3 kcal mol^{-1}), small discrimination in favor the transfer of the pro-*R* hydrogen (H_R) atom as opposed to the pro-*S* one (H_S) in almost all cases studied, and a preferential attack on the *Re*-face of the carbocation. Six-membered rings are involved in the transition-state geometries, in which the transferred hydrogen adopts a similar mode of binding to both the initial and final carbon (C–H–C distances between 1.3 and 1.4 Å).

In addition, the results shown in Table 6 point to faster [1,5]-hydrogen transfer if the β-chiral group is a methoxy, methyl or benzyloxy group with the *S* configuration and an easier rearrangement for the hydroxy group when the β-configuration is *R*, in complete agreement with the experimental results.

A chair-like transition state, as shown in Figure 2, can provide a very reasonable qualitative model for the global kinetic behavior and stereochemical outcome of our reaction. The β-chiral substituents, when located *anti* relative to the benzyloxy group, are placed equatorially in the ring, a more favorable orientation than the obligatory axial position that *syn*-substituents need to adopt. If we consider this effect to be more important than the difference in stability between the two diastereomeric starting products, we can anticipate

Table 6. Main energetic and geometric features for the semiempirical PM3(tm) treatment of hydrogen-transfer models.



Entry	R	Face[a]	H Tranf.[b]	**A**[2][c]	TS[2][c]	**B**[2][c]	$\Delta H^{\ddagger}$[c]	ΔH^{3}[c]	Imag. Freq.[d]	TS description C(+)–H[e]	C(Bn)–H[f]
1	H	*Si*	H_R	−3482.9	−3451.8	−3477.3	31.1	5.6	1057.12	1.307	1.421
2	H	*Si*	H_S	−3482.9	−3456.8	−3477.3	26.1	5.6	1057.12	1.431	1.376
3	H	*Re*	H_R	−3482.9	−3458.4	−3477.3	**24.5**	5.6	1302.56	1.405	1.394
4	H	*Re*	H_S	−3482.9	−3457.5	−3477.3	25.4	5.6	1286.83	1.423	1.371
5	**OH (R)**	*Si*	H_R	−3525.5	−3487.1	−3520.4	38.4	5.1	1173.62	1.361	1.407
6	**OH (R)**	*Si*	H_S	−3525.5	−3489.4	−3520.4	36.1	5.1	1315.91	1.440	1.357
7	**OH (R)**	*Re*	H_R	−3525.5	−3495.3	−3520.4	**30.2**	5.1	1361.66	1.418	1.397
8	**OH (R)**	*Re*	H_S	−3525.5	−3492.8	−3520.4	32.7	5.1	1312.57	1.405	1.396
9	OH (*S*)	*Si*	H_R	−3529.1	−3489.8	−3515.6	39.3	13.5	1173.79	1.340	1.446
10	OH (*S*)	*Si*	H_S	−3529.1	−3493.0	−3515.6	36.1	13.5	1406.22	1.416	1.401
11	OH (*S*)	*Re*	H_R	−3529.1	−3495.4	−3515.6	**33.7**	13.5	1349.46	1.404	1.390
12	OH (*S*)	*Re*	H_S	−3529.1	−3495.3	−3515.6	33.8	13.5	1334.04	1.403	1.385
13	MeO (*R*)	*Si*	H_R	−3518.2	−3481.9	−3514.0	36.3	4.2	1191.86	1.371	1.391
14	MeO (*R*)	*Si*	H_S	−3518.2	−3486.6	−3514.0	31.6	4.2	1277.80	1.452	1.353
15	MeO (*R*)	*Re*	H_R	−3518.2	−3486.9	−3514.0	**31.3**	4.2	1320.66	1.396	1.391
16	MeO (*R*)	*Re*	H_S	−3518.2	−3485.4	−3514.0	32.8	4.2	1286.77	1.446	1.361
17	**MeO (S)**	*Si*	H_R	−3518.8	−3484.4	−3508.9	34.4	9.9	1208.71	1.344	1.426
18	**MeO (S)**	*Si*	H_S	−3518.8	−3488.3	−3508.9	30.5	9.9	1402.66	1.422	1.391
19	**MeO (S)**	*Re*	H_R	−3518.8	−3488.6	−3508.9	30.2	9.9	1362.71	1.399	1.394
20	**MeO (S)**	*Re*	H_S	−3518.8	−3489.6	−3508.9	**29.2**	9.9	1320.37	1.402	1.378
21	Me (*R*)	*Si*	H_R	−3490.2	−3461.4	−3479.6	28.8	10.6	1271.03	1.416	1.376
22	Me (*R*)	*Si*	H_S	−3490.2	−3456.8	−3479.6	33.4	10.6	1154.43	1.343	1.445
23	Me (*R*)	*Re*	H_R	−3490.2	−3457.6	−3479.6	**32.6**	10.6	1327.97	1.426	1.399
24	Me (*R*)	*Re*	H_S	−3490.2	−3456.2	−3479.6	34.0	10.6	1312.57	1.424	1.379
25	**Me (S)**	*Si*	H_R	−3486.6	−3460.8	−3474.0	25.8	12.6	979.65	1.304	1.454
26	**Me (S)**	*Si*	H_S	−3486.6	−3463.1	−3474.0	23.5	12.6	1231.59	1.363	1.412
27	**Me (S)**	*Re*	H_R	−3486.6	−3463.0	−3474.0	23.6	12.6	1304.78	1.394	1.390
28	**Me (S)**	*Re*	H_S	−3486.6	−3463.4	−3474.0	**23.2**	12.6	1306.58	1.418	1.378
29	BnO (*R*)	*Si*	H_R	−3490.1	−3455.5	−3488.4	34.6	1.7	1185.01	1.369	1.393
30	BnO (*R*)	*Si*	H_S	−3490.1	−3460.2	−3488.4	29.9	1.7	1275.31	1.445	1.352
31	BnO (*R*)	*Re*	H_R	−3490.1	−3460.4	−3488.4	**29.7**	1.7	1311.47	1.391	1.392
32	BnO (*R*)	*Re*	H_S	−3490.1	−3457.6	−3488.4	32.5	1.7	1331.14	1.389	1.371
33	**BnO (S)**	*Si*	H_R	−3489.7	−3456.2	−3483.8	33.5	5.9	1173.92	1.339	1.449
34	**BnO (S)**	*Si*	H_S	−3489.7	−3456.2	−3483.8	33.5	5.9	1412.50	1.420	1.339
35	**BnO (S)**	*Re*	H_R	−3489.7	−3459.6	−3483.8	30.1	5.9	1368.91	1.397	1.398
36	**BnO (S)**	*Re*	H_S	−3489.7	−3461.8	−3483.8	**27.9**	5.9	1315.21	1.406	1.372

[a] *Prochiral face* of the carbocation assuming the $Co_2(CO)_6$-acetylenic group to be the highest ranking group in the Cahn–Ingold–Prelog system. [b] H_R = pro-*R*, H_S = pro-*S*. [c] Energy in kcal mol^{-1}. [d] Imaginary frequencies obtained in the harmonic vibrational frequency analysis. [e] Distance between transferred H and propargylic cation, in Å. [f] Distance between transferred H and initial benzylic carbon, in Å.

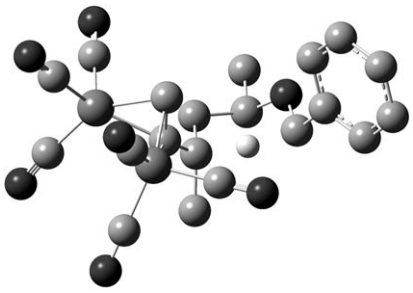


Figure 2. Chair-like transition-state geometry for pro-*R*-hydride transfers and *Re*-attack on the carbocation.

a faster reaction of the substituent when located *anti*, again in complete agreement with the experimental results. The only exception, the hydroxy group, can also be accommodated by this model because the axial transition state is now stabilized by a five-membered ring hydrogen bond (Figure 3).

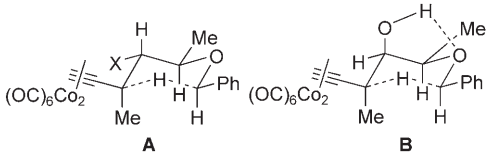


Figure 3. Chair-like transition states in which substituents are placed in the pseudo-equatorial position are preferred (**A**). With a β-hydroxy group, an internal hydrogen bond permits stabilization of an axially located group (**B**).

Conclusion

Herein, we have reported on a novel process of [1,3]-transfer of chirality in γ-benzyl-protected $Co_2(CO)_6$-α,γ-acetylenic diols under the Nicholas reaction conditions, in which a benzylic hydrogen is stereoselectively transferred to the propargylic cation. From the experimental results and semiempirical calculations, we can conclude that preferential transfer of the benzylic pro-*R* hydride in a chair-like transition state favors β-substituents and a $Co_2(CO)_6$-acetylene complex located at the equatorial positions. In addition, the methodology offers a mild and general solution to the problem of controlling the stereochemistry in any alkyl group introduced in a hydrocarbon chain, a relevant topic in the field of the synthesis of natural products.[32,37]

Experimental Section

General methods and materials: ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on Bruker Avance-400 and/or 300 spectrometers with samples in $CDCl_3$ solution, and chemical shifts are reported relative to Me_4Si. Low- and high-resolution mass spectra were obtained by using a Micromass Autospec spectrometer. Elemental analyses were performed on a Fisons Instruments EA 1108 CHNS-O analyzer. Optical rotations were determined for solutions in chloroform or *n*-hexane with a Perkin–Elmer model 241 polarimeter. Infrared spectra were recorded on a Bruker IFS 55 spectrophotometer. Column chromatography was performed on Merck silica gel, 60 Å and 0.2–0.5 mm. Spots were visualized under UV light and/or by staining with phosphomolybdic acid in ethanol. All solvents were purified by standard techniques.[38] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

General method for the preparation of enantiomeric 3-benzyl-protected 1,3-diols: preparation of (3*S*)-3-(benzyloxy)hexan-1-ol (4, $R^1 = n$-C_3H_7): Red-Al (27.8 mL, 3.4 M solution in toluene, 94.6 mmol) was slowly added to a solution of **3**[19] (5.0 g, 43.0 mmol) in dry THF (215 mL) at 0 °C under argon. The reaction mixture was stirred for 2.5 h, after which time TLC showed no remaining epoxide. Water (20 mL) and HCl (5% w/v in water) (30 mL) were then sequentially added, and the mixture was stirred until clear phases were obtained (0.5 h). The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to afford the 1,3-diol as a colorless oil.

A catalytic amount of CSA (1.0 g, 4.3 mmol) and benzaldehyde dimethyl acetal (7.8 mL, 51.6 mmol) were sequentially added to a stirred solution of the crude 1,3-diol in dry CH_2Cl_2 (140 mL) at room temperature. The reaction mixture was stirred for 1 h, after which time TLC showed complete conversion to the benzylidene derivative. Et_3N was then added until pH ≈ 7 was reached, and the mixture was stirred for 5 min and then concentrated under reduced pressure.

DIBALH (172 mL, 1 M solution in cyclohexane, 172 mmol) was slowly added to a solution of the aforementioned crude product in dry CH_2Cl_2 (140 mL) at 0 °C. After this addition, the mixture was allowed to warm to room temperature over a period of 15 min with stirring, then diluted with CH_2Cl_2 and aqueous HCl (5% w/v in water) was added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated, and the product obtained was purified by column chromatography to afford **4** ($R^1 = n$-C_3H_7) as a colorless oil (6.61 g, 74% overall yield): $[\alpha]_D^{25} = +20.7$ ($c = 1.9$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.2$ Hz, 3H), 1.34–1.39 (m, 2H), 1.48–1.56 (m, 1H), 1.62–1.67 (m, 1H), 1.76–1.83 (m, 2H), 3.63–3.66 (m, 1H), 3.73–3.81 (m, 2H), 4.49 (d, $J = 11.4$ Hz, 1H), 4.64 (d, $J = 11.4$ Hz, 1H), 7.27–7.35 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$ (q), 18.4 (t), 35.7 (t), 35.8 (t), 60.7 (t), 70.9 (t), 78.4 (d), 126.9 (d), 127.7 (d), 127.8 (d), 128.4 (d), 138.4 ppm (s); IR (film): $\tilde{\nu}_{max} = 3420, 2958, 2872, 1717, 1454, 1275, 1068$ cm^{-1}; MS: *m*/*z* (%): 208 $[M]^+$ (0.5), 191 $[M - CH_3]^+$ (1), 147 (8), 107 (19), 91 (100); HRMS calcd. for $C_{13}H_{20}O_2$: 208.14633; found 208.14683.

General method for performing a [1,5]-hydrogen transfer in γ-benzyloxy propargylic alcohols: preparation of (4*S*)-11-(*tert*-butyldiphenylsilanyloxy)undec-7-yn-4-ol (6b): SO_3-Py complex (0.48 g, 3.00 mmol) was added to a stirred mixture of **4** ($R^1 = n$-C_3H_7) (200 mg, 0.96 mmol), Et_3N (0.68 mL, 4.8 mmol), dry DMSO (1.97 mL, 10.27 mmol), and dry CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred until TLC showed completion of the reaction (ca. 2 h). It was then diluted with further CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide the aldehyde in a sufficiently pure state for use in the next step without further purification.

*n*BuLi (0.60 mL, 1.9 M in hexanes, 1.12 mmol) was added to a solution of *tert*-butyl-pent-4-ynyloxy-diphenylsilane[39] (370.8 mg, 1.15 mmol) in dry THF (2.7 mL) at −78 °C. After the addition, the mixture was allowed to warm to room temperature over a period of 0.5 h. It was then cooled to −78 °C once more and a solution of the aldehyde in dry THF (2.5 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 1 h, and then the reaction was quenched with saturated NH_4Cl solution and Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the secondary alcohol **5b** (405 mg, 80% overall yield) as a mixture of diastereoisomers in which one slightly predominated (ca. 1.5:1).

$[Co_2(CO)_8]$ (341 mg, 0.90 mmol) was added to a solution of **5b** in dry CH_2Cl_2 (8 mL) at room temperature and the mixture was stirred until TLC showed complete conversion to the hexacarbonyldicobalt complex (ca. 1 h). The mixture was then filtered through a pad of silica gel and concentrated to yield a brown solid, which was used directly in the next step.

$BF_3{\cdot}OEt_2$ (61 μL, 0.79 mmol) was slowly added to a stirred solution of the crude $Co_2(CO)_6$ complex in dry CH_2Cl_2 (9 mL) at −20 °C. The reaction mixture was stirred for 10 min and then poured into saturated aqueous $NaHCO_3$ at 0 °C. The resulting mixture was vigorously stirred for 15 min and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the $Co_2(CO)_6$ complex, which was employed in the next step without further purification.

CAN (1.72 g, 0.56 mmol) was added in one portion to a stirred solution of the complexed acetylene in dry acetone (9 mL) at 0 °C. The reaction mixture was stirred at 0 °C until TLC showed completion of the reaction (ca. 5 min). The mixture was then concentrated and the residue was diluted with water and extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography yielded **6b** as a colorless oil (223.7 mg, 69% yield overall). $[\alpha]_D^{25} = 4.15$ ($c = 2.12$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 6.9$ Hz, 3H), 1.07 (s, 9H), 1.30–1.35 (m, 2H), 1.58 (br s, 4H), 1.65–1.75 (m, 2H), 2.24–2.32 (m, 4H), 3.73 (t, $J = 5.9$ Hz, 3H), 7.35–7.44 (m, 6H), 7.65–7.73 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (q), 15.3 (t), 18.7 (t), 18.7 (t), 19.2 (s), 26.5 (q), 31.9 (t), 36.1 (t), 39.5 (t), 62.5 (t), 71.0 (d), 79.8 (s), 80.5 (s), 127.6 (d), 129.5 (d), 139.9 (s), 134.8 (s), 135.5 ppm (d); IR (film): $\tilde{\nu}_{max} = 3420, 2957, 2930, 2858, 1388, 1110$ cm^{-1}; MS: *m*/*z* (%): 421 $[M-1]^+$ (0.1), 365 $[M-t\text{Bu}]^+$ (5), 287 (100); elemental analysis calcd (%) for $C_{27}H_{38}O_2Si$: C 76.72, H 9.06; found: C 76.70, H 9.42.

General procedure for the preparation of enantiomeric β-benzyloxy ketones: preparation of (*S*)-4-(benzyloxy)heptadecan-2-one (14a): PCC (742 mg, 3.44 mmol), powdered 4 Å molecular sieves, and a small amount of NaOAc (42 mg, 0.51 mmol) were added sequentially to a solution of the alcohol **4** ($R^1 = n$-$C_{13}H_{27}$) (600 mg, 1.72 mL) in dry CH_2Cl_2 (15 mL). The heterogeneous mixture was stirred for 4 h, filtered through a pad of silica gel, and concentrated to provide the aldehyde, which was sufficiently pure for use in the next step without further purification.

MeMgCl (0.69 mL, 3 M in THF, 2.06 mmol) was added dropwise to a solution of the crude aldehyde in THF (17 mL) at −78 °C. After the mixture had been stirred for 0.5 h, saturated NH_4Cl solution was added, and the resulting slurry was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. The residual oil was used in the next step without further purification.

PCC (742 mg, 3.44 mmol), powdered 4 Å molecular sieves, and a small amount of NaOAc (42 mg, 0.51 mmol) were added sequentially to a solution of the crude diastereomeric alcohols in dry CH_2Cl_2 (15 mL). The heterogeneous mixture was stirred for 4 h, filtered through a pad of silica gel, and concentrated. The resulting viscous oil was purified by flash column chromatography to yield the ketone **14a** as a colorless oil (377.7 mg, 61% overall yield). $[\alpha]_D^{25} = +5.1$ ($c = 3.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.6$ Hz, 3H), 1.26 (br s, 20H), 1.37–1.58 (m, 4H), 2.15 (s, 3H), 2.45 (dd, $J = 15.8$, 4.8 Hz, 2H), 2.73 (dd, $J = 15.7$, 7.5 Hz, 1H), 3.91–3.95 (m, 1H), 4.49 (d, $J = 4.7$ Hz, 2H), 7.28–7.45 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (q), 22.6 (t), 25.1 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.1 (q), 31.9 (t), 34.3 (t), 48.6 (t), 71.8 (t), 75.6 (d), 127.6 (d), 127.8 (d), 128.3 (d), 138.4 (s), 207.7 ppm (s); IR (film): $\tilde{\nu}_{max} = 2929$, 2854, 1714, 1466, 1068 cm^{-1}; MS (FAB): m/z (%): 361 $[M+1]^+$ (14), 360 $[M]^+$ (15), 359 $[M-1]^+$ (11), 345 $[M-CH_3]^+$ (14), 253 $[M-OBn]^+$ (100); elemental analysis calcd (%) for $C_{24}H_{40}O_2$: C 79.94, H 11.18; found: C 80.02, H 11.32.

General procedure for the preparation of stereochemically defined α-alkyl-bis-homoprogargylic alcohols: preparation of (4*S*,6*R*)-6-methyltridec-7-yn-4-ol (17a): *n*BuLi (0.79 mL, 1.50 mmol, 1.9 M in *n*-hexane) was added dropwise to a solution of 1-heptyne (0.21 mL, 1.63 mmol) in dry THF (13 mL) under argon at −78 °C. The reaction mixture was allowed to warm to −20 °C and stirred for 15 min at this temperarure. It was then cooled to −78 °C once more, whereupon a solution of the ketone **14a** (300 mg, 0.83 mmol) in dry THF (3 mL) was added. The reaction mixture was stirred for 1 h, after which time TLC showed complete conversion. The mixture was poured into saturated aqueous NH_4Cl solution and diethyl ether and the aqueous phase was extracted with further diethyl ether. The combined organic solutions were dried over $MgSO_4$ and concentrated and the crude product was used in the next step without purification.

The tertiary carbinol thus obtained was subjected to the same procedure as used above to obtain **6b** from **5b**, furnishing **17a** as a colorless oil (231 mg, 79% overall yield). $[\alpha]_D^{25} = -6.2$ ($c = 0.32$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 3.6$ Hz, 3H), 0.88 (t, $J = 3.7$ Hz, 3H), 1.16 (d, $J = 23.3$ Hz, 3H), 1.25–1.36 (m, 26H), 1.43–1.51 (m, 4H), 1.54 (t, $J = 6.0$ Hz, 2H), 2.14 (m, 3H), 2.51 (t, $J = 7.3$ Hz, 1H), 3.75 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9$ (q), 14.0 (q), 18.6 (t), 21.9 (q), 22.1 (t), 22.6 (t), 23.9 (d), 25.4 (t), 28.7 (t), 29.3 (t), 29.6 (t), 31.0 (t), 31.9 (t), 37.4 (t), 44.7 (t), 71.3 (d), 82.0 (s), 84.5 ppm (s); IR (film): $\tilde{\nu}_{max} = 3346$, 2929, 2856, 1462 cm^{-1}; MS: m/z (%): 351 $[M+1]^+$ (25), 350 $[M]^+$ (32), 333 $[M-OH]^+$ (53), 332 $[M-H_2O]^+$ (26), 295 (51), 238 (45), 210 (80), 199 (100); elemental analysis calcd (%) for $C_{24}H_{46}O$: C 82.21, H 13.22; found: C 82.27, H 13.01.

General procedure for the preparation of stereochemically defined α-alkyl-(*Z*)-bis-homoallylic esters: preparation of (1*S*,3*R*,4*Z*)-acetic acid 3-methyl-1-tridecyl-dec-4-enyl ester (19a): A mixture of **17a** (200 mg, 0.57 mmol) and Lindlar's catalyst (5 mg) in dry EtOAc (6 mL) was stirred at room temperature under a H_2 atmosphere (ca. 1 atm). After 2 h, TLC analysis showed the reaction to be complete. The solution was filtered through a pad of Celite and the pad was washed with EtOAc. The combined organic phases were concentrated, and the crude product thus obtained was used in the next step without purification.

At 0 °C under argon, DMAP (83 mg, 0.68 mmol) and acetic anhydride (65 μL, 0.68 mmol) were added sequentially to a solution of the alkene obtained as described above in dry CH_2Cl_2 (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h, and then quenched with brine and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography yielded **19a** as a colorless oil (197.6 mg, 88% overall yield). $[\alpha]_D^{25} = +3.9$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$–0.92 (m, 6H), 0.95 (d, $J = 7.1$ Hz, 3H), 1.25 (br s, 29H), 1.35–1.58 (m, 3H), 2.02 (d, $J = 6.6$ Hz, 3H), 2.44–2.49 (m, 1H), 4.11 (dd, $J = 14.2$, 7.1 Hz, 1H), 4.85–4.90 (m, 1H), 5.17 (t, $J = 9.7$ Hz, 1H), 5.26–5.30 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (q), 21.0 (q), 21.2 (q), 22.5 (t), 22.6 (t), 25.2 (t), 27.3 (t), 28.5 (q), 29.3 (t), 29.5 (t), 29.6 (t), 31.5 (t), 31.9 (t), 34.3 (t), 41.8 (t), 72.9 (d), 128.5 (d), 135.3 (d), 170.7 ppm (s); IR (film): $\tilde{\nu}_{max} = 2929$, 1740, 1464, 1374, 1260, 1095 cm^{-1}; MS: m/z (%): 335 $[M-OAc]^+$ (22), 334 (80), 263 (42), 124 (75), 81 (100); elemental analysis calcd (%) for $C_{26}H_{50}O_2$: C 79.12, H 12.77; found: C 79.35, H 12.94.

General procedure for the preparation of *cis*-α,γ-disubstituted butyrolactones: preparation of (3*R*,5*S*)-3-methyl-5-tridecyldihydrofuran-2-one (20a): $NaIO_4$ (160 mg, 0.75 mmol) and a catalytic amount of $RuCl_3$ were added to a solution of the acetate **19a** (100 mg, 0.25 mmol) in a mixture of $CH_3CN/CCl_4/H_2O$ (3:2:2) (2.5 mL). The mixture was vigorously stirred for 30 min, after which time TLC analysis showed complete conversion to the acid derivative. It was then diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred for 15 min, then filtered through a pad of Celite and concentrated. The residue was dissolved in Et_2O (1 mL) and a solution of NaOH (30% w/v in water, saturated with NaCl) was added. The resulting mixture was vigorously stirred for 1 h at room temperature. After this time, concentrated HCl was added until pH ≈ 2 was attained, and the acidified mixture was diluted with Et_2O. Saturated aqueous NaCl solution was added, and the resulting mixture was extracted with Et_2O. The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to afford the lactone **20a** as a white solid (50.7 mg, 72% yield). M.p. 43 °C; $[\alpha]_D^{25} = -8.6$ ($c = 1.91$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.4$ Hz, 3H), 1.21–1.38 (br s, 22H), 1.38–1.62 (m, 5H), 1.72 (m, 1H), 2.48 (m, 1H), 2.65 (m, 1H), 4.31 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (q), 14.0 (q), 22.2 (t), 22.4 (t), 22.6 (t), 25.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 31.9 (t), 35.5 (t), 35.9 (d), 37.3 (t), 78.7 (d), 179.6 ppm (s); IR (film): $\tilde{\nu}_{max} = 3440$, 2922, 2851, 1751, 1645 cm^{-1}; MS: m/z (%): 283 $[M+1]^+$ (3), 282 $[M]^+$ (13), 265 $[M-OH]^+$ (1), 264 $[M-H_2O]^+$ (6), 211 $[M-C_5H_{11}]^+$ (2), 205 (10), 149 (41), 111 (29), 99 (100); elemental analysis calcd (%) for $C_{18}H_{34}O_2$: C 76.54, H 12.13; found: C 76.89, H 11.85.

General procedure for the preparation of *trans*-α,γ-disubstituted butyrolactones: preparation of (3*S*,5*S*)-3-methyl-5-tridecyldihydrofuran-2-one (22): *n*BuLi (0.21 mL of a 1.9 M solution in hexane, 0.39 mmol) was slowly added to a solution of diisopropylamine (64 μL, 0.44 mmol) in THF/HMPA (4:1) (3 mL) at −78 °C under argon. The mixture was stirred for 15 min and then a solution of the lactone **21**[40] (100 mg, 0.37 mmol) in THF/HMPA (4:1) (0.5 mL) was added dropwise. The resulting mixture was stirred for 20 min at −78 °C, whereupon a solution of MeI (24 μL, 0.44 mmol) in THF/HMPA (4:1) (0.5 mL) was added. The mixture was allowed to warm to −40 °C, stirred for 3 h at this temperature, and then treated with an aqueous solution of HCl (5% w/v) (2 mL). It was then diluted with Et_2O, saturated aqueous NaCl solution was added, and the resulting mixture was extracted with Et_2O. The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to afford the lactone **22** as a colorless oil (80.3 mg, 77% yield). $[\alpha]_D^{25} = +10.4$ ($c = 4.66$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 5.6$ Hz, 3H), 1.25–1.36 (br s, 22H), 1.36–1.44 (m, 1H), 1.67–1.69 (m, 1H), 1.97–2.07 (m, 1H), 2.08–2.11 (m, 1H), 2.70 (dd, $J = 6.5$, 5.6 Hz, 1H), 4.50 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (q), 15.9 (q), 22.7 (t), 25.3 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 34.0 (d), 35.4 (t), 78.4 (d), 180.1 ppm (s); IR (film): $\tilde{\nu}_{max} = 3440$, 2920, 2849, 1751, 1645 cm^{-1}; MS: m/z (%): 283 $[M+1]^+$ (5), 282 $[M]^+$ (16), 265 $[M-OH]^+$ (2), 264 $[M-H_2O]^+$ (10), 211 $[M-C_5H_{11}]^+$ (3), 205 (10), 99 (100); elemental analysis calcd (%) for $C_{18}H_{34}O_2$: C 76.54, H 12.13; found: C 76.82, H 12.23.

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