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INTRAMOLECULAR REACTIONS OF COMPOUNDS DERIVED FROM SUGARS. PART III.[1] HIGH DIASTEREOSELECTION IN THE INTRAMOLECULAR DIELS-ALDER REACTION OF SUGAR BASED 1,7(E,Z),9-DECATRIENES

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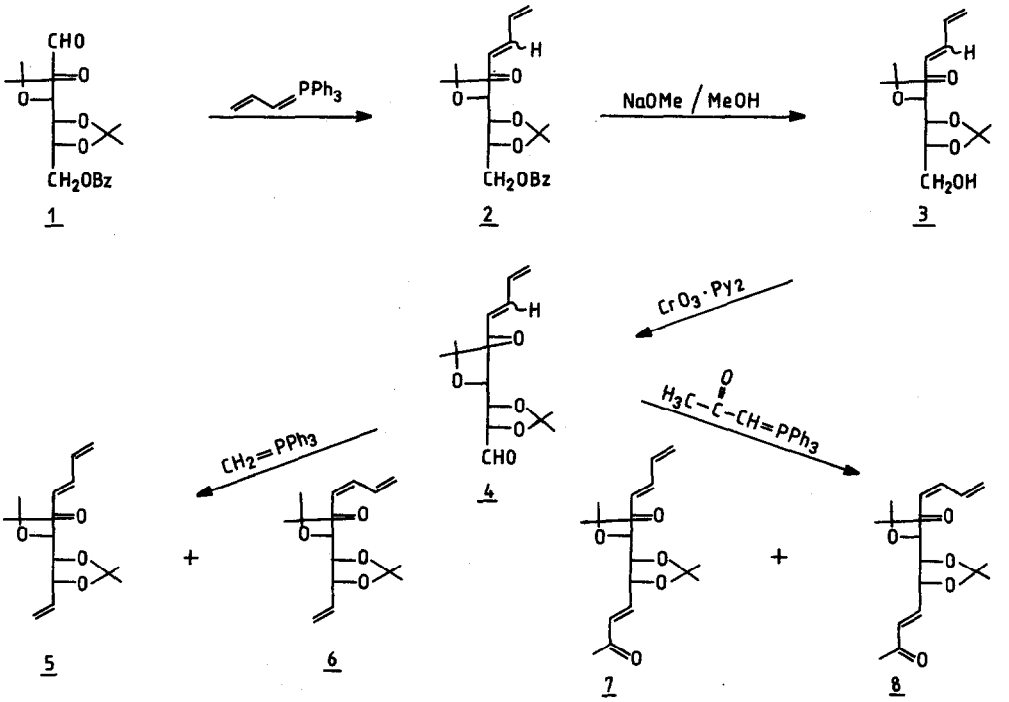
Abstract: A mixture of tetrachiral deca-1,7E,9-triene 5 and its 7Z isomer 6 was prepared from D-glucose by the use of two Wittig olefination reactions. When 5 or 6 were subjected to intramolecular Diels-Alder reaction under thermal conditions the same, cis-fused octahydronaphtalene enantiomer 9 was formed exclusively. This phenomenon can be explained by Z→E isomerization of 6 to 5. Similarly, when a mixture of trienones 7 and 8 was heated at 160° the formation of a single product 10 was observed. Stereochemical outcome of the reactions can be rationalized by inspection of the possible conformers leading to transition states.

A great number of papers have been published in the past decade dealing with the use of intramolecular Diels-Alder reactions for the synthesis of complex natural products[2,3]. Numerous efforts have been made to elaborate very highly stereocontrolled versions of this reaction[4-10].

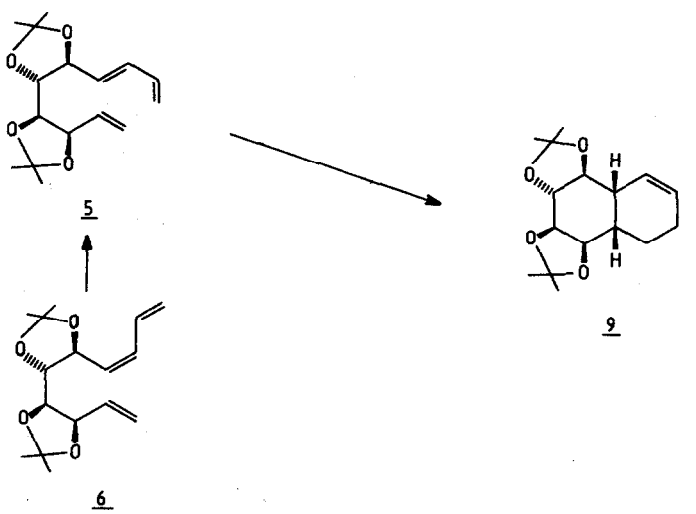
Recently we have observed exceptionally good diastereoselection in the intramolecular Diels-Alder cyclizations of a 1,6(E,Z),8-nonatriene and of a 1-aza-6(E,Z),8-nonatriene[1,11], both prepared from D-xylose. Since it can be assumed that alkoxy substituents on the linking chain exert a strong directing effect on the cyclization we have continued to study that influence on other sugar based trienes.

The decatrienes 5, 6, 7 and 8 were synthesized from 1 which can be prepared[12] from D-glucose. Reaction of 1 with allylidenetriphenylphosphorane[13] led to an inseparable mixture of 2 E and Z dienes. These last two were debenzoylated with sodium methoxide in methanol to give 3. Oxidation of 3 with chromium(VI) oxide dipyridine[15] afforded the aldehyde 4 which in a reaction with methylenetriphenylphosphorane[13] resulted a mixture of trienes 5 and 6. These could be separated partially by column chromatography.

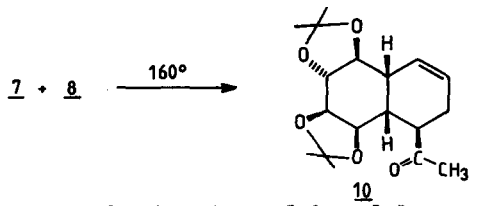
Reaction of 4 with acetylmethylenetriphenylphosphorane[14] led to the formation of a 5:1 mixture of the trienes 7 and 8.



When the E isomer triene 5 was heated at 160° for 16 h in toluene it gave the cis-fused octahydronaphtalene isomer 9 exclusively, in a 89.7 % yield. Interestingly, under similar conditions 6 resulted the same product.

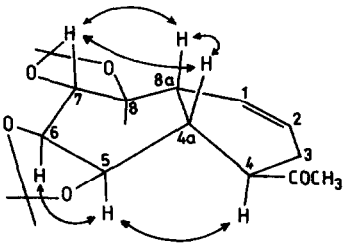


When the inseparable mixture of 7 and 8 was subjected to the thermal cyclization, 10 was formed as the sole product.

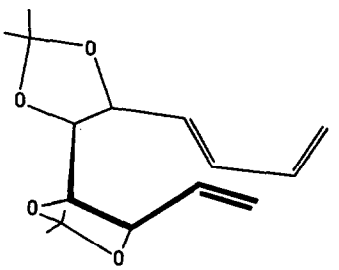


10

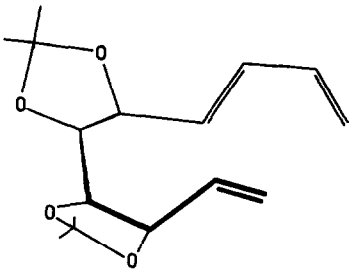
The assigned stereochemistries of 9 and 10 could be supported by NOE experiments and ^{1}H-NMR coupling constants. On irradiation of H-7 NOE enhancements were observed for H-4a and H-8a signals and conversely, upon irradiation of H-4a or H-8a similar effects were obtained. Analogous interactions could be detected for H-4 and H-5 in the case of 10. For octahydronaphtalenes of such a type the values of the $J_{4a,8a}$ coupling constants are usually less then 4 Hz in the cis-fused species and 11 Hz for the trans-fused ones. For 9 and 10 the $J_{4a,8a}$ is about 7-8 Hz. Having compared all of the coupling constants with the molecular model it was concluded that because of the presence of dioxolane rings presumably the cyclohexane ring adopts a distorted boat conformation. In this case all of the oxygen substituents can be found in equatorial positions. Axial orientation of C-4 acetyl group in 10 can be supported by the $J_{4,4a} \simeq J_{3ax,4} \simeq J_{3eq,4} \simeq 3$ Hz coupling constants.



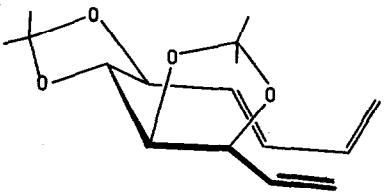
The high diastereoselectivity of these cyclizations can be explained by the inspection of the possible conformations for E and Z dienes leading to transition states. For the 7E isomer conformation A seems to be the most favourable one, because the oxygens are oriented equatorially. In the case B steric repulsion between the diene and the adjacent substituent can occur. For C and D axial position of the substituents on the linking chain is strongly destabilizing. It is interesting to note that there are only a few reports on such cases where an intramolecular Diels-Alder reaction proceeds via boat conformation. Recently Roush and Coe[4] have given evidence of an example similar to our findings. However, in our products the boat conformation seemed to be preserved.



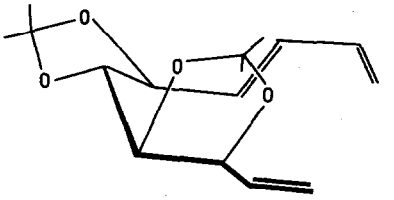
A



B

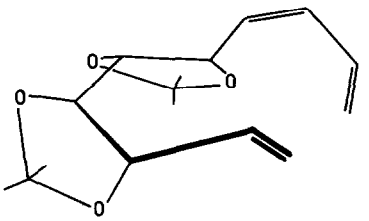


C

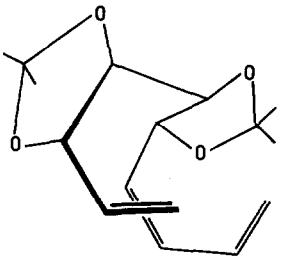


D

Conformations A' and B' for the 7Z isomer are very strained, and product formation is improbable.



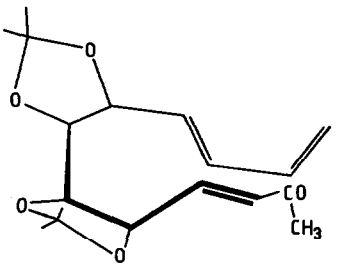
A'



B'

Nevertheless, a heating of 6 led to the formation of the same 9, and therefore a thermal isomerization of 6 to 5 could be assumed. Indeed, upon heating of 6 at 160°, GC-MS monitoring of the mixture showed simultaneous formation of 5 and 9. This phenomenon is rare: the only experimentally supported examples until now have been reported by Borch et al.[16].

For 7 the most probable conformation leading to 10 is the following one:



The high diastereoselectivity of the cyclizations of sugar based trienes presents the importance of the directing effects of the linking chain substituents. Since they led enantiomerically pure, multichiral products, their use in the synthesis of complex, natural products seems to be promising.

EXPERIMENTAL

General methods: Melting points were measured on a Kofler block and are uncorrected. Kieselgel 60 was used for column chromatography. Infrared spectra were obtained on a Perkin-Elmer 283B spectrometer. Proton NMR spectra were taken with a Bruker WP-200 SY instrument at 200 MHz. GC-MS measurements were carried out with a VG-7035 spectrometer operated at 70 eV and a Hewlett-Packard 5710A gas chromatograph equipped with a 6 ft. column filled with OV-101 on Chromosorb W-HP (80/100). Elemental analyses were performed in our microanalytical department. Optical rotations were measured with a Perkin-Elmer 141 MC polarimeter.

(2R,3R,4R,5S)-1-O-Benzoyl-2,3:4,5-di-O-methylethylidene-nona-6(E,Z),8-diene-1,2,3,4,5-pentaol 2 : Allyltriphenylphosphonium bromide (9.8 g, 25.6 mmol) in dry toluene (100 mL) was treated with 1.6 M n-butyllithium (15.6 mL, 25 mmol) for 1 h under nitrogen. 1 (6.66 g, 18.3 mmol) was added in toluene (10 mL) and the mixture was stirred for 1.5 h. After filtration it was washed with water, dried ($MgSO_4$) and the crude product was fractionated on a column using hexane-ether 8:2 mixture as eluent to afford 3.45 g (46.8%) of 2 as a syrup, containing E and Z isomers. MS m/e: 389 (M^+). Anal.: Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 68.12; H, 7.14.

(2R,3R,4R,5S)-2,3:4,5-Di-O-methylethylidene-nona-6(E,Z),8-diene-1,2,3,4,5-pentaol 3: 2 (3.7 g) was debenzoylated in dry methanol (30 mL) using a catalytic amount of sodium methoxide. After 12 h at room temperature a few grams

of dry ice was added, the solvent was evaporated and the residue was chromatographed using chloroform and hexane-aceton 7:3 mixtures successively to give 2.5 g (92.6 %) of 3 as a syrup. IR: 3440 cm^{-1} (OH). MS m/e: 269 (M^+-CH_3). Anal. : Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.10; H, 8.48.

(2S,3S,4R,5S)-2,3:4,5-Di-O-methylethylidene-nona-6(E,Z),8-diene-1-al-2,3,4,5-tetraol 4: Chromium(VI) oxide (3.38 g, 0.034 mol) was added to a stirred solution of pyridine (5.45 mL, 0.069 mol) in dry dichloromethane (50 mL). After 15 min 3 (2.4 g, 0.0085 mol) was added in the same solvent (10 mL). After 15 min the reaction mixture was poured onto the top of a silica column in ethyl acetate and the product was eluted with the same solvent to give 4 (2.18 g, 91 %) sufficiently pure for the next step. IR: 1730 cm^{-1} (C=O). MS m/e: 267 (M^+-CH_3). ^{1}H-NMR ($CDCl_3$): δ 9.64 (d, 1H, -CHO) ppm.

(3R,4R,5R,6S)-3,4:5,6-Di-O-methylethylidene-deca-1,7(E),9- and 1,7(Z),9-triene-3,4,5,6-tetraols 5 and 6: 1.6 M n-butyllithium solution (1.9 mL, 0.003 mol) in hexane was added to a stirred suspension of methyltriphenylphosphonium bromide (1.24 g, 0.0035 mol) in toluene (30 mL) under nitrogen. After 0.5 h a solution of 4 (0.65 g, 0.0023 mol) in toluene (10 mL) was dropped to the mixture. In 5 min the yellow color disappeared and the mixture was poured into water. The organic layer was washed with brine, dried ($MgSO_4$) and after evaporation the residue was separated on a column using hexane-ethyl acetate 9:1 mixture as eluent. The Z isomer was eluted first (99.2 mg). $[\alpha]_D^{20}$ -56.6 (c 1.84, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 6.63 (m, 1H, $J_{9,10a}$=16.6 Hz, $J_{9,10b}$= 10.8 Hz, H-9); 6.12 (dd, 1H, $J_{7,8}$=10.8 Hz, H-8); 5.95 (m, 1H, $J_{1a,2}$= 17.0 Hz, $J_{1b,2}$= 10.0 Hz, $J_{2,3}$= 8.5 Hz, H-2); 5.28 (m, 1H, H-7); 5.10-5.30 (m, 4H, H-10a, H-10b, H-1a, H-1b); 4.89 (dd, 1H, $J_{5,6}$= $J_{6,7}$= 8.4 Hz, H-6); 4.62 (dd, 1H, $J_{3,4}$= 7.1 Hz, H-3); 3.98 (dd, 1H, $J_{4,5}$=1.9 Hz, H-4); 3.54 (dd, 1H, H-5) ppm. Anal.: Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.53. Found: C, 68.50; H, 8.45

Intermediate fractions: 170 mg.

Eluted second was the E isomer 5. ^{1}H-NMR ($CDCl_3$): δ 6.3-6.4 (m, 2H, H-8, H-9); 6.05 (m, 1H, $J_{1a,2}$= 18 Hz, $J_{1b,2}$= 8.5 Hz, $J_{2,3}$= 8.5 Hz, H-2); 5.60 (dd, 1H, $J_{7,8}$= 14.8 Hz, $J_{6,7}$= 8.6 Hz, H-7); 5.1-5.4 (m, 4H, H-1a, H-1b, H-10a, H-10b); 4.63 (dd, 1H, $J_{3,4}$= 6.8 Hz, H-3); 4.40 (dd, 1H, $J_{5,6}$=$J_{6,7}$= 7.8 Hz, H-6); 4.05 (dd, 1H, $J_{4,5}$= 2.1 Hz, H-4); 3.58 (dd, 1H, H-5) ppm. Anal.: Found: C, 68.75; H, 8.68.

(4aS,5R,6R,7R,8S,8aR)-5,6:7,8-Di-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydronaphtalene-5,6,7,8-tetraol 9: a., A solution of Z isomer 9160 mg) in

dry toluene (30 mL) was heated at 160° in an autoclave for 20 h. After evaporation the product was chromatographically purified using hexane-ether 9:1 mixture as eluent to give 9 (57.2 mg, 35.8 %). M.p. 148-149°. $[\alpha]_D^{20}$= -80.9 (c 0.2, $CHCl_3$). MS, m/e: 280 (M^+); 265 (M^+-CH_3). ^{1}H-NMR ($CDCl_3$): δ 5.80 (m, 2H, H-1, H-2); 4.23 (dd, 1H, H-6); 4.20 (dd, 1H, H-5); 3.77 (dd, 1H, $J_{6,7}$= 7.6 Hz, $J_{7,8}$= 10.0 Hz, H-7); 3.25 (dd, 1H, $J_{8,8a}$= 10.0 Hz, H-8); 2.55 (m, 1H, $J_{4a,8a}$= 7.0 Hz, H-8a); 2.33 (m, 1H, $J_{4,4a}$= 5.0 Hz, $J_{4a,5}$= 8.0 Hz, H-4a); 2.08 (m, 2H, $J_{2,3}$= 3.5 Hz, $J_{2,3'}$= 6.5 Hz, H-3, H-3'); 1.70 (m, 2H, H-4, H-4'); 1.48; 1.46; 1.40; 1.35 (ss, 3-3H, methylethylidene methyls) ppm. Anal.: Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.70.
b., When the E isomer 5 (35 mg) was treated as above it gave 34.1 mg of 9 (89.7 %).

(5R,6R,7R,8S)-5,6:7,8-Di-O-methylethylidene-dodeca-3(E),9(E,Z),11-triene-2-one-5,6,7,8-tetraol 7 and 8: A solution of 4 (350 mg, 1.24 mmol) and of acetylmethylenetriphenylphosphorane (470 mg, 1.47 mmol) in benzene (30 mL) was boiled for 3 h. After evaporation the residue was purified by column chromatography with a hexane-ether 9:1 mixture to give syrupy 7 and 8 (277 mg, 69.3 %), as a 5:1 mixture of 3(E),9(Z) : 3(E),9(E) isomers. ^{1}H-NMR ($CDCl_3$) : δ 6.88 (dd, 1H, $J_{3,4}$= 16.0 Hz, $J_{4,5}$= 8.0 Hz H-4); 6.70 (dddd, 1H, $J_{11,12a}$= 16.0 Hz, $J_{11,12b}$= 11.0 Hz, $J_{10,11}$= 10.0 Hz, $J_{9,11}$=1.0 Hz H-11); 6.23 (ddd, 1H, $J_{9,10}$= 10.0 Hz, H-10); 6.19 (dd, 1H, $J_{3,5}$= 1.0 Hz, H-3); 5.13-5.43 (m, 3H, H-12a, H-12b, H-9); 4.93 (ddd, 1H, $J_{8,9}$= 9.0 Hz, $J_{7,8}$= 8.5 Hz, $J_{8,10}$= 1.0 Hz, H-8); 4.78 (ddd, 1H, $J_{5,6}$= 5.0 Hz, $J_{4,5}$= 7.5 Hz, $J_{3,5}$= 1.0 Hz, H-5); 4.14 (dd, 1H, $J_{5,6}$= 7.0 Hz, $J_{6,7}$= 2.1 Hz, H-6); 3.48 (dd, 1H, H-7); 2.25 (s, 3H, $CO-CH_3$); 1.60; 1.55; 1.50 (ss, 12H, methylethylidene methyls) ppm. For the minor component: δ 6.75 (dd, 1H, $J_{3,4}$= 16.0 Hz, $J_{4,5}$= 8.0 Hz, H-4); 6.20 (dd, 1H, H-3) ppm. MS m/e: 323 (M^+); 307 (M^+-CH_3). Anal.: Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.13; H, 8.05.

(4R,4aS,5R,6R,7R,8S,8aR)-4-Acetyl-5,6:7,8-di-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydronaphtalene-5,6,7,8-tetraol 10: A mixture of 7 and 8 (277 mg) was heated in dry toluene (30 mL) at 160° in an autoclave for 16 h. After evaporation the product was isolated by column chromatography with a hexane-ether 9:1 mixture to give crystalline 10 (133 mg, 48.0%). No other isomer could be isolated . The moderate yield can be attributed to polymerization of the starting compounds. M.p. 131-132°. $[\alpha]_D^{20}$ 4.8 (c 0.27, $CHCl_3$). MS m/e: 322 (M^+); 307 (M^+-CH_3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.75 (m, 2H, H-1, H-2); 4.30 (dd, 1H, $J_{6,7}$= 7.0 Hz, $J_{5,6}$= 8.2 Hz, H-6); 4.00 (dd, 1H, $J_{7,8}$= 10.5 Hz, H-7); 3.24 (dd, 1H, $J_{8,8a}$= 9.7 Hz, H-8); 2.87 (m, 1H, H-4); 2.60 (m, 1H, H-8a, 2.60 (dddd, 1H, $J_{4a,8a}$= 8.1 Hz, H-4a); 2.38 (m, 2H, H-3a, H-3b); 2.18 (s, 3H,

CO-CH_3); 1.48; 1.46; 1.44 (ss, 12H, methylethylidene methyls) ppm.
Anal.: Calcd for $C_{18}H_{26}O_5$. Found: C, 67.15; H, 8.28.

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