in 10 mL of dry pyridine was heated at 115 °C for 3 h under a blanket of nitrogen. The solution was cooled, the pyridine was removed by evaporation under vacuum, and the residue was washed with two 50-mL portions of ether. The ether-insoluble residue consisted of 0.34 g (26%) of unreacted I. Thin-layer chromatography on silica gel of the ether-soluble fraction (1.04 g) yielded a lower melting and a higher melting compound. The lower melting compound (R_f 0.7; $CHCl_3$) was recrystallized from pentane to give IV-A as a colorless solid: mp 197–199 °C dec; IR (KBr) 3430 (br, weakly H-bonded OH), 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.15–6.55 (m, 16, ArH), 4.25–3.15 (m, 25, $ArCH_2Ar$, ArOH, and SO_2CH_2), 2.1 (br s, $COCH_2$), 1.5–1.1 (m, 72, $C(CH_3)_3$), 1.0 (m, 11, CH_2 and CH in camphor).

Anal. Calcd for $C_{98}H_{126}O_{11}S$: C, 77.88; H, 8.34; S, 2.12. Found: C, 77.70; H, 8.47; S, 2.12.

Bis(camphorsulfonyl) Derivative of Calix[8]arene from *p*-*tert*-Butylphenol (IV-B). The higher melting compound from the thin-layer chromatography described above was recrystallized from hexane–ethanol to give a colorless solid: dec 210–214 °C without melting; IR (KBr) 3450 (br, weakly H-bonded OH), 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 6.97 (br s, 16, ArH), 4.1–3.6 (br d, 16, $ArCH_2Ar$), 2.5–1.8 (m, 18, CH_2 and CH of camphor), 1.3–0.5 (m, 80, $C(CH_3)_3$ and CH_3).

Anal. Calcd for $C_{108}H_{140}O_{14}S_2$: C, 75.17; H, 8.12. Found: C, 75.09; H, 8.16.

Acknowledgment. This research was supported by Grant GM-23534 from the National Institutes of Health.

Registry No. I (n = 8), 68971-82-4; II-B (n = 1, m = 7), 71370-09-7; IV-A (n = 1, m = 7), 71370-10-0; 2,4-dinitrochlorobenzene, 97-00-7; *N*-(2,4-dinitrophenyl)pyridinium chloride, 4185-69-7; camphorsulfonyl chloride, 21286-54-4.

Studies on the Synthesis of α-Functionalized Quinols: Synthesis of Jacaranone

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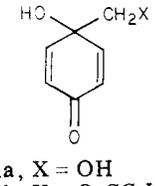
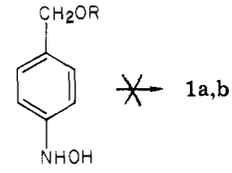
Received March 6, 1979

The potential of quinols and protected quinols[1] as synthetic intermediates prompted us to study the preparation and reactivity of quinols substituted in the α position (**1**). We have prepared and characterized three such α-substituted quinols, including the natural product jacaranone (**1e**).[2]



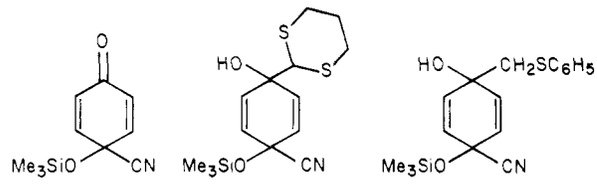
1a, X = OH
b, X = $O_2CC_6H_5$
c, X = SC_6H_5
d, X = $OCH_2C_6H_5$
e, X = CO_2CH_3

The classical preparation of quinols[3] by acid-catalyzed hydrolysis of para-substituted phenylhydroxylamines failed completely when applied to [*p*-(hydroxymethyl)phenyl]hydroxylamine (**2a**) or to its benzoate (**2b**), affording polymeric material in each case.



2a, R = H
b, R = COC_6H_5

Addition of unsubstituted Grignard or alkyllithium reagents to the protected cyanohydrin of benzoquinone followed by deprotection of the carbonyl affords quinols in good yield.[4] Therefore, we attempted to effect the 1,2-addition of α-substituted carbanions to the protected dienone **3**.

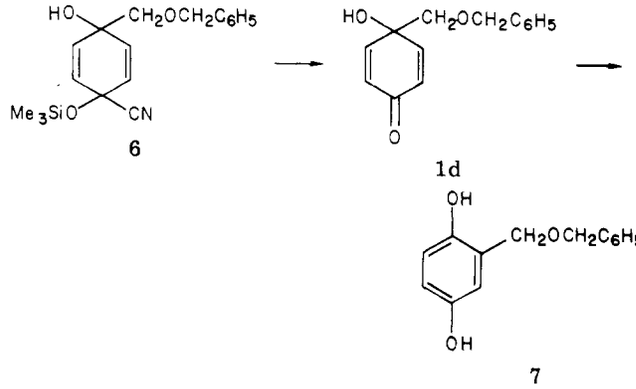


3 **4** **5**

A number of substituted alkyllithium reagents added efficiently to the carbonyl of dienone **3**. Thus, 2-lithio-1,3-dithane[5] reacted with **3** at −90 to −100 °C to give a 95% yield of crude adduct **4**, from which a single isomer[6] was obtained in 30% yield overall on recrystallization.

Likewise [(phenylthio)methyl]lithium added to dienone **3** to give a quantitative yield of the crude adduct **5**. Deprotection of the masked carbonyl with silver fluoride[4] gave the quinol **1c** in 61% yield.

Addition of [(benzyloxy)methyl]magnesium chloride[7] to dienone **3** gave only 11% of the 1,2-adduct **6**; *p*-cyanophenol, presumably the product of one-electron reduction of the dienone, was identified as one of the byproducts from this reaction. Adduct **6** was obtained in good yield,



6 **7**

however, when dienone **3** was added to [(benzyloxy)-

(1) (a) D. A. Evans and J. M. Hoffman, *J. Am. Chem. Soc.*, **98**, 1983 (1976); (b) D. A. Evans and R. W. Wong, *J. Org. Chem.*, **42**, 350 (1977). (c) See also the Ichihara synthesis of crotepoxide which uses a protected quinone: K. Oda, A. Ichihara, and S. Sakamura, *Tetrahedron Lett.*, 3187 (1975).

(2) (a) M. Ogura, G. A. Cordell, and N. R. Farnsworth, *Lloydia*, **40**, 157 (1977); (b) *ibid.*, **39**, 255 (1976).

(3) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957).

(4) D. A. Evans, J. M. Hoffman, and L. K. Truesdale, *J. Am. Chem. Soc.*, **95**, 5822 (1973).

(5) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).

(6) We found that several of the isomeric mixtures of Me_3SiCN protected quinols were separable by fractional crystallization; for our purposes, here, however, separation offered no advantage, and deprotection was generally performed on the mixture of isomers.

(7) B. Castro, *Bull. Soc. Chim. Fr.*, 1533 (1967).

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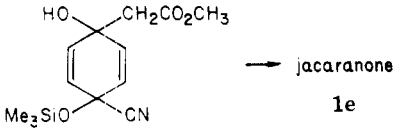
methyl]lithium.[8] The crude adduct, containing a small amount of tetrabutyltin, was converted to the quinol **1d** by silver fluoride. Attempts to purify quinol **1d** by chromatography or distillation led to significant amounts of hydroquinone **7**, by a 1,2-alkyl shift,[3] involving the exceptionally good migrating group (benzyloxy)methyl.

The isolation of α-substituted quinols from the addition/deprotection sequence had been shown to be feasible, however; therefore, we applied it to the synthesis of jacaranone **1e**,[2,9] a component of extracts of *Jacaranda caucana* Pittier, which has been shown to have significant antitumor activity against P388 lymphocytic leukemia in vivo.

The lithium enolate of methyl acetate[10] added to dienone **3** at −100 °C; the crude adduct, **8**, obtained in 81% yield was converted to quinol **1e**, jacaranone, in 89% yield. Spectroscopic properties of this material were identical with those reported for the natural product.



8

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 257 grating spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed at Schwartzkopf Microanalytical Laboratory, Inc., Woodside, N.Y., and at Galbraith Laboratories, Inc., Knoxville, Tenn.

Additions to Dienone 3. Dithiane Adduct 4. A solution of 2.08 g (10.0 mmol) of dienone **3** in 20 mL of THF was added over 0.5 h to 2-lithio-1,3-dithiane (from 1.24 g = 10.3 mmol of dithiane and 10.7 mmol of *n*-BuLi) at −100 °C. After the solution was warmed to −15 °C, the reaction mixture was allowed to stand for 42 h and was quenched with saturated NH_4Cl solution. The reaction mixture was then partitioned between ether and water; the organic solution was dried and concentrated to afford 3.11 g (95%) of a yellow semisolid. Crystallization from chloroform/hexane gave 979 mg (30%) of a light beige solid, mp 142.5–145 °C.

Recrystallization from the same solvent system gave analytically pure adduct: mp 146.5–147.5 °C; IR ($CHCl_3$) 3465, 3400, 1425, 1418 cm^{-1}; NMR ($CDCl_3$) δ 6.18 (m, 4 H), 4.22 (s, 1 H), 2.92 (m, 5 H), 2.00 (bm, 2 H), and 0.26 (s, 9 H); *m/e* (M^+) 327.

Anal. Calcd for $C_{14}H_{21}O_2NS_2Si$: C, 51.33; H, 6.46; N, 4.28; S, 19.58. Found: C, 51.24; H, 6.62; N, 4.17; S, 19.68.

Thioanisole Adduct 5. A solution of [(phenylthio)methyl]lithium, from 3.9 mL (4.1 g = 33 mmol) of thioanisole in THF and 25.4 mL of *s*-BuLi (at 1.26 M = 32 mmol), was prepared at −76 °C (20 min). A 6.32-g sample of dienone **3** (30 mmol) in 17 mL of THF was added; the solution was allowed to warm to 5 °C over 8 h and quenched with aqueous NH_4Cl. Partitioning of this mixture between ether and water gave 10.93 g (~100%) of a tan semisolid. Fractional crystallization from hexane resulted in recovery of two isomers. Materials from a comparable experiment were characterized. Isomer I: mp 101–102 °C; IR ($CHCl_3$) 3580, 2250 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (m, 5 H), 6.06 (m, 4 H), 3.17 (s, 2 H), 2.60 (s, OH), and 0.22 (s, 9 H); *m/e* (M^+) 331. Isomer II: mp 56.5–57 °C: IR ($CHCl_3$) 3590, 2250 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (m, 5 H), 5.98 (m, 4 H), 3.19 (s, 2 H), 2.67 (s, OH), and 0.21 (s, 9 H); *m/e* (M^+) 331.

Anal. Calcd for $C_{17}H_{21}NO_2SSi$: C, 61.59; H, 6.39; N, 4.25; S, 9.67. Found for isomer I: C, 61.26; H, 6.60; N, 4.03; S, 9.42. Found for isomer II: C, 61.53; H, 6.50; N, 4.17; S, 9.79.

[(Benzyloxy)methyl]lithium Adduct 6. A solution of ~11.2 mmol of [(benzyloxy)methyl]lithium[8] in 40 mL of THF was cooled to −110 °C; to this, 2.23 g (10.8 mmol) of dienone **3** in 35 mL of THF was added over 30 min. After the solution was warmed to 0 °C over 3 h, the reaction mixture was hydrolyzed with aqueous NH_4Cl.

The reaction mixture was partitioned between ether and water, and the organic phase was dried and concentrated to give a two-phase crude product. This was cooled with dry ice, and the upper phase was decanted; the lower phase was shaken with hexane at room temperature then cooled, and the decanting procedure was repeated. Concentration of the remaining material gave 3.46 g (86%) of semicrystalline material (9:1 **6**–Bu_4Sn). The IR and NMR spectra of this crude product were identical with those obtained from the reaction with [(benzyloxy)methyl]-magnesium chloride; however, the NMR spectrum showed some additional small peaks, including those for Bu_4Sn. (Bu_4Sn could be removed from the crude product by extraction with pentane but with considerable loss of adduct.)

An analytical sample of adduct **6** obtained from the reaction of dienone **3** with [(benzyloxy)methyl]magnesium chloride was characterized: mp 100.5–101 °C (from CH_3Cl_3–hexane); IR ($CHCl_3$) 3580, 1615, 1090 cm^{-1}; NMR ($CDCl_3$) δ 7.42 (s, 5 H), 6.17 (finely split m, 4 H), 4.62 (s, 2 H), 3.45 (s, 2 H), 2.98 (s, OH), and 0.17 (s, 9 H); *m/e* (M^+) 329.

Anal. Calcd for $C_{18}H_{23}O_3$ NSi: C, 65.62; H, 7.04; N, 4.25. Found: C, 65.63; H, 7.02; N, 4.42.

Adduct 8 (Dienone 3 and Methyl Lithioacetate). To a solution of LDA (from 1.4 mL of $HN(i\text{-}Pr)_2$ = 1.01 g (10 mmol)) and 4.9 mL of 2.04 M BuLi (10 mmol) in 20 mL of anhydrous THF at −100 °C was slowly added 0.79 mL (0.74 gm = 10 mmol) of methyl acetate in 10 mL of THF. After the solution was warmed to −90 °C over 30 min, the reaction mixture was cooled to −100 °C, and 2.05 g (9.9 mmol) of dienone **3** in 20 mL of THF was added over 1 h. The reaction mixture was warmed to 0 °C over 2.5 h, quenched with aqueous NH_4Cl, and partitioned between ether and water. The organic phase was dried and concentrated to give (81%) 2.36 g of a viscous liquid: IR ($CHCl_3$) 3550, 3480, and 1723 cm^{-1}; NMR ($CDCl_3$) δ 6.45–5.82 (complex m, 4 H), 3.87, 3.72, and 3.69 (bs, s and s, 4 H), 3.62 and 3.59 (two s, 2 H), and 0.22 (s, 9 H).

Deprotection Procedure. Synthesis of Quinols 1c–e. A 0.133 M solution of protected quinol in THF–H_2O (10:1) was prepared and covered with Al foil. Silver fluoride (1.03 equiv) was added. When TLC showed the absence of adduct, the reaction was terminated.

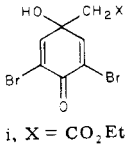
4-Hydroxy-4-[(phenylthio)methyl]-2,5-cyclohexadienone (1c). A 527 mg-sample (1.59 mmol) of adduct afforded 377 mg of crude quinol. Recrystallization from ethyl acetate–hexane gave 203 mg of beige crystals, mp 92–92.5 °C. A second recrystallization gave analytically pure off-white crystals: mp 92.5–93.5 °C; IR ($CHCl_3$) 3580, 3380, 1672, 1635 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.80 (d, J = 10 Hz, 2 H), 6.10 (d, J = 10 Hz, 2 H), 3.50 (s, OH), and 3.26 (s, 2 H); *m/e* (M^+) 232.

Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21; S, 13.81. Found: C, 67.34; H, 5.33; S, 13.94.

4-Hydroxy-4-[(benzyloxy)methyl]-2,5-cyclohexadienone (1d). Rearrangement to [(Benzyloxy)methyl]hydroquinone 7. A 929-mg sample of crude adduct **6** (containing 10% Bu_4Sn) was subjected to AgF deprotection. The reaction mixture was partitioned between CH_2Cl_2 and H_2O, dried, and concentrated to afford 695 mg of an amber oil: IR ($CHCl_3$) 3540, 1670, and 1635; NMR ($CDCl_3$) δ 7.30 (s, 5 H), 6.90 (d, J = 10 Hz, 2 H), 6.16

(8) W. C. Still, *J. Am. Chem. Soc.*, **100**, 1481 (1978). We are grateful to Professor Still for communicating his results to us prior to publication and for a gift of [(benzyloxy)methyl]tributylstannane.

(9) This strategy was also employed by Evans and Wong in the synthesis of the two naturally occurring quinols i and ii (see ref **1b**).



i, X = CO_2Et
ii, X = $CONH_2$

(10) T. R. Kelly, J. C. McKenna, and P. A. Christensen, *Tetrahedron Lett.*, 3501 (1973).

(d, J = 10 Hz, 2 H), 4.56 (s, 2 H), 3.80 (s, OH), and 3.50 (s, 2 H).

Attempted purification of quinol **1d** by bulb-to-bulb distillation (120–155 °C (0.04 mm)) or by chromatography on silica gel, Florisil, and neutral alumina (Woehm, Activity Grade I) afforded varying amounts of a viscous oil identified as hydroquinone **7**: IR (CH_2Cl_2) 3570, 3390, and 1698 cm^{-1}; NMR ($CDCl_3$–acetone-d_6) δ 7.34 (s, 5 H), 7.00 (s, 2 OH), 6.73 and 6.67 (two m, 3 H), and 4.66 and 4.58 (two s, 4 H); m/e (M^+) 230.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.87; H, 6.28.

Jacaranone (1e). A 1.11-g sample of adduct **8** was subjected to deprotection conditions in 28 mL of THF–H_2O. The reaction mixture was diluted with 300 mL of H_2O; 100 mL of pentane was added, and the two-phase mixture was filtered. Unreacted starting material was isolated from the pentane layer. The aqueous phase was saturated with NaCl and extracted with five 100-mL portions of methylene chloride, which were combined, dried, and concentrated to afford 614 mg (89%) of jacaranone, mp 75.5–78 °C. Recrystallization from ether–hexane gave colorless crystals: mp 80–81 °C (lit.[2b] mp 76–77 °C); IR (CH_2Cl_2) 3560, 3480, 1738, 1720, 1675, and 1635 cm^{-1}; NMR ($CDCl_3$) δ 7.04 (d, J = 10 Hz, 2 H), 6.21 (d, J = 10 Hz, 2 H), 4.20 (s, OH), 3.77 (s, 3 H), and 2.74 (s, 2 H); m/e (M^+) 182.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.47; H, 5.66.

Acknowledgment. We are pleased to acknowledge helpful discussions with Professors David A. Evans and W. Clark Still. This work was supported by the National Cancer Institute, Department of Health, Education, and Welfare (Grant No. CA 16524). K.A.P. gratefully acknowledges additional support in the form of an Alfred P. Sloan Foundation Fellowship.

Registry No. 1c, 71316-87-5; **1d**, 71316-88-6; **1e**, 60263-07-2; **3**, 40861-57-2; **4**, 71316-89-7; *cis*-**5**, 71316-90-0; *trans*-**5**, 71316-93-3; **6**, 71316-91-1; **7**, 71316-92-2; **8**, 71316-94-4; 2-lithio-1,3-dithiane, 36049-90-8; [(phenylthio)methyl]lithium, 13307-75-0; [(benzyloxy)methyl]lithium, 71316-95-5; methyl lithioacetate, 57570-85-1.

Optical Activity as a Probe in the Examination of Alkoxyaluminohydride Disproportionations

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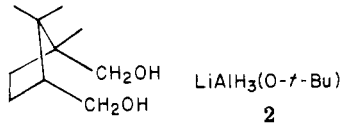
Received April 30, 1979

We recently described the effect of achiral alcohols upon the asymmetric reduction of acetophenone, using (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane (**1**)–lithium aluminum hydride solutions.[1] It was apparent from this study that the disproportionation of intermediate alkoxyaluminohydrides was resulting in a decrease in the enantiomeric excess of methylphenylcarbinol.

There have been a variety of investigations into the alkoxyaluminohydride disproportionation process using stereochemical,[2,3] kinetic probes,[4] and direct chemical analysis.[5] In particular, the kinetic results of Wiegers and Smith[4] suggest that reducing solutions prepared from lithium aluminum hydride and methanol results in a disproportionation process which produces lithium aluminum hydride as the sole reducing agent. In contrast, their results suggest that reducing solutions prepared from lithium aluminum hydride and *tert*-butyl alcohol produce both lithium aluminum hydride and lithium *tert*-butoxyaluminotrihydride (**2**) as active reducing agents.



1 **2**

We felt that optical activity could furnish a complementary third probe by which to investigate these disproportionation processes. If reducing solutions prepared from lithium aluminum hydride and methanol did produce lithium aluminum hydride as the sole reducing species, then the addition of **1** to this solution should produce the same reducing species as that obtained from lithium aluminum hydride and **1** prepared independently. We have previously shown[1] that this latter species gave a 7.7% enantiomeric excess of (+)-methylphenylcarbinol from the reduction of acetophenone.

Experimentally, this hypothesis was tested by adding a molar equivalent of methanol to lithium aluminum hydride in ether–THF (3:1).[6] After 1 h of reflux, a molar equivalent of **1** was added, and after an additional 1.5 h of reflux, a molar equivalent of acetophenone was added. This procedure resulted in a 70% reduction of acetophenone with a 7.4% enantiomeric excess of (+)-methylphenylcarbinol. This result is consistent with the Wiegers–Smith model for the alkoxyaluminohydride disproportionation where methoxide is the alkoxide species.

On the other hand, reducing solutions prepared from lithium aluminum hydride and *tert*-butyl alcohol which produce **2** and lithium aluminum hydride as the active reducing species, according to the Wiegers–Smith model, should produce two chiral reducing agents upon the addition of **1**. The chiral reagent derived from lithium aluminum hydride and **1** has just been described above. The effect of the other chiral reagent, derived from **2** and **1**, could be approximated from reducing solutions derived from lithium aluminum hydride and **1** followed by the addition of *tert*-butyl alcohol. We have previously described[1] this reducing solution and obtained a 13.1% enantimeric excess of (+)-methylphenylcarbinol in the reduction of acetophenone. Consequently, the addition of **1** to reducing solutions derived from lithium aluminum hydride and *tert*-butyl alcohol should give (+)-methylphenylcarbinol with an enantiomeric excess somewhere between 7.7% and 13.1% from the reduction of acetophenone. A theoretical value would be difficult to predict due to several factors: (1) the unknown molar ratio of lithium aluminum hydride to **2** under these conditions; (2) the difference in the rate reduction between the species derived from lithium aluminum hydride and **1** and the species derived from **2** and **1**; and (3) the former reducing species is a dihydride, whereas the latter species is a monohydride.

Experimentally, this hypothesis was tested by adding a molar equivalent of *tert*-butyl alcohol to lithium aluminum hydride in ether–THF (3:1).[7] After 1 h of reflux, a molar equivalent of **1** was added, and after an additional

(1) Johnson, T. H.; Klein, K. C. *J. Org. Chem.* **1979**, *44*, 461.
(2) For a review, see Malek, J.; Cerny, M. *Synthesis* **1972**, 217.
(3) Ashby, E. C.; Sevenair, J. P.; Dobbs, F. R. *J. Org. Chem.* **1971**, *36*, 197. Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. Haubenstock, H.; Eliel, E. L. *J. Am. Chem. Soc.* **1962**, *84*, 2363. Brown, H. C.; Deck, H. R. *Ibid.* **1965**, *87*, 5620.
(4) Wiegers, K. E.; Smith, S. G. *Ibid.* **1977**, *99*, 1480. Wiegers, K. E.; Smith, S. G. *J. Org. Chem.* **1978**, *43*, 1126.
(5) Brown, H. C.; Shoaf, C. J. *J. Am. Chem. Soc.* **1964**, *86*, 1079.
(6) This solvent system is identical with the one which resulted in the 7.7% enantiomeric excess described in the preceding paragraph and ref 1.
(7) This solvent is identical with the one which resulted in both the 7.7 and 13.1% enantiomeric excesses described in the preceding paragraph.

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