Pergamon

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Tetrahedron Letters 44 (2003) 431–433

TETRAHEDRON LETTERS

The *exo*-selectivity of the new non-natural chiral auxiliary (+)-(1*R*,*endo*)-2-benzonorbornenol in an asymmetric aza-Diels–Alder reaction

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Received 14 November 2002; revised 15 November 2002; accepted 18 November 2002

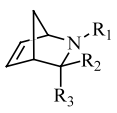
Abstract—The recently reported compound (+)-(1*R*,*endo*)-2-benzonorbornenol (**2**) proved to be an efficient chiral auxiliary in the asymmetric aza-Diels–Alder reaction between cyclopentadiene and the *N*-benzyl imine of its glyoxylate, which afforded a virtually all-*exo* mixture of cycloaducts with a 1*S*:1*R* diastereomeric ratio of 63:37. © 2002 Elsevier Science Ltd. All rights reserved.

The past 20 years have seen great progress in the development and use of chiral auxiliaries for asymmetric synthesis.[1] Many of the most widely used as menthol,[2] 8-phenylmenthol[3] and *trans*-2-phenylcyclohexanol[4] are based on the cyclohexane frame.[5] Most chiral auxiliaries are natural products or are derived from natural products, with the result that in many cases one or the other enantiomer is not available. This problem does not arise with non-natural auxiliaries obtained by resolution of a racemate, which also have the further advantage that their structure can be optimized for use in a specific asymmetric target reaction.[6]

Our research group recently prepared the pure enantiomers of the auxiliary 8-phenylmenthol;[7] this was done in the course of work[8] on asymmetric aza-Diels–Alder reactions leading to 3-substituted 2-azabicyclo[2.2.1]hept-5-enes (**1**) and similar species, which can be used as intermediates in the synthesis of a variety of compounds of biological and/or pharmaceutical interest.[9] Investigation of the utility of the pure 8-phenylmenthol enantiomers for asymmetric aza-Diels–Alder reactions[10] suggested that it would be fruitful to explore the chiral induction capacities of other rigid cycloalkanols bearing an aromatic ring.

In this work we describe the use of (+)-(1*R*)-*endo*-2-benzonorbornenol (**2**), obtained by enzymatic resolution of its racemic mixture,[11] as a chiral auxiliary in aza-Diels–Alder reactions.

The asymmetric reaction chosen to study the application of (+)-(1*R*,*endo*)-2-benzonorbornenol (**2**) as chiral auxiliary, was the aza-Diels–Alder reaction,[12] between cyclopentadiene and the imine ion formed in the reaction of benzyl amine with (+)-(1*R*,*endo*)-2-benzonorbornenyl glyoxylate (**4**). The cycloadduct obtained (**5**) can be transformed, with recovery of the chiral auxiliary employed, into amino alcohol **6**, which in turn can be used as starting material in the preparation of novel carbonucleosides and isoazanucleosides, potentially useful as antivirals and/or antineoplastics.



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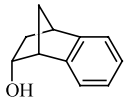

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Reaction of (+)-(1*R*,*endo*)-2-benzonorbornenol (**2**) with acryloyl chloride in the presence of triethylamine and DMAP,[13] followed by treatment of the resulting acrylate **3** either with ozone (with dimethyl sulfide quenching) or with osmium tetroxide, afforded glyoxylate **4**,[14] the identity of which was confirmed following conver-

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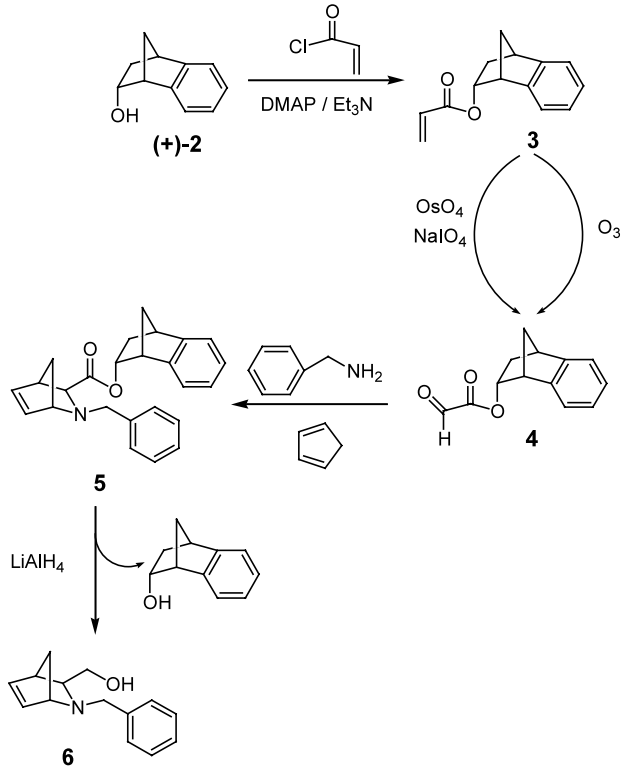
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02599-6

sion to its 2,4-dinitrophenylhydrazone derivative. Treatment of **4** with equimolar amounts of benzylamine, trifluoroacetic acid and boron trifluoride etherate in dichloromethane generated the corresponding iminiun ion, which was reacted in situ with excess cyclopentadiene at −78°C.[15] Following purification of the resulting cycloadduct, **5**, as a mixture of diastereomers (yield 83%), a ^{1}H NMR study showed it to contain only the two *exo* adducts. Treatment of **5** with $LiAlH_4$ then afforded the corresponding mixture of aminoalcohols **6** while allowing recovery of the chiral auxiliary **2** in 93% yield (Scheme 1).[16]

The enantiomeric composition of **6** was determined (a) by examination of ^{1}H NMR spectra recorded in the presence of the chiral shift reagent europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]; and (b) by comparison of the specific optical rotation of the mixture **6** [$[\alpha]_D$ −18 (*c* 1, $CHCl_3$)] with that of previously prepared[10] enantiomerically pure (1*S*,*exo*)-**6** [$[\alpha]_D$ −71 (*c* 1, $CHCl_3$)]. Both methods showed the mixture to have a 1*S*:1*R* enantiomeric ratio of 63:37.

The iminiun ion generated by treatment of benzylamine with (+)-(1*R*,*endo*)-2-benzonorbornenyl glyoxylate (**4**) in the presence of TFA and $BF_3{\cdot}Et_2O$ reacted smoothly with cyclopentadiene, affording a virtually all-*exo* mixture of cycloadducts with a 1*S*:1*R* diastereomeric ratio of 63:37. These results illustrate the utility of *endo*-2-benzonorbornenol as an easily recovered stereocontrolling auxiliary, since although chiral induction with (+)-**2** is not very high (*ee* = 26%) its use affords products that are 100% *exo*, whereas analogous chiral auxiliaries



Scheme 1.

such as 8-phenylmenthol[10] afford *endo*/*exo* mixtures that must then be separated.

Acknowledgements

The authors thank the Xunta de Galicia for financial support of this work under project PGIDT01PXI20302PR.

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13. *(+)-(1R,endo)-2-Benzonorbornenyl acrylate*, **3**. A solution of acryloyl chloride (0.82 mL; 10.16 mmol) in dry dichloromethane (10 mL) was added dropwise under argon to a solution of (+)-(1*R*,*endo*)-2-benzonorbornenol, [(+)-**2**] (780 mg; 4.87 mmol)], triethylamine (983 mg; 2 equiv.) and 4-(dimethylamino)pyridine (84 mg; 0.69 mmol) in dry dichloromethane (100 mL) at 0°C. The mixture was stirred for 2 h at room temperature and was then treated with a saturated $NaHCO_3$ solution (60 mL) and extracted with Cl_2CH_2 (3×70 mL). The pooled organic layers were washed with a saturated $NaHCO_3$ solution (2×60 mL) and brine (1×100 mL), and were then dried with Na_2SO_4. The solvent was removed in a rotary

evaporator, and purification of the resulting residue on a short column of silica gel using 9:1 Et_2O:EtOAc as eluent afforded **3** as a yellow oil. Yield 970 mg (93%). $[\alpha]_D$ +137 (*c* 1, $CHCl_3$). IR (NaCl): 2973, 2871, 1720, 1617, 1608, 1559, 1540, 1458, 1406, 1297, 1270, 1201, 1111, 1056, 985, 810, 754 cm^{-1}. ^1H NMR ($CDCl_3$): 1.06–1.12 (d×t, 1H, $J_{3'endo-3'exo}=12.85$ Hz, $J_{3'endo-2'exo}=3.30$ Hz, $3'_{endo}$-H), 1.72–1.75 (d, 1H, $J_d=9.50$ Hz, 9′-H), 1.85–1.90 (d×t, 1H, $J_d=9.50$ Hz, $J_t=1.80$ Hz, 9′-H), 2.38–2.47 (d×d×d, 1H, $J_{3'exo-3'endo}=12.97$ Hz, $J_{3'exo-2'exo}=9.06$ Hz, $J_{3'exo-4'}=4.08$ Hz, $3'_{exo}$-H), 3.34–3.35 (d, 1H, $J=2.40$ Hz, 1′-H), 3.66–3.67 (d, 1H, $J=2.97$ Hz, 4′-H), 5.45–5.49 (d×d×d, 1H, $J_{2'exo-3'exo}=8.92$ Hz, $J=4.10$ Hz, $J=3.20$ Hz, $2'_{exo}$-H), 5.63–5.67 (d×d, 1H, $J=10.28$, 1.65 Hz, –CH=C$\underline{H}_2$), 5.82–5.91 (d×d, 1H, $J=17.19$, 10.28 Hz, –C$\underline{H}$=CH_2), 6.09–6.15 (d×d, 1H, $J=17.19$, 1.65 Hz, –CH=C$\underline{H}_2$), 7.08–7.25 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): 36.28 (C-3′), 43.83 (C-4′), 48.23 (C-1′), 48.55 (C-9′), 74.68 (C-2′), 120.77 (C-5′), 123.95 (C-8′), 126.02 (C-7′), 126.69 (C-6′), 128.95 (C-2), 130.73 (C-3), 142.98 (C-8a), 148.60 (C-4a), 166.58 (C(O)).

14. *(+)-(1R,endo)-2-Benzonorbornenyl glyoxylate*, **4**. **Method A**. A vigorously stirred solution of **3** (0.93 g; 4.34 mmol) in 75 mL of 8:2 MeOH:Cl_2CH_2 at −78°C was bubbled for 20 min with ozone at a rate of 6 g/h in a 60 L/h current of O_2 (as specified by the manufacturers of the Fischer Mod. 503 ozone apparatus). Following addition of Me_2S (1 mL; 0.82 g; 7 mmol), stirring was continued under argon for a further 12 h, after which the solvent was evaporated and the residue was extracted with Cl_2CH_2 (3×50 mL). The pooled organic layers were washed with water (60 mL) and brine (60 mL) and dried with Na_2SO_4, the solvent was removed in a rotary evaporator, and purification of the resulting oily yellow residue on a short column of silica gel using 3:1 hexane:EtOAc as eluent afforded **4** as a mixture of the glyoxylate and its hydrate that was used without further purification. Yield 900 mg (89%). $[\alpha]_D$ +123 (*c* 1, $CHCl_3$). IR (NaCl): 3454, 2973, 2886, 1740, 1458, 1445, 1287, 1225, 1094, 980, 766, 702 cm^{-1}. **Method B**. A mixture of **3** (1.76 g; 8.22 mmol), osmium tetraoxide (0.03 g; 0.12 mmol), water (9 mL) and dioxane (29 mL) was stirred at room temperature for 5 min during which time the mixture became dark brown. Then sodium periodate (3.6 g; 16.9 mmol) was added in portions over 30 min, and the mixture (now pale brown) was stirred at room temperature for another 2 h and then extracted thoroughly with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated, affording a yellow oil that upon filtration through a short column of silica gel using 3:1 hexane:EtOAc as eluent afforded **4** as a mixture of the glyoxylate and its hydrate that was used without further purification. Yield 1.92 g (91%).

15. *(+)-(1R,endo)-2-Benzonorbornenyl 3-exo-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate*, **5**. A suspension of benzylamine (0.4 mL; 3.70 mmol) in dry Cl_2CH_2 (10 mL) was added under argon to a stirred suspension of **4** (800 mg; 3.40 mmol) and 3 Å molecular sieve pearls (2 g) in dry Cl_2CH_2 (20 mL) at 0°C. When the addition was complete the reaction mixture was cooled to −78°C and treated successively with trifluoroacetic acid (0.28 mL; 3.70 mmol), boron trifluoride etherate (0.46 mL; 3.70 mmol) and freshly distilled cyclopentadiene (0.7 mL; ca. 8 mmol). After 6 h a mixture of saturated aqueous $NaHCO_3$ solution (11 mL) and solid $NaHCO_3$ (1.1 g) was added, and after slowly returning to room temperature the reaction mixture was filtered. The organic layer was separated from the filtrate and washed with water and Cl_2CH_2 on a Celite pad, after which the organic layer of the resulting mixture was separated and put aside, and the aqueous layer was extracted with Cl_2CH_2 (3×50 mL). The pooled organic layers were washed with saturated $NaHCO_3$ solution (50 mL) and brine (60 mL), and were dried with Na_2SO_4. Removal of the solvent in a rotary evaporator left an oily residue that upon chromatography on silica gel with 4:1 hexane:EtOAc as eluent afforded **5** as a colourless oil. Yield 1.01 g (83%). $[\alpha]_D$ +91 (*c* 1, $CHCl_3$). IR (NaCl): 3059, 2973, 2870, 1736, 1654, 1604, 1560, 1454, 1341, 1322, 1234, 1169, 1110, 1029, 909, 843, 738, 699 cm^{-1}. ^1H NMR ($CDCl_3$): 0.80–1.23 (m, 4H), 1.59–1.80 (m, 2H), 1.94–1.97 (d, 1H, $J=5.50$ Hz), 2.20–2.35 (m, 1H), 2.78 (s, 1H), 3.08–3.67 (m, 4H), 5.20–5.31 (m, 1H, $2'_{exo}$-H), 6.05–6.08 (d×d, 1H, $J=5.50$, 1.92 Hz, 5-H), 6.25–6.28 (d×d, 1H, $J=5.50$, 3.35 Hz, 6-H), 6.76–7.28 (m, 9H, ArH).

16. *3-exo-2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-ylmethanol*, **6**. A solution of **5** (1.00 g; 2.70 mmol) in dry Et_2O (20 mL) was added dropwise under argon to a suspension of $LiAlH_4$ (0.61 g; 16.07 mmol) in dry Et_2O (20 mL) at 0°C. The reaction mixture was stirred for 12 h at room temperature and a mixture of MeOH (30 mL) and H_2O (100 mL) was added dropwise at 0°C, and the resulting mixture was extracted with AcOEt (4×100 mL). The pooled organic layers were washed with water (2×100 mL) and brine (1×100 mL) and dried with Na_2SO_4. Removal of the solvent in a rotary evaporator left a residue that when chromatographed on silica gel with 3:1 hexane:EtOAc as eluent afforded the chiral auxiliary (+)-**2** (0.40 g; 93%) in the early fractions and compound **6**, as an oil, in the later fractions. Yield 0.58 g (94%). $[\alpha]_D$ −18 (*c* 1, $CHCl_3$). IR (NaCl): 3364, 3060, 2985, 2870, 1495, 1452, 1367, 1324, 1208, 1134, 1028, 910, 717 cm^{-1}. ^1H NMR ($CDCl_3$): 1.25–1.28 (d, 1H, $J=8.40$ Hz, 7_{anti}-H), 1.68–1.71 (d, 1H, $J=8.40$ Hz, 7_{sin}-H), 1.82–1.86 (t, 1H, $J=5.55$ Hz, 3-H), 2.32 (s.a., 1H, OH), 2.69 (s, 1H, 4-H), 3.32–3.44 (m, 4H, C$\underline{H}_2$OH+C$\underline{H}_2$Ph), 3.69 (s, 1H, 1-H), 6.10–6.13 (d×d, 1H, $J=5.65$, 1.80 Hz, 5-H), 6.41–6.45 (d×d, 1H, $J=5.65$, 3.24 Hz, 6-H), 7.16–7.28 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): 46.13 (C-7), 47.16 (C-4), 59.34 (N$\underline{C}H_2$Ph), 64.43 (C-1), 64.98 (C-3), 65.66 ($\underline{C}H_2$OH), 127.55 (C-4′), 128.80 (C-2′+C-6′), 129.43 (C-3′+C-5′), 132.71 (C-5), 138.27 (C-6), 140.11 (C-1′).