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Synthesis and evaluation of new chiral diols based on the dicyclopentadiene skeleton

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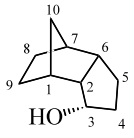
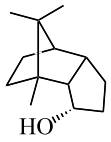
Abstract—The resolution by Lipase PS of *rac*-**5** (from reduction of ketone **6**, obtained from dicyclopentadiene with a new environment-friendly synthesis) gives (2*S*)-**5**, which was further reduced to the *endo* (2*R*)-**1a** alcohol. The *endo* (2*S*)-**1b** alcohol was obtained from camphor with a multistep synthesis. Pinacol couplings of **3a**,**b**, carried out with Mg/Hg or Corey's general procedure respectively, afforded with high diastereoselectivity the C_2 symmetry diols (2*R*,2′*R*)-**2a** and (2*S*,2′*S*)-**2b**, with *endo* oriented OH functions. The enantiogenic power of the *endo* alcohol (2*R*)-**1a** and (2*S*)-**1b** and of the diols (2*R*,2′*R*)-**2a** and (2*S*,2′*S*)-**2b** was tested towards the $LiAlH_4$ reduction of acetophenone. The C_2 symmetry appears to play a fundamental role.

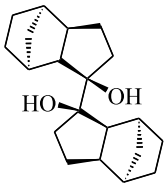
Optically active 1,2-diols are of widespread use as chiral auxiliaries in asymmetric synthesis and a large number of such compounds have been reported so far.[1] Among them, C_2-symmetrical diols are of particular interest, due to the numerous additional advantages of the C_2 auxiliaries over the asymmetrical ones.[2] In this work we describe the synthesis of new enantiopure, C_2-symmetrical diols based on the *endo*-dicyclopentadiene skeleton, and a preliminary evaluation of their enantiogenic power. Actually, the **1a** and **1b** alcohols, with *endo* oriented OH groups, are attractive substrates for the development of chiral auxiliaries, by virtue of their most interesting steric feature: the two faces of the five-membered ring are strongly differentiated by the wrapping of the bicyclo moiety, thus making the *endo* face much more hindered than the *exo* one. This potential ability may also be shared by the enantiopure diols **2a** and **2b**, which in addition offer the advantage of C_2 symmetry.



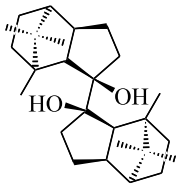
endo-**1a**



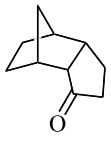
endo-**1b**



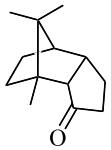
2a



2b



3a



3b

The synthetic approach towards chiral diols **2a** and **2b** is based on the pinacol coupling of enantiopure ketones **3a** and **3b**, which occurs exclusively via an *exo–exo* approach of the two monomers, because of the steric hindrance exerted by the wrapping to the *endo* face.[3] The OH groups of the diols are therefore pushed toward the *endo* face of the dicyclopentadiene skeleton, thus achieving the presumably greatest enantiodifferentiating capability.

The synthesis of the enantiopure ketone **3a**, is achieved via resolution of the suitable substrate by Lipase PS enzyme.[4,5] The resolution may be performed on either the *exo* alcohol **4** or on the *endo* alcohol **5**. The *exo* alcohol **4**, in the racemic form, was directly obtained from oxidation of the cyclopentadiene dimer by seleni-

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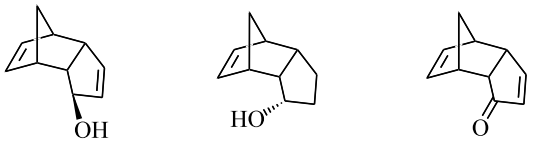
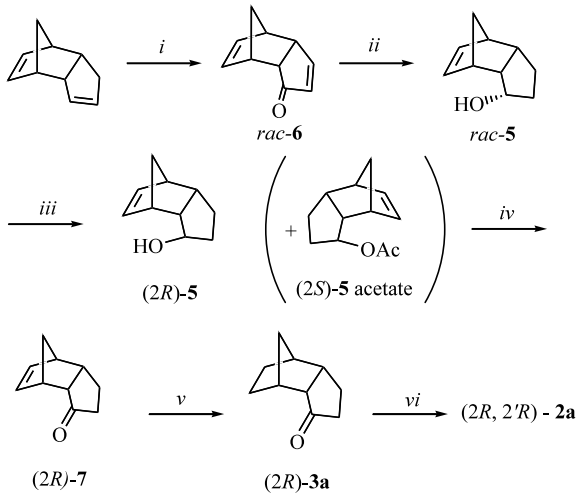
um(IV) oxide.[6] The Lipase PS resolution then gives (2*R*)-**4**,[5] which was then further oxidized to ketone (2*R*)-**6** with MnO_2.



4 **5** **6**

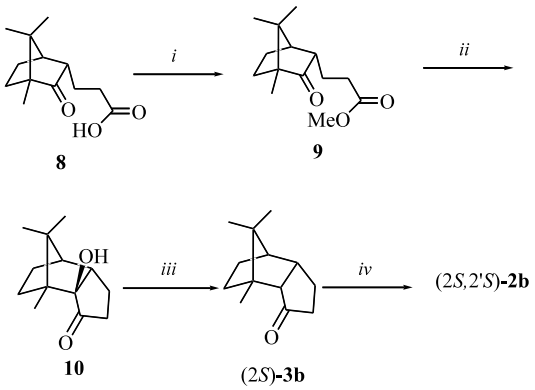
With the aim to avoid the use of toxic selenium(IV), we selected the alternative synthetic sequel described in Scheme 1. This sequel considers the direct formation of ketone *rac*-**6**, followed by reduction to the *endo* alcohol *rac*-**5**. The ketone was obtained in the past by photochemical allylic oxidation of dicyclopentadiene with singlet oxygen, followed by a multistep procedure,[7] which however turned out to be unpractical for a large-scale preparation. Therefore, we tested a new methodology to obtain *rac*-**6** in high yields and free from traces of metals, namely the one-pot allylic oxidation by Mihelich and Eickhoff, catalyzed by tetraphenylporphyrin (TPP).[8] This methodology proved to be highly effective for the synthesis of *rac*-**6**,[9] that was obtained as the sole product (after work-up the only contaminant was highly colored TPP, that was not detected in the ^{1}H NMR spectra). The two-step reduction of *rac*-**6** afforded the *endo* alcohol *rac*-**5**.[10] The Lipase PS resolution of the *endo* alcohol gave satisfactory results, with the separation of the enantiopure (2*R*)-**5** *endo* alcohol from the (2*S*)-**5** acetate.[5,11] Jones' oxidation of the alcohol afforded the (2*R*)-**7** ketone,[12] whose enantiomeric purity was confirmed after titration with Eu(tfc)$_3$, monitored by NMR. The catalytic hydrogenation of (2*R*)-**7** gave the sought-for (2*R*)-**3a** ketone in almost quantitative yield.[13]



Scheme 1. *Reagents and conditions* (yields): (i) O_2, Ac_2O, Py., *hv*, CH_2Cl_2, 6 h (quant.); (ii) (1) Zn(0), AcOH, (2) $LiAlH_4$, THF, rt (70% overall); (iii) vinyl acetate, Lipase PS, *t*-BuOMe, 38°C, 7 days (48%); (iv) Jones' oxidation (80%); (v) H_2, Pd/C, AcOEt (98%); (vi) Mg/Hg, TMSCl, THF, rt (80%).

The ketone was then coupled in the presence of magnesium amalgam.[3] The enantiomeric purity was also confirmed by the coupling reaction, which afforded the pinacol (2*R*,2′*R*)-**2a** as sole product (a single set of ^{13}C NMR signals).[14] On the contrary, when *rac*-**3a** (obtained with the same synthetic sequel, but skipping the resolution step) was reacted under the same conditions, a 1:1 mixture of the racemic *dl* pinacols [(2*S*,2′*S*)-**2a** and (2*R*,2′*R*)-**2a**] and the of *meso* pinacol [(2*S*,2′*R*)-**2a**] was obtained (two sets of ^{13}C NMR signals).[15] As already pointed out, in both cases the coupling resulted from an *exo–exo* approach of the two ketones, because of the steric hindrance exerted by the wrapping to the *endo* face.

The optically pure diol (2*S*,2′*S*)-**2b** was synthesized starting from the known enantiopure, camphor-derived, acid **8**,[16] according to the reaction sequence shown in Scheme 2. After quantitative esterification to **9** with methyl iodide in acetone,[17] the key step for the generation of the tricyclic system is the intramolecular acyloin condensation, which occurred in 80% yield by slow addition (5 h) of ester **9** to a solution of lithium naphthalenide in THF at −78°C.[18] Dehydroxilation of the α-hydroxyketone **10** with trimethylsilyl iodide in $CHCl_3$ afforded (2*S*)-**3b** in good yield.[19]



Scheme 2. *Reagents and conditions* (yields): (i) CH_3I, Na_2CO_3, acetone, rt (94%); (ii) Li-Naph., THF, −78°C (80%); (iii) TMSI, $CHCl_3$ (quant.); (iv) Mg(Hg)/$TiCl_4$, THF, −10°C (80%).

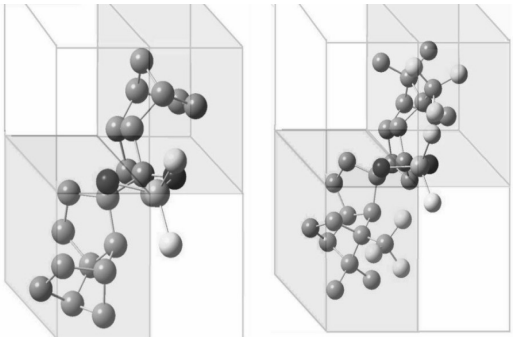


Figure 1. Schematic representation of the steric hindrance exerted on the reaction center by the bridgehead positions in the complexes of diols **2a** (left) and **2b** (right) with $LiAlH_4$.

Table 1. Enantiogenic power of *endo* alcohols (2*R*)-**1a** and (2*S*)-**1b** and of diols (2*R*,2′*R*)-**2a** and (2*S*,2′*S*)-**2b** towards the $LiAlH_4$ reduction of acetophenone, in THF at −78°C

Alcohol or diol	$LiAlH_4$:alcohol or diol ratio	Ethanol:diol ratio	Time (h)	Conversion (%)	E.e. (%)
(2*R*)-**1a**	1:3	–	2	80	0
(2*S*)-**1b**	1:3	–	2	60	5
(2*R*,2′*R*)-**2a**	1:1	–	2	75	15
(2*R*,2′*R*)-**2a**	1:1	1:1	6	27	30
(2*S*,2′*S*)-**2b**	1:1	–	2	75	35
(2*S*,2′*S*)-**2b**	1:1	1:1	2	60	17

Unexpectedly, the procedure for pinacol coupling with magnesium amalgam is not effective for ketone **3b**. After unsuccessful investigations of alternative coupling reagents, such as SmI_2 or Li/NH_3, the diol (2*R*,2′*R*)-**2b** was finally obtained with a satisfactory 80% yield by the Corey's general procedure for the reductive coupling of carbonyl compounds.[20,21]

Finally, stereoselective reduction of (2*R*)-**3a** and (2*S*)-**3b** by $LiAlH_4$ gave the corresponding *endo* alcohols (2*R*)-**1a** and (2*S*)-**1b** with excellent yields.

To test the enantiogenic capability of diols (2*R*,2′*R*)-**2a** and (2*S*,2′*S*)-**2b**, the asymmetric reduction of acetophenone with the diol/$LiAlH_4$ adducts was examined.[22] Because of the steric repulsion between the two norbornane moieties, these latter units and the hydroxy groups in free **2a** or free **2b** are reciprocally *gauche* oriented. However, when the diol **2a** or the diol **2b** combine with $LiAlH_4$, the C–O bonds should assume an almost eclipsed conformation around the central C–C bond, thus acquiring an increased rigidity and a C_2 axial symmetry, with steric shielding exerted by the norbornane units at the opposing angles of a quadrant, as represented in Figure 1. It is worth noting that the bridgehead positions are strategically oriented towards the reaction center, and thus affecting the asymmetric induction. The diol **2b**, which bears a methyl substituent at the bridgehead positions, is then expected to exert a greater asymmetric induction than the unsubstituted diol **2a**.

Moreover, it may be wondered whether the enantiogenic power is to be attributed to the C_2 structure of diols **2a** and **2b**, or it is rather already present in the monomeric alcohol units. Actually, the hydroxyl group in the *endo* alcohol (2*R*)-**1a** and (2*S*)-**1b** is positioned inside an helically-shaped scaffold, characterized by structural rigidity and presenting the faces of the hydroxycyclopentane ring strongly differentiated as for the steric shielding.

The answer to these questions comes from the comparative experiments reported in Table 1. The (2*R*)-**1a** promoter, in a 3:1 ratio with $LiAlH_4$, induces no appreciable enantiomeric excess, while the (2*S*)-**1b** promoter gives only 5% e.e., favoring the *R* enantiomer. On the contrary, equimolar amounts of pinacol (2*R*,2′*R*)-**2a** and $LiAlH_4$ reduces acetophenone with a 15% e.e., and with the excess of the same enantiomer. Similarly to other chiral diols with C_2 symmetry,[23] the e.e. is increased to 30% by the participation of an equimolar amount of ethanol. As expected, diol (2*S*,2′*S*)-**2b** gives the best results: the reduction of acetophenone with equimolar $LiAlH_4$ gives 35% e.e. Curiously, the addiction of an equimolar amount of ethanol reduces, in this case, the e.e. to 17%, probably because of the strong steric strain of the $LiAlH_4$–**2b**–EtOH complex, which promotes his disproportionation into less selective species.[22a]

These results clearly highlight the importance of the C_2 symmetry. The observed enantioselectivity is modest, however comparable to that of other chiral C_2 aliphatic diols.[24] Actually, it is not clear if the low e.e. should be attributed to the modestly efficient steric shielding of the norbornane units or by electronic effects, which seems to favor aromatic chiral auxiliary over aliphatic ones in the asymmetric reduction of ketones.[22b,c] In the continuation of this research further modifications of the norbornane structure will be evaluated, together with alternative applications of these promising molecules.

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9. Photosynthesis of tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one **6**. A solution of dicyclopentadiene (13.0 mL, 98 mmol), acetic anhydryde (10.0 ml, 100 mmol), pyridine (4.0 ml, 49 mmol), dimethylaminopyridine (240 mg, 2.0 mmol) and tetraphenylporphyrin (20 mg, 0.03 mmol) in CH_2Cl_2 (90 mL) was irradiated with a halogen lamp (500 W) for 5 h under O_2 bubbling and vigorous stirring. The mixture was diluted in CH_2Cl_2 (100 ml), washed in sequence with saturated aqueous $NaHCO_3$ (2×50 ml), 1 M HCl (2×50 ml), saturated aqueous $CuSO_4$ (2×20 ml), brine (100 ml), and dried over Na_2SO_4. The volatile materials were removed by suction to afford 13.0 g of **6** as a dark-red oil, pure enough (^{1}H NMR) to be used in the following steps without further manipulations.
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14. Representive procedure for the reductive coupling of ketone **3a** to diol (2*R*,2′*R*)-**2a**. A solution of the enantiopure ketone (2*S*)-**3a** (2.00 g, 13.5 mmol) in anhydrous THF (10 ml) was added at 0°C in 30 min to a mixture of magnesium amalgam (obtained from 380 g of Hg and 5 g of Mg) and trimethylchlorosilane (12 ml, 94 mmol) in anhydrous THF (40 ml). The mixture was then stirred under argon for 32 h at room temperature. The organic phase was decanted, and the remaing metal washed several times with CH_2Cl_2 and THF. After evaporation, the combined organic layers were dissolved in ethanol (10 ml) and water (40 ml) and refluxed for 30 min. After acidification with diluited HCl, the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. Crystallization from hexane afforded 1.55 g (80% yield) of (2*R*,2′*R*)-**2a**. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 2.48 (2H, m, H_2), 2.38 (2H, m, H_6), 2.20 (4H, bs, H_1 and H_7), 2.09 (2H, m, H_{9endo}), 1.84 (2H, m, H_{4endo}), 1.69 (2H, m, H_{4exo}), 1.63 (2H, bs, H_{5endo} or H_{5exo}), 1.53 (2H, m, H_{10s}), 1.49 (2H, m, H_{5endo} or H_{5exo}), 1.42 (2H, m, H_{10a}), 1.39 (2H, m, H_{9exo}); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 88.13 (2C, C_3), 50.31 (2C, C_2), 45.29 (2C, C_6), 43.00 (2C, C_{10}), 41.99 (2C, C_1 or C_7), 41.31 (2C, C_7 or C_1), 36.95 (2C, C_4), 24.69 (2C, C_9), 24.30 (2C, C_8), 22.40 (2C, C_5).
15. ^{13}C NMR signals of the *meso* diol (2*S*,2′*R*)-**2a**. ($CDCl_3$, 100 MHz), δ: 88.50 (2C, C_3), 50.66 (2C, C_2), 50.59 (2C, C_6), 45.32 (2C, C_{10}), 43.37 (2C, C_1 or C_7), 41.65 (2C, C_7 or C_1), 41.27 (2C, C_4), 37.48 (2C, C_9), 24.51 (2C, C_8), 22.61 (2C, C_5).
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21. (2*S*,2′*S*) - 7,8,8,7′,8′,8′ - Hexamethylhexadecahydro[1,1′]bi-[4,7-methanoindenyl]-1,1′-diol **2b**: ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 2.63 (2H, m, H_6), 2.36 (2H, d, J=11.1 Hz, H_2), 2.27 (2H, m, H_{9endo}), 1.56 (10H, m, $4H_8$ and $4H_5$, $2H_7$), 1.35 (2H, tdd, J=14.9, 4.6, 2.5 Hz, H_{9exo}), 0.96 (6H, s, Me_{10s}), 0.89 (6H, s, Me_1), 0.88 (6H, s, Me_{10a}); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 88.90 (2C, C_3), 52.43 (2C, C_2), 48.84 (2C, C_9), 44.10 (2C, C_6), 36.41 (2C, C_4), 29.70 (2C, C_9), 29.19 (2C, C_5), 24.76 (2C, C_8), 19.35 (2C, Me_{10a}), 19.27 (2C, Me_{10s}), 16.48 (2C, Me_1).
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