Tetrahedron Letters, Vol. 34, No. 19, pp. 3123-3126, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Highly Stereoselective 15-Ketoreduction of Halogenated Carbacyclin-precursors

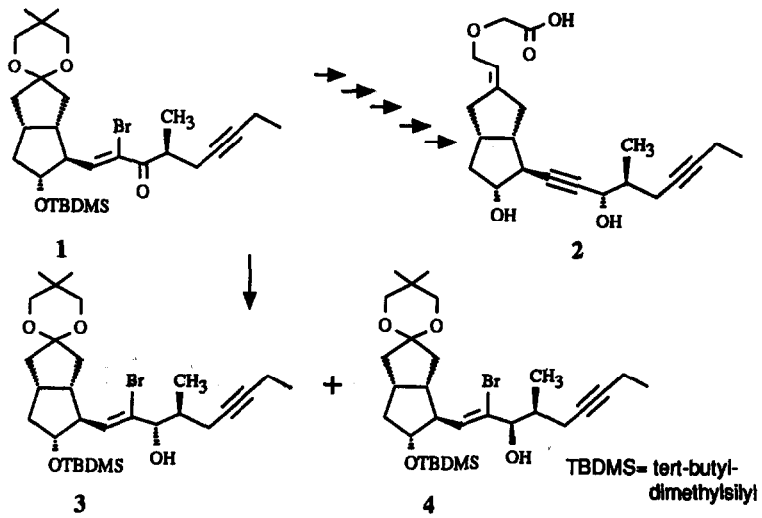
Michael Harre*, Klaus Nickisch and Jürgen Westermann

Chemical and Microbiological Development and Production
Schering AG, Berlin, D-1000, Berlin 65

Abstract: The stereoselectivity in the carbonyl-reduction of a series α-halovinyl ketones with various reducing agents was studied

Bromoketone **1** is a precursor to the chemically and metabolically stable carbacyclin-analogue Cicaprost (**2**) [1,2,3].

In the prostaglandin and prostacyclin field, much work has been devoted to generate the 15α-hydroxy-group in analogues of (2) stereoselectively from the corresponding 15-ketone.



Impressive results have been reported by using special protecting groups at C11 or certain chiral reducing agents [4, 5, 6, 7] on nonhalogenated vinylketones.

Less is known about the stereochemistry in the reduction of α-halovinyl ketones [8, 9, 10].
The stereochemical outcome of the reduction of bromoketone **1** is not easily predicted because of the remote stereocenters and the bromine at C14. To study the stereochemistry of the reduction of bromoketone **1**, a variety of reducing agents was tested. The results are shown in table 1.
L-Selectride® or $LiBEt_3H$ gave mainly the undesired anti-Cram product **4** (with respect to the C16 methyl group). Reduction under the conditions of Luche ($CeCl_3/NaBH_4$) [11] gave mainly the Cram product **3**.

Excellent results were obtained with 1.5 equivalents of diisobutyl-aluminium-2,6-di-tert-butyl-4-methyl-phenoxide in toluene at -78°C (Yamamoto method) [12], which produced the desired 15α-epimer **3** almost exclusively.

This method is very sensitive to temperature (entries 9-11). Solvents other than toluene gave lower stereoselectivity .

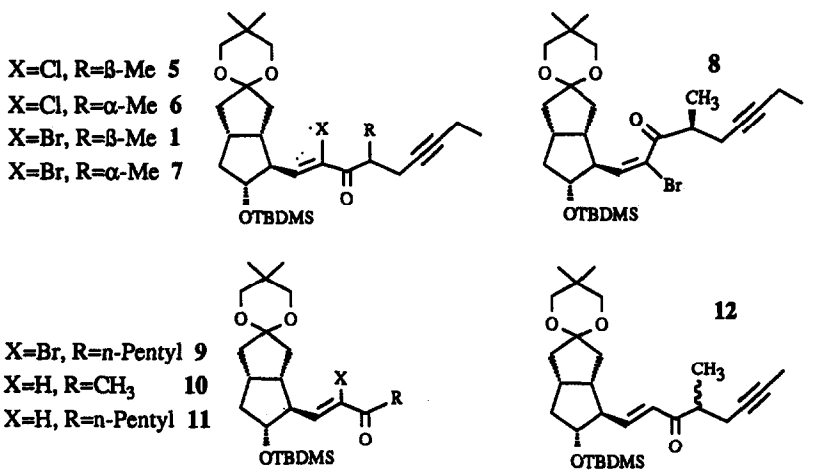
In the Dibah/Ionol case a free 11-hydroxy group [4,5,6,7] is not necessary for the stereoselectivity. Whether a free 11-hydroxy group would have the same directing effect could not be determined, because we were not able to deprotect bromoketone **1** to the 11-hydroxy compound without decomposition.

Table 1:

No.	Red.agent	Solvent	Temp.	Time	3 : 4
					15α 15ß
1	Dibah-T	Toluene	-78°C	1 h	60.8 : 39.2
2	R-Alpine-hydride®	THF	-78°C	45 min	23.3 : 76.7
3	S-Alpine-hydride®	THF	-78°C	45 min	11.5 : 88.5
4	$LiBEt_3H$	THF	-78°C	1 h	4.8 : 95.2
5	NBu_4BH_4	$MeCl_2$	0°C	4 h	ca. 3 : 7
6	L-Selectride®	THF	-78°C	1 h	3.1 : 96.9
7	$NaBH_4/CeCl_3$	MeOH	-70°C	1 h	86.4 : 13.6
8	$LiBH_4$	THF	-78°C	3 h	68.5 : 31.5
9	Dibah/Ionol	Toluene	-78°C	2 h	97.4 : 2.6
10	Dibah/Ionol	Toluene	-50°C	8 h	ca. 7 : 3
11	Dibah/Ionol	Toluene	-20°C	6 h	no reaction
12	Aluminium-isopropylate	i-PrOH	+80°C	6 h	88.0 : 12.0

ca. = TLC-estimates

To explore the stereoselectivity of the reduction further, the following series of ketones was reduced with L-Selectride®, according to the Luche method and the Yamamoto method [13].



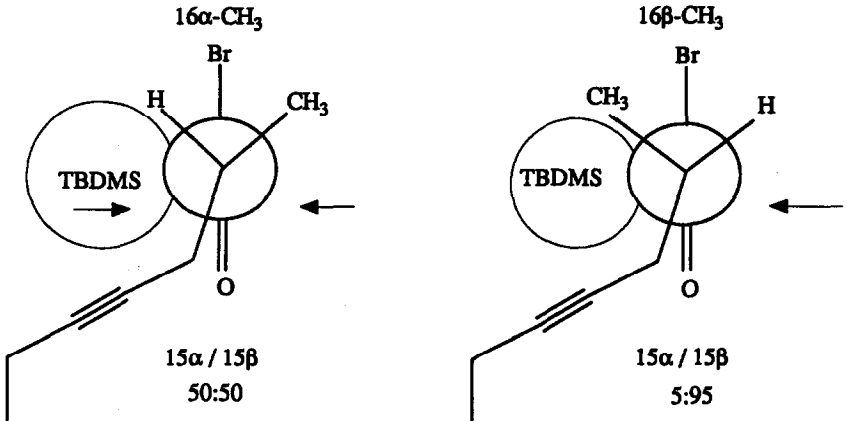
The results are shown in table 2.

No.	Ketone	Reagent	15α : 15ß [13]
1	Z-16ß-methyl-14-chloro-ketone **5**	$NaBH_4/CeCl_3$	86.6 : 13.2
		Dibah/Ionol	97.0 : 3.0
		L-Selectride®	7.1 : 92.9
2	Z-16α-methyl-14-chloro-ketone **6**	$NaBH_4/CeCl_3$	96.5 : 3.5
		Dibah/Ionol	96.4 : 3.6
		L-Selectride®	50 : 50
3	Z-16ß-methyl-14-bromo-ketone **1**	$NaBH_4/CeCl_3$	86.4 : 13.6
		Dibah/Ionol	97.4 : 2.6
		L-Selectride®	3.1 : 96.9
4	Z-16α-methyl-14-bromo-ketone **7**	$NaBH_4/CeCl_3$	95.9 : 4.1
		Dibah/Ionol	92.7 : 7.3
		L-Selectride®	49.2 : 50.8
5	E-16ß-methyl-14-bromo-ketone **8**	$NaBH_4/CeCl_3$	97.1 : 2.9
		Dibah/Ionol	4.1 : 95.9
		L-Selectride®	95 : 5
6	Z-demethylbromo-ketone **9**	Dibah/Ionol	88.0 : 12.0

The nonhalogenated ketones **10** to **12** were reduced with 20 Eq. of Dibah/Ionol and gave ca. 50:50 mixtures at approximately 10% conversion.

Discussion: Reduction with L-Selectride®

In the 16α-methyl series reduction with L-Selectride® gives a ca. 1:1 mixture of the 15α and 15ß-epimer.
We assume the following conformation for the ketone in which the interactions between the bromine and the substituents at C-16 are minimized:



In the 16α-methyl case one side of the carbonyl group is hindered by the C16-methyl group, the other is hindered by the remote 11-TBDMS group.
In the 16ß-methyl case the hydride attacks from the less hindered side giving the 15ß-epimer almost exclusively.

Reductions with Dibah/Ionol and $NaBH_4/CeCl_3$:

Reduction of the α-halo-enones with Dibah/Ionol or $NaBH_4/CeCl_3$ gives the 15α-hydroxy-epimers with high stereoselectivity, the Dibah/Ionol method being slightly more selective than the borohydride/ $CeCl_3$ method with the 16ß-epimers.

The configuration at C16 exhibits little influence on the outcome of the reduction, both 16α-methyl and 16ß-methyl-ketones giving mainly the 15α-epimer.
We believe that prior to reduction the metals complex to the carbonyl oxygen. We assume that there is also some interaction between bromine and the metals.
If this is true then one can anticipate that the bulky TBDMS group at C-11 and the large 2,6-tert-butyl-4-methyl-phenyl group are on opposite sides of the carbonyl group, the isobutyl group delivering the hydride preferentially from the side of the TBDMS group, giving rise to the 15α-epimer in the reduction of the Z-isomers **1**, **5**, **6**, **7** and **9** irrespective of the configuration at C-16.

The inverse result is obtained in the reduction of the E-isomer **8**, but in this case $NaBH_4/CeCl_3$ and Dibah/Ionol give opposite results.
The nonhalogenated, 11-TBDMS protected ketones **10**, **11** and **12** are reduced only sluggishly even with a large excess of Dibah/Ionol (20 eq.) and the stereoselectivity is low.

We thank S.Radau and S.Martschinke for analytical work and the spectroscopical department for recording spectral data.

REFERENCES:

1. R.C.Nickolson, M.H.Town, H.Vorbrüggen Med. Chem. Rev. **1985**, 5, 1.
2. W.Skuballa, H.Vorbrüggen Angew. Chem. Int. Ed. **1981**, 20, 1046.
3. M.Harre, J.Westermann, J.Trabandt Liebigs Annalen **1989**, 1081.
4. H.Yamamoto, S.Iguchi, H.Nakai, M.Hayashi J. Org.Chem. **1979**, Vol. 44, 1363.
   S.Harashima, O.Oda, S.Amemiya, K. Kojima Tetrahedron **1991**, Vol.47, 2773.
5. W.Bartmann, G.Beck, G.Jähne, U.Lerch Liebigs Annalen **1987**, 321.
6. E.J.Corey, S.Ohuchida, R.Hahl J.Am.Chem.Soc. **1984**, Vol. 106, 3875.
7. E.J.Corey, K.Becker, R.Varma J.Am.Chem.Soc. **1972**, Vol. 94, 8616.
8. E.J.Corey, C.P. Chen, G.A.Reichard Tetrahedron Lett. **1989**, Vol.30, 5547
   E.J.Corey, J.O.Link Tetrahedron Lett. **1989**, Vol.30, 6275
   G.A.Tolstikov, S.A.Ismailov, L.Y.Vel'der, M.S.Miftakhov Zh.Org.Khim. **1991**, Vol.27 , 90.
9. S.Wilson, M.Haque Tetrahedron Lett. **1984**, 25(30), 3131.
10. H.Sasai, M.Shibasaki Tetrahedron Lett. **1987**, Vol.28, 333.
11. J.L.Luche J.Am.Chem.Soc **1978**, Vol.100, 2226.
    J.L.Luche JCS Chem.Comm. **1978**, 601.
    A. Krief, D. Surleraux Synlett **1991**, 273.
12. H. Yamamoto, S.Iguchi, H.Nakai, M.Hayashi Bull.Chem.Soc. Jp. **1981**, Vol.54, 3033.
13. All ketones and alcohols gave satisfactory elemental analyses, spectral data agree with given structures. Selected data for **1**: oil, $[\alpha]_D$ +19.1° (c=1, $CHCl_3$), IR (KBr, cm^{-1}): 2950, 2860, 1740, 1685, 1615, 1280, 1120; ^1H NMR ($CDCl_3$, 300 MHz): δ 0 (6H, d, $SiMe_2$), 0.8 (9H, s, SitBu), 0.87 (3H, s, ketal CH_3), 1.03 (3H, s, ketal CH_3), 1.10 (3H, tr, j=7.5, 21 CH_3), 1.21 (3H, d, j=7.5, 16 CH_3), 1.5-2.55 (13H, m), 3.14 (1H, ddd, j=10, j=10, j=10, H_{12}), 3.4-3.6 (4H, m, ketal CH_2), 4.0 (1H, m, H_{11}), 6.95 (1H, d, j=10, H_{13}) Anal. calc. for $C_{29}H_{47}BrO_4Si$:C 61.36, H 8.34, Br 14.08, found C 61.46, H 8.04, Br 13.90; for **3**: oil, $[\alpha]_D$ +23.6° (c=1, $CHCl_3$), IR (KBr, cm^{-1}): 3450, 2960, 1470, 1460, 1255, 1120; ^1H NMR ($CDCl_3$, 300 MHz): δ 0 (6H, s, $SiMe_2$), 0.86 (9H, s, SitBu), 0.92 (3H, d, j=7, 16 CH_3), 0.92 (3H, s, ketal CH_3), 1.0 (3H, s, ketal CH_3), 1.13 (3H, tr, j=7, 21 CH_3), 1.5-2.5 (14H, m), 2.9 (1H, ddd, j=10, j=10, j=10, H_{12}), 3.5 (4H, m, ketal CH_2), 3.8-3.95 (2H, m, H_{11}+ H_{15}), 5.75 (1H, d, j=10, H_{13}) Anal.calc. for $C_{29}H_{49}BrO_4Si$: C 61.14 H 8.67, Br 14.02, found C 61.36, H 8.28, Br 13.20; for **4**: oil, $[\alpha]_D$ -27.6° (c=1, $CHCl_3$), IR (KBr, cm^{-1}): 3450, 2950, 2850, 1650, 1470, 1460, 1255, 1115; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04 (6H, s, $SiMe_2$), 0.86 (9H, s, SitBu), 0.9 (3H, s, ketal CH_3), 1.02 (3H, s, ketal CH_3), 1.04 (3H, d, j=7, 16 CH_3), 1.12 (3H, tr, j=7.5, 21 CH_3), 1.6-2.3 (13H, m), 2.42 (1H, m, H_{16}), 2.9 (1H, m, H_{12}), 3.5 (4H, m, ketal CH_2), 3.9 (1H, m, H_{11}), 4.1 (1H, m, H_{15}), 5.85 (1H, d, j=10, H_{13}), Anal. calc. for $C_{29}H_{49}BrO_4Si$: C 61.14, H 8.67, Br 14.02, found C 61.27, H 8.48, Br 13.82; for **5**: oil; $[\alpha]_D$ +11.1° (c=1, $CHCl_3$), Anal. calc. for $C_{29}H_{47}ClO_4Si$: C 66.57, H 9.05, Cl 6.78, found C 66.76, H 8.95, Cl 6.78; for **7**: oil, $[\alpha]_D$ -4.4° (c=1, $CHCl_3$), Anal. calc. for $C_{29}H_{47}BrO_4Si$: C 61.36, H 8.34, Br 14.08, found C 61.34, H 8.11, Br 13.85, for **9**: oil, $[\alpha]_D$ +4.5° (c=1, $CHCl_3$), Anal. calc. for $C_{27}H_{47}BrO_4Si$: C 59.65, H 8.71, Br 14.70, found C 59.94, H 8.40, Br 14.34.
    The configuration at C15 of the corresponding alcohols from **1** and **7** were confirmed by elaboration of the major epimer to the Cicaprost-16-epimers, the alcohols from **11** and **12** were assigned by comparison with known compounds. The C15 configuration of the alcohols derived from **5** to **6** and **8** to **10** was tentatively assigned by TLC behavior. (K.Kojima, S.Amemiya, K.Koyama, K.Sakai Chem.Pharm.Bull. **1985**, Vol. 33, 2688).

(Received in Germany 14 January 1993)