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Homochiral Matching in the Diels-Alder Cyclodimerization of 2-Vinyl-7-oxabicyclo[2.2.1]hept-2-ene Derivatives.

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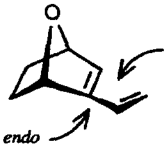
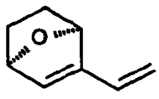
Keywords: *Face selectivity, [4+2]-cycloadditions, chiral recognition, (1R,2S,3S,4R,7R, 11S,12R)-11-ethenyl-15,16-dioxapentacyclo[10.2.1.*$1^{4,7}.0^{3,8}.0^{2,11}$*]hexadec-8-en-6,13-dione, (1R,2R,3R,4R,7R,11R,12R)-11-ethenyl-15,16-dioxapentacyclo[10.2.1.*$1^{4,7}.0^{3,8}.0^{2,11}$*]hexadec-8-en-5,14-dione and their ethylene acetals.*

Abstract : Racemic 6-vinyl-7-oxabicyclo[2.2.1]hept-5-en-2-one, 5-vinyl-7-oxabicyclo[2.2.1]hept-5-en-2-one and their ethylene acetals undergo highly stereoselective Diels-Alder cyclodimerizations. The optically pure semicyclic dienes give the corresponding optically pure dimers with the same ease.

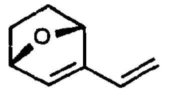
As for butadiene[1] and substituted derivatives[2] 2-vinyl-7-oxabicyclo[2.2.1]hept-2-ene (**1**) is expected to undergo Diels-Alder cyclodimerization. In the case of the optically pure (1*S*,4*R*)-**1** reacting as a dienophile there are two regioisomeric approaches for both the endocyclic and the exocyclic double bond and two faces for each olefinic moieties which can attack the *exo* or *endo* face of (1*S*,4*R*)-**1** adding as a diene thus leading to 16 possible cyclodimers! In the case of racemic (1*RS*,4*SR*)-**1** for each or the above-mentionned 16 possibilities there is the option of racemic matching (i.e. reactions of (1*R*,4*S*)-**1** + (1*S*,4*R*)-**1** being preferred) or homochiral matching (i.e. reactions of (1*R*,4*S*)-**1** + (1*R*,4*S*)-**1** and (1*S*,4*R*)-**1** + (1*S*,4*R*)-**1** being preferred).



(1*S*,4*R*)-**1**

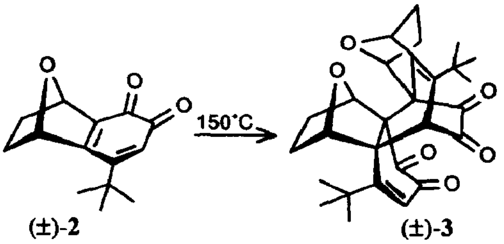


(1*S*,4*R*)-**1**

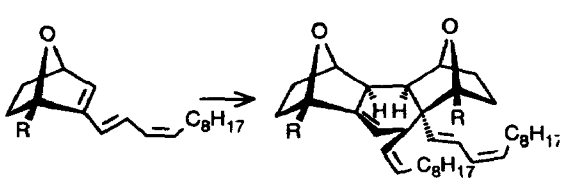


(1*R*,4*S*)-**1**

For derivative (±)-**2**, Sims and Wege[3] found the cyclodimer (±)-**3** to be formed selectively, the *exo* face of both the diene and dienophile partners being preferred over their *endo* face. Apparently reactions of (+)-**2** + (-)-**2** were preferred over homochiral matching. In the case of the related triene (±)-**4**, Djuric et al.[4] found that (±)-**5** was the major product of dimerization again suggesting a racemic rather than a homochiral matching for the Diels-Alder cyclodimerization. In contrast with these results we report here that

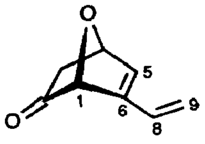


(±)-**2** (±)-**3**

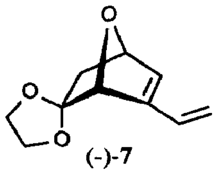


(±)-**4** R=$(CH_2)_3COOMe$ (±)-**5**

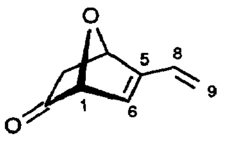
homochiral matching is preferred for the Diels-Alder cyclodimerization of the 5-vinyl and 6-vinyl-7-oxa-bicyclo[2.2.1]hept-5-en-2-yl derivatives (±)-**6**, (±)-**7**, (±)-**8** and (±)-**9**. Furthermore we shall show that the rates of these reactions depend on the nature (oxo vs. ethylidenedioxy) and on the position of the remote substituent of the bicyclic skeleton.



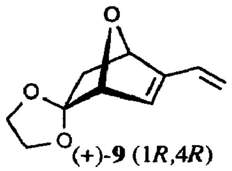
(+)-**6**



(-)-**7**

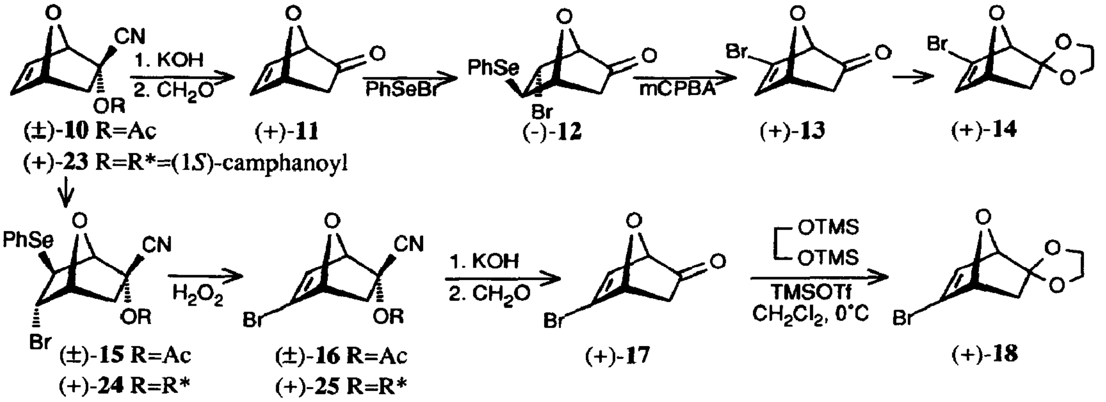


(+)-**8**



(+)-**9** (1*R*,4*R*)

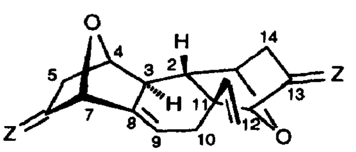
The racemic dienes (±)-**6** and (±)-**7** were prepared from bromoenone (±)-**13** derived from (±)-**11**, the product of saponification of the Diels-Alder adduct (±)-**10** of furan with 1-cyanovinyl acetate.[5] Stille's coupling[6] of (±)-**13** with CH_2=$CHSn(Bu)_3$ and a catalytic amount of $Pd(Ph_3P)_4$ (DMF, 55°C, sealed pyrex tube, 3 h) gave (±)-**6** (70%). Acetalization of (±)-**13** with 1,2-bis[(trimethylsilyl)oxy]ethane and $TMSOSO_2CF_3$ (CH_2Cl_2, 0°C) provided (±)-**14** (60%) which was converted as above to (±)-**7** (58%). PhSeBr addition to (±)-**10** followed by oxidative elimination of the selenide and saponification furnished bromoenone (±)-**17**[7] which was converted to the corresponding ethyleneacetal (±)-**18** (93%). Stille's coupling (as above) of (±)-**17** and (±)-**18** with CH_2=$CHSn(Bu)_3$ provided (±)-**8** (60%) and (±)-**9** (94%), respectively.[8]



(±)-**10** R=Ac (+)-**23** R=R*=(1*S*)-camphanoyl; (+)-**11**; (-)-**12**; (+)-**13**; (+)-**14**

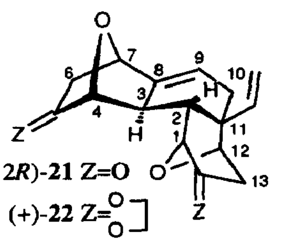
(±)-**15** R=Ac (+)-**24** R=R*; (±)-**16** R=Ac (+)-**25** R=R*; (+)-**17**; (+)-**18**

Dienone (±)-**6** could not be isolated as it was dimerized instantaneously at 0°C on concentrating CH_2Cl_2 solutions containing it! Dienes (±)-**7**, (±)-**8** and (±)-**9** were dimerized much more slowly and could be obtained pure at 20°C. Their dimerization occurred in the condensed state on staying at 25°C for several days. For 1% CD_3CN solutions, the rate constants of dimerization were ranging from $0.5 \cdot 10^{-5}$ to $12 \cdot 10^{-5}$ $moldm^{-3}s^{-1}$ at 80°C (by 360 MHz ^1H-NMR). The dimerizations of (±)-**6**, (±)-**7**, (±)-**8** and (±)-**9** were highly stereoselective and gave the pentacyclic compounds (±)-**19**, (±)-**20**, (±)-**21** and (±)-**22**, respectively with



(+)-(1*R*,2*S*,3*S*,4*R*,7*R*,11*S*,12*R*)-**19** Z=O

(+)-**20** Z=O O



(+)-(1*R*,2*R*,3*R*,4*R*,7*R*,11*R*,12*R*)-**21** Z=O

(+)-**22** Z=O O

yields >90% (360 MHz ^{1}H-NMR of the crude reaction mixture). The optically pure dienes (+)-**6**, (-)-**7**, (+)-**8** and (+)-**9** derived from the "naked sugar" (+)-**23**[8] (following the same procedures as for the preparation of the racemic dienes)[9] were dimerized with the same rates as the corresponding racemic dienes and gave the optically pure cyclodimers (+)-**19**,[10] (+)-**20**,[11] (+)-**21**[12] and (+)-**22**[13] with yields better than 90%. Their relative configurations were established by their ^{1}H-NMR spectra which showed no coupling between H-1/H-2 and H-3/H-4 proton pairs,[14] thus demonstrating that the *exo* face was preferred for both the diene and dienophile partners, probably for steric reasons. NOESY 2-D spectra showed cross-peaks between H-1/H-3 and H-2/H-4 proton pairs. No NOE's were detected between the protons of the 11-vinyl group and H-3.

Table. Frontier orbital coefficients and energies, and heats of formation of dienes, **6**, **7**, **8** and **9** (SYBYL)

diene	*s-cis*[a)]	C-5	C-6	C-8	C-9[b)]	ε_i(eV)	ΔH_f°[c)]
6	HOMO	0.5633	0.4292	-0.3466	-0.4814	-9.4328	-5.70
	LUMO	0.5987	-0.4751	-0.3253	0.5093	-0.2173	
7	HOMO	-0.5571	-0.4300	0.3239	0.4638	-9.080	-56.44
	LUMO	0.5720	-0.4485	-0.3436	0.5052	0.1732	
8	HOMO	0.4356	0.5421	-0.3347	-0.4706	-9.4245	-5.80
	LUMO	0.4739	-0.5736	0.3310	-0.5155	-0.2605	
9	HOMO	0.4505	0.5519	-0.3277	-0.4764	-9.0663	-56.92
	LUMO	0.4519	-0.5787	0.3646	-0.5335	0.1602	
diene	*s-trans*[d)]						
6	LUMO	-0.5960	0.4792	0.3127	-0.4792	-0.2063	-5.28
	HOMO	-0.5631	-0.4359	0.3480	0.4581	-9.4362	
7	LUMO	0.5847	-0.4649	-0.3511	0.5030	0.1627	-55.75
	HOMO	0.5693	0.4502	-0.3330	-0.4612	-9.0938	
8	LUMO	-0.4772	0.5748	-0.3293	0.4885	-0.2804	-5.27
	HOMO	0.4432	0.5394	-0.3264	-0.4489	-9.4572	
9	LUMO	0.4558	-0.5793	0.3609	-0.5053	0.1403	-56.41
	HOMO	0.4603	0.5502	-0.3201	-0.4543	-9.0964	

a) The *s-cis* conformers were calculated to have planar diene moieties.

b) The 2p coefficients perpendicular to the diene plane are given. Contributions by 2s and 2p coefficients in the plane of the diene moiety are very small and can be neglected.

c) Heats of formation in Kcal/mol

d) The *s-trans* conformers are slightly less stable than the *s-cis* conformers probably because of a gauche interaction between the bridgehead hydrogen and the vinyl group. Their diene moieties showed slight distortions (3-5°) from planarity.

From the frontier orbital properties calculated by the AM1 method (Table) and applying the PMO theory,[15] one sees that the endocyclic double bonds in **6**-**9** are better dienophiles than the exocyclic vinylic moieties since larger atomic coefficients are calculated for the former than for the latter olefinic units. The regioselectivity observed for the cyclodimerizations of **6**-**9** are also predicted by the coefficients of the HOMO's and LUMO's of these dienes. The fastest Diels-Alder cyclodimerization should occur with the diene presenting the largest perturbation term between its LUMO/HOMO pairs as given, to a first approximation, by H = sum of (LUMO/HOMO overlaps)^2/(ε_{LUMO}-ε_{HOMO}). If one considers the coefficients at C-5/C-9 (C-6/C-9) of the *s-cis*-diene (diene partner) and at C-5/C-6 of the *s-trans*-diene (dienophile partner) one obtains H = 0.0357, 0.0335, 0.0322 and 0.0337 for **6**, **7**, **8** and **9**, respectively, suggesting that dienone **6** must dimerize faster than **7** - **9**, as observed.

Work is underway in our laboratory to define the limits of the homochiral matching principle disclosed here and to apply it to the asymmetric synthesis of compounds of biological interest.

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References and Notes

1. Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478-7485 and ref. cited therein.
2. Berson, J. A.; Malherbe, R. *J. Am. Chem. Soc.* **1975**, *97*, 5910-5912; Rimmelin, J.; Jenner, G. *Tetrahedron* **1974**, *30*, 3081-3085; Jenner, G.; Rimmelin, J. *Tetrahedron Lett.* **1980**, *21*, 3039-3042.
3. Sims, C. G.; Wege, D. *Aust. J. Chem.* **1992**, *45*, 1983-1990.
4. Djuric, S. W.; Huff, R. M.; Penning, T. D.; Clare, M.; Swenton, L.; Kachur, J. F.; Villani-Price, D.; Krivi, G. G.; Pyla, E. Y.; Warren, T. G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1367-1370.
5. Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341-5348.
6. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508-524; Mitchell, T. N. *Synthesis* **1992**, 803-815.
7. Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10587-10602.
8. Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1865-1871; Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348-5353; Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173-185.
9. Data of (+)-**6**: yellow oil, dimerizes quickly; $[\alpha]_D^{25}$ ~390 (c≅0.93, CH_2Cl_2). UV ($CHCl_3$) λ_{max}=243 nm (ε≅10 000); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 6.50 (dd, ^3J=17.5, 11.0); 6.50 (m, H-5), 5.42 (d, ^3J=17.5), 5.38 (m, H-4); 5.33 (d, ^3J=11.0); 4.83 (s, H-1); 2.38 (dd, ^2J=16, ^3J=4, H-3*exo*); 2.02 (d, ^2J=16, H-3*endo*). Data of (-)-**7**: oil, $[\alpha]_D^{25}$ -74 (c=0.90, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 6.59 (dd, ^3J=18, 11); 6.36 (d, ^3J=1.8); 5.23 (d, ^3J=18); 5.04 (ddd, ^3J=5.0, 1.8, ^4J=1.0); 4.68 (s); 4.12-3.95 (m, 4H); 2.22 (dd, ^2J=12, ^3J=5); 1.72 (d, ^2J=12). Data of (+)-**8**: oil, $[\alpha]_D^{25}$ +1280 (c=0.74, CH_2Cl_2); IR (film) ν: 1705, 1575, 1515 cm^{-1}; UV (CH_3CN) λ_{max}=241 nm (ε=5700); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 6.56 (dd, ^3J=17.5, 11); 6.17 (m, H-6); 5.40 (d, ^3J=4.5, H-4); 5.36 (d, ^3J=17.5); 4.65 (d, ^3J=2.0, H-1); 2.35 (dd, ^2J=16, ^3J=4.5, H-3*exo*); 1.82 (d, ^2J=16, H-3*endo*). Data of (+)-**9**: oil, $[\alpha]_D^{25}$ +420 (c=0.67, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 6.51 (dd, ^3J=17.5, 10.5); 6.19 (d, ^3J=1.5); 5.21 (d, ^3J=10.5); 5.20 (d, ^3J=17.5); 5.15 (br.d, ^3J=5.0); 4.50 (dd, ^3J=1.5, ^4J=1.0); 4.13-3.86 (m, 4H); 2.21 (dd, ^2J=12, ^3J=5); 1.59 (d, ^2J=12).
10. Data of (+)-**19**: $[\alpha]_D^{25}$ +191 (c=0.94, CH_2Cl_2); CD(CH_3CN): $\Delta\varepsilon_{308}$ +2.13; IR (film) ν: 2950, 2920, 1760, 1405 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 6.00 (dm, ^3J=7, H-9); 5.71 (dd, ^3J=17, 11), 5.04 (d, ^3J=11), 4.95 (d, ^3J=17, CH_2=CH); 4.82 & 4.73 (2d, ^3J=6, H-1, H-4); 4.61 (s, H-7); 3.98 (s, H-12); 2.65 (dd, ^2J=17, ^3J=6); 2.54 (dd, ^3J=17.5, ^3J=6); 2.39 (dd, ^2J=14, ^3J=7, H-10eq); 2.20 (d, ^3J=9.5, H-3); 2.17 (d, ^2J=14, H-10ax); 2.15 (d, ^2J=17); 2.06 (d, ^2J=17.5); 2.03 (d, ^3J=9.5, H-2). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ_C: 208.8, 206.5 (2s, CO); 139.5 & 116.3 (vinyl); 137.0 (s, C-8); 122.0 (d, C-9); 87.6, 82.3, 82.1, 79.3 (C-1, C-4, C-7, C-12); 51.5 (C-11); 46.8 (C-3), 43.1 (C-2); 43.0 (C-5, C-14); 33.6 (C-10).
11. Data of (+)-**20**: $[\alpha]_D^{26}$ +46 (c=0.63, CH_2Cl_2); ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ_C: 142.7 & 116.0 (vinyl); 140.6 (C-8), 119.0 (C-9); 115.1 & 114.3 (C-6, C-13); 86.4, 82.7, 82.2, 80.2 (C-1, C-4, C-7, C-12); 65.3, 65.2, 64.4, 63.4 (2 OCH_2CH_2O); 53.1 (C-11); 52.5 (C-3), 47.0 (C-2); 43.4, 42.3 (C-5, C-14); 33.4 (C-10).
12. Data of (+)-**21**: $[\alpha]_D^{26}$ +156 (c=1.32, CH_2Cl_2); CD(CH_3CN): $\Delta\varepsilon_{308}$ +1.36; IR (film) ν: 2950, 2920, 1760, 1405 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H: 6.00 (dm, ^3J=7.3, H-9); 5.73 (dd, ^3J=17.3, 10.8); 5.06 (d, ^3J=10.8), 4.95 (d, ^3J=17.3, CH_2=CH-); 4.82 (d, ^3J=6, H-7); 4.73 (d, ^3J=6.1, H-12); 4.62 (s, H-4); 3.98 (s, H-1); 2.68 (ddd, ^2J=17.2, ^3J=6, ^4J=0.9, H-6*exo*); 2.55 (ddd, ^2J=17.5, ^3J=6.1, ^4J=1.2, H-13*exo*); 2.40 (dd, ^2J=14, ^3J=7.3, H-10eq); 2.22 (dm, ^3J=9.6, H-3); 2.19 (dm, ^2J=14, H-10ax); 2.17 (d, ^2J=17.2, H-6*endo*); 2.07 (d, ^2J=17.5, H-13*endo*); 2.04 (d, ^3J=9.6, H-2); ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ_C: 208.8, 206.5 (2 CO); 139.5, 116.3 (vinyl); 137.0 (C-8), 122.0 (C-9); 87.6, 82.3, 82.1, 79.3 (C-1, C-4, C-7, C-12); 51.5 (C-11); 46.8 (C-3); 43.1 (C-2); 43.0 (C-6, C-13); 33.6 (C-10).
13. Data of (+)-**22**: $[\alpha]_D^{26}$ +47 (c=0.54, CH_2Cl_2); ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ_C: 144.8 (C-8), 142.2, 114.0 (vinyl); 114.9 (C-9); 114.5 (C-7, C-14); 87.1 (C-4), 84.9 (C-7); 83.6 (C-1); 79.1 (C-12); 65.2, 64.4, 64.2 (OCH_2CH_2O); 54.7 (C-11); 45.3 (C-3), 40.5 (C-2); 42.7, 39.9 (C-6, C-13); 33.1 (C-10).
14. Ramey, K. C.; Lini, D. C. *J. Magn. Reson.* **1970**, *3*, 94-102; Nelson, W. L.; Allen, D. R. *J. Heterocycl. Chem.* **1972**, *9*, 561-568; Kienzle, F. *Helv. Chim. Acta* **1975**, *58*, 1180-1183.
15. Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092-4094; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779-807; Alston, P. V.; Ottenbrite, R. M.; Guner, O. F.; Shillady, D. D. *Tetrahedron* **1986**, *42*, 4403-4408; Sauer, J.; Sustmann, R.; Siangouri-Feulner, I. *Chem. Ber.* **1993**, *126*, 1241-1245.

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