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Enantiopure (9-Anthryl)(2-piperidyl)- and (9-Anthryl)(2-pyridyl)methanols – Their Use as Chiral Modifiers for Heterogeneous Hydrogenation of Keto Esters over Pt/Al_2O_3

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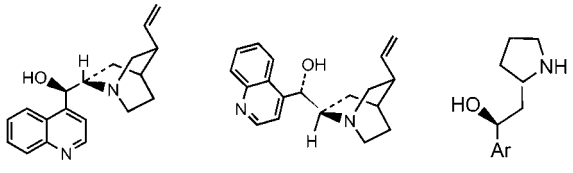
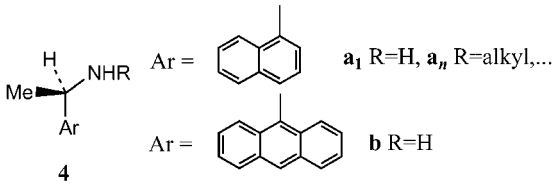
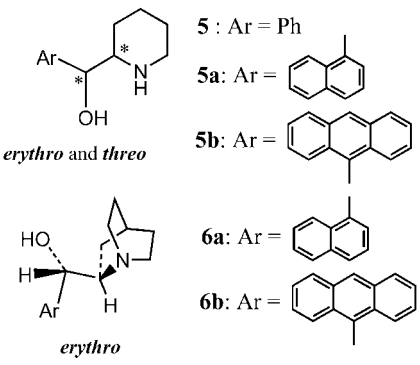
A route toward the synthesis of the *erythro* isomer of (9-anthryl)(2-piperidyl)methanol is presented as well as resolution and assignment of the structure (through NMR). The use of both the *erythro* and *threo* enantiopure isomers of this new amino alcohol, and its precursor [(9-anthryl)(2-pyridyl)methanol], as chiral modifiers for the Pt/Al_2O_3 hydrogenation of ethyl lactate showed that the *erythro* isomer is not necessarily the most efficient chiral modifier. This is probably because of the 9-anthryl group. The enantioselectivities that this compound provides are not, as one would expect, higher than those observed with the naphthyl group.

Introduction

Asymmetric heterogeneous hydrogenation of α-keto esters over supported platinum catalysts with the use of cinchona alkaloids (Orito reaction[1]) has been known for about thirty years and has been the subject of numerous reviews.[2] When we started our work in this field in 1998,[3] it was already known that cinchonidine **1** was the most efficient chiral modifier[2] and apart from cinchonidine or cinchonine derivatives[4] the only different modifiers tested were type **3** amino alcohols (1994)[5] and type **4** amines (1995).[6a,6b] Our target was then amino alcohol **5a**[3] which had the same –CH(OH)–CH(N)– link as cinchona alkaloids and one chiral carbon less. Moreover, both enantiomers of both the *erythro* and *threo* diastereomers could be available which would provide straightforward conclusions. With the use of **5a**, for the first time we clearly showed (2001) that the *erythro* isomer was a more efficient chiral modifier than the *threo* isomer[3] and almost as efficient as cinchonidine **1** (which is also an *erythro* isomer). Until 2002, it also seemed that the anthryl group had a tendency to provide higher enantioselectivities than the naphthyl group (when located on the carbon bearing the hydroxy







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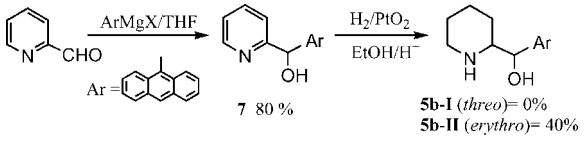
group). Therefore, we decided to synthesize and study *erythro* and *threo* amino alcohols **5b**. By the time this work was completed, other results appeared that dealt with the comparison of anthryl and naphthyl groups in the case of amines **4**[6c–6e] and amino alcohols **6**.[7]

We present here the synthesis and resolution of both the *erythro* and *threo* diastereomers of anthryl amino alcohol **5b**, a synthesis of the pure *erythro* isomer (lower overall yield but no difficulty with the separation of diastereomers), the use of **5b** as a chiral modifier for the heterogeneous hydrogenation of ethyl pyruvate over Pt/Al_2O_3, as well as the use of precursor **7** to test the effect of the possible in situ hydrogenation of **7** into **5b** during hydrogenation of pyruvate.

Synthesis

Condensation of the 9-anthryl Grignard reagent with 2-pyridinecarboxaldehyde proceeded smoothly in THF to provide anthrylpyridyl alcohol **7** in 80% yield (Scheme 1). Heterogeneous hydrogenation of **7** with the use of PtO_2 (from Aldrich) in EtOH/HCl (1 equiv.)[8,9] then provided pure *erythro* **5b-II** in 40% yield (**5b-I**/**5b-II** = 0/100).



Scheme 1.

It is worth noting that *threo* isomer **5b-I** (necessary for structure determination) can be obtained (as the major isomer) from formamidine **8**, Scheme 2, by following Meyers' procedures,[10,11] (overall yield 50%, after chromatographic purification).

Table 1. NMR spectroscopic data for *threo* and *erythro* configurations.

Amino alcohol	$^3J_{1-2}$ $CDCl_3$ [Hz]	Δ^3J [Hz]	δ(1-H) [ppm]	Configuration
5-I (Ar = Ph)	7.5	2.5	4.36	*threo*[a]
5-II (Ar = Ph)	5.0		4.56	*erythro*[a]
(1*S*,2*S*)-Pseudoephedrine	8.2	4.3		*threo*[a]
(1*R*,2*S*)-Ephedrine	3.9			*erythro*[a]
5a-I (67%)	6.0	2	5.24	*threo*[a]
5a-II (33%)	4.0		5.44	*erythro*[a]
5b-I (80%)	9.5	2	6.03	*threo*
5b-II (20%)	7.5		6.10	*erythro*

[a] Known compounds, cf. refs.[12,13]

The ratios of **I**/**II** have been determined with the use of the 1-H proton doublets (between δ = 6.0 ppm and 6.2 ppm, Table 1).

Determination of *threolerythro* Structure of 5b-I and 5b-II

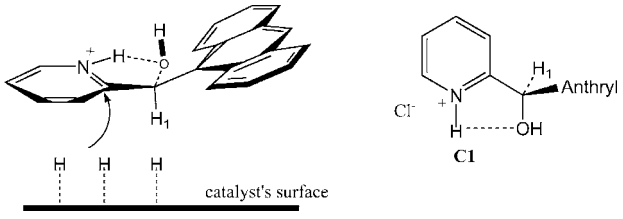
threolerythro Structure from NMR

In amino alcohols having the CH(OH)–CH(NH) system and of known structure, Table 1, the *erythro* isomer has the smallest coupling constant. Therefore, the *erythro* structure has been assigned to isomer **5b-II**, which exhibits the smallest coupling constant: 7.5 Hz versus 9.5 Hz for isomer **5b-I**.

Moreover, the 1-H doublets in the *erythro* isomers are always the most deshielded, which is the case here too (δ = 6.10 ppm compared to δ = 6.03 ppm for the *threo* isomer in this case).

erythro Structure from Model

The *erythro* structure assigned by NMR to isomer **II**, the only isomer obtained from hydrogenation over PtO_2, is consistent with the model shown in Scheme 3, as it is reasonable to postulate that the hydrogen (located on the catalyst surface) approaches from the less hindered side of the H-bonded **C1** conformer of substrate **7** (1-H side).

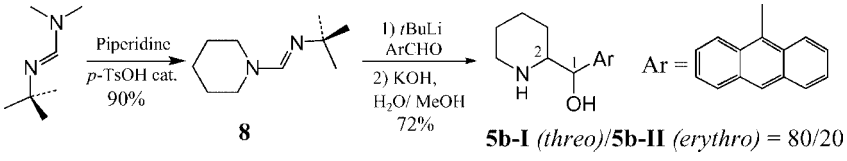


Scheme 3.

Resolution of Piperidyl Alcohol 5b-I and 5b-II

Diastereomeric separation of the *threo* isomer from the *erythro* isomer was performed first by preparative supercritical fluid chromatography with a Chromegabond Amine column (25 cm × 23 mm ID, 5 μm 60 Å, ES Industries) at a flow rate of 50 mL/min with a mobile phase of 25% methanol in carbon dioxide (100 bar outlet pressure) with UV detection at 257 nm.

Analytical separation of racemic pure *threo* isomer **5b-I** was further performed with a CHIRALCEL OD-RH column (150 × 4.6 mm, 5 μm) with acetonitrile/ethanolamine, 100:0.1, as the mobile phase (flow rate = 0.5 mL/min) and UV detection at 235 nm.



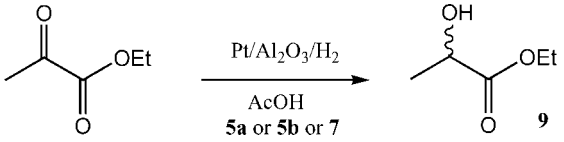
Scheme 2.

On a preparative scale, a CHIRALCEL OD column (250 × 50 mm, 20 μm) and the same mobile phase (100 mL/min) were then used. After recrystallization from acetonitrile (to completely remove ethanolamine as seen from ^{1}H NMR) of the two fractions having the highest *ee*, the specific rotations of enantiomers *threo* **5b-I1** and *threo* **5b-I2** were determined: *threo* **5b-I1**: $[\alpha]_D$ = +11.0 (*c* = 0.45, $CHCl_3$), *ee* = 99%; *threo* **5b-I2**: $[\alpha]_D$ = –10.8 (*c* = 0.50, $CHCl_3$), *ee* = 99%.

The *erythro* isomer (**5b-II**) was obtained pure and the enantiomers were then preparatively obtained by supercritical fluid chromatography with the use of a CHIRALPAK AD column (250 × 20 mm, 10 μm) at a flow rate of 50 mL/min with a mobile phase of 16% methanol (containing 25 mM of isobutylamine) in carbon dioxide (100 bar outlet pressure) with UV detection at 257 nm, with the isolation of two fractions: *erythro* **5b-II1** negative CD at 263 nm, *ee* = 99%; *erythro* **5b-II2** positive CD at 263 nm, *ee* = 99%. $[\alpha]_D$ = +17 (*c* = 0.24, $CHCl_3$).

Resolution of Pyridyl Alcohol 7

Analytical separation of *rac*-**7** was performed with a CHIRALCEL OD column (250 × 4.6 mm, 10 μm) with hexane/EtOH/diethylamine, 8:2:0.5, as the mobile phase (flow rate = 1 mL/min) and UV detection at 254 nm. On a preparative scale, a CHIRALCEL OD column (0.46 × 25 cm, 10 μm) and the same mobile phase (120 mL/min) were used with the isolation of two fractions: (–)-**7**, chemical purity >95% (by 400 MHz ^{1}H NMR). $[\alpha]_D$ = –171 (*c* = 0.36, $CHCl_3$), *ee* = 100% (from analytical chromatography); (+)-**7**, chemical purity >95% (by 400 MHz ^{1}H NMR). $[\alpha]_D$ = +97 (*c* = 0.37, $CHCl_3$), *ee* = 57% (from specific rotation).



Asymmetric Pt/Al_2O_3 Hydrogenation of Ethyl Pyruvate

After hydrogenation and distillation, the enantiomeric excesses of the ethyl lactate samples were determined by gas chromatography with a Cyclodex-B capillary column (30 m) with the use of an HP 5890 GC-FID instrument and the *ee* values were reproducible within 1%.

The well-defined catalyst 5% Pt/Al_2O_3 4759 from Engelhard was activated before use (3 h, 300 °C, under H_2 flow); AcOH was used as the solvent. The reactions were run at room temperature for 2 h with stirring at a rate of ca. 500 rpm, and the pyruvate, purchased from Aldrich, was distilled before used. The results are given in Table 2.

Table 2. Ethyl pyruvate hydrogenation over 5% Pt/Al_2O_3 at room temperature for 2 h.

Modifier	Conversion [%]	(*R*)/(*S*)	*ee* [%]
None	13	–	–
(+)-**5b-II2** *erythro*	100	68:32	36
(–)-**5b-II1** *erythro*	100	32.5:67.5	35
(–)-**5b-I2** *threo*	100	27:73	46
(+)-**5b-I1** *threo*[a]	100	73.5:26.5	47
(–)-**7**	100	37:63	26

[a] Cf. ref.[3]

It is worth noting that, contrary to the cinchona alkaloids generally used, **5b-I1** and **5b-I2** (as well as **5b-II1** and **5b-II2**) are true enantiomers; therefore, the samples of **5b-I1** and **5b-I2** (as well as **5b-II1** and **5b-II2**) that were used that have identical enantiomeric purities (cf. above) provide identical (*R*)/(*S*) ratios to ethyl lactate, within the reproducibility of the method used, for the determination of these ratios (compare 68:32 with 32.5:67.5 and 27:73 with 73.5:26.5). It appears that (*S*)-lactate is obtained from (–)-**5b-II** (*erythro*) and (–)-**5b-I** (*threo*) while (+)-**5b-II** and (+)-**5b-I** provide (*R*)-lactate. It is also worth noting that the *threo* isomers provide slightly higher enantioselectivities than the *erythro* isomers (46–47% versus 35–36% *ee*).

Precursor **7**, which under these conditions undergoes slow hydrogenation[14] into desired **5b-II**, is less efficient probably because hydrogenation of pyruvate is too rapid and that **7** is a less efficient chiral modifier.

Conclusions

These results show that the *erythro* isomer is not necessarily the most efficient chiral modifier as was suggested from previous results obtained by using compound **5a**[3] and cinchona alkaloids[4,15] (Table 3).

Table 3. Hydrogenation of ethyl pyruvate with the use of various chiral modifiers.

Modifier	Conversion [%]	(*R*)/(*S*)	*ee* [%]
Cinchonidine (9*R*,8*S*) *erythro*	100	93.5:6.5	87
Epiquinidine (*threo*)[a]	?	1:1	0
(–)-(1*R*,2*S*)-**5a-II** *erythro*	100	86.5:13.5	73
(+)-(1*S*,2*R*)-**5a-II** *erythro*[b]	100	14:86	72
(–)-**5a-I** *threo*	100	27:73	46
(+)-**5a-I** *threo*[b]	67	67.5:32.5	35[c]
(+)-**6a**-(1*S*,2*R*) *erythro*[d]	–	6:94	88
(+)-**6b**-(1*S*,2*R*) *erythro*[d]	–	10.5:89.5	79

[a] Cf. ref.[15] [b] Cf. ref.[3], note that the absolute configuration of *erythro* **5a-II** was determined from the stereo-outcome of the hydrogenation of pyruvate and confirmed by VCD (ref.[13]). [c] This sample of the *threo* isomer that was used contained 1.8% of one enantiomer of the *erythro* isomer (ref.[13]). [d] Cf. ref.[7]

The results also corroborate that the anthryl group is not necessarily a more efficient modifier than the naphthyl group, and it may provide lower enantioselectivities for both *erythro* and *threo* isomers as in the case of type **5** amino alcohols (compare Table 2 and Table 3) or compara-

ble enantioselectivities in the case of type **6** *erythro* amino alcohol (Table 3).

As in the case of (–)-**5a-II**, for which the (1*R*,2*S*) configuration was determined from the stereo-outcome of the reaction (pyruvate hydrogenation) and corroborated by VCD, one could postulate from the stereo-outcome of the pyruvate hydrogenation reaction that (+)-**5b-II**, which also provides (*R*)-lactate, has the (1*R*,2*S*) configuration.

Experimental Section

General Procedure for Anthryl Grignard Addition onto 2-Pyridincarboxaldehyde: It is worth noting that the 9-anthryl grignard formed from 9-bromoanthacene must be generated in THF heated at reflux. A solution of bromoanthracene (3.36 g, 13 mmol) in anhydrous THF (80 mL) was added dropwise whilst stirring to a suspension of Mg (0.31 g, 13 mmol) in anhydrous THF (30 mL) and 1,2-dibromoethane (0.2 mL). The mixture was heated at reflux and stirring was maintained until all of the Mg disappeared. After cooling to room temperature, a solution of 2-pyridincarboxaldehyde (0.7 g, 6.5 mmol) in anhydrous THF (30 mL) was added dropwise whilst stirring overnight. Then, a saturated aqueous solution of NH_4Cl was added, THF was evaporated under vacuum, and the aqueous phase was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried with Na_2SO_4, the solvent removed under reduced pressure, and the amino alcohol isolated and purified by chromatography on silica gel (ether/hexane, 3:2). **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.9 (br. s, 1 H), 6.72 (d, ^3J = 7.5 Hz, 1 H), 7.2 (dd, ^3J = 7.5, 5 Hz, 1 H), 7.29 (s, 1 H), 7.44 (m, 5 H), 8.02 (m, 2 H), 8.31 (m, 2 H), 8.49 (s, 1 H), 8.71 (d, ^3J = 5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.7, 120.8, 122.1, 124.8, 125.0, 127.2, 128.9, 129.3, 130.7, 131.8, 132.3, 137.0, 147.6, 161.8 ppm. $C_{20}H_{15}NO$ (285.22): calcd. C 84.17, H 5.30; found C 84.00, H 5.42.

General Procedure for PtO_2 Hydrogenation: To a solution of **7** (0.2 g, 0.7 mmol) in EtOH (10 mL) in a glass tube that exactly fits inside of a stainless steel autoclave were added successively concentrated HCl (0.05 mL, 0.7 mmol) and PtO_2 (30 mg). After being purged twice (vacuum/H_2 admission), the mixture was stirred under 50 bar H_2 and at 0 °C for 6 h. The catalyst was filtered out, NaOH (1 equiv.) and H_2O (5 mL) were added, the mixture was extracted with CH_2Cl_2 (10 × 10 mL), the combined organic phases were dried with Na_2SO_4, the solvent was removed under vacuum, and the amino alcohol was then purified by chromatography on silica gel (ether/hexane, 9:1). *threo* **5b-I**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (br. d, ^3J = 12.0 Hz, 1 H, 2-H$_e$), 1.0 (m, 1 H, 3-H), 1.10 (br. q, 1 H, 2-H$_a$), 1.36 (m, 1 H, 4-H), 1.48 (m, 2 H, 3-H, 4-H), 2.69 (td, ^2J = 12 Hz, ^3J = 12 Hz, 2.5 Hz, 1 H, 5-H$_a$), 3.09 (br. d, J = 12 Hz, 1 H, 5-H$_e$), 3.52 (td, ^3J = 9.5 Hz, 9.5 Hz and 4 Hz, 1 H, 1-H), 3.60 (br. s, 1 H), 6.03 (d, ^3J = 9.5 Hz, 1 H), 7.47 (m, 4 H), 8.00 (m, 2 H), 8.40 (s, 1 H), 8.72 (br., 2 H)[16] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 26.0, 29.4, 46.7, 62.0, 73.5, 125.1, 125.2, 125.7, 128.4, 129.6, 130.7, 132.0, 133.8 ppm. $C_{20}H_{21}NO$ (291.22): calcd. C 82.44, H 7.26; found C 81.79, H 7.34. *erythro* **5b-II**: All signals overlapped with those of *threo* **5b-I**, except: δ = 2.72 (br. t, ^2J = ^3J = 12 Hz, 1 H, 5-H$_a$) and 6.10 (d, ^3J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.2, 28.2, 46.6, 62.2, 73.7, 124.8, 125.7, 128.4, 129.1, 130.2, 131.6, 132.1 ppm.

General Procedure for Aldolization of Formamidine 8: To a solution of piperidine formamidine **8** (2.0 g, 11.88 mmol, 1.0 equiv.) in an ether/THF mixture (15:4 mL) was added (at –78 °C) *tert*-butyllithium (1.7 M, 8.5 mL, 14.25 mmol, 1.2 equiv.). The solution was stirred at –20 °C for 1 h, which resulted in the formation of a white precipitate. The reaction mixture was cooled to –78 °C, the desired aldehyde (1.1 equiv.) added, and the mixture slowly warmed up to 0 °C over 5 h. The solution was poured into 10% HCl (30 mL) and extracted with diethyl ether (2 × 10 mL). The aqueous layer was then made basic (pH 12) with 20% NaOH and extracted several times with dichloromethane. The combined organic phases were then concentrated under vacuum. A solution of the resulting crude product in MeOH (25 mL) and water (4 mL) and KOH (4 g) was heated at 60 °C for 24 h. After cooling, the mixture was extracted with dichloromethane (5 × 15 mL). The combined dichloromethane phases were dried with Na_2SO_4, the solvents removed under reduced pressure, and the amino alcohol isolated and purified by chromatography on silica gel (CH_2Cl_2/MeOH, 4:1).

General Procedure for Pt/Al_2O_3 Hydrogenation: A mixture of ethyl pyruvate (5 mL, 3500 equiv.) and the desired chiral modifier (1 equiv.), stirred for 30 min before used, was poured into a glass tube that exactly fits inside of a stainless steel autoclave. AcOH (10 mL) and the activated catalyst (50 mg, 1 equiv. in Pt) were then added successively. After being closed tightly, the device was purged three times (through successive vacuum-H_2 admission), the H_2 pressure was fixed at 40 bar, and the mixture was stirred for 2 h. The conversion was determined by using ^{1}H NMR of the crude products, then ethyl lactate was separated from other components through distillation and the *ee* was determined by chromatography (cf. text above). **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, ^3J = 7 Hz, 3 H), 1.35 (d, ^3J = 7 Hz, 3 H) 3.15 (br. s, 1 H, OH), 4.17 (2 H, CH_2 and 1 H, CH overlapped q).

Resolution of Piperidyl Alcohols 5b-I and 5b-II and Pyridyl Alcohol 7: Diastereomeric separation of the *threo* isomer from the *erythro* isomer was first necessary (cf. above). Analytical separation of racemic pure *threo* isomer **5b-I** was then performed further with a CHIRALCEL OD-RH (150 × 4.6 mm, 5 μM) column with acetonitrile/ethanolamine, 100:0.1 as the mobile phase (flow rate = 0.5 mL/min), the chromatographic parameters obtained are: R_{t_1} = 9.15 min, R_{t_2} = 11.04 min, k'_1 = 1.54, k'_2 = 2.07, alpha = 1.34. Then, on a preparative scale, 483 mg of *rac*-**5b-I** was resolved by using a larger CHIRALCEL OD column (250 × 50 mm, 20 μm) and the same mobile phase (100 mL/min), with isolation of three fractions whose enantiomeric purities were determined by using the analytical conditions (93% of the starting material was recovered): 250 mg (52%) *threo*: enantiomer 1 (**5b-I1**), chemical purity = 95%, *ee* = 100%; 90 mg (19%) *threo*: enantiomer 2 (**5b-I2**), *ee* = 86.8%; 109 mg (22%) *threo*: enantiomer 2 (**5b-I2**), chemical purity = 94%, *ee* = 98.5%. The enantiomers of **5b-II** were preparatively obtained by supercritical fluid chromatography by using a CHIRALPAK® AD column (250 × 20 mm, 10 μm) from Chiral Technologies, Inc. and recovery of 81% of the starting material (the enantiomeric purities of the fractions have been determined by using the analytical conditions): *erythro* **5b-II1** (70 mg), first eluted: R_t = 16.21 min, negative CD at 263 nm, *ee* = 99%; *erythro* **5b-II2**(108 mg), second eluted: R_t = 17.31 min, positive CD at 263 nm, *ee* = 99%. Analytical and preparative separation of *rac*-**7** were performed with CHIRALCEL OD columns with different sizes (either 250 × 4.6 mm, 10 μM or 0.46× 25 cm, 10 μM) and the same mobile phase. The analytic chromatographic parameters obtained are: R_{t_1} = 14.50 min, R_{t_2} = 16.00 min. On the preparative scale, 167 mg of *rac*-**7** was resolved with isolation of two fractions and recovery of 74% of the starting material (the enantiomeric purities of the fractions have been determined by using the analytical conditions): 52 mg enantiomer (–)-**7**, chemical purity >95% (by 400 MHz ^{1}H

NMR); 71 mg enantiomer (+)-**7**, chemical purity >95% (by 400 MHz ^{1}H NMR).

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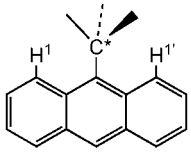

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