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Access to the spiro hydrindandione ring system of Fredericamycin A through spiroalkylation and oxidation.

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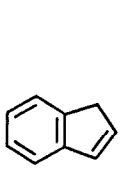
ABSTRACT : *Indene could be spiro alkylated with bis-1,2-bromomethyl benzene derivatives. Further functionalization of the benzylic positions led to the dihydroxy dibenzospiro 4,4 nonane dione ring system of Fredericamycin A.*

A second access to the spiro hydrindandione system of Fredericamycin A (see preceding letter) was based on the spiro alkylation of indene (1) with 1,4-dibromoderivatives.

Indene 1 could be spiro alkylated with 1,2-bisbromomethyl benzene 2a using a modification of Makosza's two phase procedure (2) to give 3a m.p. 88-90°C (MeOH).

The Kharasch-Sosnovsky reaction (3) (excess $(tBuO)_2$; AcOH ; PhCl ; CuBr, 3 days 110°C) led mainly (51% yield (7)) to mono acetoxylation 7a. After hydrolysis, hydrogenation of the double bond and oxidation, monoketone 8 was obtained (54% yield for the 3 steps).



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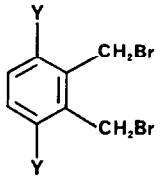
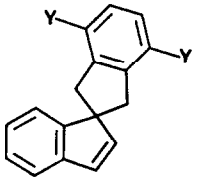
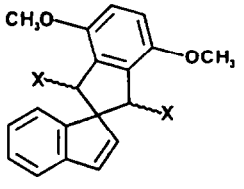


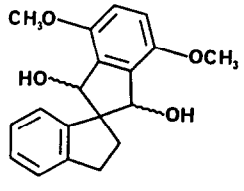
2a Y = H
2b Y = OCH_3



3a Y = H
3b Y = OCH_3



4a X = Br
4b X = OAc
4c X = OH



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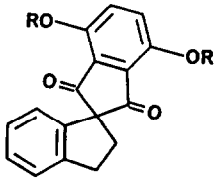
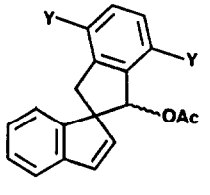
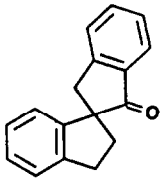


6a R = CH_3
6b R = H



7a Y = H
7b Y = OCH_3



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2,3-Bis(bromomethyl)-1,4-dimethoxybenzene 2b (4) and indene reacted (THF, aq. NaOH 50% ; trimethylbenzylammonium hydroxide, 50°C, 4h) to give the spiro compound 3b (34%)(m.p. 75-76°C).

The Kharasch-Sosnovsky reaction again led to monofunctionalization 7b (yield 58% (7). Bromination of 3b (NBS, CCl_4) however gave mainly a mixture of 1,3-dibromoderivatives 4a (hydrindane numbering) which was treated with silver acetate (AcOH, reflux, 4h)(5). Conversion of the diacetates 4b into the diols 4c was achieved with lithium aluminium hydride in ether at room temperature. Catalytic hydrogenation of the double bond (Pd/C/5% ; Et_2O ; 50 bar) gave the corresponding saturated diols 5 which were readily oxidized (PCC, CH_2Cl_2, at room temperature (6)) to give the dione 6a after chromatography (m.p. 249°C with decomposition (MeOH, Et_2O)).

This compound proved identical with the sample prepared in the accompanying letter. It could be demethylated ($AlCl_3$, benzene, 50°C, 6h) to give 6b (63%)(m.p. 179-180°C (heptane)). The overall yield from 3b to 6a was 20% (not optimized).

Thanks are due to the CNRS (LA32) for generous support and for a scholarship (to B.P.) and to the Rhone Poulenc Company for a scholarship (to G.E.).

All the compounds gave analytical results ^1H, ^{13}C NMR, MS in agreement with their proposed structure.

3b ^{13}C NMR : δ($CDCl_3$) : 151.6 ; 150.1(2C) ; 144.3 ; 142.7 ; 132(2C) ; 128.3 ; 126.5 ; 125.1 ; 120.8(2C) ; 108.9(2C) ; 60 ; 55.6(2C) ; 38.4(2C).

^1H NMR δ($CDCl_3$) : 3.21(s,4H) ; 3.81(s,6H) ; 6.56(d,1H,J=5.Hz) ; 6.73(d, 1H,J=5.5Hz) ; 6.75 (s,2H) ; 7.14 to 7.4(m,4H).

MS(EI) m/z : 278(100) ; 247(94) ; 263(57) ; 202(50) ; 203(46).

6a ^{13}C NMR δ($CDCl_3$) : 198.8(2C) ; 151.1(2C) ; (145.3 ; 141.7 ; 129.7)(4C) ; 127.8 ; 126.3 ; 124.8 ; 122.6 ; 119.9(2C) ; 67.4 ; 56.5(2C) ; 32.9 ; 32.1.

^1H NMR δ($CDCl_3$) : 2.55(t,2H,J=7.5Hz) ; 3.28(t,2H,J=7.5Hz) ; 4.02(s,6H,OCH_3) ; 6.76(d,1H, 7Hz) ; 7.09(d,d,1H,7Hz) ; 7.24(d,d,1H,7Hz) ; 7.36(d,1H, 7Hz) ; 7.36(s,2H).

MS(EI) m/z : 308(100) ; 115(36) ; 163(26) ; 76(26) ; 309(25) ; 193(24).

6b ^1H NMR($CDCl_3$) : 2.58(t,2H,J=7.5Hz) ; 3.32(t,2H,J=7.5Hz) ; 6.85(d,1H,J=7Hz) ; 7.2(d,d,1H, J=7Hz) ; 7.33(s,2H) ; 7.34(d,d,1H,J=7Hz) ; 7.43(d,1H,J=7Hz).

MS(EI) m/z : 280(100) ; 115(84) ; 265(42) ; 108(32) ; 116(29).

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