ORGANIC LETTERS

2000
Vol. 2, No. 3
335−337

Enantiocontrolled Synthesis of Trialkyl-Substituted Stereogenic Carbons. A General Route to *cis*-3,5-Dialkyl γ-Lactones

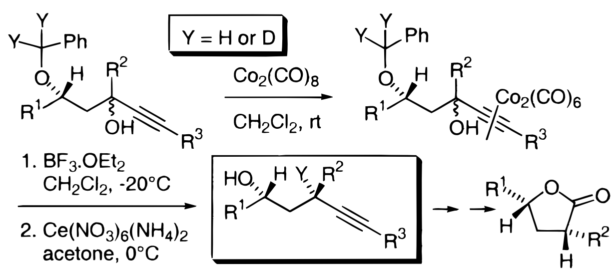
David Díaz and Víctor S. Martín*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna, C/Astrofisico Francisco Sánchez, 2, 38206 La Laguna, Tenerife, Spain

vmartin@ull.es

Received November 30, 1999

ABSTRACT



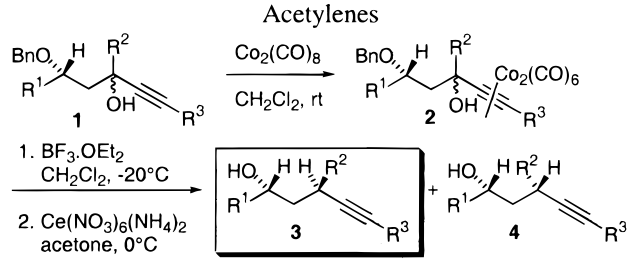
Lewis acid treatment of tertiary $Co_2(CO)_6$-propargylic alcohols having a stereochemically defined benzyloxy group at the γ-benzyl position yielded after cobalt demetalation *sec*-dialkyl bishomopropargylic alcohols in good yields. The reaction is highly stereoselective and predictable, providing pure stereoisomers. The use of benzyl-α,α'-d_2 ethers permitted the stereoselective *d*-labeling of methines and methylenes. Very simple chemical manipulations provided a general methodology to obtain the enantiomers of 3,5-dialkyl-γ-lactones.

Carbon−carbon σ-bond formation is usually the main objective in an organic synthesis.[1] The coupling between an acetylide and an alkylating agent could be considered to be a standard procedure for the synthesis of dialkyl acetylenes.[2] However, due to competitive elimination reactions, this procedure is inefficient for the preparation of *sec*-dialkyl acetylenes.[2] One alternative procedure that overcomes this difficulty is the reduction of the cobalt complex of α-acetylenic alcohols with sodium borohydride in trifluoroacetic acid.[3] Recently, we described a new procedure for the synthesis of bishomopropargylic alcohols based on the Lewis acid treatment of γ-benzyl-protected $Co_2(CO)_6$-α,γ-acetylenic diols and further demetalation.[4]

In this paper, we present the possibility of extending such an intramolecular reduction to the stereocontrolled synthesis of *sec*-dialkyl bishomopropargylic alcohols (Scheme 1).[5] The γ-benzyl-protected α,γ-propargylic alcohols **1** were obtained in accordance with Scheme 2. Chiral 2,3-epoxy alcohols **5**

Scheme 1. Stereoselective Synthesis of *sec*-Dialkyl Acetylenes

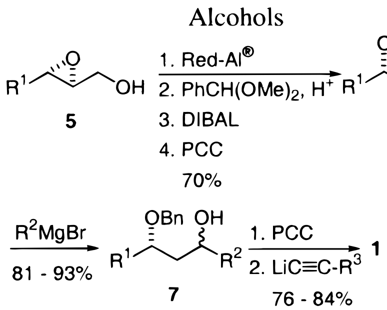
Acetylenes



(1) *Comprehensive Organic Synthesis*; Trost, B. M., et al., Eds.; Pergamon Press: Oxford, 1991; Vol. 3.
(2) (a) Brandsma, L. In *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988. (b) Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., et al., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 271−292.

10.1021/ol991287b CCC: $19.00
Published on Web 01/20/2000

Scheme 2. Synthesis of γ-Benzyl Protected α,β-Propargylic Alcohols



were regioselectively opened to the corresponding 1,3-diols. Benzylidene protection and regioselective reduction provided the secondary benzyl ether. Oxidation of the primary alcohol furnished the aldehyde **6**, which was treated with a suitable Grignard reagent to yield the secondary alcohols **7**. Oxidation to the corresponding ketone and lithium acetylide addition provided **1** as a mixture of diastereoisomers.[6]

The $Co_2(CO)_6$-acetylenic complex **2** was obtained by simple treatment of **1** with $Co_2(CO)_8$ in a CH_2Cl_2 solution. The addition of 1 equiv of $BF_3{\cdot}OEt_2$ to a CH_2Cl_2 solution of the $Co_2(CO)_6$-acetylenic complex **2**, at -20 °C, provided within minutes the corresponding complexed bishomopropargylic alcohol in a straightforward manner.[7] In all cases, the $Co_2(CO)_6$-bishomopropargylic alcohols were satisfactorily demetalized in the standard manner ($Ce(NO_3)_6(NH_4)_2$, acetone, 0 °C) to obtain the free acetylenes. Representative examples with different R^2 groups are outlined in Table 1.[8]

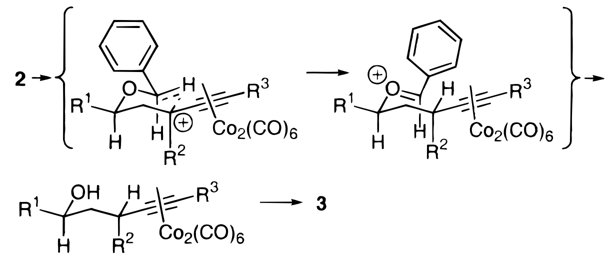
Table 1. Stereoselective Intramolecular Propargylic Reduction in γ-Benzyl-Protected $Co_2(CO)_6$-α,γ-Acetylenic Diols under Lewis Acid Treatment

entry	**2** ($R^1 = C_{13}H_{27}$-*n*, $R^3 = C_5H_{11}$-*n*)	**3**:**4**	(yield, %)[a]
1	**2a**, $R^2 = CH_3$	100:0	89 (79)
2	**2b**, $R^2 = C_5H_{11}$-*n*	100:0	86 (82)
3	**2c**, $R^2 = $ Ph	100:0	87 (84)
4	**2d**, $R^2 = $ Pr-*i*	30:1	81 (72)
5	**2e**, $R^2 = $ Bu-*t*	1:1	79 (70)

[a] Yields are not optimized (the overall yield from **1** to **3** + **4** is given in parentheses).

As can be seen from Table 1, the configuration of the stereogenic center in which the benzyl-protected group was located remains unaffected. However, the most interesting feature of our process was that the reduction of a tertiary propargylic alcohol, when the R^2 is not very bulky, provided the corresponding *sec*-dialkyl acetylene as a sole diastereoisomer regardless the stereochemistry of the carbinol propargylic center (entries 1 and 2).[9] Even when the R^2 substituent was a phenyl group, the reduction provided only one stereoisomer (entry 3). *These products represent compounds in which the chirality of the γ-carbon has been completely transferred to the sec-position relative to the acetylene.* When the R^2 increased the steric influence (isopropyl group), a tiny amount of **4d** was isolated (entry 4). The reaction lacks stereoselectivity when R^2 is a *tert*-butyl group. These facts are consistent with our previously reported mechanism based on a hydride transfer of one benzylic proton to the propargylic carbocation (Scheme 3).[4]

Scheme 3. Proposed Mechanism for the Stereoselective Hydride Transfer to $Co_2(CO)_6$-Propargylic Cations



The chairlike transition state locates the bulkiest group in a pseudoequatorial position. The cobalt complex substituent is such a group when R^2 is not highly demanding from a steric viewpoint. However, when the size of R^2 was very large, as occurred, for example, with a *tert*-butyl group, competition between the group and the complexed acetylene led to poor selectivity.

To establish the stereochemistry of the newly created stereocenter, we envisioned the possibility of transforming **3** into a 3,5-disubstituted γ-lactone. Thus, **3** was selectively hydrogenated to the *cis*-olefin **8** that after acetylation and cleavage of the olefin afforded the corresponding carboxylic acid. Alkaline hydrolysis of the acetate group and further acid treatment afforded in excellent yield the corresponding γ-lactone (Table 2). The methodology was quite general, except for the case for R^2 = phenyl, in which we had to cleave the double bond via the formation of the corresponding *cis*-diol (OsO_4, NMO) and further oxidative fragmentation ($KMnO_4$, K_2CO_3, $NaIO_4$). The cis relationship between

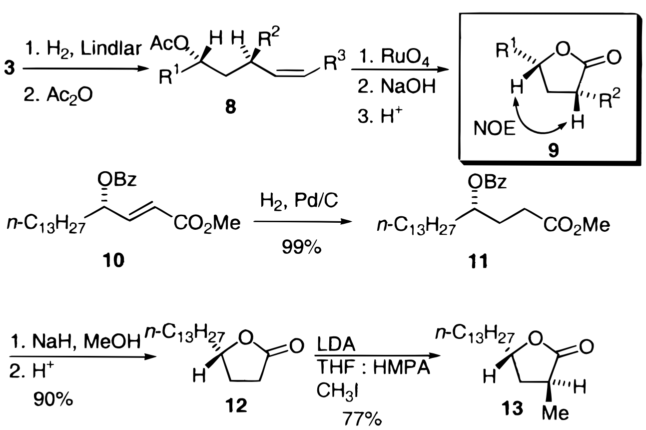
(3) Nicholas, K. M.; Siegel, J. *J. Am. Chem. Soc.* **1985**, *107*, 4999.
(4) Díaz, D. D.; Martín, V. S. *Tetrahedron Lett.* **1999**, in press.
(5) For other examples of "ionic hydrogenations" of alcohols, see: (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633 and references therein. (b) Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955. (c) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758. (d) Olah, G. A.; Arvanaghi, M.; Ohannecian, L. *Synthesis* **1987**, 770. (e) Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* **1988**, *29*, 5793 and references therein.
(6) The propargylic alcohol is usually obtained as a mixture in which one of the diastereoisomers slightly predominates (ca. 1.5:1).
(7) Blank experiments performing the acidic treatment over **1** gave inseparable mixtures, and in any case, traces of **3** were detected.
(8) In our previous work, we have shown that the propargylic reduction is compatible with a broad kind of functional group.
(9) We have performed the reaction with both diastereoisomers of **2b** leading to **3b** as the sole isolated product.
(10) Prepared by the method shown in: Rodríguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 4461.
(11) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 4, pp 2−110 and references therein.
(12) The dibenzyl alcohol **18** was obtained in accordance with the method described in Scheme 2, with the exception of the step relative to the reduction of the benzylidene derivative. In this case, we had to use $NaBH_3(CN)-(CH_3)_3SiCl$, in CH_3CN, to obtain the secondary benzyl ether since the use of DIBAL provided the benzyl ether in the primary position. Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2371.

Table 2. Stereoselective Synthesis of *cis*-3,5-Disubstituted γ-Lactones

entry	**3** ($R^1 = C_{13}H_{27}$-*n*, $R^3 = C_5H_{11}$-*n*)	**3** (yield, %)	**9** (yield, %)
1	**3a**, $R^2 = CH_3$	88	72
2	**3b**, $R^2 = C_5H_{11}$-*n*	85	71
3	**3c**, R^2 = Ph	87	64
4	**3d**, R^2 = Pr-*i*	85	63

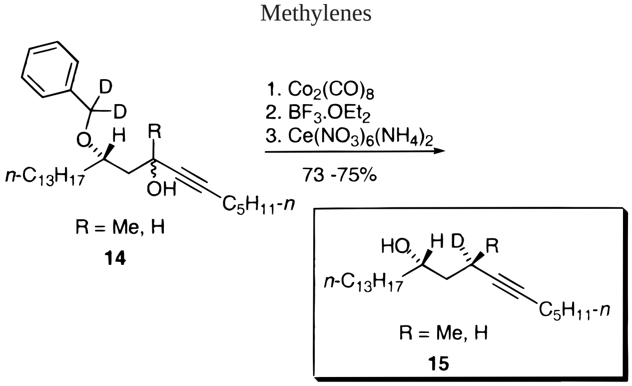
the 3,5-substituents was clearly determined by NOE experiments over the γ-lactones **9** (Scheme 4). To ensure that such studies were reliable, we prepared the alternative *trans*-lactone by a different procedure. Thus, the 4-benzoyloxy-α,β-unsaturated ester **10**[10] was submitted to catalytic hydrogenation to yield the saturated diester **11** that was submitted to basic hydrolysis and further acidic treatment to afford the lactone **12**. The alkylation under standard basic conditions led mainly to the expected trans-3,5-disubtituted γ-butyrolactone **13**.[11] The NMR studies were in accord with the stereochemistry.

Scheme 4. Stereoselective Synthesis of 3,5-Disubstituted γ-Lactones



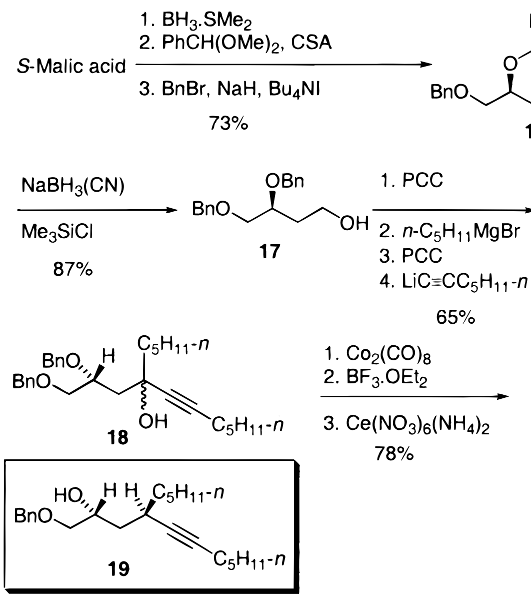
One exciting option of our method is the stereoselective *d*-labeling of methines and methylenes. The only preparation of the suitable benzyl-α,α'-d_2 ethers **14** and further application of our methodology provided cleanly the corresponding deutero compounds **15** (Scheme 5).

Scheme 5. Stereoselective *d*-Labeling of Methines and Methylenes



From a practical viewpoint, the high regioselectivity of the reaction is another very important feature since only those benzyl ethers located at the γ-position are able to participate in the reduction of the propargylic alcohol. Thus, we prepared the dibenzyl alcohol **18** from *S*-malic acid in accordance with Scheme 6,[12] and it was then submitted to the above-mentioned conditions, yielding only the reduced compound **19**.

Scheme 6. Only Benzyl Groups Located in the BisHomopropargylic Position Are Able to Transfer Hydrides



In summary, the intramolecular hydride transfer from a secondary γ-benzyloxy group with defined absolute stereochemistry to a $Co_2(CO)_6$-complexed propargylic cation generated under Nicholas conditions occurs with excellent stereoselectivity, providing a new method to obtain *sec*-dialkyl acetylenes with absolute stereochemical control. Since the stereochemistry of the reduction is highly predictable, the judicious choice of the different substituents may provide access to stereochemically defined tricarbon-substituted methines in their enantiomeric forms. Application of this methodology to the synthesis of some natural products is underway and will be published in due course.

Acknowledgment. This research was supported by the DGES (PB95-0751) of Spain and the Consejería de Educación, Cultura y Deportes del Gobierno de Canarias. D. D. thanks the M. E. C. of Spain for a F. P. I. fellowship.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for **3a**–**e**, **4e**, **9a**–**d**, **15**, and **19**. NOE studies for **9a**–**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991287B