Tetrahedron Letters, Vol. 34, No. 19, pp. 3181-3184, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# A Two-Step Chirality Transfer from (-)- Endo- to (-)-Exo-Tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one

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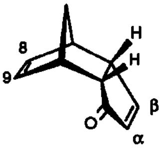
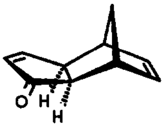
*__Abstract__: An effective synthesis of enantiopure (-)-*exo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one* exo-1 *is realized starting from enantiopure (-)-*endo-1 *applying Diels-Alder/retro-Diels-Alder methodology. The unusually high* exo-*stereoselectivity observed in the [4+2]-cycloaddition of (-)-*endo-1 *with cyclopentadiene has been evaluated by semi-empirical AM1 transition state calculations.*

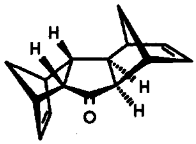
*Endo*- and *exo*-tricyclo[5.2.1.$0^{2,6}$]decadienones 1 have great potential as synthetic building blocks in cyclopentenoid natural product synthesis[1]. The *endo*-tricyclodecadienone system, *endo*-1, both racemic and enantiopure[2], is readily accessible, however, its *exo*-congener, *exo*-1, has only been obtained as a racemic mixture and in low yield after laborious syntheses[3,4]. For our studies on the steric and electronic features of the *endo*- and *exo*-tricyclodecadienone systems 1, we needed an effective synthesis of both racemic and enantiopure *exo*-1. For this purpose, we explored the Diels-Alder reaction of enantiopure (-)-*endo*-1 with cyclopentadiene and studied the thermal cycloreversion of its major adduct (-)-2a. On thermodynamic and kinetic grounds we reasoned that cycloreversion of 2a, would preferably lead to formation of *exo*-1. AM1 energy calculations[5] show that *exo*-1 is thermodynamically slightly more stable than *endo*-1, while, on the basis of microscopic reversibility, [4+2]-cycloreversion of *endo*-adducts is expected to be kinetically favored over that of *exo*-adducts. Hence, thermal cycloreversion of enantiopure 2a under suitable conditions may give access to enantiopure *exo*-1.



(-)-endo-1



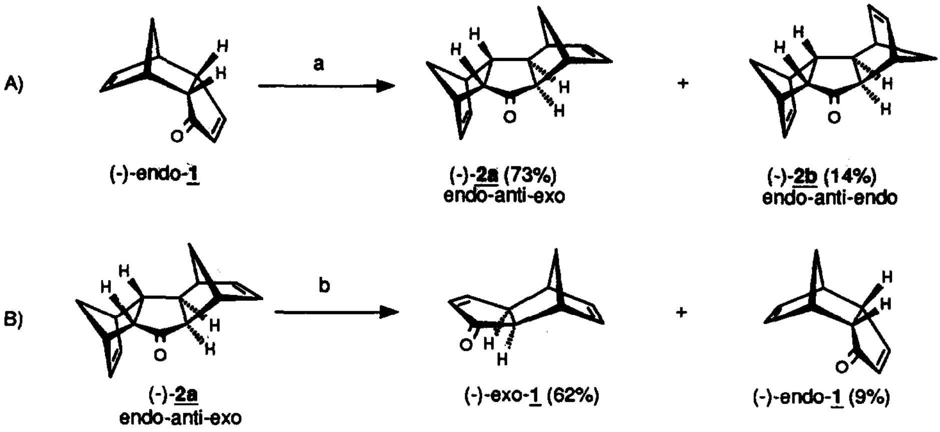
(-)-exo-1



(-)-2a

Cookson and co-workers[4] studied the Diels-Alder reaction of (±)-tricyclodecadienone *endo*-1 with cyclopentadiene in the presence of aluminum chloride as catalyst. The formation of *endo-anti-exo*-adduct 2a and *endo-anti-endo*-adduct 2b was reported, however, without mention of exact yields or ratios.

Treatment of a mixture of enantiopure (-)-*endo*-tricyclodecadienone *endo*-1[2a] {0.72 g, $[\alpha]_D = -140.3°$ (c=0.548,MeOH)} and 0.2 equiv. of dry aluminum chloride in 15 ml dry benzene for four hours at room



(a) 2 equiv. cyclopentadiene, 0.2 equiv. $AlCl_3$, benzene, R.T. , 4 h; (b) o-dichlorobenzene, reflux, 17 h.

Scheme 1. Synthetic route to enantiopure (-)-*exo*-tricyclodecadienone 1.

temperature with 2 equiv. of cyclopentadiene gave a mixture of two adducts in 89% yield (Scheme 1A[6]). Separation was accomplished by flash chromatography[7a] to yield the pure diastereomers (-)-2a[8,9] {0.76 g, $[\alpha]_D$= -441.2° (c=0.668,$CHCl_3$)} and (-)-2b[8,10] {0.15 g, $[\alpha]_D$= -278.7° (c=0.590,$CHCl_3$)} in 73% and 14% yield, respectively. Neither *endo-syn-endo-* nor *endo-syn-exo*-adduct was detected in the reaction mixture.

Thermal cycloreversion of *endo-anti-exo*-adduct (-)-2a (0.30 g) was most conveniently carried out by heating it in *o*-dichlorobenzene for 17 hours at 180 °C (Scheme 1B[6]). Desired (-)-*exo*-1 was formed in 62% yield together with 9% of (-)-*endo*-1. This result shows that the *endo*-norbornene moiety in 2a is indeed preferentially cleaved in this cycloreversion reaction. Removal of solvent and (-)-*endo*-1 (0.02 g) by flash chromatography[7b] gave optically pure (-)-*exo*-1[8,11] {0.13 g, $[\alpha]_D$= -200.5° (c=0.578,MeOH)} in 45% overall yield, starting from enantiopure (-)-*endo*-1.

Attempts to convert (-)-*endo*-1 to (-)-*exo*-1 in a one-pot procedure applying cyclopentadiene in *o*-dichlorobenzene at 180 °C in a sealed tube with or without aluminum chloride resulted in either complete recovery of (-)-*endo*-1 or considerable decomposition.

The observation of a highly stereoselective *exo*-addition of cyclopentadiene to norbornene annelated cyclopentenone *endo*-1 contrasts sharply the moderate to strong preference of cyclopentadiene for *endo*-addition to monocyclic cyclopentenones[12]. Recently, a second example of predominant *exo*-addition to *endo*-1 was reported by Takano *et al.*[1j] who applied 6-methoxy-1-vinyl-3,4-dihydronaphthalene (Dane's diene) as the diene. To shed light on this unusual *exo*-stereoselectivity of *endo*-1 in the [4+2]-cycloaddition reaction, semi-empirical AM1 transition state calculations[5,13] were carried out for all four conceivable Diels-Alder products 2. The calculated TS bond distances between the interacting atoms $\alpha$, $\alpha^*$ and $\beta$, $\beta^*$ confirm the anticipated concerted character of this cycloaddition in all cases, the $\beta$-$\beta^*$ bond being somewhat stronger than the $\alpha$-$\alpha^*$ bond for 2a,b and the *endo-syn-exo*-adduct, due to a more effective orbital overlap. Strong steric congestion near the $\beta$-$\beta^*$ bond in the transition state leading to the *endo-syn-endo*-adduct is responsible for the somewhat stronger $\alpha$-$\alpha^*$ bond and somewhat weaker $\beta$-$\beta^*$ bond in this case. The calculated heats of activation are in agreement with the observed *exo-anti*-stereoselectivity. The transition state leading to *endo-anti-exo*-adduct 2a is 0.91 kcal/mol more stable than that producing *endo-anti-endo*-adduct 2b.

Table 1. Calculated TS-Properties for the Diels-Alder Reaction of *endo*-1 with Cyclopentadiene.

| product | $\Delta H_{act.}$ [a] | d(α,α*) [b] | d(β,β*) [c] |
|---|---|---|---|
| *endo-anti-exo*-2a | + 31.90 | 2.16 | 2.11 |
| *endo-anti-endo*-2b | + 32.81 | 2.14 | 2.10 |
| *endo-syn-endo* | + 46.53 | 2.08 | 2.18 |
| *endo-syn-exo* | + 42.02 | 2.16 | 2.12 |

Table 2. Calculated TS-Properties for the Cycloreversion of 2a.

| product | $\Delta H_{act.}$ [a] | d(α,α*) [b] | d(β,β*) [c] |
|---|---|---|---|
| *endo*-1 | + 55.84 | 2.16 | 2.11 |
| *exo*-1 | + 54.95 | 2.15 | 2.10 |

[a] Heat of activation in kcal/mol [b] distance between interacting atoms α and α* in TS in Å [c] *ibid.* for β and β*.

Moreover, the experimental (*i.e.* 5.2:1) and calculated (*i.e.* 4.7:1)[17] ratios of 2a:2b are in good agreement. The transition states leading to *syn*-adducts, in which the diene must add at the sterically hindered concave face of *endo*-1, are highly destabilized, and accordingly no *syn*-adducts were formed. These calculations demonstrate that the observed *exo-anti*-stereoselectivity is inherent to the spatial arrangement of the atoms in *endo*-tricyclodecadienone *endo*-1. A directing influence of the $C_8$-$C_9$ double bond in *endo*-1 on the *endo*/*exo*-stereoselectivity of its Diels-Alder reaction with cyclopentadiene can be ruled out, since both *endo*-1 and its 8,9-hydrogenated analog display a strong *exo*-stereoselectivity in their [4+2]-cycloaddition with cyclopentadiene[4]. The somewhat higher heat of activation calculated for the *endo-anti-endo*-transition state can probably be attributed to steric interaction of the $C_2$ and $C_6$ protons in *endo*-1 with cyclopentadiene, which is more severe in the *endo*- than in the *exo*-addition mode. Apparently this steric effect is large enough to overrule the electronically favored *endo*-addition.

Transition state calculations similarly confirm that the observed regioselective fragmentation of the *endo*-fused norbornene moiety in the cycloreversion of 2a is also inherent to the spatial arrangement of its atoms (Table 2). It is kinetically preferred over fragmentation of the *exo*-fused norbornene ring since it involves a larger loss of steric strain and it is thermodynamically favored because it leads to thermodynamically more stable *exo*-1. In this case however, the observed selectivity (*i.e.* 6.9:1) is significantly higher than that predicted by the difference in the calculated heats of activation (*i.e.* 2.7:1)[18].

The above results show that enantiopure *exo*-tricyclodecadienone (-)-*exo*-1 can conveniently be synthesized in good yield from readily available enantiopure (-)-*endo*-1 in a simple two-step procedure. Furthermore, semi-empirical AM1 calculations show that *endo*-tricyclodecadienone *endo*-1 typically undergoes *exo*-addition in Diels-Alder reactions.

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1. For some recent representative examples see: (a) Klunder, A.J.H.; Huizinga, W.B.; Sessink, P.J.M.; Zwanenburg, B. *Tetrahedron Lett.*, **1987**, *28*, 357 (b) Klunder, A.J.H.; Houwen-Claassen, A.A.M.; Kooy, M.G.; Zwanenburg, B. *ibid.*, **1987**, *28*, 1329 (c) Lange, J.H.M.; Klunder, A.J.H.; Zwanenburg, B. *ibid.*, **1989**, *30*, 127 (d) Houwen-Claassen, A.A.M.; Klunder, A.J.H.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7134 (e,f) Grieco, P.A.; Abood, N. *J. Org. Chem.*, **1989**, *54*, 6008 and *J. Chem. Soc., Chem. Commun.*, **1990**, 410 (g) Garland, R.B.; Miyano, M.; Pireh, D.; Clare, M.; Finnegan, P.M.; Swenton, L. *J. Org. Chem.*, **1990**, *55*, 5854 (h) Klunder, A.J.H.; Zwanenburg, B.; Liu, Z.-Y. *Tetrahedron Lett.*, **1991**, *32*, 3131 (i) Lange, J.H.M.; Klunder, A.J.H.; Zwanenburg, B. *Tetrahedron*, **1991**, *47*, 1509 (j) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.*, **1992**, *33*, 1909 and references cited therein.

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4. Cookson, R.C.; Henstock, J.; Hudec, J. *J. Am. Chem. Soc.*, **1966**, *88*, 1059.
5. Use of the services and facilities of the Dutch National NWO/SURF Expertise Center CAOS/CAMM, University of Nijmegen, under grant numbers SON 326-052 and STW NCH99.1751, is gratefully acknowledged.
6. All compounds in schemes 1A and 1B are drawn in their correct absolute configuration.
7. $SiO_2$ 60H (Merck), *n*-hexane:ethylacetate = (a) 19:1, $R_f$(2a)= 0.37, $R_f$(2b)= 0.18 (b) 3:1, $R_f$(*exo*-1)= 0.34, $R_f$(*endo*-1)= 0.24.
8. The optical purities of (-)-*exo*-1, (-)-2a and (-)-2b all exceeded 98% as was shown by means of $^1$H-NMR-studies, using Eu(hfc)$_3$ as chiral shift reagent.
9. 2a: white powder (*n*-pentane). m.p.: 95.5 - 96.5 °C (subl.: 80 °C). $^1$H-NMR (400 MHz,CDCl$_3$): $\delta$ 6.17 A of AB (dd, J=3.0 and 5.7 Hz, 1H), 6.14 A of AB (dd, J=3.1 and 5.7 Hz, 1H), 6.09-6.05 B of AB (m, 2H), 3.22-3.20 (m, 1H), 3.11-3.07 (m, 2H), 2.97 (bs, 1H), 2.83 (bs, 1H), 2.51 (ddd, J=2.1, 4.1 and 8.6 Hz, 1H), 1.94 A of AB (d, J=7.7 Hz, 1H), 1.78 B of AB (d, J=7.7 Hz, 1H), 1.51 A of AB (d, J=8.4 Hz, 1H), 1.37-1.33 (m, 2H), 1.27 (d, J=8.4 Hz, 1H). $^{13}$C-NMR (400 MHz,H-dec.,CDCl$_3$): $\delta$ 222.8 (quat.), 138.4/137.1/135.9/135.5 (tert.), 60.4/59.1 (tert.), 51.2 (sec.), 49.9/48.0/47.6/47.3/46.8/46.5 (tert.), 45.6 (sec.). IR ($CH_2Cl_2$): $\upsilon$ 3020-2830 (C-H,sat.), 1715 (C=O) cm$^{-1}$. EI/MS: m/e (%) 212 (2,M$^+$), 147 (86,-$C_5H_5$), 81 (8,-$C_5H_5$,-$C_5H_6$), 66 (100,$C_5H_6^+$). Found: C 84.68, H 7.45 (calc. for $C_{15}H_{16}O$: C 84.87, H 7.60).
10. 2b: white powder (*n*-pentane). m.p.: 130.0 - 131.5 °C (subl.: 100 °C). $^1$H-NMR (400 MHz,CDCl$_3$): $\delta$ 6.20 A of AB (dd, J=3.0 and 5.6 Hz, 2H), 6.07 B of AB (dd, J=2.9 and 5.6 Hz, 2H), 3.07 (bs, 4H), 2.60 A of AB (dd, J=4.7 and 8.2 Hz, 2H), 2.42 B of AB (dd, J=3.6 and 8.2 Hz, 2H), 1.45 A of AB (d, J=8.2 Hz, 2H), 1.28 B of AB (d, J=8.2 Hz, 2H). $^{13}$C-NMR (400 MHz,H-dec.,CDCl$_3$): $\delta$ 224.4 (quat.), 137.1/136.1 (tert.), 59.7 (tert.), 51.4 (sec.), 47.5/46.5/45.8 (tert.). IR ($CH_2Cl_2$): $\upsilon$ 3010-2840 (C-H,sat.), 1720 (C=O) cm$^{-1}$. EI/MS: m/e (%) 212 (1,M$^+$), 147 (97,-$C_5H_5$), 81 (11,-$C_5H_5$,-$C_5H_6$), 66 (100,$C_5H_6^+$). Found: C 84.45, H 7.45 (calc. for $C_{15}H_{16}O$: C 84.87, H 7.60).
11. An analytically pure sample of (-)-*exo*-1 was obtained by Kugelrohr distillation (70 °C/9-10 mmHg).
12. For some representative examples see: (a) Sauers, R.R.; Henderson, T.R. *J. Org. Chem.*, **1974**, *39*, 1850 (b) Kienzle, F.; Minder, R.E. *Helv. Chim. Acta*, **1987**, *70*, 1537 (c) Alonso, I.; Carretero, J.C.; Garcia Ruano, J.L. *Tetrahedron Lett.*, **1989**, *30*, 3853 (d) Dols, P.P.M.A.; Lacroix, L.; Klunder, A.J.H.; Zwanenburg, B. *ibid.*, **1991**, *32*, 3739.
13. All calculations were performed using the AM1 Hamiltonian[14]. After energy-minimization of the product (EF-routine in MOPAC 6.0[15]), a preliminary TS-structure was calculated using the VAMP-program[16]. The Diels-Alder reaction was simulated by simultaneously elongating both bonds formed during the reaction in steps of 0.1 Å from their initial length (around 1.55 Å) up to 2.55 Å (SYMMETRY-routine in combination with a path calculation). Subsequently, two structures (mostly those at 1.95 and 2.35 Å) close to the approximate TS (near 2.15 Å) were used in a SADDLE-calculation, which provided a preliminary TS-structure. Final refinement of this structure, was best achieved using the TS-routine implemented in MOPAC 6.0. All six transition structures obtained in this way, were found to have a single imaginary vibrational frequency as required for a genuine transition state.
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15. MOPAC version 6.0. Quantum Chemistry Program Exchange (QCPE), Program Number 455, **1990**.
16. VAMP 4.3 is a vectorized semi-empirical MO program, derived from Dewar's AMPAC 1.0 and Stewart's MOPAC 4.0 and is developed and maintained at the University of Erlangen.
17. $k_{2a}/k_{2b} = \exp(-\Delta\Delta H_{act.}/RT)$, $\Delta\Delta H_{act.} = (\Delta H_{act.})_{2a} - (\Delta H_{act.})_{2b} = 68.96 - 69.87 = -0.91$ kcal/mol = -3.81 kJoule/mol, T = 298 K.
18. $k_{exo\text{-}1}/k_{endo\text{-}1} = \exp(-\Delta\Delta H_{act.}/RT)$, $\Delta\Delta H_{act.} = (\Delta H_{act.})_{exo\text{-}1} - (\Delta H_{act.})_{endo\text{-}1} = 54.95 - 55.84 = -0.89$ kcal/mol = -3.72 kJoule/mol, T = 453 K.

**Acknowledgment.** This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

(Received in UK 8 March 1993)