## A NEW STEREO- AND REGIOSELECTIVE SYNTHESIS OF (±)-SESAMIN INVOLVING A $\beta$ -SCISSION OF ALKOXYL RADICALS AS THE KEY STEP<sup>1</sup>

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Abstract: A new stereo- and regioselective synthesis of  $(\pm)$ -sesamin (a representative lignan) based on our general method for the transformation of a cyclopentanone ring into a tetrahydrofuran ring involving a regioselective  $\beta$ -scission of the alkoxyl radicals is reported

The 2,6-diaryl-3,7-dioxabicyclo[3 3 0]octanes comprise the largest group of lignans<sup>2</sup> to which many biologically-active natural products belong <sup>3</sup> Sesamin<sup>4</sup> is one of the representative lignans which have been known for many years. The first synthesis of this interesting molecule was achieved by Beroza<sup>5</sup> and by Freudenberg<sup>5</sup>, an enantio-controlled synthesis of (-)-sesamin has recently been reported <sup>6</sup>

In this paper we report on a new stereo- and regioselective synthesis of  $(\pm)$ -sesamin 11 A method for the transformation of a cyclopentanone ring into a tetrahydrofuran ring involving a regioselective  $\beta$ -scission of the alkoxyl radicals (previously reported by us<sup>7</sup>) was applied to the key step in this synthesis The sequence is outlined in Schemes 1 and 2

The lithiation of 4-bromo-1,2-methylenedioxybenzene 1 with butyllithium followed by a reaction of the resulting lithio derivative with tributyltin chloride (according to the procedure by Locksley and collaborators<sup>8</sup>) gave 3,4-methylenedioxytributyltinbenzene 2 in 52% yield Treatment of the tributyltinbenzene 2 with lead tetraacetate<sup>9</sup> in dichloromethane for 25 h at 46°C under ultrasonication in an ultrasonic cleaner gave crystalline 3,4-methylenedioxyphenyllead triacetate  $3^{10}$  in 94% yield (Scheme 1)

According to the procedure modified the method<sup>11</sup> developed by Pinhey and collaborators, 3,4-methylenedioxyphenyllead triacetate **3** and dibenzyl 3,7-dioxobicyclo[3 3 0]octane-2,6-dicarbonate  $5^{12}$  (prepared in 72% yield by heating dimethyl 3,7-dioxabicyclo[3 3 0]octane-2,6-dicarbonate  $4^{13}$  and excess benzyl alcohol in dry toluene containing a catalytic amount of 4-dimethylaminopyridine (4-



Scheme 1. Reagents and conditions 1, BuL1 - Et<sub>2</sub>O,  $-78^{\circ}$ C 11, Bu<sub>3</sub>SnCl - Et<sub>2</sub>O, reflux 11, Pb(OAc)<sub>4</sub> - CH<sub>2</sub>Cl<sub>2</sub>, 46°C



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(11)

1,  $C_6H_5CH_2OH - 4-DMAP$  - toluene, reflux 11, 3,4-OCH<sub>2</sub>OC<sub>6</sub>H<sub>3</sub>Pb(OAc)<sub>3</sub> - pyridine - CH<sub>2</sub>Cl<sub>2</sub>, reflux 111, 10% Pd-C - H<sub>2</sub> - MeOH, 25°C 11v, MCPBA - CH<sub>2</sub>Cl<sub>2</sub>, 25°C v, DIBAL - CH<sub>2</sub>Cl<sub>2</sub>, -78°C v1, HgO - I<sub>2</sub> - benzene, 25°C v11, hv > 300 nm v111, NaBH<sub>4</sub> - MeOH, reflux

DMAP) under reflux for 16 h according to the method by Taber and collaborators<sup>14</sup>) in dry dichloromethane were heated under reflux in an atmosphere of nitrogen for 24 h under ultrasonication in an ultrasonic cleaner to give dibenzyl [2,5-bis(3,4methylene-dioxyphenyl)]-3,7-dioxobicyclo[3 3 0]-octane-2,6-dicarbonate  $6^{15}$  in 72% yield Hydrogenolysis of the dibenzyl dicarbonate 6 in the presence of a 10% palladium on carbon in methanol in an atmosphere of hydrogen for 20 h resulted in a spontaneous loss of CO<sub>2</sub> to give 2,6-[bis(3,4-methylenedioxyphenyl)]-3,7-dioxobicyclo[3 3 0]octane  $7^{16}$  in 74% yield Irradiation of the signal at  $\delta$  3 11 (1 $\alpha$ -H and  $5\alpha$ -H) in the <sup>1</sup>H NMR spectrum resulted in an enhancement of the areas of the signals at  $\delta$  2 72 (4 $\alpha$ -H), 6 61 (6'-H) and 6 63 (2'-H) This NOE measurement established the *cis* disposition of the two methylenedioxyphenyl groups as well as the angular hydrogens, as outlined in Scheme 2

The Baeyer-Villiger oxidation of 2,6-diaryl-3,7-dioxabicyclooctane 7 with MCPBA (*meta*-chloroperbenzoic acid) in dichloromethane at room temperature for 10 days gave 2,7-bis(3,4-methylenedioxyphenyl)-3,8-dioxabicyclo[4 4 0]decane-4,9-dione  $8^{17}$  in 28% yield <sup>18</sup>

The reduction of dilactone 8 with DIBAL in dichloromethane at -78°C for 35 h gave 2,7-bis(3,4-methylenedioxyphenyl)-3,8-dioxabicyclo[4 4 0]decane-4,9-diol  $9^{19}$  in 44% yield <sup>18</sup> The dilactol 9 in benzene was first treated with mercury(II) oxide and iodine (each 3 equivalents) in benzene, the resulting hypoiodite in benzene was then irradiated with a 100-W high pressure Hg arc through a Pyrex-filter for 12 h at room temperature (according to a procedure of Suginome and Yamada<sup>7</sup>) to give an oily iodo-formate 10 The <sup>1</sup>H NMR of the formate 10 exhibited formyl protons at 8 13 The crude iodo-formate 10, obtained by the usual work-up, was immediately dissolved in methanol containing NaBH<sub>4</sub> The solution was then heated under reflux for 12 h to give (±)-sesamin<sup>20</sup> (28% from dilactol 9 Its <sup>1</sup>H and <sup>13</sup>C NMR spectra were in agreement with those published in the literature <sup>21-23</sup>

The present method may be generally applicable to the synthesis of a variety of 2,6-diaryl-3,7-dioxabicyclo[330]octane lignans with the geometry of the natural series and with their two 2,6-diaryl groups substituted symmetrically by alkoxyl and/or hydroxyl groups  $^{24}$ 

## **REFERENCES AND NOTES**

- 1 Photoinduced Molecular Transformations Part 125 Part 124 K Kobayashi, A Sasaki, Y Kanno, and H Suginome, *Tetrahedron*, in press
- 2 For a review, D A Whiting, Nat Prod Rep , 1985, 2, 191
- 3 For a review, W D MacRae and G H N Towers, Phytochem, 1984, 23, 1207
- Isolation S H Bertram, J P K van der Steur, and H I Waterman, Biochem Z, 1928, 197, 1, K Peinemann, Arch Pharm, 1896, 234, 238 Structure W D Cohen, Rec Trav Chim, 1938, 57, 653, F von Bruchhausen and H Gerhard, Ber, 1939, 72, 830 Stereochemistry K Freudenberg and G S Sidhu, Ber, 1961, 94, 851, E D Becker and M Beroza, Tetrahedron Lett, 1962, 157

- 5 M Beroza and M S Schechter, J Am Chem Soc, 1956, 78, 1242, K Freudenberg, and E Fischer, Naturwiss, 1956, 43, 16, Ber, 1956, 89, 1230
- 6 S Takano, T Ohkawa, S Tamori, S Satoh, and K Ogasawara, J Chem Soc, Chem Communn, 1988, 189
- 7 H Suginome and S Yamada, J Org Chem, 1985, 50, 2489
- 8 H Halim, H D Locksley, and J J Memon, J Chem Soc, Perkin Trans 1, 1980, 2331
- 9 R P Kozyrod and J T Pinhey, Tetrahedron Lett, 1983, 24, 1301
- 10 Mp 117~118°C
- 11 J T Pinhey and B A Rowe, Aust J Chem, 1979, 32, 1561, 1980, 33, 113, 1983, 36, 789, Tetrahedron Lett, 1980, 21, 965
- M p 104~106°C (methanol) <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 2 40~3 70 (6H, m, 1-, 4-, 5-, and 8-H), 3 50~3 58 (2H, m, 2- and 6-H), 5 18 and 5 25 (each 2H, each d, J 8 8 Hz, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7 36 (10H, s, aromatic H)
- 13 a) S P Bahtnagar and U Weiss, J Org Chem, 1977, 18, 3089 b) S H Bertz, G Rihs, and R B Woodward, Tetrahedron, 1982,38, 63
- 14 D F Taber, J C Amedio, Jr, and Y K Patel, J Org Chem, 1985, 50, 3618
- 15 M p 153-155°C (dichloromethane-diethyl ether) IR (Nujol) 1763 and 1738 cm<sup>-1</sup>, <sup>1</sup>H NMR (270 MHz)  $\delta$  2 26 (2H, dd, J 20 2 and 9 2 Hz, 4 $\beta$  and 8 $\beta$ -H), 2 72 (1H, ddd, J 20 2, 7 7, and 2 9 Hz, 4 $\alpha$  and 8 $\alpha$ -H), 3 45 (2H, ddd, J 9 2, 5 98 and 6 00 (each 2H, each d, J 1 1 Hz, -OCH<sub>2</sub>O-), 6 81 (2H, d, J 0 7 Hz, 2'-H), 6 81 (2H, d, J 1 5 Hz, 5'-H), and 6 85 (2H, dd, J 1 5 and 0 7 Hz, 6'-H)
- 16 M p 215-217°C (dichloromethane-diethyl ether) <sup>1</sup>H NMR (270 MHz)  $\delta$ 2 62 (2H, d, J 19 5 Hz, 4 $\beta$ -H and 8 $\beta$ -H), 2 72 (2H, dd, J 19 5 and 4 4 Hz, 4 $\alpha$ -H and 8 $\alpha$ -H), 3 11 (2H, d, J 4 4 Hz, 1 $\alpha$ -H and 5 $\alpha$ -H), 3 12 (2H, br s, 2 $\beta$ -H and 6 $\beta$ -H), 5 97 (4H, s, two methylenedioxy groups), 6 61 (2H, dd, J 7 8 and 1 9 Hz, 6'-H), 6 63 (2H, d, J 1 9 Hz, 2'-H), and 6 81 (2H, d, J 7 8 Hz, 5'-H)
- 17 M p > 300°C (2 1 dichloromethane-methanol) IR (Nujol) 1734 cm<sup>-1</sup>, <sup>1</sup>H NMR (270 MHz)  $\delta$  2 24 (2H, dd, J 15 2 and 6 2 Hz, 5 $\alpha$ - and 10 $\alpha$ -H), 2 35 (2H, dd, J 15 2 and 10 9 Hz, 5 $\beta$ - and 10 $\beta$ -H), 2 66 (2H, m, 1 $\alpha$ - and 6 $\alpha$ -H), 4 94 (2H, d, J 10 3 Hz, 2 $\beta$ - and 7 $\beta$ -H), 6 02 (4H, s, -OCH<sub>2</sub>O-)
- 18 The remaining products were ill-defined compounds
- 19 M p 200~203°C (methanol), IR (Nujol) 3372 cm<sup>-1</sup> (OH)
- 20 M p 129~130°C (ethanol), <sup>1</sup>H NMR (270 MHz)  $\delta$  3 05 (2H, ddd, J 7 3, 4 4, and 3 9 Hz, 1- and 5-H), 3 87 (2H, dd, J 9 3 and 3 9 Hz, 4 $\alpha$  and 8 $\alpha$ -H), 4 23 (2H, dd, J 7 8 Hz, 5'-H), 6 80 (2H, dd, J 7 8 and 6 5 Hz, 6'-H), and 6 85 (2H, d, J 1 5 Hz, 2'-H)
- 21 K Takahashi and T Nakagawa, Chem Pharm Bull, 1966, 14, 641
- 22 K Weinges and R Sanig, Chem Ber, 1968, 101, 3010
- 23 A Pelter, R S Ward, D J Watson, P Collins, and I T Kay, J Chem Soc Perkin Trans 1, 1982, 175
- 24 All the new compounds described in this paper gave satisfactory combustion or high resolution mass spectrometric data

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