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Remote control of Diels–Alder additions. Enantioselective synthesis of (2*R*)-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalen-2-yl methyl ketone (Wong's anthracycline intermediate) from furfural

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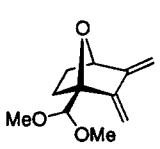
Abstract: The enantiomerically pure (1*S*,4*R*,4′*S*,5′*S*)-1-(4′,5′-dimethyl-dioxolan-2′-yl)-5,6-dimethylidene-7-oxabicyclo[2.2.1]hept-2-ene derived from the acetal of furfural and (2*S*,3*S*)-butane-2,3-diol underwent addition to 1-acetylvinyl *para*-nitrobenzoate in the presence of an excess of *t*-BuMe$_2$SiOSO$_2$CF$_3$ to yield an 83:17 mixture of two diastereomeric products which was converted into (2*R*)-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalen-2-yl methyl ketone. © 1997 Elsevier Science Ltd

Introduction

The Diels–Alder cycloadditions of diene **1** and tetraene **2** have been shown to be regioselective when using methyl vinyl ketone or 2-butynone as dienophiles. The regioselectivity is at its highest when the reactions are carried out at low temperature in the presence of a large excess of a strong Lewis acid.[1,2] Regio- and stereo-control by the 1-(dimethoxymethyl) group are quite good with 1-acetylvinyl esters **3**. For instance, the $BF_3 \cdot Et_2O$-promoted Diels–Alder addition of 1-acetylvinyl RADO(Et)-ate (**3a**; RADO(Et)=(1*R*,7*R*)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carbonyl)[3] to tetraene **2** leads to an 87:13 mixture of the monoadducts **4** and **4′**. Adduct **4** was converted into (–)-4-demethoxy-7-deoxydaunomycinone and led to a new class of enantiomerically pure anthracycline analogues.[4]

Recently we described the synthesis of enantiomerically pure triene (+)-**5**, derived from the acetal of furfural and (2*S*,3*S*)-butane-2,3-diol in four steps.[5] We report here the results of our studies on its cycloaddition to 1-acetylvinyl 4-nitrobenzoate **3b** and the conversion of the adducts obtained into Wong's intermediate,[6,7] of use to generate anthracycline anti-tumor drugs.[8,9]



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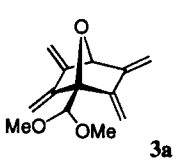
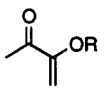
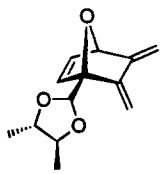


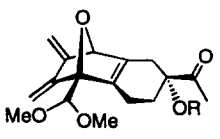
2



3a R=RADO(Et)
3b R=4-NO_2-C_6H_4CO=PNB



(+)-**5**



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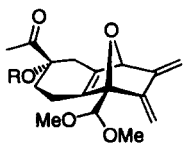

4′

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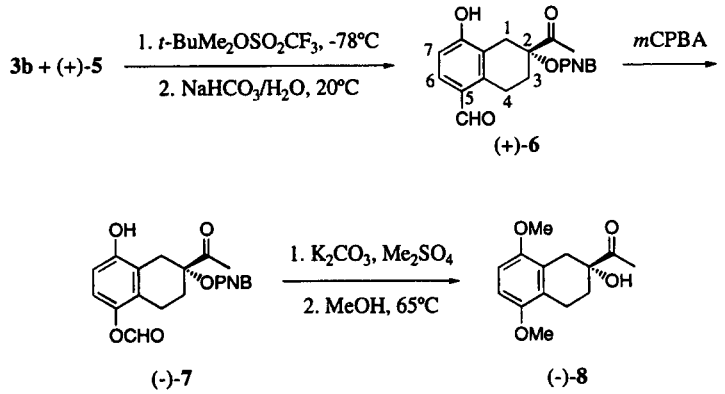
Results and discussion

As expected[10], triene (+)-**5** was much less reactive than diene **1** and tetraene **2** towards all kinds of dienophiles. With **3b**,[11] Lewis acids such as $B(OMe)_3$, $BF_3 \cdot Et_2O$, $Yb(OTf)_3$ were not capable of promoting the Diels–Alder cycloaddition without extensive polymerization. We eventually found that *t*-$BuMe_2SiOSO_2CF_3$ (4 equivalents) was capable of inducing a smooth addition (CH_2Cl_2, −78°C, 7 days) providing aldehyde (+)-**6** (70%) after work-up with aqueous $NaHCO_3$. Bayer–Villiger oxidation of (+)-**6** with *meta*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 (0°C) led to tetraline (−)-**7** (80%) with an e.e.=66%, as measured by ^{19}F-NMR of its Mosher's ester.[12] Its absolute configuration (2*R*) was established as follows (Scheme 1): methylation of (−)-**7** with K_2CO_3, Me_2SO_4 in THF (65°C, 2 days, Ar) followed by methanolysis (MeOH, 65°C, 2 h) furnished the known Wong's intermediate (−)-**8** (62%).[7]



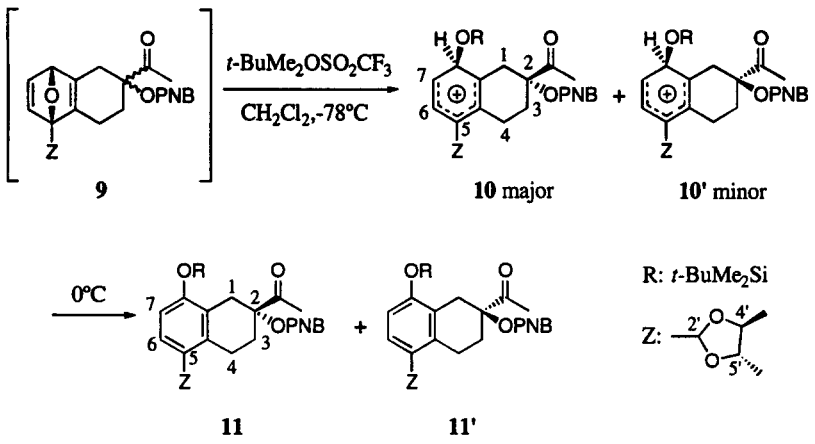
Scheme 1.

The enantiomeric excess of 66% obtained for (−)-**8** does not arise from epimerization which has been reported to occur under acidic conditions.[13] When the cycloaddition between **3b** and (+)-**5** was carried out in a NMR tube (CD_2Cl_2, −78°C), the slow formation of two diastereomeric cyclohexadienyl cations **10** and **10′** was observed indicating that the Lewis-acid (*t*-$BuMe_2SiOSO_2CF_3$) used to promote the Diels–Alder addition induces a fast oxa-ring opening of the 7-oxanorbornadiene intermediates **9**. Structures of cations **10** and **10′** were given by their ^{13}C-NMR characteristics (see Experimental part) which compared well with those reported for the 1,3,5-trimethylcyclohexadienyl cation in super-acid media.[14] On warming the solution to 0°C, cations **10** and **10′** eliminated a proton providing a 83:17 mixture of silyl phenolates **11** and **11′** (as given by their ^{13}C-NMR data). At 20°C, and in the presence of H_2O, **11** and **11′** were rapidly hydrolyzed to (+)-**6** (Scheme 2).

These observations demonstrate that the incomplete enantiomeric purity of (+)-**6**, (−)-**7** and (−)-**8** arises from an incomplete stereoselectivity of the Diels–Alder addition of **3b** to triene (+)-**5**. As in the case of the cycloaddition of **3b** to tetraene **2**, the cycloaddition **3b**+(+)-**5** is highly regioselective but the face and/or *Alder* vs anti-*Alder* stereoselectivity of the reaction is incomplete, in contrast with the cycloaddition **2**+**3a**→**4**+**4′**.[4]

Conclusion

The enantiomerically enriched (e.e. 66%) Wong's intermediate for anthracycline synthesis has been derived in seven steps from the acetal of furfural and (2*S*,3*S*)-butane-2,3-diol. Our approach features a highly regioselective but incompletely stereoselective Diels–Alder addition of 1-acetylvinyl *para*-nitrobenzoate to (1*S*,4*R*,4′*S*,5′*S*)-1-(4′,5′-dimethyldioxolan-2′-yl)-5,6-dimethylidene-7-oxabicyclo[2.2.1]hept-2-ene.



Scheme 2.

Experimental

General, see Ferritto and Vogel.[15] None of the procedures were optimized. All solvents were distilled prior to use. CH_2Cl_2 was distilled from P_2O_5. TLC monitoring: Merck silica gel 60 F_{254} plates, detection by UV light or phosphomolybdic acid and heat. Flash chromatography (FC): Merck silica gel 60 (63–200 μm).

(2R)-Acetyl-5-formyl-1,2,3,4-tetrahydro-8-hydroxynaphthalen-2-yl para-*nitrobenzoate (+)-6*

1-Acetylvinyl *p*-nitrobenzoate[11] (50 mg, 0.247 mmol) was dissolved in anh. CH_2Cl_2 (1 ml) and was cooled to −78°C under an Ar atmosphere. *t*-$BuMe_2SiOSO_2CF_3$ (90 μl, 0.392 mmol) was added and the solution was stirred at −78°C for 1 h. Triene (+)-**5**[5] (20 mg, 0.908 mmol) was then added and the mixture was allowed to react at −78°C without stirring for 1 week. The solution was then poured into sat. aq. $NaHCO_3$ sol. (3 ml) and ice (4 g) and was stirred for 1 h. The mixture was then extracted with CH_2Cl_2 (10 ml, twice). The organic phases were washed with water (5 ml), sat. aq. NaCl sol. (5 ml), dried ($MgSO_4$) and the solvent was evaporated without heating. The residue was purified by FC (Florisil, light petroleum/EtOAc 2:1) yielding 25 mg (70%), (colourless oil); e.e.=66% as determined for (−)-**7**. $[\alpha]_{589}^{25}$=310, $[\alpha]_{578}^{25}$=346, $[\alpha]_{546}^{25}$=381, $[\alpha]_{436}^{25}$=890 (*c*=0.42, $CHCl_3$). UV (CH_3CN): 268 (11000); 227 (6000). IR (KBr): 3420, 1723, 1674, 1580, 1527, 1351, 1293, 1231, 1104, 721. ^{1}H-NMR (250 MHz, $CDCl_3$): 10.02 (*s*, CHO); 8.27 (*d*, ^3J=8.8, PNB); 8.12 (*d*, ^3J=8.8, PNB); 7.62 (*d*, ^3J=8.3, H–C(6)); 6.83 (*d*, ^3J=8.3, H–C(7)); 3.57 (*ddd*, ^2J=18.5, ^3J=5.5, 4.2, H–C(4)); 3.32 (*br. s.*, H_2–C(1)); 3.25 (*ddd*, ^2J=18.5, ^3J=11.3, 5.5, H–C(4)); 2.62 (*ddd*, ^2J=14.0, ^3J=5.5, 4.2, H–C(3)); 2.30 (*s*, Me); 2.11 (*ddd*, ^2J=14.0, ^3J=11.3, 5.5, H–C(3)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 205.6 (*s*, CO); 192.1 (*d*, ^1J(C,H)=172, CHO); 163.9 (*s*, COO); 159.3, 150.8, 139.4 (3*s*, C(arom)); 135.1, 130.9, 123.6 (3*d*, ^1J(C,H)=169, 171, C(arom)); 121.1 (*s*, C(arom)); 112.5 (*d*, ^1J(C,H)=161, C(arom)); 84.4 (*s*, C(2)); 29.4, 27.5, 22.9 (3*t*, ^1J(C,H)=129, 131, 130, C(1), C(3), C(4)); 24.0 (*q*, ^1J(C,H)=128, Me). CI-MS (NH_3): 402 (0.5, $[M+NH_4]^+$), 337 (0.5, $[M-NO_2]^+$), 260 (21, $[M-C_6H_5NO_2]^+$), 217 (2, $[M-CO_2C_6H_4NO_2]^+$), 179 (14), 178 (42), 169 (44), 167 (52), 139 (41), 111 (48), 86 (63), 84 (100), 83 (39), 72 (49). Anal. calc. for $C_{20}H_{17}NO_7$ (383.1): C 62.66, H 4.47, N 3.65; found: C 62.59, H 4.62, N 3.67.

(2R)-2-Acetyl-5-formyloxy-1,2,3,4-tetrahydro-8-hydroxynaphthalen-2-yl para-*nitrobenzoate ((−)-7)*

A mixture of (+)-**6** (70 mg, 0.204 mmol), $NaHCO_3$ (35 mg, 0.408 mmol) and anh. CH_2Cl_2 (7 ml) was cooled to 0°C. *m*-CPBA (100%, 44 mg, 0.2548 mmol) was added and the solution was stirred at 0°C for 3 h. The mixture was poured into water and ice (10 ml) and extracted with CH_2Cl_2 (20 ml, 3 times). After drying ($MgSO_4$), the solvent was evaporated and the residue was purified by FC

(silica gel, CH_2Cl_2/light petroleum/EtOAc 8:1:1), yielding 66 mg (80%), yellowish powder (e.e.=66%, Mosher's ester, ^{19}F-NMR). $[\alpha]_{589}^{25}=-18.5$, $[\alpha]_{577}^{25}=-19.5$, $[\alpha]_{546}^{25}=-23.0$, $[\alpha]_{435}^{25}=-33.4$(*c*=1.1, $CHCl_3$). IR (KBr): 3434, 2937, 1723, 1528, 1465, 1351, 1321, 1293, 1244, 1117, 1103, 737, 720. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.28 (*s*, HCOO); 8.26 (*md*, ^3J=8.7, H(arom)); 8.09 (*md*, ^3J=8.7, H(arom)); 6.87, 6.67 (2*d*, ^3J=8.6, H–C(6), H–C(7)); 3.37 (*br. d*, ^2J=18.2, H–C(1)); 3.18 (*br. d*, ^2J=18.2, H–C(1)); 2.85 (*br. ddd*, ^2J=17.7, ^3J=5.9, 2.7, H–C(3)); 2.68 (*br. m*, H–C(3)); 2.59 (*br. m*, H–C(4)); 2.31 (*s*, CH_3); 2.10 (*m*; H–C(4)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 205.7 (*s*, CO); 164.1 (*s*, COO); 159.6 (*d*, ^1J(C,H)=231, HCOO); 152.0, 150.8, 140.9, 134.5 (4*s*, C(arom)); 131.0 (*d*, ^1J(C,H)=170, C(arom)); 128.1 (*s*, C(arom)); 123.7 (*d*, ^1J(C,H)=172, C(arom)); 121.0 (*s*, C(arom)); 119.6, 112.9 (2*d*, ^1J(C,H)=164, 162, C(arom)); 84.6 (*s*, C(2)); 29.7, 26.8 (2*t*, ^1J(C,H)=130, 131, C(1), C(3)); 24.2 (*q*, ^1J(C,H)=129, CH_3); 20.0 (*t*, ^1J(C,H)=130, C(4)). CI-MS (NH_3): 415 (7, $[M+NH_4]^+$), 400 (4, $[M+H]^+$), 399 (2, M^+), 343 (8), 281 (6), 234 (19), 233 (54), 232 (100), 204 (19), 189 (20), 187 (79), 161 (27), 150 (78), 137 (34), 120 (62), 92 (43).

(2R)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dihydroxynaphthalen-2-yl para*-nitrobenzoate*

This compound was formed quantitatively when (−)-**7** was left in presence of air. Colourless oil. IR (film): 3385 (*br*), 2921, 2360, 2339, 1722, 1716, 1651, 1537, 1489, 1351, 1292, 1103, 720. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.27 (*dm*, ^3J=8.9, H(arom)); 8.10 (*dm*, ^3J=8.9, H(arom)); 6.57, 6.54 (2*d*, ^3J=9.5, H–C(6), H–C(7)); 4.52, 4.42 (2*br. s*, 2×OH); 3.33 (*br. dd*, ^2J=17.6, ^4J=1.5, H–C(1)); 3.16 (*br. d*, ^2J=17.6, H–C(1)); 2.95, 2.66, 2.12 (3*m*, H_2–C(3), H_2–C(4)); 2.30 (*s*, CH_3). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 205.5 (*s*, CO); 163.9 (*s*, COO); 150.7, 147.3, 146.7 (3*s*, C(arom)); 130.9, 123.7, 123.6 (3*d*, C(arom)); 122.7, 120.6 (2*s*, C(arom)); 112.6 (*d*, C(arom)); 84.9 (*s*, C(2)); 29.9, 26.6, 20.2 (3*t*, C(1), C(3), C(4)); 24.2 (*q*, CH_3). CI-MS (NH_3): 389 (43, $[M+NH_4]^+$), 388 (26), 387 (100), 372 (25 $[M+H]^+$), 371 (20, M^+), 370 (71), 313 (24), 295 (18), 254 (11), 216 (19), 199 (28), 152 (71), 108 (29), 91 (42).

(2R)-1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxynaphthahalen-2-yl methyl ketone ((−)-8)

A mixture of (−)-**7** (20 mg, 0.050 mmol), anh. THF (5 ml), K_2CO_3 (200 mg, 1.45 mmol) and Me_2SO_4 (100 µl, 0.793 mmol) was refluxed under Ar for 2 days. Anh. MeOH (1 ml) was then added and the solution was refluxed for 2 hours (TLC control, silica gel, CH_2Cl_2/light petroleum/EtOAc 8:1:1). The mixture was then poured into 1 N aqueous HCl (10 ml) and extracted with CH_2Cl_2 (20 ml, 3 times). After drying ($MgSO_4$), the solvent was evaporated and the residue was purified by FC (silica gel, CH_2Cl_2/light petroleum/EtOAc 17:2:1), yielding 7.8 mg (62%), colourless oil (e.e.=66%). $[\alpha]_{589}^{25}=-22$ (*c*=0.8, $CHCl_3$). All spectral data were identical to those reported for this compound.[6,7] Anal. calc. for $C_{14}H_{18}O_4$ (250.29): C 67.18, H 7.25; found C 67.31, H 7.08.

Characteristics of the major intermediates **10** and **11** formed during the *t*-$BuMe_2SiOSO_2CF_3$-promoted cycloaddition of **3b** to (+)-**5**. ^{13}C-NMR (CD_2Cl_2, 100.6 MHz, −78°C) of **10**: 207.7 (CO), 174.1 (C(5)), 166.0 (COO), 150.9, 150.0 (C(7), C(8a)), 100.3 (C(2′)), 94.5 (C(8)), 85.0 (C(2)), 72.7, 72.3 (C(4′), C(5′)), 24.8, 22.9 (Me–C(4′), Me–C(5′)). ^{13}C-NMR (CD_2Cl_2, 100.6 MHz, 0°C) of **11**: 207.2 (CO), 166.0 (COO), 105.2 (C(2′)), 85.1 (C(2′)), 81.5, 80.5 (C(4′), C(5′)), 18.3, 17.7 (Me–C(4′), Me–C(5′)). Signals for C(1), C(3), C(4), C(4a), C(6) and MeCO are overlapped with those of the reactants.

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