Tetrahedron Letters No. 35, pp 3309 - 3310.

0040-4039/79/0822-3309$02.00/0

A NEW STEREOCONTROLLED SYNTHESIS OF D-RING AROMATIC STEROID.

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Summary: D-Ring aromatic steroid (11) having 19-methyl and C_6-nitro group has been stereoselectively synthesised by an intramolecular cycloaddition of the o-quinodimethane (A) derived thermally from 5-acetoxy-2-[2-(1-cyano-4-methoxybenzocyclobutenyl)-1-nitroethyl]-1-ethenyl-1-methylcyclohexane (10).

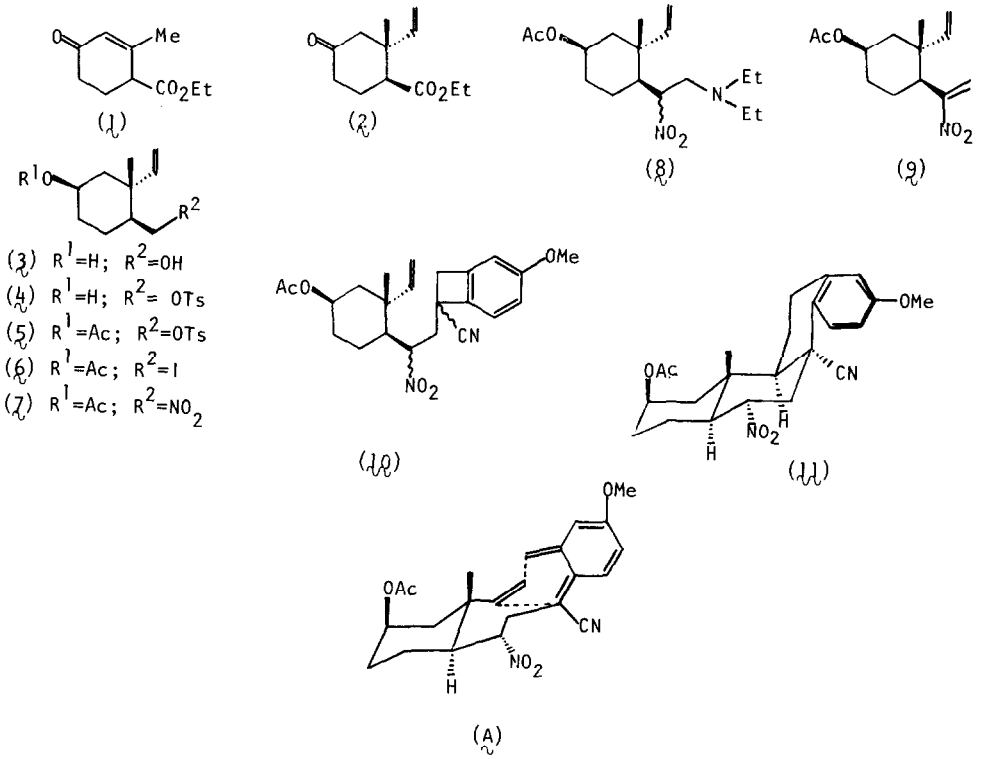
The intramolecular cycloadditions of o-quinodimethanes have been successfully applied to the synthesis of polycyclic natural products and A-ring aromatic steroids, and the compounds thus obtained were the target molecules of choice for several groups including ourselves[1-3], mainly because of pharmaceutically interesting activity as sex hormones. As none of these provides an efficient route to the steroid having 19-methyl group, we have investigated the synthesis of D-ring aromatic steroids having 19-methyl and a nitro group at C_6-position. Here, we wish to report a new stereocontrolled synthesis of D-ring aromatic steroid.

The olefinic ester (2) [ir 1725 cm^{-1}, NMR (CCl_4) 1.1 (3H, s, Me) and 4.7 - 6.1 (3H, m, olefinic-H), m/e 210 (M^+)], prepared by 1,4-addition of vinylmagnesium bromide, in the presence of CuI, to Hagemann's ester (1)[4], was converted into the tosylate (5) via the diol (3) and hydroxy tosylate (4) in the usual manner by successive reduction ($LiAlH_4$ in THF), tosylation (TsCl in pyridine) and acetylation (Ac_2O in pyridine). The tosylate (5) was then transformed into the nitro derivative (7) [ir 1725, 1550, and 1380 cm^{-1}, m/e 241 (M^+)] through the iodide (6), by successive treatment of (5) with NaI in acetone and $NaNO_2$ in DMF. The nitro derivative (7) on reaction with formalin and diethylamine gave the Mannich base (8) which was treated with hydrogen chloride in boiling benzene to afford the nitro olefin (9) [ir 1725 cm^{-1}, NMR (CCl_4) 1.1 (3H, s, Me), 4.6 - 6.0 (4H, m, olefinic-H), and 6.4 br (1H, s, olefinic-H), m/e 253 (M^+)]. Michael addition of 1-cyano-4-methoxybenzocyclobutene[5] to the nitro olefin (9) in the presence of $NaNH_2$ in liq. NH_3 yielded the key intermediate (10)[6] [ir 2230, 1752, 1550 and 1360 cm^{-1}, NMR (CCl_4) 1.2 (3H, s, Me), 2.0 (3H, s, COMe), 7.77 (3H, s, OMe), 4.6 - 6.0 (4H, m, olefinic-H and $CHNO_2$), and 6.5 - 7.2 (3H, m, Ar-H), m/e 412 (M^+)] which was heated in o-dichlorobenzene at 180°C for 2 h in a current of nitrogen to afford the D-ring aromatic steroidal compound (11) as an oil [ir 2220, 1725, 1550, and 1360 cm^{-1}, NMR (CCl_4) 0.35 (3H, s, Me), 1.77 (3H, s, COMe), 3.8 (3H, s, OMe), 4.5 (1H, distorted t, J=12 Hz, $CHNO_2$), 5.1 br (1H, s, CHOAc) and 6.7 - 7.5 (3H, m, Ar-H), m/e 412 (M^+)] in 94 % yield.

The signals which could be attributed to C_2-H and C_6-H were observed at 5.1 and 4.5 ppm as broad singlet and distorted triplet in the nmr spectrum, respectively, indicating acetoxy and nitro groups to be oriented as axial and equatrial respectively and the fact that the methyl group resonated at abnormally high field in the nmr spectrum suggested the stereochemistry of this product (11) to be that shown in scheme 2, in which the methyl group is located over the benzene ring and could be

shielded by its ring current. Although the possible intermediate leading to compound (11) is thought to be the o-quinodimethane (A), the details of this reaction mechanism is now under investigation.

Scheme



REFERENCES

1. W. Oppolzer, Synthesis, 798 (1978). References cited therein.
2. R. L. Funk and K. P. C. Vollhardt, J. Amer. Chem. Soc., 101, 215 (1979).
3. T. Kametani, H. Nemoto, M. Tsubuki, and M. Nishiuchi, Tetrahedron Letters, 27 (1979).
4. L. I. Smith and G. F. Rouault, J. Amer. Chem. Soc., 65, 631 (1943).
5. T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, J. Amer. Chem. Soc., 98, 8185 (1976).
6. All the reaction sequences from (1) to (10) proceeded in moderate to high yields.

(Received in Japan 24 May 1979)