626 *J. Org. Chem.* **2001,** *66,* 626−628

A Novel Silylcopper Catalyst for the Reductive Bromination of Hajos Dione. Improved Preparation of a CD Synthon for the Synthesis of Vitamin D

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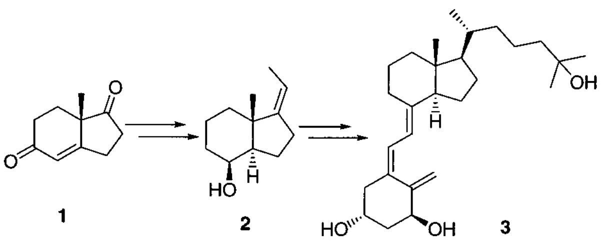
Received October 5, 2000

(3a*R*,4*S*,7a*S*)-(*Z*)-Ethylidene-7a-methyloctahydro-1*H*-4-indenol (**2**) is a well-known, versatile synthon in the field of vitamin D chemistry.[1] It has been converted into 1α,25-dihydroxyvitamin D_3 (**3**) (Scheme 1),[2] the hormonally active metabolite of vitamin D_3, as well as many other analogues including the 16-ene series,[3] some of which were evaluated as clinical candidates at Hoffmann-La Roche for a variety of indications. One of the intrinsic problems associated with the synthesis of **2** is the construction of the thermodynamically unfavorable *trans*-hydrindane system—a well-recognized problem in steroid synthesis. Many methods have been developed for the stereoselective generation of this ring system, and this topic was the subject of a recent review by Wicha and co-workers.[4]

For the synthesis of **2**, Hajos dione (**1**) is an attractive starting material since it is easily accessible in pure enantiomeric form by asymmetric intramolecular aldol condensation using proline as a catalyst,[5] and most of the reported methods are based on this commercially available material. The most efficient synthesis of **2** to date is via the reductive bromination of **1** to give bromodione **4**, which was then converted in five steps to **2** in 22% overall yield, as shown in Scheme 2.[6]

Scheme 1



Scheme 2

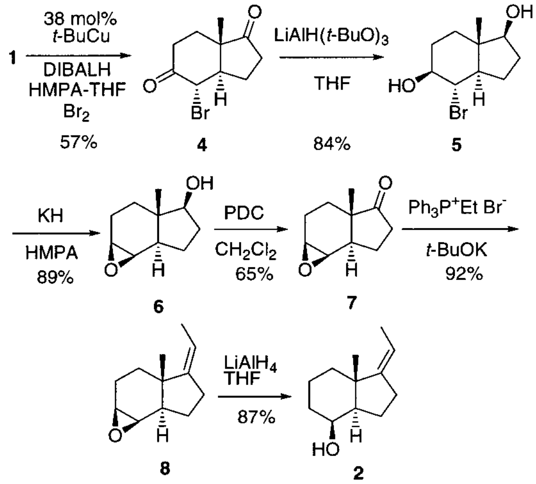


Table 1. Stereo- and Regioselectivities in the Reduction of Hajos Dione (1)

entry	RCu	mol %	stereo-selectivity **11**:**12**	regio-selectivity (**11**+**12**):**13**	isol yield of **4**, %
1	HCu	20	1:4	ca. 6:4	-
2[a]	MeCu	20	5:4	ca. 7:3	-
3[a]	n-BuCu	20	2:1	ca. 7:3	-
4[a]	*t*-BuCu	20	10:1	ca. 7:3	57[b]
5	Me_3SiCu	8	8:1	ca. 9:1	59[c]
6	Ph_3SiCu	8	5:1	>19:1	60[c]
7	$PhMe_2SiCu$	6.5	8:1	>19:1	70[c]

[a] Reference 9. [b] Reference 6. The product was isolated by chromatography. [c] Isolated by crystallization.

The reductive bromination step consists of a stereoselective 1,4-reduction of **1** with DIBALH in the presence of 38 mol % of *tert*-butylcopper(I) catalyst and HMPA, to establish the requisite *trans*-hydrindane system, and subsequent bromination of the resulting enolate to introduce the functionality necessary for subsequent transformations. Product **4** was isolated in 57% yield after purification by silica gel chromatography and then crystallization. However, the thermal instability of *tert*-butylcopper(I), due to its tendency to undergo β-elimination to give isobutylene and copper hydride, make this reaction difficult to reproduce on large scale. The copper hydride thus formed gives mostly the undesired *cis*-isomer (entry 1 in Table 1), which is thermodynamically more stable. Moreover, use of the relatively large quantity of cuprous iodide, the copper source, caused the formation of an undesirable amount of the corresponding iodo-dione via bromide−iodide exchange of **4**. The iodide, thus formed, undergoes unproductive reductive de-iodination upon treatment with the aluminum hydride reagent in the next step. Other copper sources, such as cuprous bromide or cyanide, were found to be not as effective as cuprous iodide in this reaction. In this paper, we describe a new catalyst for this crucial reductive bromination reaction, which eliminates the drawbacks associated with the *tert*-butylcopper catalyst, as well as improvements in the overall sequence leading to synthon **2**.

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[1] Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877 and references therein. For another review on vitamin D Chemistry, see: Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383.

[2] Baggiolini, E. G.; Jacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

[3] (a) Uskokovic, M. R.; Studzinski, G. P.; Gardner, J. P.; Reddy, S. G.; Campbell, M. J.; Koeffler, H. P. *Curr. Pharm. Des.* **1997**, *3*, 99. (b) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200. (c) Kensler, T. W.; Dolan, P. M.; Gange, S. J.; Lee, J. K.; Wang, Q.; Posner, G. H. *Carcinogenesis* **2000**, *21*, 1341.

[4] Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071.

[5] (a) Hajos, Z. G.; Parish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Hajos, Z. G.; Parish, D. R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 363.

[6] Daniewski, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, *53*, 5534. For a recent application of *t*-BuCu catalyst, see: Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710.

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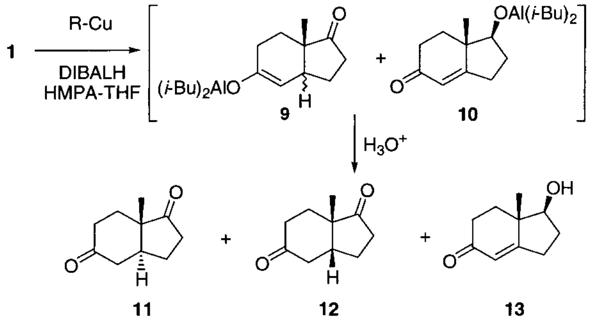
Scheme 3

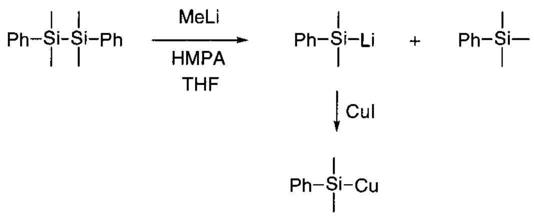


To study stereo- and regioselectivities of the copper-catalyzed reduction of **1**, the reaction mixture was quenched with dilute hydrochloric acid (Scheme 3), and the stereoselectivity, **11**:**12**, was determined by NMR analysis. The regioselectivity, (**11**+**12**):**13**, was estimated by TLC analysis of the reaction mixture, compared to known standards of the mixture. It should be noted that either the 1,4-reduction of the unsaturated ketone to give enolate **9** or the 1,2-reduction of the saturated carbonyl group to give alkoxide **10** occurs in this reaction, not both—one of the very interesting characteristics of this copper-catalyzed reduction.[7]

Silylcopper catalysts were attractive to us, since they are as bulky as the *tert*-butylcopper catalyst—the key to achieve high stereoselectivity. Moreover, a silylcopper catalyst would be more stable than the *tert*-butylcopper catalyst because β-elimination is unfavorable due to the high energy of the carbon−silicon double bond. Three silylcopper catalysts (Me_3SiCu, Ph_3SiCu, and $PhMe_2SiCu$; entries 5−7, Table 1), that are easily prepared from commercially available disilanes,[8] were examined. These catalysts were found to be more effective in the 1,4-reduction of Hajos dione (**1**) and, as expected, more stable than the *tert*-butylcopper catalyst previously used (entry 4). As a consequence, the catalyst loading could be reduced to 6−8% while maintaining the reproducibility of the reaction. Although the stereoselectivities (entries 5−7) were somewhat lower than that achieved using the *tert*-butylcopper catalyst (entry 4), the silylcopper catalyst exhibited higher regioselectivities. With arylsilylcoppers (entries 6 and 7), only trace amounts of the 1,2-reduction product **13** were detected. Of these silylcopper catalysts, dimethylphenylsilylcopper(I) was found to be the best in terms of product yield to give, after bromination of the intermediate enolate and crystallization of the reaction product (no chromatographic purification required), the desired bromo-dione **4** in 70% isolated yield.

The dimethylphenylsilylcopper(I) catalyst was prepared in situ from 1,2-diphenyltetramethyldisilane, methyllithium, and cuprous iodide, as shown in Scheme 4. Thus, 1,2-diphenyltetramethyldisilane in a mixture of THF and HMPA was treated with a slight deficiency of methyllithium in order to ensure complete consumption of the methyllithium to give dimethylphenylsilyllithium,[10] along with inert phenyltrimethylsilane. The silyllithium thus formed was treated with a sub-stoichiometric amount of cuprous iodide at −35 °C to give the desired dimethylphenylsilylcopper(I) catalyst as a fine black suspension in a pale yellow supernatant. Excess cuprous iodide, if used, will be converted to copper hydride, which generates predominantly the undesired cis isomer (entry1, Table 1). To the freshly prepared catalyst was added a freshly prepared solution of DIBALH[11] in a mixture of THF and HMPA below −68 °C. Then, a solution of Hajos dione (**1**) in THF and HMPA was added to the mixture maintained at that temperature. Addition of **1** at higher temperatures reduced the stereoselectivity. The resulting aluminum enolate **9** was then treated with bromine and, after acidic workup, bromo-dione **4** was isolated in 70% yield as a crystalline solid. This procedure was carried out on 200-g scale uneventfully. Interestingly, with the new silylcopper catalyst, although cuprous iodide is still employed as the copper source, the iodo-dione via bromide−iodide exchange of **4** has not been observed in the reaction mixture.

Scheme 4



Having established the improved method to the key intermediate, bromo-dione **4**, the remaining sequence leading to **2** was also improved. The reduction of **4** with a 1 M solution of lithium tri-*tert*-butoxyaluminohydride in THF was carried out at −20 °C since the reaction at 0 °C was found to cause some reductive elimination of the bromohydrin group. Crystalline **5** was thus obtained in 85% yield. The next two steps were then carried out as a one-pot procedure, using potassium *tert*-butoxide as the base for the epoxidation and sodium hypochlorite in the presence of a catalytic amount of ruthenium chloride for the oxidation to give epoxy-ketone **7** in 93% yield. This new procedure is a considerable improvement over the original two-step procedure that utilized potassium hydride and chromium oxide, which gave the product in only 57% yield (Scheme 2). Wittig olefination of **7** and subsequent reduction of **8** with lithium aluminum hydride were carried out essentially as described previously but with modified workup which allowed isolation of **2** in 85% yield over these two steps without chromatography (Scheme 5).

In conclusion, we have shown that the new silylcopper catalyst, dimethylphenylsilylcopper(I), is more efficient in the reductive bromination of Hajos dione (**1**) than the *tert*-butylcopper(I) previously described. In addition, the new procedure is reproducible, easier to scale-up, and higher yielding. With additional improvements described in this paper, especially in the transformation of diol **5** into epoxy-ketone **7**, the overall yield of synthon **2** from Hajos dione (**1**) was increased to 47% from the 22% previously described.[6]

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(7) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537.

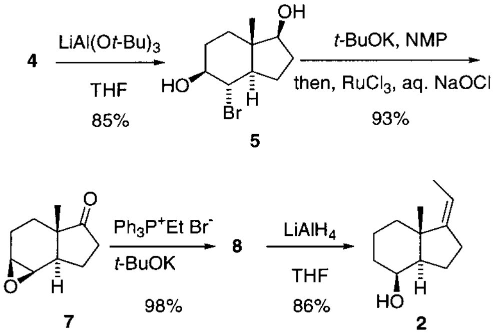
(8) These silylcopper catalysts were prepared by treating Me_6Si_2, $Me_3SiSiPh_3$, or $(PhMe_2Si)_2$ with MeLi,[10] followed by CuI (see Scheme 4).

(9) Daniewski, A. R.; Kiegiel, J. *Synth. Commun.* **1988**, *18*, 115.

(10) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063. Also see: Hevesi, L.; Dehon, M. *Tetrahedron Lett.* **1994**, *35*, 8031.

(11) The solution was prepared from commercially available, neat DIBALH immediately prior to use. Commercially available solutions in THF or dichloromethane were not effective.

Scheme 5



Experimental Section

THF was distilled from sodium/benzophenone, and HMPA from CaH_2 at 80 °C/0.5 mmHg. Commercial DIBALH (neat) and CuI (off-white to beige) were used as received (Aldrich). Hajos dione (**1**) was prepared following the literature method.[5b] All reactions were conducted under nitrogen. All compounds obtained here have been characterized previously.[6]

(3a*R*,4*S*,7a*S*)-4-Bromo-7a-methyloctahydro-1*H*-indene-1,5-dione (4). A solution of MeLi (1.4 M in diethyl ether, 31.0 mL, 43.4 mmol) was added to a solution of 1,2-diphenyltetramethyldisilane (13.7 g, 50.6 mmol) in THF (320 mL) and HMPA (120 mL) at −5 °C. The mixture was stirred at 0 °C for 30 min and, after cooling to −60 °C, cuprous iodide (7.6 g, 40.0 mmol) was added in one portion. The solid that remained on the wall of the reaction flask was rinsed into the reaction mixture with THF. The reaction mixture was warmed to −35 °C over 25 min and then stirred for 30 min. During that time a black solid precipitated, and the supernatant became almost colorless/pale yellow. A solution of DIBALH, freshly prepared by adding DIBALH (neat, 132 mL 732 mmol) to a mixture of THF (100 mL) and HMPA (176 mL) at −10 °C, was then added to the reaction mixture at <−68 °C via cannula. Then, a solution of **1** (100 g, 609 mmol) in HMPA (100 mL) and THF (100 mL) was added to the mixture at <−68 °C over 1 h. The mixture was then stirred for 5 min, and bromine (60 mL, 1.16 mol) was added over 10 min. An exotherm ensued that raised the temperature to −20 °C. After stirring at −20 °C for 5 min, the reaction mixture was poured into ice−water (1.3 kg) containing sulfuric acid (80 mL). After stirring for 20 min, the mixture was extracted with EtOAc (2 × 1.5 L). The combined extracts were washed with 5% sulfuric acid (2 × 500 mL) and then with saturated aqueous $NaHCO_3$ solution (150 mL). The resulting emulsion was filtered through a Celite pad, and the organic layer was separated, dried, and concentrated. The residue was dried under high vacuum and then triturated with hexane (250 mL). The supernatant was removed by decantation, and the residue was treated similarly with 50 mL of hexane. The remaining solid was dried under reduced pressure and then triturated with diethyl ether (250 mL). After being cooled in a freezer (−20 °C) for 5 min, the white crystals were collected by filtration, washed with cold diethyl ether, and dried to give 106 g (70.9%) of **4**.[6]

(1*S*,3a*R*,4*S*,5*S*,7a*S*)-4-Bromo-7a-methyloctahydro-1*H*-indene-1,5-diol (5). A solution of LiAl(O*t*-Bu)$_3$ (1 M in THF, 420 mL) was added over 40 min to a suspension of **4** (49.8 g, 203 mmol) in THF (130 mL) at −50 °C. The mixture was warmed to −20 °C and stirred for 30 min. After cooling to −30 °C, the reaction mixture was quenched by the addition of 20% H_2SO_4 (600 mL). The bulk of the aqueous layer was then separated, and the wet organic layer was concentrated under reduced pressure to give a thick suspension. The solids were collected by filtration, washed with cold water (2 × 50 mL) and diethyl ether (50 mL), and dried to give 43.1 g (85.2%) of **5**.[6]

(3a*R*,4*R*,5*S*,7a*S*)-4,5-Epoxy-7a-methyloctahydro-1*H*-inden-1-one (7). A solution of *t*-BuOK (1.66 M in THF, 95 mL, 157 mmol) was added to a solution of **5** (28.1 g, 113 mmol) in NMP (170 mL) at 5 °C, and the mixture was stirred at room temperature for 50 min. After the mixture was cooled to 5 °C, 10% aqueous $KHCO_3$ solution (275 mL) and $RuCl_3$ hydrate (40.9% Ru, 1.77 g, 7.2 mmol) were added. Then, with vigorous stirring, an aqueous solution of NaOCl (1.04 M, 300 mL) was added to the mixture at 15−25 °C over 2 h. The reaction was quenched with methanol (30 mL) and, after stirring for 5 min, the mixture was diluted with water (300 mL) and extracted with 1:2 hexane:diethyl ether (6 × 300 mL). The combined extracts were concentrated, and the residue was dissolved in 1:1 hexane: diethyl ether (250 mL). The solution was then washed with saturated NaCl solution (2 × 50 mL), dried, and concentrated to give 17.4 g (93.0%) of **7** as a colorless oil.[6]

(3a*R*,4*R*,5*S*,7a*S*)-(*Z*)-4,5-Epoxy-7a-methyl-1-ethylidene-octahydro-1*H*-indene (8). A solution of *t*-BuOK (1 M in THF, 324 mL) was added to a suspension of (ethyl)triphenylphosphonium bromide (122 g, 329 mmol) in THF (500 mL) at −15 °C. The mixture was warmed to 7 °C over 40 min and then cooled to 0 °C, and a solution of **7** (35.9 g, 216 mmol) in THF (250 mL) was added. The mixture was stirred at room temperature for 23 h, and then the reaction was quenched by the addition of acetaldehyde (3.25 mL). The mixture was concentrated to a volume of ca. 600 mL, and water (500 mL) was added. The mixture was then extracted with hexane (500 mL). The aqueous layer was diluted with methanol (300 mL) and again extracted with hexane (2 × 250 mL). The combined extracts were concentrated to a volume of ca. 200 mL, diluted with hexane (200 mL), and washed with 2:1 methanol:water (2 × 200 mL, each containing 10 mL of 30% hydrogen peroxide). The combined washes were back-extracted with hexane (3 × 100 mL). The combined extracts were dried and concentrated to give 37.7 g (97.8%) of **8** (containing a small amount of Ph_3PO).[6]

(3a*R*,4*S*,7a*S*)-(*Z*)-1-Ethylidene-7a-methyloctahydro-1*H*-4-indenol (2). A solution of $LiAlH_4$ (1 M in THF, 90 mL) was added to a solution of **8** (37.7 g, 211 mmol) in THF (200 mL) at 5 °C. The mixture was stirred at room temperature for 30 min and then cooled to 5 °C, and 5% hydrochloric acid (600 mL) was added cautiously. The mixture was extracted with hexane (2 × 250 mL). The combined extracts were washed with saturated aqueous $KHCO_3$ solution (300 mL), dried, and concentrated to give 37.4 g of crude **2**. This material was dissolved in hexane (150 mL) and filtered though silica gel (TLC grade, 50 g) with the aid of 10:1 hexane:ethyl acetate (500 mL). The filtrate was concentrated to give 32.8 g (86.2%) of **2** as a colorless oil.[6]

Acknowledgment. We are thankful to Drs. M. Okabe, M. Kabat, S. Wolff, and C. Exon for support, scientific discussion, and help in preparation of the manuscript.

JO0014414