Tetrahedron Vol. 49, No. 26, pp. 5817-5822, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

Dienes as Chiral Templates : Easy Access to Pure (2*S*,3*S*,4*R*)-4-Hydroxy-2,3-epoxycyclohex-5-en-1-one

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(*Received in Germany* 11 *March* 1993)

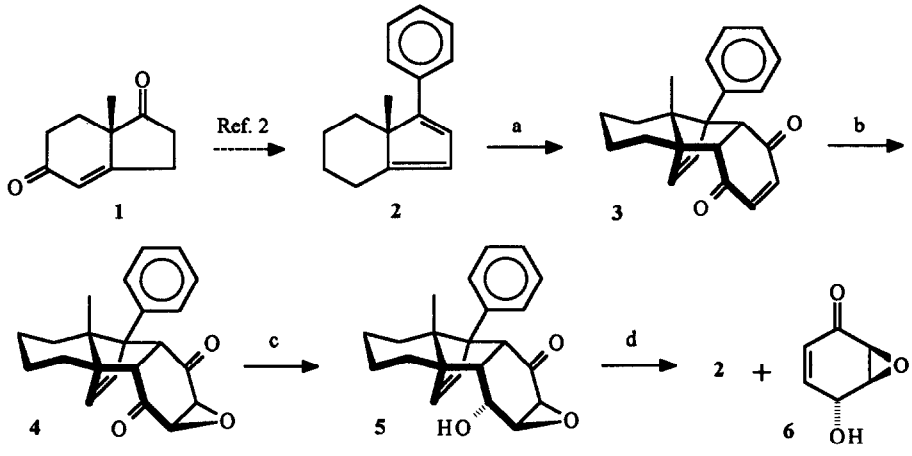
Key words : Chiral diene, chiral template, retro Diels-Alder reaction, flash vacuum thermolysis, Favorskii rearrangement.

***Abstract** : The title compound 6 was obtained stereospecifically through a concise sequence including a Diels-Alder reaction with the chiral diene 2 and the retro reaction. The Favorskii rearrangement starting from the intermediate epoxide 4 was found to be regioselective.*

Asymmetric induction using a chiral diene is a very powerful synthetic method leading to enantiomerically pure products in good yields after a retro Diels-Alder reaction[1]. In this paper, we wish to describe the facile synthesis of 4-hydroxy-2,3-epoxycyclohex-5-en-1-one (**6**), which we believe to be a very versatile intermediate in organic synthesis.

The synthesis of the chiral template diene **2** was described earlier[2], starting from the Hajos-Wiechert ketone **1** (Scheme 1). The Diels Alder reaction with 1,4-benzoquinone had to be performed under pressure, at 6.5 Kbar, thus avoiding the appearance of the hydroquinone by-product[3,4]. Treatment of the cycloadduct[5] **3** with $NaOH/H_2O_2$ gave the epoxide **4**, stable and crystalline, in 98% yield, provided that the two reagents were mixed prior to the reaction (this improvement was already mentioned in the case of the hydroboration[6], where it was claimed to be milder) and that the work up was achieved within 60 sec. The reaction proved to be highly stereoselective. Alternatively, sodium perborate could be used, although with moderate yields (71%). Disappointingly, the reaction of **4** with L-Selectride® in toluene at -78°C gave the reduced compound **5** as a single regioisomer albeit in very poor yields which we eventually attributed to the acidic work up. Thus, treatment with 1N NaOH or saturated $NaHCO_3$ furnished 98% of **5**, which could not be chromatographed, probably due to the lability of the epoxide functionnality. However, crystallization from CH_2Cl_2/Et_2O gave

pure **5**. Two recrystallizations were performed prior to the retro Diels-Alder reaction. For this transformation, we used the flash vacuum thermolysis procedure at 300°C under high vacuum. The reaction proceeded cleanly, in 90% yield, according to this procedure, and the desired (2*S*,3*S*,4*R*)-4-hydroxy-2,3-epoxycyclohex-5-en-1-one could be separated from our chiral template by two crystallizations.



a 1,4-Benzoquinone, CH_2Cl_2, 6.5 Kbar, 25°C, 3 days (95%) **b** 5 eq. $NaOH/H_2O_2$, THF-H_2O 4:1, 0°C, 45 s (98%) **c** L-Selectride®, toluene, -78°C, 15 mn, sat. $NaHCO_3$ (98%) **d** 300°C, 1.10^{-2} atm. (90%).

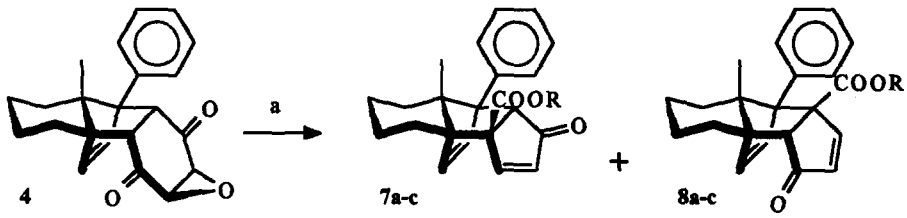
Scheme 1

Pure **6** was obtained in this way, in four steps starting from **2** and 1,4-benzoquinone, in 64% yield from 1,4-benzoquinone and without any chromatography. The chiral diene **2** was recovered in 90% yield. A similar but multistep route was used recently[7] in a synthesis of conduritol C, although with a symmetrical diene.

Our attempts to synthesize the corresponding cyclopropane failed, with Corey's reagent trimethyloxosulfonium ylide, as well as with the with diazomethane/palladium acetate or rhodium acetate. Enolization occurred with the former, while the latter did not react.

In addition to this sequence, we did examine the Favorskii rearrangement of epoxide **4**. This reaction has been described in the literature before[8,9], however, with symmetrical compounds only. In our case we expected regioselectivity and in the event treatment of **4** with potassium methoxide at 45°C turned out to be regioselective indeed (Scheme 2). A 95 : 5 ratio of the two isomers **7a** and **8a** was obtained in 81% yield, the ring contraction being preponderant opposite to the phenyl substituent. The isomer ratio was determined from the NMR signals of the tertiary proton next to the carbonyl group in **7a** and **8a**, which appeared at 4.31 and 3.21 ppm, respectively. The two

regioisomers could not be separated on silica, however one simple crystallization from petroleum ether/Et_2O and then Et_2O gave pure **7a**.



7a R = Me
b R = Et
c R = iPr

a K_2CO_3, ROH-THF-H_2O, 45-70°C, 75 mn-8 h (**7a**, 81% ; **7b**, 44% ; **7c**, traces).

Scheme 2

Unfortunately, we failed to improve the regioselectivity by changing to potassium ethoxide or isopropoxide : while the reaction rate was decreasing, the yield dropped, giving only a trace of **6c** with the isopropoxide at 70°C, without changing the regioselectivity. Crown ether 18-6 decreased the reaction time but did neither improve the yield nor the regioselectivity.

EXPERIMENTAL

Melting points were measured on a Büchi hotstage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200. MS assays (MS m/z) were obtained using a Finnigan MAT 312 spectrometer with an ionization potential of 70 eV. IR spectra were recorded in $CHCl_3$ or in KBr with a Perkin-Elmer 580. UV spectra were measured on a Beckmann 3600 spectrometer. Elemental analysis were obtained using a Heraeus CHN rapid analyzer. For flash chromatography Baker silica gel 30-60 μ was used, TLC analysis were carried out on DC aluminium foils, covered with silica gel $^{60}F_{254}$ (E. Merck) ; the spots were detected by UV (254 nm) an in addition to that by a dipping bath of Cer(IV)-sulphate/phosphormolybdic acid reagent. Optical rotations were measured on a Perkin-Elmer 241. Organic solvents were purified by standard procedures. Anhydrous THF was distilled from potassium/benzophenone and for the reaction which are air sensitive, air- and moisture-sensitive reactions were carried out in flame-dried reaction vessels under nitrogen using dry syringes.

Diels Alder reaction to (4a*S*,4b*S*,8a*R*,9*R*,9a*S*)-9a-methyl-9-phenyl-1,2,3,4,4b,8b,9,9a-octahydro-4a,9-etheno-4a*H*-fluorene-5,8-dione (3)

A solution of the diene **2** (5.00 g, 23.8 mmol) and 1,4-benzoquinone (2.57 g, 23.8 mmol) in freshly distilled CH_2Cl_2 (10 ml) was placed in a Teflon® tube and pressurized at 6.5

Kbar for 3 days at room temperature. Evaporation of the solvent and crystallization from CH_2Cl_2/Et_2O gave 7.19 g of the Diels Alder product **3** (95% yield), which was stored in the dark under inert atmosphere.

3 : **mp**=150-151°C (decomp.) ; $[\alpha]^{23}_D$=-329 (c=1.0, $CHCl_3$) ; **TLC** R_f (PE/Et_2O : 1/1)=0.65 ; **MS** m/z 318 (M^+, 2), 222 (13), 211 (100), 196 (41), 182 (33), 167 (65), 165 (39) ; **IR** ν^{-1} (KBr) 2950s, 1663s, 1607s, 1497s, 1446s, 1304s, 1119s, 751s, 700s cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 0.52 (bd, J=13 Hz, 1H), 0.81 (bs, 3H), 2.25 (bd, J=13 Hz, 1H), 3.15 (d, J=8 Hz, 1H), 4.07 (d, J=8 Hz, 1H), 5.96 (d, J=6 Hz, 1H), 6.12 (d, J=6 Hz, 1H), 6.47 (d, J=10 Hz, 1H), 6.55 (d, J=10 Hz, 1H), 7.22-7.42 (m, $w_{1/2}$=8 Hz, 5H) ; **^{13}C NMR** ($CDCl_3$) δ 15.0 (CH_3), 21.2 (CH_2), 23.6 (CH_2), 25.8 (CH_2), 27.9 (CH_2), 50.1 (CH), 52.9 (CH), 62.1 (C), 64.5 (C), 72.1 (C), 126.9 (CH), 127.8 (CH), 127.9 (CH), 136.3 (CH), 136.5 (C), 138.5 (CH), 141.7 (CH), 142.8 (CH), 198.5 (C), 199.4 (C) ; **UV** (CH_3CN) λ_{max} nm (ε) 229 (8900). **Microanalysis** calc. for $C_{22}H_{22}O_2$ (318.42) ; C, 82.99 ; H, 6.96. Found : C, 82.50 ; H, 6.93%.

Stereoselective epoxidation to (1a*R*,2a*S*,2b*S*,6a*S*,7*R*,7a*R*,8a*S*)-6a-methyl-7-phenyl-1a,2a,3,4,5,6,6a,7,7a,8a-decahydro-2b,7-etheno-2b*H*-fluoreno[2,3-*b*]oxirene-2,8-dione (4)

A solution of NaOH (314 mg, 7.85 mmol) and 30% H_2O_2 (800 µl, 7.85 mmol) in H_2O (4 ml) was added in one portion to a solution of **3** (500 mg, 1.57 mmol) in THF (16 ml) cooled to 0°C, with the help of an addition funnel. The mixture became homogeneous within 45 to 60 sec. and was extracted 3 times with CH_2Cl_2 (15 ml). The combined organic layers were washed 2 times with 5% aqueous $FeSO_4$ (20 ml), dried over $MgSO_4$ and evaporated to dryness, leading to pure **4** (515 mg, 98%), which was crystallized from CH_2Cl_2/Et_2O.

4 : **mp**=162-163°C ; $[\alpha]^{25}_D$=-176° (c=1.0, $CHCl_3$), **TLC** R_f (CH_2Cl_2)=0.46 ; **MS** m/z 334 (M^+,6), 239 (28), 221 (16), 210 (100), 167 (25), 69 (15) ; **IR** ν^{-1} ($CHCl_3$) 3048s, 2922s, 2859s, 1716s, 1443s, 771s, 694s cm^{-1} ; **^{1}H NMR** (CD_2Cl_2) δ 0.49 (bd, J=13 Hz, 1H), 0.79 (d, J=1 Hz, 3H), 3.43 (d, J=1 Hz, 1H), 3.51 (bt, J=4 Hz, 2H), 4.38 (d, J=10 Hz, 1H), 6.03 (d, J=6 Hz, 1H), 6.09 (d, J=6.0 Hz, 1H), 7.18-7.40 (m, $w_{1/2}$=29 Hz, 5H) ; **^{13}C NMR** (CD_2Cl_2) δ 15.2 (CH_3), 21.5 (CH_2), 23.7 (CH_2), 26.6 (CH_2), 27.9 (CH_2), 50.0 (CH), 50.7 (CH), 52.7 (CH), 58.6 (CH), 59.5 (C), 60.5 (C), 65.6 (C), 126.8 (CH), 127.2 (CH), 128.3 (CH), 138.5 (C), 138.6 (CH), 140.4 (CH), 203.7 (C), 204.9 (C) ; **UV** (MeOH) λ_{max} (ε) nm 264 (170), 258 (250), 252 (240), 246 (230), 218 (7000). **Microanalysis** calc. for $C_{22}H_{22}O_3$ (334.42) ; C, 79.02 ; H, 6.63. Found : C, 79.05 ; H, 6.70%.

Regioselective reduction to (1a*S*,2*R*,2a*S*,2b*S*,6a*S*,7*R*,7a*R*,8a*S*)-6a-methyl-7-phenyl-1a,2a,3,4,5,6,6a,7,7a,8a-decahydro-2b,7-etheno-2b*H*-fluoreno[2,3-*b*]oxirene-8(2*H*)-one (5)

To a solution of **4** (400 mg, 1.20 mmol) in dry toluol (8 ml) at -78°C was added a solution of L-Selectride® 1M in THF (1.2 ml, 1.20 mmol) dropwise and under inert atmosphere. After 5 to 10 min, the reaction mixture was poured into a 1M solution of NaOH (20 ml) and extracted 3 times with CH_2Cl_2 (10 ml). The organic phase was evaporated, dissolved in a small amount of CH_2Cl_2 (2 ml) and diluted with petroleum ether (20 ml). After

washing 2 times with water (20 ml), the organic phase was dried over $MgSO_4$ and evaporated to give **5** (394 mg, 98%), which was crystallized from CH_2Cl_2/Et_2O. A second crystallization was performed prior to the retro Diels-Alder experiment.

5 : mp=199-201°C ; $[\alpha]^{23}_D$=+8.8 (c=1.0, $CHCl_3$) ; TLC R_f (Et_2O)=0.30 ; MS m/z 336 (M^+, 14), 236 (34), 221 (43), 210 (97), 165 (38), 149 (100), 115 (37) ; IR ($CHCl_3$) ν^{-1} 3564w, 2928s, 1712s, 1444s, 1384s, 1088s cm^{-1} ; ^1H NMR (CD_2Cl_2) δ 0.54 (bd, J=13 Hz, 1H), 0.77 (d, J=1 Hz, 3H), 2.94 (dd, J_1=11 Hz, J_2=6Hz, 1H), 3.28 (d, J=4 Hz, 1H), 3.60 (dd, J_1=4 Hz, J_2= 3 Hz, 1H), 4.08 (d, J=11 Hz, 1H), 4.60-4.72 (m, $w_{1/2}$=13 Hz, 1H), 6.18 (bs, 2H), 7.17-7.37 (m, $w_{1/2}$=22 Hz, 5H) ; ^{13}C NMR (CD_2Cl_2) δ 15.7 (CH_3), 21.7 (CH_2), 23.6 (CH_2), 26.1 (CH_2), 28.3 (CH_2), 50.1 (CH), 54.5 (CH), 55.6 (CH), 60.1 (C), 60.2 (CH), 63.1 (C), 65.0 (C), 67.0 (CH), 126.7 (CH), 127.4 (CH), 128.3 (CH), 136.3 (CH), 139.1 (C), 140.1 (CH), 207.3 (C) ; UV (CH_3CN) λ_{max} (ε) 278 (350), 275 (390), 258 (480), 252 (490), 247 (480), 225 (4500). Microanalysis calc. for $C_{22}H_{24}O_3$ (336.43) ; C, 78.54 ; H, 7.19. Found : C, 78.37 ; H, 7.17%.

retro Diels-Alder reaction to (2*S*,3*S*,4*R*)-4-hydroxy-2,3-epoxycyclohex-5-en-1-one (6)

A 60 cm quartz thermolysis tube was connected with "O"-ring joints on a 25 ml flask containing crystals of **5** (162 mg, 0.48 mmol.) and on a cold trap, the thermolysis tube was heated to 300°C under a vacuum of 1.10^{-2} atm. The starting material was then heated to 250°C with the help of a kugelrohr apparatus, until it disappeared (about 15 min). We trapped 90% from a 1 : 1 mixture of the diene **2** and **6**. Crystallization from PE and Et_2O followed by a second one in Et_2O gave pure **6** (70%).

6 : mp=84-86°C ; $[\alpha]^{23}_D$=-341 (c=0.46, $CHCl_3$) ; TLC R_f (Et_2O)=0.31 ; MS m/z 126 (M^+, 11), 110 (15), 97 (100), 82 (16), 71 (29), 69 (50), 55 (46) ; IR (KBr) ν^{-1} 3235w, 2926s, 1683s, 1039s, 799s cm^{-1} ; ^1H NMR (CD_2Cl_2) δ 2.43 (bs, 1H), 3.44 (ddd, J_1=3.6 Hz, J_2=1.8 Hz, J_3=1.0 Hz, 1H), 3.78 (ddd, J_1=3.6 Hz, J_2=2.4 Hz, J_3=1.2 Hz, 1H), 4.68 (bs, 1H), 5.98 (ddd, J_1=10.4 Hz, J_2=2.0 Hz, J_3=1.2 Hz, 1H), 6.70 (ddd, J_1=10.4 Hz, J_2=4.6 Hz, J_3=2.4 Hz, 1H) ; UV (CH_3CN) λ_{max} (ε) 307 (400), 224 (3900). Microanalysis calc. for $C_6H_6O_3$ (126.11) ; C, 57.14 ; H, 4.80. Found : C, 56.91 ; H, 4.85%.

Favorskii rearrangement to methyl (3a*R*,3b*R*,7a*S*,8*R*,8a*S*)-7a-methyl-1-oxo-8-phenyl-5,6,7,7a,8,8a-hexahydro-1*H*-3b,8-ethenocyclopenta[*a*]indene-3a(4*H*)-carboxylate (7a) and methyl (3a*R*,3b*S*,7a*S*,8*R*,8a*S*)-7a-methyl-3-oxo-8-phenyl-4,5,6,7,7a,8-hexahydro-3*H*-3b,8-ethenocyclopenta[*a*]indene-8a(3a*H*)-carboxylate (8a)

To a solution of **4** (100 mg, 0.30 mmol) in THF (2 ml) was added K_2CO_3 (414 mg, 3.00 mmol) in H_2O/MeOH 1/1 (4 ml). The reaction mixture was heated at 45°C for 75 mn and cooled to room temperature. It was then extracted 3 times with Et_2O (10 ml) and dried over $MgSO_4$. After evaporation of the ethereal phase, chromatography over silica gel, eluted with petroleum ether/Et_2O gave **7a** and **8a** which were crystallized from Et_2O to give pure **7a** (84 mg, 81%).

7a : mp=167-168°C ; $[\alpha]^{23}_D$=-380 (c=1.0, $CHCl_3$) ; TLC R_f (MTBE/PE : 1/1)=0.51 ; MS m/z 348 (M^+, 32), 289 (20), 210 (100), 195 (50), 181 (40), 167 (75), 165 (53), 91 (50) ; IR ($CHCl_3$) ν^{-1} 2932m, 1724s, 1704s, 1444s, 1268s, 844s cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.71 (bd, J=13 Hz, 1H), 0.87 (d, J=1 Hz, 3H), 3.78 (s, 3H), 4.31 (s, 1H), 5.83 (d, J=6 Hz, 1H), 5.88 (d, J=6 Hz, 1H), 6.62 (d, J=6 Hz, 1H), 7.32 (d, J=6 Hz, 1H), 7.22-7.46 (m, $w_{1/2}$=18 Hz, 5H) ; ^{13}C NMR ($CDCl_3$) δ 15.6 (CH_3), 21.2 (CH_2), 23.7 (CH_2), 25.2 (CH_2), 32.1 (CH_2), 52.5 (CH), 55.4 (CH_3), 63.3 (C), 67.6 (C), 68.5 (C), 69.6 (C), 126.9 (CH), 127.8 (CH), 128.0 (CH), 135.5 (CH), 136.7 (C), 137.3 (CH), 138.7 (CH), 161.8 (CH), 172.3 (C), 208.1 (C) ; UV (CH_3CN) λ_{max} (ε) 237 (6000), 226 (7000). **Microanalysis** calc. for $C_{23}H_{24}O_3$ (348.45) ; C, 79.28 ; H, 6.94. Found : C, 79.23 ; H, 6.90%.

Ethyl (3a*R*,3b*R*,7a*S*,8*R*,8a*S*)-7a-methyl-1-oxo-8-phenyl-5,6,7,7a,8,8a-hexahydro-1*H*-3b,8-ethenocyclopenta[*a*]indene-3a(4*H*)-carboxylate (7b)

7b : TLC R_f (PE/Et_2O : 1/1)=0.32 ; MS m/z 362 (M^+, 2), 289 (2), 245 (8), 210 (6), 200 (17), 91 (86), 85 (88), 83 (100) ; IR ν^{-1} ($CHCl_3$) 2932m, 2864s, 1716s, 1700s, 1584s, 1460s, 1444s, 1384s, 1332s, 1268s, 1132s, 908s, 620m cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.71 (bd, J=13 Hz, 1H), 0.88 (d, J=1 Hz, 3H), 1.32 (t, J=7 Hz, 3H), 4.24 (q, J=7 Hz, 2H), 4.30 (s, 1H), 5.82 (d, J=5 Hz, 1H), 5.97 (d, J=5 Hz, 1H), 6.02 (d, J=6 Hz, 1H), 7.34 (d, J=6 Hz, 1H), 7.22-7.45 (m, $w_{1/2}$=16 Hz, 5H) ; **Microanalysis** calc. for $C_{24}H_{26}O_3$ (362.47) ; C, 79.53 ; H, 7.23. Found : C, 79.50 ; H, 7.33%.

Acknowledgement : We are grateful to the *Alexander Von Humboldt foundation* for a post-doctoral fellowship to A.M..

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