Tetrahedron Letters,Vol.24,No.14,pp 1497-1500,1983 0040-4039/83/141497-04$03.00/0
Printed in Great Britain

CONTROL OF THE DIELS-ALDER ADDITION REGIOSELECTIVITY BY REMOTE SUBSTITUENTS. SYNTHESIS OF ANTHRACYCLINE PRECURSORS.

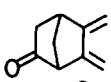
Joaquin Tamariz, Luis Schwager, John H. A. Stibbard and Pierre Vogel*

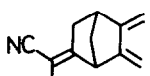
Institut de chimie organique de l'Université, 2, rue de la Barre,
CH-1005 Lausanne, Switzerland.

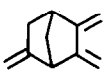
Summary. *The 2,3,5-tris(methylene)norbornane adds to methyl propynoate with "para" regioselectivity. This principle is applied to the regioselective synthesis of a daunomycinone precursor.*

The Diels-Alder reactivity of an exocyclic *s-cis*-butadiene moiety grafted onto norbornane[1] and bicyclo[2.2.2]octane[2] skeletons can be affected by remote substitution of the bicyclic systems. For instance, 5,6-bis(methylene)-2-norbornanone (2) is less reactive than the parent diene 1 toward strong dienophiles[3], perhaps because of the electron withdrawing effect of the homoconjugated carbonyl group (inductive effect). Nevertheless, the "para" regioselectivity of


1

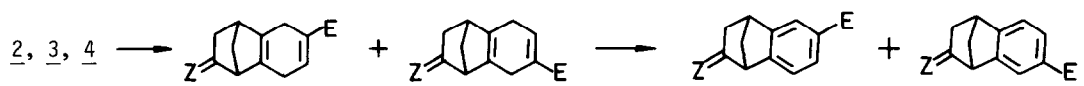

2


3


4

the cycloadditions of 2 to methyl vinyl ketone (MVK) and methyl propynoate suggested that the carbonyl may also act as an electron donating group[4]. This interpretation was confirmed by the regioselectivity of the electrophilic additions of the C-C double bonds in norborn-5-en-2-one and bicyclo[2.2.2]oct-5-en-2-one[5], and was supported by MO calculations[4,6].

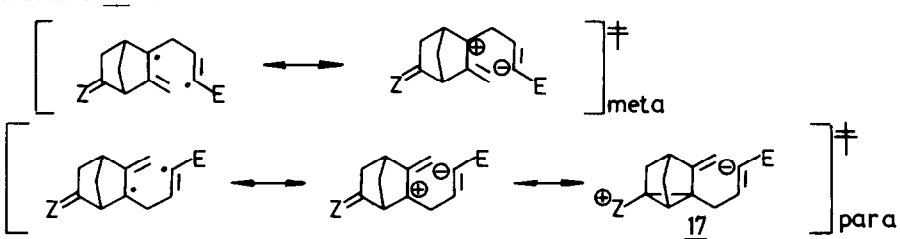
We have prepared the new trienes 3 and 4, and now present the results of our preliminary investigations of their Diels-Alder reactivity. The methylene group at C(5) in 4 was found to induce a "para" orienting effect on the regioselectivity, and this result suggested a new approach to the regioselective synthesis of anthracyclines which is also reported.



	"para"	"meta"		E = $COOCH_3$
Z = $(NC)_2C$:	5 (47 %)	6 (53 %)	7	8
H_2C :	9 (77 %)	10 (23 %)	11	12
O :	13 (75 %)	14 (25 %)	15	16

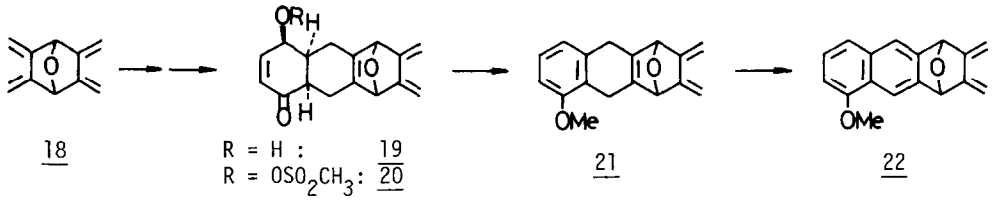
The reaction of malodinitrile with ketone 2 (MeOH, piperidine, 60°, 5 h)[7] gave triene 3 (53 %)[8]. When heated with a 7-fold excess of methyl propynoate, an adduct mixture of 5/6 (47:53) was formed (99 %)[8]. Triene 4 was prepared from 2 following Nozaki's technique[9](Zn, CH_2Br_2, $TiCl_4$, THF) in ca. 50 % yield[8]. It added to methyl propynoate (C_6H_6, 80°, 1.5 h) and gave the adducts 9/10 (77:23) in near quantitative yield[8]. The structures of the adducts 5/6 and 9/10 were established by oxidation with dichlorodicyanobenzoquinone (DDQ, C_6H_6, 80°, 4 h) to yield the corresponding benzoates 7/8 and 11/12, whose structures were determined by a combination of ^{13}C- and ^1H-NMR spectroscopy. Alkaline hydrolyses of 7 and 8 (which were easily separated by chromatography) gave the known ketones 15 and 16[4], respectively. Oxidative cleavage ($NaIO_4$, OsO_4, *t*BuOH, CH_2Cl_2, 52°, 3 h) of the methylene groups in 11/12 furnished 15/16 (76 %), respectively.

The dicyanomethylene substituent effects have often been considered as analogous to those of the carbonyl group[10]. The absence of regioselectivity in the Diels-Alder additions of 3[11] contrasts with the observed selectivity with dienone 2[4]. The latter was attributed to n(CO),σC(1,2) ↔ πC(5,6) hyperconjugative interaction in 2. Such an effect is obviously absent in the case of the dicyanomethylene substituted system 3. The "para" regioselectivity in the cycloaddition of triene 4 suggests that the methylene group at C(5) can act as an electron donating group on the homoconjugated diene at C(2,3). This property is tentatively ascribed to a through-space interaction which intervenes more strongly in the transition state of the reaction giving the "para" adduct than in that giving the "meta" isomer. This effect can be visualized by the diradicaloid ↔ charge-transfer-limiting-structure model[12], as depicted below. This model also "explains" the absence of any regioselectivity observed with 3: the cyano substituents destabilizing the limiting structure 17[13].

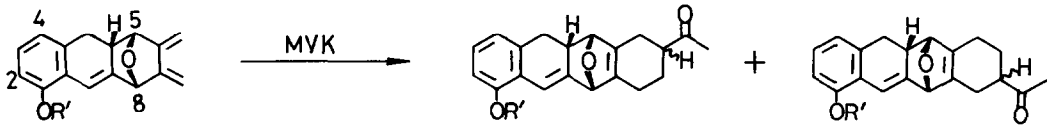


Tetrakis(methylene)-7-oxanorbornane (18)[14] adds sequentially two different dienophiles and thus can generate in a simple way a wide variety of anthracycline precursors[15]. The selective reduction of the benzoquinone monoadduct of 18 gave alcohol 19[16], whose mesylate 20 (m.p. 110°) furnished 21[17] upon treatment with 2 mol equiv of *t*BuOK (THF, 0-20°, 2 h) followed by reaction with 3-fold excess of CH_3I (20°, 12 h). Oxidation with DDQ (C_6H_6, 20°, 2 h) gave 22[17] (62 % from 19). The Diels-Alder additions of methyl vinyl ketone (MVK) and methyl propynoate to the dienes 21 and 22 were not regioselective.

When 4-6 mol equiv of *t*BuOK were used to eliminate mesylic acid from 20, a mixture of phenolates was obtained that gave the α-naphthoates 23/24 in a 7:3 ratio upon quenching with α-naphthoyl chloride. The double bond in the 7-oxanorborn-2-ene portion of 20 migrates and becomes conjugated with the aromatic ring. The regioselectivity and the high stereoselectivity



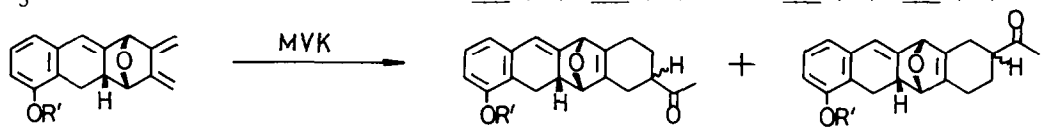
18 — R = H: 19; R = OSO_2CH_3: 20 — 21 — 22



R'= α-naphthoyl: 23 — toluene, 90°: 25β (61), 25α (7)[18]; 26β (19), 26α (13)

$BF_3 \cdot Et_2O$, CH_2Cl_2, -85°: (86), (<2); (14), (<1)

R'= CH_3 : 29 — " " , -78°: 30β (90), 30α (<2); 31β (10), 30α (<1)



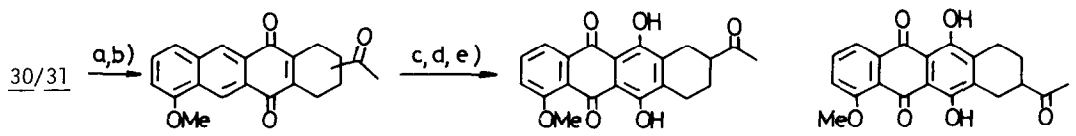
R'= α-naphthoyl: 24 — toluene, 100°: 27β (65), 27α (7); 28β (18), 28α (10)

$ZnCl_2$, CH_2Cl_2, -78°: (67), (<3); (33), (<1)

$BF_3 \cdot Et_2O$, CH_2Cl_2, -78°: (81), (<3); (19), (<1)

(no trace of either the *Hendo*-C(5a) isomer of 23 or the *Hendo*-C(8a) isomer of 24 were observed) of this isomerization is not yet understood. The new trienes 23 and 24[17] were separated by HPLC. In a manner analogous to that of 4, 23 and 24 added to MVK with "para" regioselectivity giving the adducts 25/26 and 27/28, respectively. The additions were also stereoselective in the sense that the adducts with the acetyl side chain in the β (or *exo*) position were the major products. The mixtures of β- and α-isomers were easily separated by column chromatography on SiO_2.

The "para" regioselectivity (9:1), the β-acetyl stereoselectivity (>98 %), and the isolated yield (80 %) were best when the methoxy derivative 29 was employed and when the addition of MVK (20 mol equiv) was carried out at - 78° in the presence of $BF_3 \cdot Et_2O$ (6 mol equiv, CH_2Cl_2). The triene 29[17] was prepared in 96 % yield by saponification of 23 followed by treatment with NaH and CH_3I. The structures of 23-31 were determined using 360 MHz ^{1}H-NMR spectroscopy involving double irradiation experiments[8]. The mixture of adducts 30/31 (9:1) was transformed into the known (±)-7,9-dideoxydaunomycinone (32)(m.p. 243-4°, lit. 243-5°[19], 244-5°[20]) according to the scheme below. The minor isomer 33 was identical with the known (±)-7,9-dideoxyisodaunomycinone (m.p. 215-6°, lit. 216-7°[19a]). Optimization of these reactions is underway. The transformation of 32 into (±)-daunomycinone has already been achieved.[19,21]



30/31 — a,b) — c,d,e) — 32 — 33

a) DDQ in C_6H_6, 80°, 24 h; b) CF_3COOH in CH_2Cl_2, then $HCrO_3Cl \cdot pyr$, CH_2Cl_2; c) Zn in Ac_2O; d) Jones' oxidation; e) 3 % HCl in CH_3OH, 70°, 12 h, then recrystallization from CH_2Cl_2/CH_3OH

Our results show that remote substituents can control the regioselectivity of the Diels-Alder additions of dienes grafted onto norbornane systems. The origin of the observed regioselectivities is not yet fully understood, nevertheless, our doubly-convergent synthesis of anthracyclinones starting from 18 is now capable of generating a wide variety of molecules of biological interest in a regioselective fashion, including daunomycinone.

Acknowledgment. We are grateful to Hoffmann-La Roche and Co., Basel, to the "Swiss National Science Foundation", to "Fonds Herbette", Lausanne and to the "Commission Fédérale des bourses pour étudiants étrangers", Zürich, for financial support.

References and Notes.

1. M. Hardy, P.A. Carrupt & P. Vogel, Helv.Chim.Acta 59, 936 (1975); L. de Picciotto, P.A. Carrupt & P. Vogel, J. Org. Chem. 47, 3796 (1982) and references therein.
2. A. Chollet, M. Wismer & P. Vogel, Tetrahedron Lett. 1976, 4271; R. Gabioud & P. Vogel, Tetrahedron 36, 149 (1980); O. Pilet & P. Vogel, Angew.Chem.Int.Ed. 19, 1003 (1980).
3. A. Chollet, C. Mahaim, C. Foetisch, M. Hardy & P. Vogel, Helv.Chim.Acta 60, 59 (1977).
4. M. Avenati, P.A. Carrupt, D. Quarroz & P. Vogel, Helv.Chim.Acta 65, 188 (1982).
5. P.A. Carrupt & P. Vogel, Tetrahedron Lett. 23, 2563 (1982).
6. P.A. Carrupt, dissertation, University of Lausanne, Nov. 1979; see also the CD spectra of bicyclic β,γ-unsaturated ketones: P.A. Carrupt & P. Vogel, Tetrahedron Lett. 22, 4721 (1981).
7. F. S. Prout, V.D. Beaucaire, G.R. Dyrkacz, W.M. Koppes, R.E. Kuznicki, T. Marlewski, J.J. Pienkowski & J.M. Puda, J. Org. Chem. 38, 1512 (1973).
8. The structure of this new compound was given by its spectral data and by elemental analysis. Details will be given in a full paper.
9. K. Takai, Y. Hotta, K. Oshima & H. Nozaki, Tetrahedron Lett. 19, 2417 (1978).
10. K. Wallenfels, K. Friedrich, J. Rieser, W. Ertel & H.K. Thieme, Angew. Chem. 88, 311 (1976).
11. Preliminary results showed similar regioselectivity for the cycloaddition of MVK.
12. W. E. McEwen, I.C.W. Huang, C.P.C. Marin, F. McCarty, E.M. Segnini, C.M. Zepp,III & J.J. Lubinkowski, J. Org. Chem. 47, 3098 (1982) and lit. cited therein; R.B. Woodward & T.J. Katz, Tetrahedron 5, 70 (1959).
13. The frontier and sub-frontier orbitals as calculated by the EHT, MNDO and *ab initio* STO 3G techniques revealed no significant differences between the coefficients at H_2C=C(2) and H_2C=C(3) in 3 and 4: P.A. Carrupt & P. Vogel, unpublished calculations.
14. C. Mahaim, P.A. Carrupt, J.P. Hagenbuch, A. Florey & P. Vogel,Helv.Chim.Acta 63, 1149 (1980).
15. P.A. Carrupt & P. Vogel, Tetrahedron Lett. 20, 4533 (1979); Y. Bessière & P. Vogel, Helv. Chim. Acta 63, 232 (1980); J. Tamariz & P. Vogel, Ibid. 64, 188 (1981).
16. A.A. Pinkerton, D. Schwarzenbach, J.H.A. Stibbard, P.A. Carrupt & P. Vogel, J. Am. Chem. Soc. 103, 2095 (1981).
17. Characteristics of 21: m.p. 145-7°; ^{1}H-NMR($CDCl_3$): 7.1(d,1H), 6.72(m,2H),5.3(s,2H),5.15(s,4H), 3.85(s,3H),3.55(m,4H); MS(70 eV): 252(25),223(100); 22: m.p. 154-5°; ^{1}H-NMR($CDCl_3$): 8.18(s, 1H),7.67(s,1H),7.38(d,1H),7.30(d,1H),6.8(dxd,1H),5.7(s,2H),5.3(s,2H),5.2(s,2H),3.95(s,3H); MS(70 eV): 250(100),235(16),221(20); 23: m.p. 183-4°; ^{1}H-NMR($CDCl_3$): 8.98(d,1H),8.46(dxd,1H), 8.05(d,1H),7.85(dxd,1H),7.5(m,3H),7.12(dxd,1H),6.99(d,2H),6.40(d,1H),5.37(s,1H),5.08(s,1H), 4.81(s,1H),4.98(s,1H),4.9(d,1H),4.89(s,1H),2,86(dxdxdxd,1H),2.75(dxd,1H),2.46(dxd,1H); 24: m.p. 139-40°; ^{1}H-NMR($CDCl_3$): 8.96(d,1H),8.45(dxd,1H),8.06(d,1H),7.87(dxd,1H),7.44(m,3H), 7.17(dxdxd,1H),6.99(dxd,1H),6.92(dxd,1H),6.39(d,1H),5.36(d,1H),5.17(s,1H),5.09(s,1H),4.96 (s,1H),4.92(s,1H),4.5(d,1H),2.92(dxd,1H),2.81(dxdxdxd,1H),2.18(dxd,1H); 29: m.p. 134-5°; ^{1}H-NMR($CDCl_3$): 7.07(t,1H),6.72(m,3H),5.44(s,1H),5.22(s,1H),5.13(s,1H),5.37(s,1H),5.01(s,1H), 4.97(d,1H),3.82(s,3H),2.9(dxdxdxd,1H),2.76(dxd,1H),2.47(dxd,1H); MS(70 eV): 252(92),223(100).
18. In parenthesis: adduct ratios as determined by 360 MHz ^{1}H-NMR.
19. a) R.D. Gleim, S. Trenbeath, R.S.D. Mittal & C.J. Sih, Tetrahedron Lett. 1976, 3385;
b) K.S. Kim, E. Vanotti, A. Suarato & F. Johnson, J. Am. Chem. Soc. 101, 2483 (1979);
c) M.J. Broadhurst & C.H. Hassal, J. Chem. Soc. Perkin Trans. I, 1982, 2227.
20. J.S. Swenton & P.W. Raynolds, J. Am. Chem. Soc. 100, 6188 (1978).
21. A.S. Kende, Y.G. Tsay & J.E. Mills, J. Am. Chem. Soc. 98, 1967 (1976).

(Received in France 19 January 1983)