JOC Article

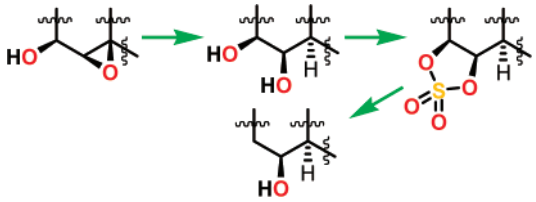
Expedited Approach to the Vitamin D *trans*-Hydrindane Building Block from the Hajos Dione. Comparative Study on Various Methods for the Selective Deoxygenation of One of the Hydroxy Groups in a Diol

Paweł Chochrek and Jerzy Wicha*

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw 48, Poland

jwicha@icho.edu.pl

Received April 3, 2007



1α,25-Dihydroxyvitamin D_3 (calcitriol, **1**) is a bioregulator important for the treatment of various human metabolic diseases and biomedical research. Herein, we report an efficient diastereoselective approach to the key *trans*-hydrindane building block for calcitriol synthesis (**2a**) starting from the readily accessible optically active tetrahydroindenedione derivative (Hajos dione, **3**). It was found that epoxide ring opening in a related hydroxy epoxide (**7**) with sodium cyanoborohydride−$BF_3 \times Et_2O$ occurs by hydride anion addition at the ring juncture position to produce a vicinal diol with the *trans*-hydrindane ring system (**6a**). Four methods for selective deoxygenation of the sterically less shielded hydroxy group in diol **6a** were examined with an approach based on a cyclic sulfate of the diol as the most efficient and operationally convenient method.

Introduction

Synthesis of 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**, Figure 1) and other derivatives of vitamin D_3 have received a great deal of attention[1] due to their application for the treatment of various human metabolic diseases and their importance in biomedical research.[2] The Hajos dione[3] **3**, produced in L-proline-catalyzed annulation of 2-methylcyclopenta-1,3-dione with methyl vinyl ketone, presents a classic precursor to the calcitriol CD ring building block[4] **2a**. However, methods currently available for saturation of the carbon−carbon double bond in **3** or its easily accessible derivatives (e.g., **4**) and for transposition of the oxygen substituent from C-5 to C-4 suffer from serious drawbacks (i.e., catalytic hydrogenation of **3** or **4** affords predominantly *cis*-hydrindane derivatives).

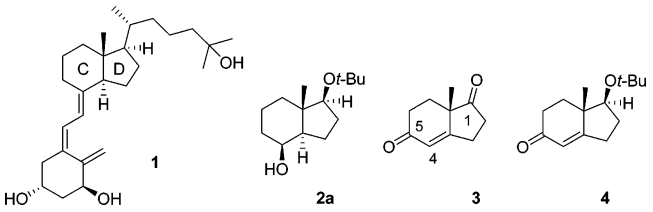


FIGURE 1.

Reduction of the carbonyl group in **4** with the Luche reagent[5] forms β-alcohol **5** selectively (Scheme 1). Several methods have

* Corresponding author. Tel.: 48-22-632-8117; fax: 48-22-632-6681.

(1) (a) Rodriguez, R.; Ollivier, C.; Santelli, M. *Synlett* **2006**, 312−314. (b) Pandey, G.; Raikar, S. B. *Tetrahedron Lett.* **2006**, *47*, 2029−2032. (c) Gomez-Reino, C.; Vitale, C.; Maestro, M.; Mourino, A. *Org. Lett.* **2005**, *7*, 5885−5887. (d) Fernandez, C.; Diouf, O.; Moman, E.; Gomez, G.; Fall, Y. *Synthesis* **2005**, 1701−1705. (e) For a review, see: Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877−1952.

(2) (a) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocrinol. Rev.* **1995**, *16*, 200−257. (b) Beckman, M. J.; DeLuca, H. F. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Oxford, A. W., Eds.; Elsevier: Amsterdam, 1998; Vol. 35, pp 1−56. (c) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889−3895.

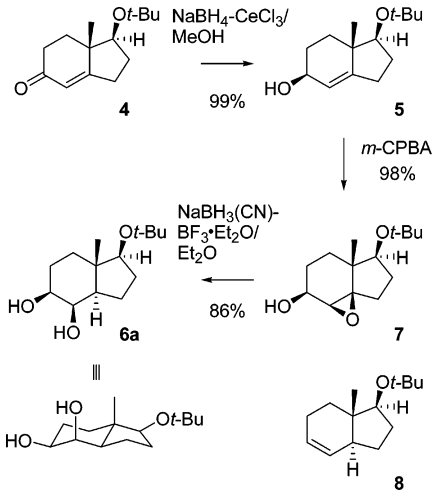
(3) (a) Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623; *Chem. Abstr.* **1971**, *75*, 129414r. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239−3243. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497.

(4) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskoković, M. R. *J. Org. Chem.* **1986**, *51*, 3098−3108.

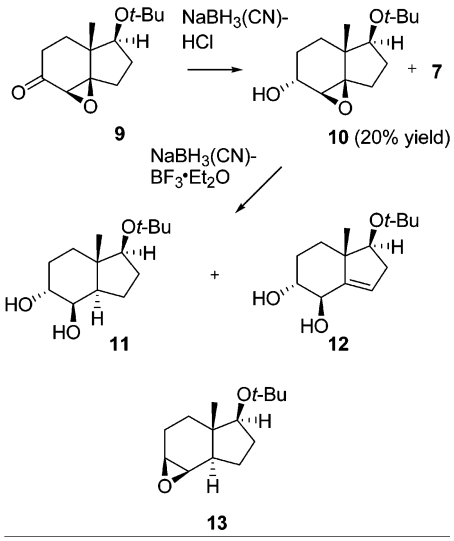
(5) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *Chem. Commun.* **1978**, 601−602.

10.1021/jo070685m CCC: $37.00
Published on Web 06/19/2007

SCHEME 1



SCHEME 2



been developed[6] for hydrogen atom delivery from the α-side of allylic alcohols related to **5** via chirality transfer. However, these methods lead to olefins, such as **8**, which have no regiocontrolling factors for further functionalization.[7,8] Direct conjugate reduction of ketones **3** with DIBAL-cuprous iodide provides a short-step approach to functionalized *trans*-hydrindane derivatives;[9] but the fragile nature of the intermediate copper hydride species may obstruct large-scale preparations. More circuitous approaches to *trans*-hydrindane derivatives, such as **2a**, starting from **3** have also been developed.[10]

We first thought that epoxide **7**, prepared from allylic alcohol **5**, could serve as a convenient intermediate en route from **4** to **2a**. A method using sodium cyanoborohydride in the presence of a Lewis acid for reductive opening of an epoxide ring at the more substituted carbon atom was reported by Hutchins et al.[11] Preliminary experiments indicated that epoxide **7** indeed could be reduced to diol **6a** in high yield.[12] With *trans*-hydrindane derivative **6a** in hand, our task became focused upon selective deoxygenation of its less shielded hydroxyl group (at C-5). In this paper, we report a method for preparing vicinal diols related to *trans*-hydrindane via opening of the respective hydroxy epoxides and scrutiny of selected methods for regioselective deoxygenation of one hydroxyl group in diols.

Results and Discussion

Reduction of the carbonyl group in **4** with the Luche reagent[5] afforded allylic alcohol **5** (Scheme 1) in 99% yield. This product was treated with *m*-CPBA in DCM to give epoxide **7** quantitatively. Reduction of **7** with sodium cyanoborohydride−BF_3·Et_2O in THF according to the Hutchins protocol[11] afforded *cis*-diol **6a** in 77% yield. Use of Et_2O as the solvent led to an increased product yield to 86%.[13] It should be noted that hydride anion addition occurred at the sterically hindered position.[14]

Several examples of the Hutchins method application for epoxide ring opening in complex hydroxy epoxides were reported.[15] However, the effect of the neighboring hydroxyl group remains unclear. Opening of diastereomeric hydroxy epoxide **10** (Scheme 2) would be of interest since the projected *trans*-diol **11**, if available, could be converted into **2** via C-5 monotosylate and β-epoxide **13**.[7] It is known that 4β,5-epoxy-5β-cholestan-3-one with an analogous keto-epoxide moiety on reduction with sodium cyanoborohydride in acidic medium affords exclusively the corresponding 3α-hydroxy derivative.[16]

Hydroxy-epoxide **7** was then smoothly oxidized[17] to **9** (Scheme 2). Reduction of **9** with sodium cyanoborohydride afforded 5β-alcohol **7** as the major product with only a small amount of expected **10** (ca. 20% yield). Nevertheless, **10** was subjected to the action of sodium cyanoborohydride−BF_3·Et_2O in ether. A mixture of two products identified as **11** and **12** was obtained. At this stage, attempts to prepare **2** from **4** via *trans*-diol **11** were abandoned.

The Barton−McCombie free radical method[18] was chosen in the first approach to selectively deoxygenate one of hydroxyl groups in diol **6a**. Accordingly, acetylation of **6a** gave diacetate **6b** (Scheme 3) that was subjected to kinetically controlled hydrolysis with potassium carbonate in aqueous methanol. After

(6) (a) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *25*, 149−152. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326−1327. (c) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429−6431. (d) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841−4844. (e) Chochrek, P.; Wicha, J. *Eur. J. Org. Chem.* **2007**, 2534−2542.

(7) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem Soc., Perkin Trans. 1* **1977**, 2608−2612.

(8) Marczak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218−2223.

(9) (a) Daniewski, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, *53*, 5534−5535. (b) Daniewski, A. R.; Liu, W. *J. Org. Chem.* **2001**, *66*, 626−628.

(10) Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071−12150.

(11) Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214−5215.

(12) A preliminary communication has been published: Chochrek, P.; Wicha, J. *Org. Lett.* **2006**, *8*, 2551−2553.

(13) In THF, partial gelling of the solvent occurred, which complicated the isolation procedure, especially on larger scale runs.

(14) (a) Cai, F.; Zhou, W. S. *Chin. J. Chem.* **2004**, *22*, 1019−1021. (b) Galagovsky, L. R.; Gros, E. G.; Ramirez, J. A. *Phytochemistry* **2001**, *58*, 973−980.

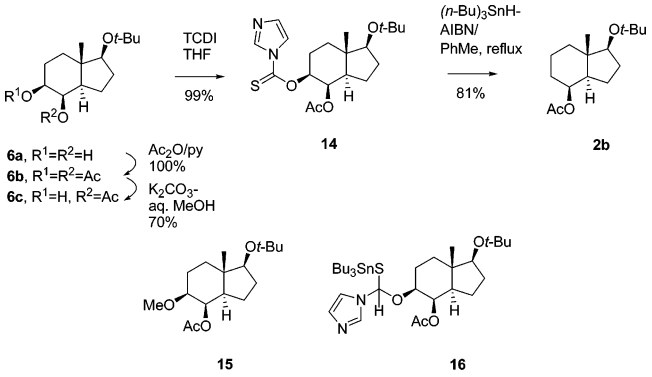
(15) (a) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004−4006. (b) Chappell, M. D.; Stachel, S. J.; Lee, C. B.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 1633−1636. (c) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399−2401. (d) Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784−13792.

(16) Boutigue, M. H.; Jacquesy, R.; Petit, Y. *Bull. Soc. Chim. Fr.* **1973**, 3062−3065.

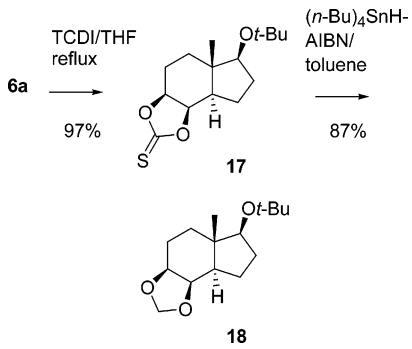
(17) Trost, B. M.; Bogdanowicz, M. J.; Frazee, W. J.; Salzmann, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 5512−5525.

(18) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

SCHEME 3



SCHEME 4

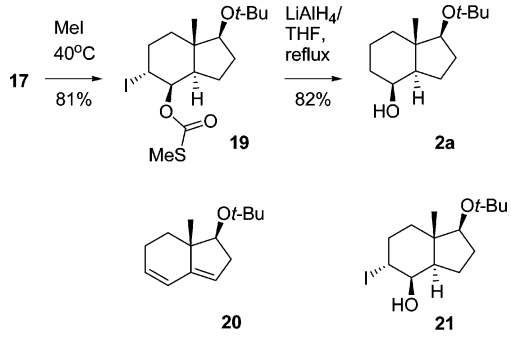


chromatography, monoalcohol **6c** was obtained in 70% overall yield along with diol **6a** (16%), unchanged diacetate **6b** (7%), and 5-*O*-acetyl derivative **6d** (not shown, 7%). Treatment of alcohol **6c** with thionocarbonyl-1,1′-diimidazole (TCDI) in THF at a reflux temperature afforded **14** that was subsequently subjected to reaction with tributyltinhydride in the presence of 2,2′-azobisisobutyronitrile (AIBN). The best results were obtained when a solution of **14** and AIBN (0.17 mol equiv) was added slowly with a syringe pump to a solution of tributyltinhydride in toluene (ca. 0.06 M, 5.1 mol equiv) at the reflux temperature, following Giese's instructions for free radical reductions.[19] The product[20] **2b** was isolated in 81% yield after chromatography.

At higher concentrations of tributyltinhydride, substantial amounts of the methoxy derivative **15** were formed along with an unstable tin containing derivative to which structure **16** was assigned (by ^{1}H NMR) as well as the alcohol **6c**. Fragmentation of **16** provides a likely mechanism for the reversion of **14** to the starting alcohol **6c**. When thionocarbamate **14** in toluene containing AIBN was added to neat Bu_3SnH at 120 °C, the methoxy derivative **15** was obtained in 78% yield. Reduction of **14** in dilute solutions but at a lower temperature (80 °C) also gave considerable amounts of **15** and **16**. These results corroborate some earlier reported observations on tributyltinhydride reduction of xanthate esters.[21]

Diol **6a** on treatment with TCDI in THF at reflux temperature gave cyclic thionocarbonate **17** in 97% yield (Scheme 4). This derivative remained unchanged when treated with tributyltinhydride and AIBN in a diluted solution under conditions applied to the reduction of **14**. When the reaction was carried out at high concentrations of tributyltinhydride (1.7 M) and in the presence of AIBN, desulfurized product **18** was obtained in 87% yield.[22]

SCHEME 5



Although the overall yield of **2a** from **4** compared rather well with those attainable by earlier reported methods, other approaches feasible for the selective removal of the C-5 hydroxyl group in diol **6a** were examined.

Treatment of **17** with methyl iodide[23,24] at 40 °C provided a crystalline and stable iodohydrine derivative **19** (Scheme 5, 81% yield after chromatography). The structure of **19** was confirmed by narrow multiplets corresponding to equatorial protons at C-4 (δ 5.33 ppm) and C-5 (δ 4.63 ppm). A ^{1}H NMR spectrum of the crude reaction product showed traces of contamination, most likely the regio-isomeric iodohydrine derivative.

Reduction of **19** with $LiAlH_4$ in THF at reflux gave alcohol **2a** in 80−85% yield along with some diene[25] **20** that was easily removed by chromatography or by crystallization. Monitoring of the reaction by TLC indicated that some intermediates were involved. Indeed, reduction of **19** at a room temperature with $LiAlH_4$ (1 mol equiv) afforded a mixture of products from which epoxide **13** (27%), iodohydrin **21** (53%), and diene **20** (18%) were isolated by chromatography.

The methyl iodide-induced opening of the thionocarbonate ring in **17** is likely to reflect the polarizability of the thionocarbonyl group. It appeared to be of interest to examine the possibility of thionocarbonate ring opening with a dipolar reagent, X^+Y^-, which would be followed by ring reclosure to give a more thermodynamically stable thiolcarbonate **22** (Scheme 6). Glyceryl thionocarbonate when treated with potassium iodide in acetonitrile at 60 °C underwent rearrangement into the corresponding thiolcarbonate.[24,26] More recently, it was reported that cyclic thionocarbonates of activated diols, such as di-(isopropyl)tartrate, rearrange to corresponding thiolcarbonates when heated in THF in the presence of a catalytic amount of

(19) Giese, B.; Groninger, K. S. *Org. Synth.* **1990**, *69*, 66−69.

(20) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskoković, M. R. *Tetrahedron* **1984**, *40*, 2283−2296.

(21) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059−4065.

(22) (a) Williams, D. R.; Moore, J. L. *Tetrahedron Lett.* **1983**, *24*, 339−342. (b) De Angelis, F.; Marzi, M.; Minetti, P.; Misiti, D.; Muck, S. *J. Org. Chem.* **1997**, *62*, 4159 − 4161.

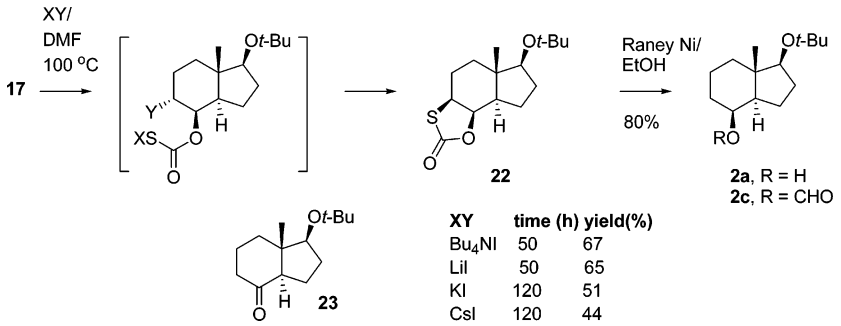
(23) (a) Mukaiyama, T.; Kuwajima, I.; Mizui, K. *J. Org. Chem.* **1966**, *31*, 32−34. (b) Vedejs, E.; Wu, E. S. C. *J. Org. Chem.* **1974**, *39*, 3641−3645. (c) Barton, D. H. R.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1773−1776. (d) Adiyaman, M.; Jung, Y. J.; Kim, S.; Saha, G.; Powell, W. S.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1999**, *40*, 4019−4022.

(24) Jones, F. N.; Andreades, S. *J. Org. Chem.* **1969**, *34*, 3011−3014.

(25) (a) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1993**, *49*, 5483−5493. (b) Tietze, L. F.; Subba Rao, P. S. V. *Synlett* **1993**, 291−292.

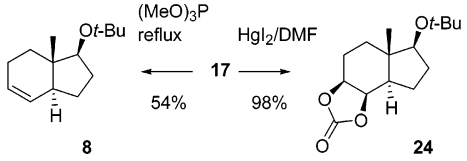
(26) Schroenberg, A.; Vargha, L. *Chem. Ber.* **1930**, *63*, 178−180.

SCHEME 6

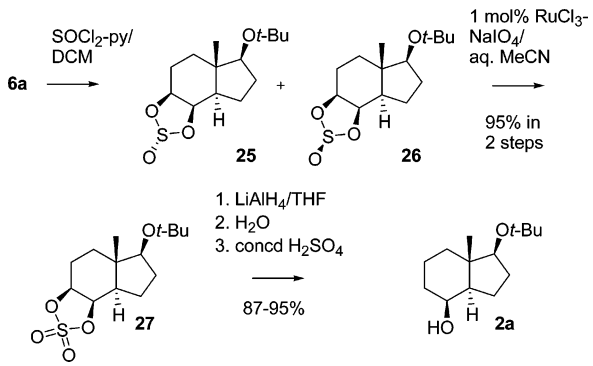


XY	time (h)	yield(%)
Bu_4NI	50	67
LiI	50	65
KI	120	51
CsI	120	44

SCHEME 7



SCHEME 8



tetrabutylammonium bromide.[27] However, rearrangement of inactivated and sterically hindered thionocarbonates have not been reported thus far. We have found that treatment of thionocarbonate **17** with tetrabutylammonium iodide (5 mol equiv) in DMF at 100 °C gives the rearranged product **22** in 67% yield. Somewhat lower yields of **22** were obtained with lithium iodide. Potassium or cesium iodides were less effective. The choice of DMF as the solvent was crucial. Notably, thionocarbonate **17** on treatment with mercuric iodide in DMF was converted into carbonate **24** in 98% yield (Scheme 7).

Thiolcarbonate derivative **22** was reduced with Raney nickel W2 in ethanol (Scheme 6). Preliminary experiments showed that alcohol **2a** (45−56% yield) along with formate **2c** (26−38%) and a small amount of ketone **23** are formed. In subsequent runs, the crude product of reduction was treated briefly with NaOH in aqueous methanol. Alcohol **2a** was then obtained in 80% yield after chromatography.

The Corey−Winter reaction[28] was examined to complete our study on reactivity of cyclic thionocarbonates. Thus, **17** in refluxing trimethylphosphite (111 °C) was converted into olefin[25] **8** isolated in only 54% yield (Scheme 7), likely owing to the product volatility.

Epoxide **13** was a potentially useful intermediate in the synthesis of **2a**, but thus far, it could be obtained only as an intermediate in the $LiAlH_4$ reduction of **19** (Scheme 5). Sharpless and co-workers have observed[29,30] that vicinal diol cyclic sulfates are "like epoxides only more reactive". To this end, diol **6a** was treated with thionyl chloride in the presence of pyridine to give isomeric sulfites **25** and **26** in 76 and 23% yield, respectively (after chromatography) (Scheme 8). Structures were assigned from single-crystal X-ray analysis of the major isomer (**25**, *R* configuration about the sulfur atom, Figure 2). Ruthenium tetraoxide (less than 1 mol %)−sodium periodate oxidation[31] of a crude sulfite gave cyclic sulfate **27** in 95% yield from diol **6a**.

Reduction of cyclic sulfates to monoalcohols with sodium borohydride in dimethylacetamide was originally recommended.[29] The intermediate sulfate esters were then hydrolyzed in a 20% aqueous H_2SO_4−ether system. Alternatively, hydrolysis could be affected with a catalytic amount of concentrated sulfuric acid and 0.5−1.0 equiv of water in THF.[32] Little attention has been devoted to the reduction of cyclic sulfates since the pioneering works.

We have found that treatment of sulfate **27** with lithiumaluminum hydride in THF (0 °C to room temperature), then quenching the reagent excess with water and aqueous Na_2SO_4, and adding a small excess of concentrated H_2SO_4 gave alcohol **2a** in excellent yields (87−95% after chromatography).

In conclusion, the Hajos dione derivative **4** was efficiently transformed into the *trans*-hydrindane related diol **6a** via allylic alcohol **5** and hydroxy epoxide **7**. Four methods for selective deoxygenation of the less sterically shielded hydroxy group in diol **6a** were examined and are summarized in Table 1.

In route A, selective hydrolysis of diacetate **6b** to **6c** accounted for the main losses of material. If all side products in the diacetate hydrolysis step could be recycled, this approach would provide a high 81% yield of **2b**. However, high dilution is required in the free radical reduction step and would hamper the efficiency of larger volume procedures. Another disadvantage is brought about by the use of toxic tin compounds in stoichiometric amounts. In route B, a large excess of methyl iodide was used, although in larger scale operations, part of this reagent could be presumably recovered. The advantage of route C consists of the use of the economic Raney nickel−ethanol system in the reduction step. Route D, however, provides the most expedited and technically convenient approach to the required product. The product **2a** was obtained in 87%

(27) Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250−6251.
(28) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677−2678.
(29) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539.
(30) For a review, see: (a) Byaun, H. S.; He, L. L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051−7091. (b) Lohray, B. B. *Synthesis* **1992**, 1035−1052.
(31) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.
(32) Kim, B. J.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655−658.

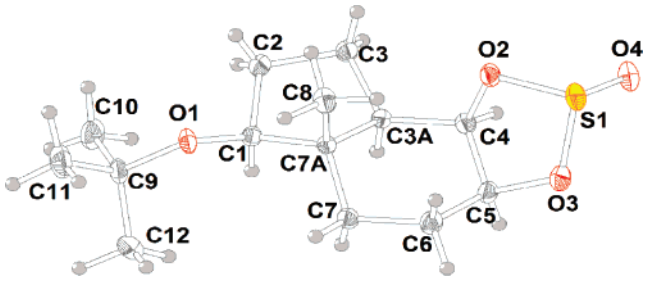


FIGURE 2. Single-crystal X-ray structure of sulfite **25** (ORTEP plot).

TABLE 1. Preparation of 2a by Selective Deoxygenation of Diol 6a

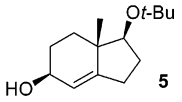
route	key step or intermediate	no. of steps	total yield (%)
A	Barton−McCombie deoxygenation	5	56[a] (81[b])
B	MeI opening of cyclic thionocarbonate **17**	3	66
C	via cyclic thiolcarbonate **22**	3	54
D	via cyclic sulfate **26**	3	87

[a] Acetate **2b** was obtained. [b] Providing complete recycling of side products in the diacetate hydrolysis step.

yield from diol **6a** with the sulfone **26** being the only isolated intermediate. Overall, the yield of **2a** from α,β-unsaturated ketone **4** amounted then to 72% (in six steps).

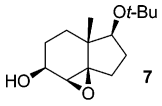
Experimental Section

(1*S*,5*S*,7a*S*)-1-*tert*-Butoxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-ol (5). Cerium(III) chloride heptahydrate (13.00 g, 35.00 mmol) was added to a stirred solution of **4** (7.72 g, 34.72 mmol) in MeOH (50 mL). After the salt has dissolved, the solution was cooled to 0 °C, and $NaBH_4$ (1.54 g, 40.71 mmol) was added in portions. The mixture was stirred for 1 h at room temperature. Acetone (5 mL) was then added, and stirring was continued for 2 h. The mixture was diluted with ether (200 mL) and set aside for 16 h. The precipitate was filtered off and washed with ether (3 × 10 mL). The combined filtrates were evaporated to give **5** (7.70 g, 99%): mp 63−65 °C; ^{1}H NMR (200 MHz) δ (ppm) 0.99 (s, 3H), 1.15 (s, 9H), 1.20−2.60 (m, 8H), 3.37 (ap. t, J = 7.4 Hz, 1H), 4.24 (m, 1H), 5.33 (m, 1H); ^{13}C NMR (50 MHz) δ (ppm) 17.2, 26.0, 28.8, 28.8, 29.8, 34.2, 43.3, 68.8, 72.6, 80.2, 122.2, 149.4, in agreement with values reported.[33]

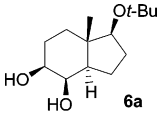


(1a*S*,2*S*,4a*R*,5*S*,7a*R*)-5-*tert*-Butoxy-4a-methyloctahydroindeno-[3a,4-*b*]oxiren-2-ol (7). *m*-CPBA (1.12 g, 70%, 4.68 mmol) was added in portions to a stirred solution of **5** (1.00 g, 4.46 mmol) in DCM (50 mL) at room temperature. After 0.5 h, the mixture was diluted with DCM (30 mL) and washed consecutively with aq $NaHCO_3$ and aq $Na_2S_2O_3$ and again with aq $NaHCO_3$. The organic extract was dried, and the solvent was evaporated to give **7** (1.05 g, a waxy solid, 98% yield): mp 80−83 °C (pentane); $[\alpha]^{23}_D$ = +13.8 (c = 1.10, $CHCl_3$); ^{1}H NMR (200 MHz), δ (ppm) 0.94 (s, 3H), 1.14 (s, 9H), 1.20−2.10 (m, 9H), 3.16 (br s, 1H), 3.55 (ap. t, J = 7.4 Hz, 1H), 3.83−4.00 (m, 1H); ^{13}C NMR (50 MHz), δ (ppm) 14.4, 25.2, 27.4, 28.8, 30.0, 33.9, 39.6, 63.5, 69.7, 71.2, 72.8, 80.0. Anal. Calcd for $C_{14}H_{24}O_3$ (240.34): C, 69.96; H, 10.06; found: C, 70.00; H, 10.02.

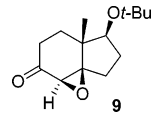
(33) Dauben, W. D.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212−1216.



(1*S*,3a*R*,4*R*,5*S*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (6a). BF_3·Et_2O (1.2 mL) was added dropwise, within 0.5 h, to a stirred solution of **7** (1.00 g, 4.16 mmol) and sodium cyanoborohydride (1.05 g, 16.67 mmol) in ether (40 mL). After 2 h, the reaction was quenched with water (70 mL), and the product was extracted with ether (2 × 50 mL). The extract was washed with brine and dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on silica gel (30 g, 25% EtOAc in hexanes) to give **6a** (crystalline mass, 867 mg, 86%): mp 131−133 °C (pentane/acetone); $[\alpha]^{23}_D$ = +13.0 (c = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.98 (d, J = 0.3 Hz, 3H), 1.12 (s, 9H), 1.02 − 1.16 (m, 1H), 1.25−1.33 (m, 1H), 1.40−1.58 (m, 2H), 1.60−1.99 (m, 5H), 2.19 (d, J = 3.0 Hz, 1H), 2.37 (d, J = 6.2 Hz, 1H), 3.31 (ap. t, J = 8.5 Hz, 1H), 3.51−3.60 (m, 1H), 3.95 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 13.1, 21.6, 26.4, 28.7, 31.0, 35.1, 41.2, 47.0, 71.7, 72.3, 73.0, 80.0. Anal. Calcd for $C_{14}H_{26}O_3$ (242.36): C, 69.38; H, 10.81; found: C, 69.41; H, 11.03.

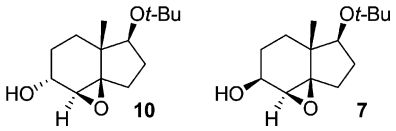


(1a*R*,4a*R*,5*S*,7a*R*)-5-(*tert*-Butoxy)-4a-methylhexahydroindeno-[3a,4-*b*]oxiren -2(1a*H*)-one (9). CrO_3 (2.79 g, 27.9 mmol) was carefully added to a stirred mixture of pyridine (4.33 mL, 53.8 mmol) and DCM (50 mL). After 15 min, a solution of **7** (637 mg, 2.65 mmol) in DCM (7 mL) was added dropwise. The mixture was stirred for 20 min and then allowed to settle, and the clear solution was decanted. The solid was washed with a small amount of DCM. The combined solutions were washed consecutively with aq $NaHCO_3$, aq 10% solution of tartaric acid, and aq $NaHCO_3$ again and dried. The solvent was evaporated, and the residue was chromatographed on silica gel (20 g, 10% EtOAc in hexanes) to give **9** (572 mg, 90%): mp 101−104 °C (pentane); $[\alpha]^{22}_D$ = +105.2 (c = 1.045, $CHCl_3$); ν_{max} (KBr) 1716 cm^{-1}; ^{1}H NMR (400 MHz) δ (ppm) 1.14 (d, J = 0.5 Hz 3H), 1.17 (s, 9H), 1.64−1.74 (m, 1H), 1.77−1.95 (m, 5H), 1.95−2.02 (m, 1H), 2.66−2.76 (m, 1H), 3.07 (d, J = 0.8 Hz, 1H), 3.66−3.73 (m, 1H); ^{13}C NMR (100 MHz) δ (ppm) 14.3, 27.0, 28.7, 30.3, 32.2, 37.7, 40.5, 61.7, 73.1, 76.4, 79.5, 209.2. Anal. Calcd for $C_{14}H_{22}O_3$ (238.33): C, 70.56; H, 9.30; found: C, 70.62; H, 9.34.

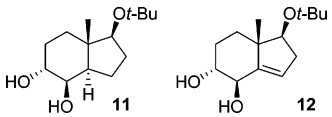


(1a*S*,2*R*,4a*R*,5*S*,7a*R*)-5-(*tert*-Butoxy)-4a-methylperhydroindeno-[3a,4-*b*]oxiren-2-ol (10) and 7. To a solution of **9** (870 mg, 3.65 mmol) and sodium cyanoborohydride (913 mg, 14.53 mmol) in THF (60 mL) containing a small amount of bromocresol green, a solution of concd aq HCl in THF (1:5) was added dropwise to maintain pH 3−4 (change of the indicator color from greenish-blue to yellow). After the starting material was consumed (TLC), the reaction was quenched with water (50 mL), and the product was extracted with ether (3 × 50 mL). The organic extract was washed with water and with brine, and the solvent was evaporated. The residue was chromatographed on silica gel (40 g, 30% EtOAc in hexanes) to give **10** (159 mg, 18%) and **7** (648 mg, 74%). **10**: mp 84−88 °C (pentane); $[\alpha]^{31}_D$ = +65.3 (c = 1.285, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.91 (s, 3H), 1.10−1.23 overlapping (m, 1H), 1.16 (s, 9H), 1.35−1.47 (m, 2H), 1.58−1.92 (m, 6H), 3.00 (s, 1H), 3.67−3.74 (m, 1H), 4.11 (br s, 1H); ^{13}C NMR (100

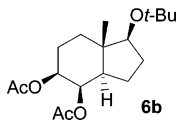
MHz) δ (ppm) 15.0, 25.0, 27.4, 27.8, 28.7, 29.5, 39.8, 62.6, 66.4, 67.4, 72.9, 179.0. Anal. Calcd for $C_{14}H_{24}O_3$ (240.34): C, 69.96; H, 10.06; found: C, 69.85; H, 10.31.



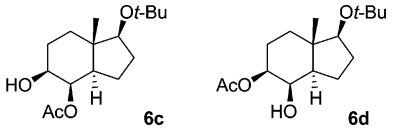
(1*S*,3a*R*,4*R*,5*R*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (11) and (1*S*,4*R*,5*R*,7a*S*)-1-*tert*-butoxy-7a-methyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-4,5-diol (12). $BF_3{\cdot}Et_2O$ (0.06 mL) was added to a stirred solution of **10** (59 mg, 0.25 mmol) and sodium cyanoborohydride (60 mg, 0.96 mmol) in ether (3 mL). After 30 min, the mixture was poured into water, and the product was extracted with ether (3 × 5 mL). The organic extract was washed with aq $NaHCO_3$ and brine, and the solvent was evaporated. The residue was chromatographed on silica gel (5 g, 40% EtOAc in hexanes) to give **11** (21 mg, 35%) and **12** (16 mg, 27%). **11**: mp 132−135 °C (hexane); $[\alpha]^{25}_D = +70.7$ ($c = 0.87$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.97 (s, 3H), 1.14 (s, 9H), 1.44−1.75 (m, 6H), 1.83−1.89 (m, 1H), 1.95−2.02 (m, 1H), 2.13−2.23 (m, 1H) 3.94 (d, $J = 4.8$ Hz, 1H), 4.01−4.06 (m, 1H), 4.38−4.43 (m, 1H); ^{13}C NMR (100 MHz) δ (ppm) 17.5, 21.4, 25.8, 28.5, 35.4, 39.2, 50.3, 73.3, 74.5, 80.1, 80.4, 101.1. Anal. Calcd for $C_{14}H_{26}O_3$ (242.36): C, 69.38; H, 10.81; found: C, 69.29; H, 10.75. **12**: mp 127−129 °C; $[\alpha]^{23}_D = -17.7$ ($c = 0.285$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 1.12 (d, $J = 0.3$ Hz, 3H), 1.16 (s, 9H), 1.48−1.66 (m, 5H), 2.10−2.25 (m, 2H), 2.31−2.39 (m, 1H) 3.83 (dd, $J =$ 8.7, 7.8 Hz, 1H), 3.96 (q, $J = 2.8$, 1H), 4.17 (d, $J = 2.8$, 1H), 5.69 (q, $J = 1.8$, 1H); ^{13}C NMR (100 MHz), δ (ppm) 18.4, 24.3, 28.7, 32.4, 37.9, 45.2, 69.7, 71.5, 72.8, 82.6, 128.1, 146.1. MS HR (ESI) calcd for $C_{14}H_{24}O_3Na$ (MNa^+): 263.16177; found: 263.16060. Anal. Calcd for $C_{14}H_{24}O_3{\cdot}1/2H_2O$ (249.39): C, 68.68; H, 10.09; found: C, 68.73; H, 10.12.



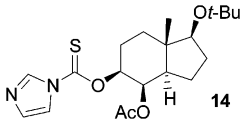
4,5-*O*,*O*′-Diacetyl-(1*S*,3a*R*,4*R*,5*S*,7a*S*)-1-*tert*-butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (6b). A mixture of **6a** (770 mg, 3.18 mmol), DCM (20 mL), pyridine (771 μL, 9.53 mmol), acetic anhydride (752 μL, 7.95 mmol), and DMAP (12 mg, 0.08 mmol) was stirred at room temperature for 24 h. DCM (50 mL) was then added, and the solution was washed consecutively with 3% aq HCl (2 × 20 mL) and brine (2 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated. The residue was chromatographed on silica gel (25 g, 10% EtOAc in hexanes) to give **6a** (1038 mg, 100%): mp 72−74 °C (MeOH/H_2O); $[\alpha]^{23}_D = -19.6$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.97 (s, 3H), 1.13 (s, 9H), 1.14−1.29 (m, 1H), 1.41−1.52 (m, 4H), 1.60−1.73 (m, 2H), 1.75−1.82 (m, 1H), 1.85−1.97 (m, 1H), 1.99 (s, 3H), 2.10 (s, 3H), 3.30−3.37 (m, 1H), 4.77−4.84 (m, 1H), 5.35 (br d, $J = 3.4$ Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.7, 21.0, 21.1, 21.5, 23.2, 28.7, 30.8, 34.8, 41.6, 45.6, 70.6, 72.4, 73.1, 79.6, 170.4, 170.7. Anal. Calcd for $C_{18}H_{30}O_5$ (326.43): C, 66.23; H, 9.26; found: C, 66.20; H, 9.27.



5-*O*-Acetyl-(1*S*,3a*R*,4*R*,5*S*,7a*S*)-1-*tert*-butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (6c) and 4-*O*-Acetyl-(1*S*,3a*R*,4*R*,5*S*,-7a*S*)-1-*tert*-butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (6d). To a solution of **6b** (1.00 g, 3.06 mmol) in methanol (52 mL), a 0.5 M aq solution of K_2CO_3 (3.00 mL) was added. The mixture was stirred for 1 h, then it was diluted with DCM (150 mL) and washed with water and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel (40 g, gradient elution hexanes/30% EtOAc in hexanes) to give consecutively: **6b** (71 mg, 7%), 5-*O*-acetyl derivative **6d** (60 mg, 7%), 4-*O*-acetyl derivative **6c** (603 mg, 70%), and **6a** (117 mg, 16%). **6c**: mp 84−86 °C (pentane); $[\alpha]^{23}_D = +1.5$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.94 (s, 3H), 1.12 (s, 9H), 1.41−1.56 (m, 4H), 1.69−1.79 (m, 4H), 1.85−2.03 (m, 2H), 2.12 (s, 3H) 3.29−3.36 (m, 1H), 3.67−3.76 (m, 1H), 5.23 (dd, $J = 3.6$, 1.8 Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.7, 21.1, 21.8, 26.6, 28.7, 30.9, 34.8, 41.5, 45.8, 72.2, 72.4, 73.8, 79.7, 172.1. Anal. Calcd for $C_{16}H_{28}O_4$ (284.40): C, 67.57; H, 9.92; found: C, 67.50; H, 9.96. 6d: mp 102−104 °C (pentane); $[\alpha]^{23}_D = +7.2$ ($c = 0.55$, $CHCl_3$); ^{1}H NMR (200 MHz) δ (ppm) 1.01 (s, 3H), 1.11 (s, 9H), 1.20−2.01 (m, 10H), 2.10 (s, 3H), 3.32 (ap. t, $J = 8.4$ Hz 1H), 4.05 (br s, 1H), 4.63−4.78 (m, 1H); ^{13}C NMR (50 MHz), δ (ppm) 13.3, 21.4, 21.5, 22.5, 28.7, 31.0, 35.1, 41.3, 46.7, 70.1, 72.3, 76.1, 80.0, 170.1. Anal. Calcd for $C_{16}H_{28}O_4$ (284.40): C, 67.57; H, 9.92; found: C, 67.64; H, 10.19.

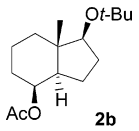


4-*O*-Acetyl-5-*O*-(1*H*-imidazol-1-ylcarbonothionyl)-(1*S*,-3a*R*,4*R*,5*S*,7a*S*)-1-*tert*-butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (14). Thionocarbonyldiimidazole (TCDI) (497 mg, 2.79 mmol) was added to a solution of alcohol **6c** (396 mg, 1.39 mmol) in THF (12 mL). The mixture was heated at reflux temperature for 4 h and cooled, and the solvent was evaporated. The residue was chromatographed on silica gel (25 g, 30% EtOAc in hexanes) to give **14** (543 mg, 99%): mp 110−112 °C (pentane); $[\alpha]^{23}_D = +8.0$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 1.02 (s, 3H), 1.14 (s, 9H), 1.27 (dt, $J = 13.1$, 4.8 Hz, 1H), 1.47−1.62 (m, 4H), 1.88 (dt, $J = 13.3$, 3.7 Hz 1H), 1.92−2.00 (m, 1H), 2.01−2.10 (m, 2H), 2.13 (s, 3H), 3.36−3.42 (m, 1H). 5.48−5.54 (m, 1H), 5.53−3.59 (m, 1H), 7.02 (dd, $J = 1.8$, 1.0 Hz, 1H), 7.54 (dd, $J = 1.7$, 1.3 Hz, 1H), 8.24 (t, $J = 1.2$, Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.8, 21.0, 21.5, 22.5, 28.7, 30.7, 34.5, 41.6, 45.6, 69.9, 72.5, 79.4, 82.5, 117.9, 130.8, 136.7, 170.4, 183.2. Anal. Calcd for $C_{20}H_{30}N_2O_4S$ (394.53): C, 60.89; H, 7.66; N, 7.10; S, 8.13; found: C, 60.82; H, 7.59; N, 7.16; S, 8.15.



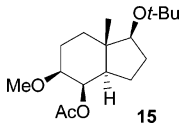
(1*S*,3a*R*,4*R*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-indene-4-ol acetate (2b). A solution of **14** (500 mg, 1.27 mmol) in toluene (40 mL) containing AIBN (36 mg, 0.22 mmol) was added by means of a syringe pump, within 1 h, to a refluxing mixture of tri-*n*-butyltinhydride (1.37 mL, 5.11 mmol) in toluene (85 mL). The mixture was heated under reflux for further 2 h and then set aside for 16 h. The solvent was evaporated, and the residue was chromatographed on silica gel (30 g, hexanes/10% EtOAc in hexanes) to give **2b** (276 mg, 81%): $[\alpha]^{23}_D = +28.1$ ($c = 1.02$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.91 (s, 3H), 0.94−1.06 (m, 1H), 1.13 (s, 9H), 1.22−1.54 (m, 6H), 1.63−1.91 (m, 4H), 2.05 (s, 3H), 3.30−3.38 (m, 1H), 5.11−5.15 (m, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.5, 17.6, 21.3, 22.3, 28.7, 30.0, 30.7, 37.3, 41.6, 46.5, 71.2, 72.2, 80.5, 170.9. MS HR Calcd for $C_{16}H_{28}O_3$:

268.20384 (M^+); found: 268.20439. In agreement with the reported data[20] ($[\alpha]_D = +20.7$).



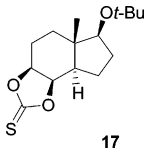
2b

(1*S*,3a*R*,4*R*,5*S*,7a*S*)-1-*tert*-Butoxy-5-methoxy-7a-methyloctahydro-1*H*-indene-4-ol Acetate (15). A solution of **14** (91 mg, 0.23 mmol) in toluene (2 mL) containing AIBN (10 mg, 0.06 mmol) was added within 1 h to tri-*n*-butyltinhydride (0.61 mL, 2.3 mmol) stirred at 120 °C (bath temperature). The mixture was heated under reflux for a further 6 h and cooled, and the solvent was evaporated. The residue was chromatographed on silica gel (30 g, 10% EtOAc in hexanes) to give **15** (54 mg, 78%): mp 64−67 °C; $[\alpha]^{23}_D = -26.2$ ($c = 0.45$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.94 (s, 3H), 1.12 (s, 9H), 1.35−1.53 (m, 4H), 1.65−1.96 (m, 5H), 2.10 (s, 3H), 3.14−3.21 (m, 1H), 3.30−3.34 (m, 1H) overlapping 3.33 (s, 3H), 5.45−5.49 (m, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.9, 21.4, 22.0, 24.6, 28.9, 31.2, 35.3, 42.1, 46.1, 56.8, 69.2, 72.6, 79.9, 81.1, 171.2. Anal. Calcd for $C_{17}H_{30}O_4$ (298.42): C, 68.42; H, 10.13; found: C, 68.52; H, 10.27.



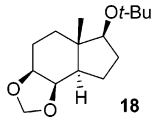
15

(3a*S*,5a*S*,6*S*,8a*R*,8b*R*)-6-*tert*-Butoxy-5a-methyloctahydro-3a*H*-indeno[4,5-*d*][1,3]dioxole-2-thione (17). TCDI (220 mg, 1.24 mmol) was added to a solution of **6a** (150 mg, 0.62 mmol) in THF (5 mL). The mixture was heated at reflux temperature for 4 h and then cooled, and the solvent was evaporated. The residue was chromatographed on silica gel (15 g, 30% EtOAc in hexanes) to give **17** (171 mg, 97%): mp 124−125 °C (pentane/acetone); $[\alpha]^{23}_D = +65.6$ ($c = 0.75$, $CHCl_3$); $\lambda_{max.}$(EtOH) 236.5 nm (ϵ 1121); ^{1}H NMR (400 MHz) δ (ppm) 0.92 (s, 3H), 1.02−1.12 (m, 1H), 1.13 (s, 9H), 1.49−1.72 (m, 3H), 1.73−1.87 (m, 2H), 1.88−2.05 (m, 2H), 2.17−2.26 (m, 1H), 3.37 (ap. t, $J = 8.2$, 1H), 4.86−4.94 (m, 2H); ^{13}C NMR (100 MHz) δ (ppm) 11.8, 21.9, 24.9, 28.6, 30.3, 32.7, 40.4, 43.9, 72.6, 79.5, 80.2, 82.5, 192.3. Anal. Calcd for $C_{15}H_{24}O_3S$ (284.41): C, 63.35; H, 8.51; S, 11.27; found: C, 63.55; H, 8.38; S, 11.25.



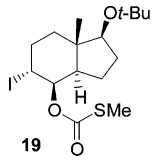
17

(3a*S*,5a*S*,6*S*,8a*R*,8b*R*)-6-*tert*-Butoxy-5a-methylperhydro-3a*H*-indeno[4,5-*d*][1,3]dioxole (18). Tributyltinhydride (0.90 mL, 3.45 mmol) was added dropwise within 15 min to a solution of **17** (88 mg, 0.31 mmol) and AIBN (10 mg, 0.06 mmol) in toluene (2 mL) and stirred at the reflux temperature (bath temperature 120 °C). The mixture was heated for further 0.5 h and cooled, and the solvent was evaporated. The residue was chromatographed on silica gel (30 g, 5% EtOAc in hexanes) to give **18** (68 mg, 87%): ^{1}H NMR (400 MHz) δ (ppm) 0.94 (s, 3H), 1.00 (dt, $J = 13.6$, 4.4 Hz, 1H), 1.13 (s, 9H), 1.45−1.52 (m, 1H), 1.53−1.65 (m, 3H), 1.67−1.75 (m, 1H), 1.78−1.90 (m, 2H), 1.90−2.02 (m, 1H), 3.34 (dd, $J = 8.7$, 7.6 Hz, 1H), 4.01 (dd, $J = 5.1$, 3.1 Hz, 1H), 4.07−4.15 (m, 1H), 4.93 (d, $J = 0.6$ Hz, 1H), 5.20 (d, $J = 0.7$ Hz, 1H);^{13}C NMR (100 MHz) δ (ppm) 12.2, 22.5, 24.7, 28.7, 30.8, 33.9, 40.6, 44.8, 72.3, 74.6, 77.1, 80.1, 94.7. MS HR Calcd for $C_{15}H_{26}O_3$ (M^+): 254.18819; found: 254.18732.



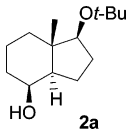
18

***O*-[(1*S*,3a*R*,4*R*,5*R*,7a*S*)-1-*tert*-Butoxy-5-iodo-7a-methyloctahydro-1*H*-inden-4-ol] *S*-Methyl Thiocarbonate (19).** A mixture of **17** (285 mg, 1.00 mmol) and methyl iodide (1.5 mL) was heated in a sealed ampule (44 °C, bath temperature) for 20 h. The excess methyl iodide was evaporated. The residue was dissolved in DCM (25 mL), washed consecutively with aq 10% $Na_2S_2O_3$ (10 mL) and water (10 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (15 g, 8% EtOAc in hexanes) to give **19** (345 mg, 81%, a crystalline mass): mp 95−98 °C (MeOH/H_2O); $[\alpha]^{24}_D = -62.8$ ($c = 1.02$, $CHCl_3$); ν_{max} (KBr) 1704 cm^{-1}; ^{1}H NMR (400 MHz) δ (ppm) 0.88 (s, 3H), 1.05−1.17 (m, 1H), 1.15 (s, 9H) overlapping 1.38−1.70 (m, 5H), 1.83−1.96 (m, 1H), 2.00−2.11 (m, 1H), 2.25−2.32 (m, 1H), 2.33 (s, 3H), 3.48 (ap. t, $J = 8.6$ Hz, 1H), 4.63 (br s, 1H), 5.33 (br s, 1H); ^{13}C NMR (100 MHz) δ (ppm) 13.0, 13.5, 21.9, 28.4, 28.7, 29.8, 30.3, 33.2, 39.9, 41.8, 72.5, 78.9, 80.0, 171.0. MS HR Calcd for $C_{16}H_{27}O_3$-SI: 426.07257 (M^+); found: 426.07167.



19

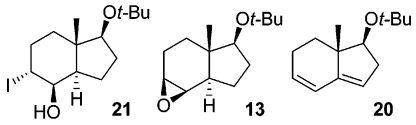
(1*S*,3a*R*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-inden-4-ol (2a). To a refluxing suspension of $LiAlH_4$ (53 mg, 1.4 mmol) in THF (4 mL) was added dropwise a solution of **19** (134 mg, 0.31 mmol) in THF (1 mL). The mixture was heated under reflux for 15 min, cooled, and quenched with saturated aq Na_2SO_4. The precipitate was filtered off and washed with Et_2O (10 mL). Combined filtrates were evaporated, and the residue was chromatographed on silica gel (7 g, 1% EtOAc in hexanes and 10% EtOAc in hexanes) to give **2a** (61 mg, 85%) and **20** (3.9 mg, 6%) (vide infra). **2a**: mp 60−63 °C (pentane); $[\alpha]^{23}_D = +31.8$ ($c = 0.74$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.97 (d, $J = 0.5$ Hz, 3H), 0.98−1.20 (m, 1H), 1.13 (s, 9H), 1.25−1.35 (m, 1H), 1.36−1.51 (m, 4H), 1.60−1.94 (m, 6H), 3.33 (dd, $J = 8.9$, 7.8 Hz, 1H), 4.04 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 13.0, 17.1, 22.1, 28.7, 30.1, 33.8, 37.6, 41.4, 47.7, 69.4, 72.2, 80.7. Anal. Calcd for $C_{14}H_{26}O_2$ (226.36) C, 74.29; H, 11.58; found: C, 74.20; H, 11.52.



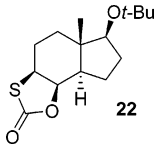
2a

(1*S*,3a*R*,4*R*,5*R*,7a*S*)-1-*tert*-Butoxy-5-iodo-7a-methyloctahydro-1*H*-inden-4-ol (21), (1a*S*,3a*S*,4*S*,6a*R*,6b*R*)-4-*tert*-butoxy-3a-methyloctahydro-1a*H*-indeno[4,5-*b*]oxirene (13), and *tert*-Butyl (1*S*,7a*S*)-7a-Methyl-2,6,7,7a-tetrahydro-1H-inden-1-yl Ether (20). $LiAlH_4$ (11 mg, 0.29 mmol) was added to a solution of **19** (130 mg, 0.31 mmol) in THF (3 mL) and stirred at room temperature. After 30 min, the reagent excess was quenched with saturated aq Na_2SO_4, and then the mixture was diluted with ether (5 mL). The solid was filtered off and washed with ether. The filtrate was evaporated, and the residue was chromatographed on silica gel (10 g, hexanes and then 10% EtOAc in hexanes) to give, consecutively, **20** (11 mg, 18%), **13** (18 mg, 27%), and **21** (58 mg, 53%). **20**: ^{1}H NMR (400 MHz) δ (ppm) 0.92 (d, $J = 0.6$ Hz, 3H), 1.18 (s, 9H), 1.20−2.20 (m, 6H), 3.78 (ap. t, $J = 8.0$ Hz), 5.28−

5.31 (m, 1H),5.70−5.76 (m, 1H), 6.10−6.15 (m, 1H); ^{13}C NMR (100 MHz) δ (ppm) 15.5, 23.5, 28.7, 33.8, 38.1, 44.7, 72.5, 81.4, 119.2, 123.4, 129.1, 145.3. MS HR Calcd for $C_{14}H_{22}O$: 206.16707; found: 206.16783. **13**: mp 54−58 °C; $[\alpha]^{27}_D = +22.2$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.88 (s, 3H), 0.93−1.05 (m, 1H), 1.11 (s, 9H), 1.37−1.48 (m, 2H), 1.55−1.84 (m, 4H), 1.85−1.98 (m, 1H), 2.04−2.14 (m, 1H), 3.08 (t, $J = 4.8$ Hz, 1H), 3.18 (d, $J = 4.3$ Hz, 1H), 3.31 (dd, $J = 8.8$, 7.7 Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.1, 21.3, 23.3, 28.7, 30.3, 33.3, 41.8, 44.1, 50.5, 55.3, 72.2, 79.9. Anal. Calcd for $C_{14}H_{24}O_2$, (224.34): C, 74.95; H, 10.78; found: C, 75.02; H, 10.75. **21**: ^{1}H NMR (400 MHz) δ (ppm) 0.95 (s, 3H), 1.13 (s, 9H), 1.40−1.54 (m, 3H), 1.62−1.77 (m, 2H), 1.80−2.00 (m, 3H), 2.11−2.22 (m, 2H), 3.46 (dd, $J =$ 8.9, 7.8 Hz, 1H), 4.23 (br s, 1H), 4.58 (br s, 1H); ^{13}C NMR (100 MHz) δ (ppm) 13.5, 21.8, 27.6, 28.7, 30.0, 33.5, 36.7, 40.6, 41.7, 72.4, 75.3, 80.3. MS HR (ESI) Calcd for $C_{14}H_{25}O_2I$ (M^+): 352.08993; found: 352.08882.

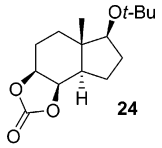


(3a*S*,5a*S*,6*S*,8a*R*,8b*R*)-6-*tert*-Butoxy-5a-methyloctahydro-3a*H*-indeno[5,4-*d*][1,3]oxathiol-2-one (22). A solution of **17** (304 mg, 1.07 mmol) and tetrabutylammonium iodide (1.89 g, 5.11 mmol) in DMF (1.7 mL) was stirred at 100 °C for 50 h. After cooling, the viscous mixture was transformed to a silica gel column (20 g, 5% EtOAc in hexanes). Elution of the column with 5% EtOAc in hexanes gave **22** (204 mg, 67%): mp 98−101 °C (pentane); $[\alpha]^{22}_D = +27.8$ ($c = 1.045$, $CHCl_3$); λ_{max} (EtOH) 204.3 nm (ϵ 814); ν_{max} (KBr) 1723 cm^{-1}; ^{1}H NMR (400 MHz) δ (ppm) 0.92 (d, $J = 0.4$ Hz, 3H), 1.08 (dt, $J = 13.6$, 3.9 Hz, 1H), 1.13 (s, 9H), 1.43−1.51 (m, 1H), 1.51−1.59 (m, 1H), 1.61−1.72 (m, 1H), 1.82 (dt, $J =$ 13.0, 3.5 Hz, 1H), 1.87−2.00 (m, 3H), 2.08−2.17 (m, 1H), 3.37 (ap. t, $J = 8.2$ Hz, 1H), 3.49−3.56 (m, 1H), 4.66 (dd, $J = 4.6$, 3.2 Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.2, 22.9, 28.6, 29.3, 30.2, 35.8, 40.6, 46.2, 48.0, 72.5, 79.8, 82.4, 173.1. Anal. Calcd for $C_{15}H_{24}O_3S$ (284.41): C, 63.35; H, 8.51; S, 11.27; found: C, 63.26; H, 8.33; S, 11.51.

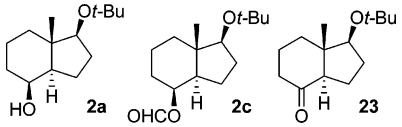


The use of LiI instead of tetrabutylammonium iodide in analogous conditions (100 °C, 50 h) gave **22** in 65% yield, KI (100 °C, 120 h) in 51% yield, and CsI (100 °C, 120 h) in 44% yield.

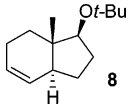
(3a*S*,5a*S*,6*S*,8a*R*,8b*R*)-6-*tert*-Butoxy-5a-methyloctahydro-3a*H*-indeno[4,5-*d*][1,3]dioxole-2-one (24). HgI_2 (840 mg, 1.85 mmol) was added to a solution of **17** (57 mg, 0.2 mmol) in DMF (1 mL). After 3 h, the suspension was diluted with DCM (10 mL) and filtered through a pad of Celite. The Celite was washed with DCM. The filtrate was evaporated, and the residue was chromatographed on silica gel (2 g, 30% EtOAc in hexanes) to give **24** (53 mg, 98%): mp 104−108 °C (pentane); $[\alpha]^{30}_D = +35.5$ ($c = 0.385$, $CHCl_3$); ν_{max} (KBr) 1778 cm^{-1}; ^{1}H NMR (200 MHz) δ (ppm) 0.92 (s, 3H), 1.17 (s, 9H), 1.32−2.06 (m, 8H), 2.10−2.28 (m, 1H), 3.36 (ap. t, $J = 8.0$ Hz, 1H), 4.58−4.78 (m, 2H); ^{13}C NMR (50 MHz) δ (ppm) 12.1, 21.9, 25.3, 28.7, 30.4, 32.8, 40.4, 44.4, 72.6, 75.8, 78.1, 79.5, 155.2. Anal. Calcd for $C_{15}H_{24}O_4$ (268.35): C, 67.14; H, 9.01; found: C, 66.90; H, 9.21.



(1*S*,3a*R*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-inden-4-ol (2a), (1*S*,3a*R*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-inden-4-ol formate (2c), and (1*S*,3a*R*,7a*S*)-1-*tert*-Butoxy-7a-methyloctahydro-1*H*-inden-4-one (23). Raney nickel W2 (ca. 300 mg) was added to a solution of **22** (130 mg, 0.46 mmol) in ethanol (5 mL), and the suspension was heated at the reflux temperature for 2 h. (If after that time the starting material was not fully consumed, an additional portion of Raney nickel, 100 mg, was added, and heating was continued for a further 1 h.) The mixture was cooled and filtered through a pad of Celite. The Celite was washed with ethanol, and the filtrate was evaporated to give a crude product. Chromatography of this product on silica gel (7 g, 5% EtOAc in hexanes and then 10% EtOAc in hexanes) gave the formate **2c** (30−35 mg, 26−38%), alcohol **2a** (47−58 mg, 45−56%), and a small amount of a ketone **23**. In further runs, the crude product was dissolved in methanol (5 mL) containing 10% aq NaOH (0.3 mL). The mixture was stirred for 3 h, and then it was diluted with DCM (15 mL) and washed with 1% hydrochloric acid and water. The solvent was evaporated, and the residue was chromatographed on silica gel (5 g. 10% EtOAc in hexanes) to give alcohol **2a** (83 mg, 80%). **2c**: ^{1}H NMR (400 MHz) δ (ppm) 0.91 (s, 3H), 0.98−1.06 (m, 1H), 1.12 (s, 9H), 1.35−1.56 (m, 6H), 1.65−1.93 (m, 4H), 3.34 (dd, $J = 8.9$, 7.6 Hz, 1H), 5.26 (br s, 1H), 8.11 (d, $J = 0.8$ Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.5, 17.5, 22.2, 28.7, 30.0, 30.8, 37.2, 41.5, 46.3, 71.3, 72.3, 80.5, 161.1. MS HR (ESI) calculated for $C_{15}H_{26}O_3Na$ (M^+): 277.17742; found: 277.17621. **23**: ν_{max} (DCM) 1716 cm^{-1}; ^{1}H NMR (400 MHz) δ (ppm) 0.68 (d, 3H, $J = 0.4$ Hz), 1.16 (s, 9H), 1.40−1.55 (m, 3H), 1.82−1.97 (m, 4H), 1.98−2.06 (m, 1H), 2.15−2.38 (m, 3H), 3.65 (ap. t, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 11.9, 18.5, 23.7, 28.7, 30.2, 36.3, 40.9, 49.4, 56.6, 72.6, 80.4, 211.6. MS HR (ESI) calcd for $C_{14}H_{24}O_2Na$ (MNa^+): 247.16685; found: 247.16796.

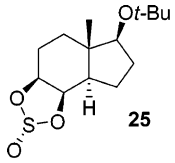


***tert*-Butyl (1*S*,3a*S*,7a*S*)-7a-Methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl Ether (8).** A solution of **17** (70 mg, 0.246 mmol) in trimethylphosphite (1 mL) was heated at the reflux temperature for 50 h. The mixture was cooled and transferred to a silica gel column (5 g, pentane). Elution of the column with pentane gave olefin **8** (28 mg, 54%): $[\alpha]^{23}_D = +123.7$ ($c = 0.96$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 0.74 (d, $J = 0.7$, 3H), 1.14 (s, 9H), 1.26−1.45 (m, 2H), 1.47−1.65 (m, 2H), 1.73−1.80 (m, 1H), 1.89−2.06 (m, 2H), 2.07−2.15 (m, 2H), 3.45 (dd, $J = 9.0$, 7.0 Hz, 1H), 5.49−5.62 (m, 2H); ^{13}C NMR (100 MHz) δ (ppm) 10.8, 24.2, 24.5, 28.7, 31.4, 34.0, 41.9, 43.2, 72.2, 79.5, 126.7, 128.1; MS (70 eV, EI) *m*/*z* (%): 208.3 (1) [M^+], 152.2 (18) [$M^+ - C_4H_8$], 134.2 (63) [$M^+ - C_4H_8 - H_2O$], 57.1 (100) [$C_4H_9^+$], 41.1 (25) [$C_3H_5^+$]. Anal. Calcd for $C_{14}H_{24}O$ (208.341): C, 80.71; H, 11.61; found: C, 80.58; H, 11.56.

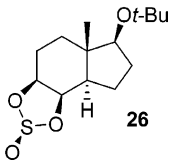


(3a*S*,5a*S*,6*S*,8a*R*,8b*R*,2′*R*)-6-*tert*-Butoxy-5a-methyloctahydro-3a*H*-2λ-4-indeno[4,5-*d*][1,3,2]dioxathiolane 2-Oxide (25) and

(3a*S*,5a*S*,6*S*,8a*R*,8b*R*,2′*S*)-6-*tert*-Butoxy-5a-methyloctahydro-3a*H*-2λ-4-indeno[4,5-*d*][1,3,2]dioxathiolane 2-Oxide (26). Thionyl chloride (0.4 mL, 0.65 g, 5.46 mmol) was added dropwise to a solution of diol **6a** (679 mg, 2.80 mmol) in DCM (10 mL) and pyridine (1 mL, 0.98 g, 12.39 mmol) and stirred at 0 °C. Stirring was continued for 15 min, and then the mixture was allowed to warm to room temperature. The reaction was quenched by careful addition of water, and then DCM (20 mL) was added. The solution was washed consecutively with 5% hydrochloric acid and aq $NaHCO_3$ and dried. The solvent was evaporated. The residue was dissolved in DCM and filtered through a pad of silica gel to give a mixture of sulfites. Re-chromatography of this mixture on silica gel (35 g, 5% EtOAc in hexanes) gave, consecutively, **26** (186 mg, 23%) and **25** (613 mg, 76%). **26**: mp 124−126 °C (pentane); $[\alpha]^{20}_D = +8.2$ ($c = 1.225$, $CHCl_3$); λ_{max} (EtOH) 202.1 nm (ϵ 202); ^{1}H NMR (400 MHz) δ (ppm) 1.04 (dt, $J = 13.8$, 3.8 Hz, 1H), 1.09 (s, 3H), 1.13 (s, 9H), 1.55−1.67 (m, 3H), 1.80−2.04 (m, 3H), 2.14−2.22 (m, 1H), 2.33−2.45 (m, 1H), 3.35 (ap. t, $J = 8.1$ Hz, 1H), 4.49−4.55 (m, 1H), 4.55−4.59 (m, 1H); ^{13}C NMR (100 MHz) δ (ppm) 11.6, 22.3, 27.1, 28.6, 30.7, 34.4, 40.8, 44.8, 72.5, 79.7, 81.1, 83.6. Anal. Calcd for $C_{14}H_{24}O_4S$ (288.40): C, 58.31; H, 8.39; S, 11.12; found: C, 58.24; H, 8.37; S, 11.14. **25**: mp 115−116 °C (pentane); $[\alpha]^{18}_D = -41.5$ ($c = 1.035$, $CHCl_3$); λ_{max} (EtOH) 196.3 nm (ϵ 207); ^{1}H NMR (400 MHz) δ (ppm) 0.92 (s, 3H), 1.02 (dt, $J = 13.8$, 3.8 Hz, 1H), 1.13 (s, 9H), 1.53−1.78 (m, 5H), 1.84−1.92 (m, 1H), 1.93−2.11 (m, 2H), 3.36 (ap. t, $J = 8.2$ Hz, 1H), 4.70−4.82 (m, 1H), 5.07 (dd, $J = 5.0$, 2.8 Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 12.1, 22.3, 26.3, 28.6, 30.6, 33.5, 40.5, 43.6, 72.5, 78.2, 79.5, 81.7. Anal. Calcd for $C_{14}H_{24}O_4S$ (288.40): C, 58.31; H, 8.39; S, 11.12; found: C, 58.39; H, 8.45; S, 11.02. For the X-ray measurements, see the Supporting Information.

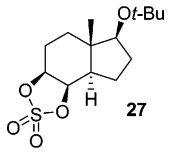


25



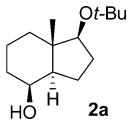
26

(3a*S*,5a*S*,6*S*,8a*R*,8b*R*)-6-*tert*-Butoxy-5a-methyloctahydro-3a*H*-2λ-4-indeno[4,5-*d*][1,3,2]dioxathiolane 2,2-Dioxide (27). Sodium periodate (723 mg, 3.38 mmol) and $RuCl_3 \cdot 3H_2O$ (6 mg, 0.02 mmol) were added to a solution of a mixture of crude **25** and **26** obtained as described previously (650 mg, 2.25 mmol) in acetonitrile (10 mL) and water (5 mL). The mixture was stirred for 2 h and then diluted with EtOAc (25 mL). The solution was washed with aq $NaHCO_3$ and brine and dried. The solvent was evaporated. The residue was chromatographed on silica gel (20 g, 20% EtOAc in hexanes) to give **27** (652 mg, 95%): mp 111−113 and 125−126 °C (dec) (acetone/pentane); $[\alpha]^{19}_D = +7.2$ ($c = 1.075$, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm) 1.01 (s, 3H) overlapping 1.01−1.14 (m, 1H), 1.13 (s, 9H), 1.45−1.53 (m, 1H), 1.54−1.72 (m, 2H), 1.78−1.91 (m, 2H), 1.93−2.05 (m, 1H), 2.17−2.26 (m, 2H), 3.36 (ap. t, $J = 8.2$ Hz, 1H), 4.84 (dt, $J = 9.1$, 4.9 Hz, 1H), 5.11 (dd, $J = 4.9$, 2.8 Hz, 1H); ^{13}C NMR (100 MHz) δ (ppm) 11.7, 21.9, 24.3, 28.6, 30.4, 33.0, 40.6, 45.0, 72.7, 79.2, 82.8, 83.6. Anal. Calcd for $C_{14}H_{24}O_5S$ (304.40): C, 55.24; H, 7.95; S, 10.53; found: C, 55.33; H, 8.11; S, 10.56.



27

Reduction of 26. $LiAlH_4$ (80 mg, 2.11 mmol) was added in portions to a solution of **26** (305 mg, 1.00 mmol) in THF (10 mL) and stirred at 0 °C. The mixture was allowed to warm to room temperature. After 1 h, saturated aq Na_2SO_4 (50 μL) and water (100 μL) were added. Stirring was continued for an additional 30 min, and then concentrated H_2SO_4 (200 μL) was added. A thick precipitate was formed. The mixture was stirred for an additional 3 h (after ca. 1 h, the precipitate has dissolved). Concentrated aq $NaHCO_3$ was carefully added (until evolution of CO_2 ceased). The product was extracted with ether (3 × 40 mL). The organic extract was washed with brine and dried with $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel (10 g, 10% EtOAc in hexanes) to give alcohol **2a** (196−215 mg, 87−95% yield).



2a

Acknowledgment. We thank Dr. Milan R. Uskoković of BioXell for the generous gift of the Hajos dione and Dr. David M. Piatak for comments about the manuscript. We are indebted to Prof. Krzysztof Woźniak and Łukasz Dobrzycki of the Chemistry Department, University of Warsaw for X-ray measurements.

Supporting Information Available: Description of general experimental methods, ^{1}H and ^{13}C NMR spectra of all new compounds (**2a**−**c**, **6a**−**d**, **7**−**15**, and **17**−**27**), and single-crystal X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070685M