A simple stereochemical assignment of 1,4-diols having a *cis*-2,3-methano bridge

Abdelhamid Benkouider,[a] James Bouquant[a] and Patrick Pale*[b]

[a] *Laboratoire des Réactions Sélectives et Applications (CNRS UMR 6519), Université de Reims-Champagne-Ardenne, 51100 Reims, France*
[b] *Laboratoire de Chimie Organique des Substances Naturelles (CNRS UMR 7509), Université Louis Pasteur, 4 rue Blaise Pascal, 67000, Strasbourg, France. E-mail: ppale@chimie.u-strasbg.fr; Fax: +1 33 390 241 517*

Received (in Montpellier, France) 13th February 2001, Accepted 2nd March 2001
First published as an Advance Article on the web 11th April 2001

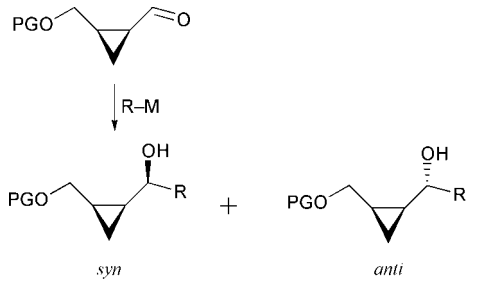
Letter

A convenient and reliable method, based on derivatization and NMR, allows for the assignment of the relative stereochemistry in various substituted *cis*-1,2-bis(hydroxymethyl)cyclopropanes.

The cyclopropyl moiety is found in a wide range of naturally occurring compounds isolated from various sources.[1] Cyclopropanes are also widely used as mimics of biologically active compounds,[2] as probes for mechanistic studies,[3] as well as building blocks in organic synthesis.[4] Owing to the importance of these 3-membered rings, numerous investigations dealing with the stereocontrolled synthesis of substituted cyclopropanes have been performed and are still ongoing. Nucleophilic additions to cyclopropyl aldehydes is one of the most convenient methods,[5] however the stereochemical identification of the so-formed diastereoisomers is not conveniently achieved and often requires X-ray analysis of a derivative,[6] or correlations with known compounds.[7,8] Here we describe a simple and convenient method for the stereochemical identification of diastereomeric *cis*-1,2-bis(carbinol)cyclopropane derivatives. This method, applied to 1,4-diols having a *cis*-2,3-methano bridge, complements the method initially described by Dana *et al.*[9] for 1,2-diols and later extended by the groups of Rychnovsky[10] and Evans[11] for 1,3-diols.

cis-1,2-Bis(carbinol)cyclopropanes—*cis*-2,3-methano-1,4-diols—are common structural motifs in various cyclopropylated compounds, especially natural products.[1] The simplest member, monoprotected 1,2-bis(hydroxymethyl) cyclopropanes, are convenient chiral building blocks for the synthesis of cyclopropylated natural products.[12,13] After oxidation and nucleophilic addition, two diastereoisomeric cyclopropyl carbinols are obtained (Scheme 1);[14] each can be further processed to provide natural products containing a *cis* or *trans* cyclopropane nucleus.[12,13]

Both products can easily be separated by chromatography but their spectroscopic properties do not allow for their stereochemical characterization as *syn* or *anti* addition products. The coupling constant between the carbinol proton and the adjacent cyclopropyl proton is expected to be different in each diastereoisomer, since the corresponding dihedral angles should be different.[15] Clearly, the observed coupling constants are an average of various conformations at the temperature used for recording NMR spectra (Table 1). Molecular calculations corroborate these observations. Several minima of lower energy were observed for each diastereoisomer of **1a** in the potential energy maps obtained after optimization of each conformation generated by incrementation of the dihedral angles between the carbinol proton and the adjacent cyclopropyl proton, and between one of the hydroxymethylene protons and the adjacent cyclopropyl proton.[16]

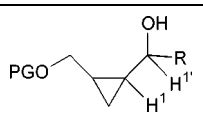


Scheme 1

The corresponding diols, **2a**–**f**, should possess a hydrogen bond between the two hydroxy groups, which may restrain the possible conformations. They were easily obtained after deprotection at the primary hydroxy group of each diastereoisomer (Scheme 2, where PG = $TxMe_2Si$). However, these diols exhibit the same trends as their progenitors **1a**–**f** (Table 1). Again, molecular calculations agree with these observations.

Converting each diastereoisomer to a cyclic derivative, particularly to a bicyclo[5-1-0] system, would ensure a locked conformation for both diastereoisomers and thus the coupling constant between the proton at the new hydroxyl center and the adjacent cyclopropyl proton would be significantly different in each diastereoisomeric derivative.[17] After several unsuccessful attempts,[18] we found that each diastereoisomer could be converted to a cyclic dimethylsilyl ether (Scheme 2). As

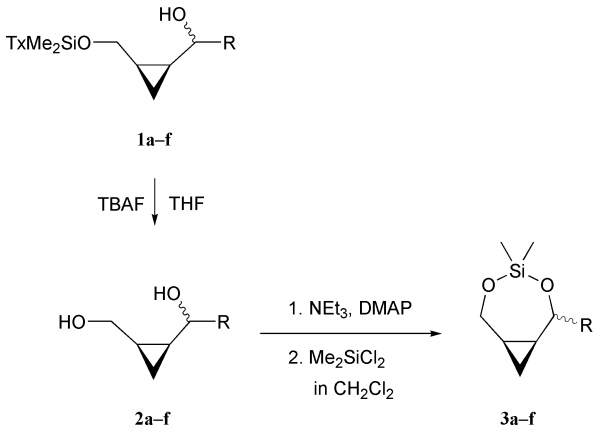
Table 1 Coupling constants $^3J_{H^1-H^{1'}}$ in various *cis*-1,2-bis(carbinol) cyclopropanes **1a**–**f** (PG = $TxMe_2Si$) and **2a**–**f** (PG = H)[a]



R		$^3J_{H^1-H^{1'}}$/Hz *anti*	*syn*
Me	**1a**	9.5	9.0
	2a	9.9	8.8
Bu^n	**1b**	9.7	8.6
	2b	9.8	7.8
$C{\equiv}CCH_2OMEM$[b]	**1c**	10.2	9.8
	2c	9.7	7.8
$C{\equiv}CCH_2OSiPh_2Bu^t$	**2d**	6.7	10.1
$CH{=}CH_2$	**1e**	9.6	8.4
	2e	10.0	8.6
cyclo-pentyl	**1f**	9.4	8.4
	2f	9.9	8.4

[a] Tx = 1,1,2-trimethylpropyl. [b] MEM = methoxyethoxymethyl.

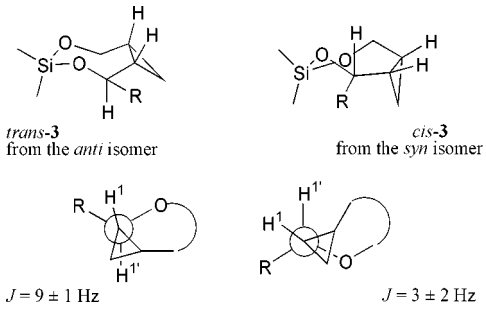
 DOI: 10.1039/b101408k



Scheme 2

expected, the above-mentioned coupling constant did indeed prove characteristic of each diastereoisomer, with a mean value of $J = 9 \pm 1$ Hz for the cyclic derivative of the *anti* diastereoisomer (less polar) and a mean value of $J = 3 \pm 2$ Hz for the compound derived from the *syn* diastereoisomer (more polar) (see Table 2 and Scheme 3). From the Karplus equation,[15] one can infer that the larger coupling constant corresponds to a dihedral angle close to 10 or 170°, and the smaller one to an angle of around 40 or 140°. These values show that the less polar diastereoisomer yields a cyclic derivative having a *trans* relationship between the cyclopropyl group and the adjacent substituent, and the more polar one a *cis* stereochemical arrangement. They are thus, respectively, the *anti* and the *syn* isomers.

A molecular calculation study supports these assignments. The silabicyclic systems obtained were analyzed using various computational tools.[16] The characteristic dihedral angle in structures **3a–e** was extracted and compared with that inferred from the NMR data (Table 2). In the cases examined, the *trans* isomers (*anti* diastereoisomers) always exhibited the expected pseudo-chair conformation for the 7-membered ring, with the substituent R being pseudo-equatorial (Scheme 3, top left). On the contrary, the conformations of the *cis* isomers (*syn* diastereoisomer) are more or less skewed and vary with the nature of the substituent. This relative flexibility probably results from the interactions between this substituent and both the cyclopropyl methylene group and the pseudoaxial methyl of the dimethylsilyl group (Scheme 3, top right). Therefore, the 2 protons H, $^1H^{1'}$ always have a quasi *trans* diaxial relationship (mean dihedral angle: $162 \pm 9°$) in the *trans* (*anti*) isomers, and thus exhibit a larger coupling constant than the *cis* (*syn*) isomers (Scheme 3, bottom).



Scheme 3

This derivatization and spectroscopic method allows for a rapid and convenient determination of the relative stereochemistry of *cis*-1,2-bis(carbinol)cyclopropanes. Once set up, this method was used as a predictive tool in the synthesis of cyclopropylated natural products.[13] Further work is in progress in order to extend this approach to other small ring carbinols and to variously substituted 1,4-diols.

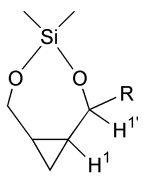
Experimental

General procedure for the formation of the silaketal **3** and selected physical data are given here. To a 0.3 M dichloromethane solution of diol **2** (*syn* or *anti*, 1 equiv.) were successively added at room temperature triethylamine (2.2 equiv.) and DMAP (0.1 equiv.). After cooling the resulting mixture to 0 °C, dichlorodimethylsilane (1.1 equiv.) was added dropwise. When TLC analysis indicated disappearance of the starting materials (0.5 to 1 h), the reaction mixture was concentrated under reduced pressure and then taken up in ether. The white precipitate formed was filtered off and the resulting solution was evaporated under reduced pressure. Chromatography of the residue (silica gel) provided the pure silaketal **3** (*cis* or *trans*) as an oil (yield 60–70%).

trans-**3a**: R_f 0.57 (SiO_2, light petroleum–ethyl acetate 95 : 5); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.09 (3H, s), 0.20 (3H, s), 0.41 (1H, ddd, J = 5.1, 5.4, 5.4), 0.86 (1H, ddd, J = 5.1, 8.4, 8.4), 1.1–25 (1H, m), 1.43 (3H, d, J = 6.1), 1.35–1.45 (1H, m), 3.44 (1H, dd, J = 11, 12.5), 3.64 (1H, dq, J = 6.1, 9.8), 4.27 (1H, dd, J = 5.9, 12.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −4.0 (q), −0.91 (q), 18.36 (t), 19.92 (d), 23.59 (q), 25.00 (d), 65.54 (t), 71.60 (d); MS (EI) *m/z* (%): 173 $[M + 1]^+$ (2), 157 (52), 149 (100), 133 (41), 114 (39), 103 (36), 75 (72), 73 (75), 55 (31); IR ($CHCl_3$): ν 2968, 2960, 2905, 1415, 1257, 1064, 814 cm^{-1}.

cis-**3a**: R_f 0.32 (SiO_2, light petroleum–ethyl acetate 95 : 5); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.08 (3H, s), 0.18 (3H, s), 0.55–0.65 (1H, m), 0.7–0.8 (1H, m), 0.9–1.0 (1H, m), 1.1–1.2 (1H, m), 1.30 (3H, d, J = 6.2), 3. 89 (1H, dd, J = 5.9, 12.4), 4.24 (1H, dd,

Table 2 Experimental coupling constants $^3J_{H^1-H^{1'}}$ and corresponding calculated (PM3) dihedral angles in the silaketals derived from diastereoisomeric addition products



3a–e

		anti		*syn*	
R		$^3J_{H^1-H^{1'}}$/Hz	Dihedral angle/°	$^3J_{H^1-H^{1'}}$/Hz	Dihedral angle/°
–Me	**3a**	9.8	−163	2.1	33
–Bu^n	**3b**	9.1	−162	2.0	20
–C≡CCH$_2$OPG	**3c,d**	8.1 ± 0.3	−153	3.5 ± 0.6	38
–CH=CH$_2$	**3e**	9.9	−170	2.3	−9

$J = 4.5$, 12.4); 4.52 (1H, dq, $J = 2.1$, 6.2 Hz), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −3.29 (q), −0.37 (q), 3.54 (t), 17.70 (q), 23.57 (d), 24.30 (d), 61.76 (t), 64.94 (d); MS (EI) *m/z* (%): 173 $[M + 1]^+$ (3), 151 (17), 149 (27), 133 (25), 98 (13), 83 (50), 75 (36), 73 (48), 58 (74), 57 (74), 55 (100); IR ($CHCl_3$): ν 2970, 2960, 2910, 1412, 1260, 1060, 820 cm^{-1}.

Acknowledgements

The authors thank the CNRS and P.P. the "Institut Universitaire de France" for financial support. A. B. thanks the French and Algerian governments for a doctoral fellowship.

Notes and references

1 (*a*) H. W. Liu and C. T. Walsh, in *The Chemistry of Cyclopropyl Group*, ed. S. Patai and Z. Rappoport, Wiley, Toronto, 1987, ch. 16, pp. 959–1025; (*b*) W. Gerwick, *Chem. Rev.*, 1993, **93**, 1807.
2 C. H. Stammer, *Tetrahedron*, 1990, **46**, 2231.
3 (*a*) C. J. Suckling, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 537; (*b*) W. B. Motherwell and D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, 1992.
4 (*a*) J. Salaün, in *The Chemistry of Cyclopropyl Group*, ed. S. Patai and Z. Rappoport, Wiley, Toronto, 1987, ch. 13, pp. 809–878; (*b*) H. U. Reissig, in *The Chemistry of Cyclopropyl Group*, ed. S. Patai and Z. Rappoport, Wiley, Toronto, 1987, ch. 8, pp. 375–443; (*c*) J. Salaün, *Chem. Rev.*, 1989, **89**, 1247.
5 A. Mengel and O. Reiser, *Chem. Rev.*, 1999, **99**, 1191; see also ref. 6 and 7.
6 (*a*) S. Ono, S. Shuto and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 221; (*b*) C. Böhm, M. Schinnerl, C. Bubert, M. Zabel, T. Laban, E. Parlsini and O. Reiser, *Eur. J. Org. Chem.*, 2000, 2955.
7 (*a*) J. Cossy, N. Blanchard and C. Meyer, *Synthesis*, 1999, 1063; (*b*) M. Lautens and P. H. M. Delanghe, *J. Org. Chem.*, 1995, **60**, 2474; (*c*) B. Lei and A. G. Fallis, *J. Org. Chem.*, 1993, **58**, 2186; (*d*) H. Nemoto, X.-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 3095.
8 Lanthanide shift reagents have also been used, see: G. Descotes, A. Menet and F. Collonges, *Tetrahedron*, 1973, **29**, 2931.
9 (*a*) J. Chuche, G. Dana and M. R. Monot, *Bull. Soc. Chim. Fr.*, 1967, 3300; (*b*) G. Dana and X. Danespajouh, *Bull. Soc. Chim. Fr., Ser. II*, 1980, 395.
10 S. Rychnovsky, B. Rogers and G. Yang, *J. Org. Chem.*, 1993, **58**, 3511.
11 D. A. Evans, D. L. Rieger and J. R. Gage, *Tetrahedron Lett.*, 1990, **31**, 7099.
12 D. Grandjean, P. Pale and J. Chuche, *Tetrahedron*, 1991, **47**, 1215.
13 (*a*) C. Barloy-Da Silva, A. Benkouider and P. Pale, *Tetrahedron Lett.*, 2000, **41**, 3077; (*b*) A. Benkouider and P. Pale, *J. Chem. Res. (S)*, 1999, 104; (*c*) C. Barloy-Da Silva and P. Pale, *Tetrahedron: Asymmetry*, 1998, **9**, 3951.
14 Medium to excellent stereoselectivity was achieved, depending on the nature of the organometallic and the conditions used. These results will be reported at a later date.
15 M. Karplus, *J. Phys. Chem.*, 1959, **30**, 11.
16 Molecular mechanics and quantum (AM1, PM3) calculations were performed using Hyperchem and CAChe.
17 ^{13}C-NMR values were also anticipated to be of help in distinguishing diastereoisomers, as for 5- or 6-membered acetonides (see ref. 9–11) but they proved to be useless in our cases.
18 The formation of acetonide, ketal from benzaldehyde, silaketal from other dichlorosilanes under various conditions was unsuccessful or gave unreliable results, usually with one of the diastereoisomers reacting and not the other.