Syntheses of Aryltetralin Lignans: Concise Syntheses of (±)-Isopodophyllotoxone, (±)-Picropodophyllone and Their Related Compounds

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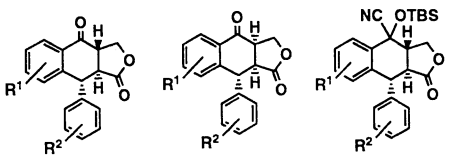
Synopsis. (±)-Isopodophyllotoxone and (±)-picropodophyllone were synthesized stereoselectively from the *O*-(*t*-butyldimethylsilyl) cyanohydrins (**3a**) in good yields. This new method was successfully applied to the syntheses of a variety of lignans of the aryltetralin series.

Lignans of the aryltetralin series, e.g., (±)-isopodophyllotoxone (**1a**) and (±)-picropodophyllone (**2a**) (Fig. 1), have recently become of considerable interest as useful intermediates in the synthesis of (±)-podophyllotoxin and its related compounds having intriguing biological activities.[1] The synthetic methods of this series of lignans so far reported include those based on the Stobbe condensation,[2] the Lewis acid-catalyzed rearrangement of a cyclopropyl ketone,[3] and the tandem Michael addition-cyclization reaction.[4] These methods, however, require a number of steps. In connection with our synthetic studies in search of new compounds having interesting biological activities from lignan derivatives,[5–7] we now report on a new method for the stereoselective syntheses of aryltetralin lignans (**1**, **2**) from the common intermediates (**3**).



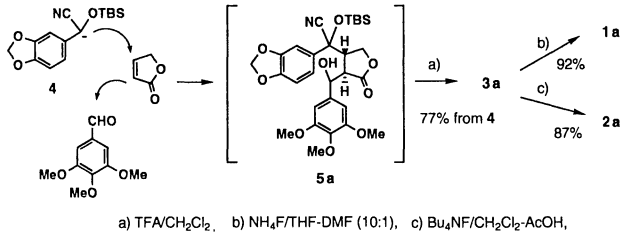
1a—d **2a—d** **3a—d**

TBS=*t*-butyldimethylsilyl

	R^1	R^2
a:	6,7-OCH_2O-	3,4,5-$(OMe)_3$
b:	7-OMe	3,4-$(OMe)_2$
c:	6,7-OCH_2O-	3,4-$(OMe)_2$
d:	6,7-$(OMe)_2$	3,4,5-$(OMe)_3$

Fig. 1.

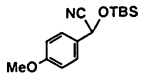
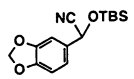
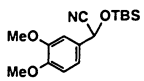
The requisite *O*-(*t*-butyldimethylsilyl) cyanohydrin (**3a**) was prepared based on the tandem conjugate addition-aldol reaction. The conjugate addition of the anion generated by the reaction of **4** with lithium diisopropylamide to 2-butenolide in tetrahydrofuran (THF) at −78 °C, followed by trapping the resulting enolate with 3,4,5-trimethoxybenzaldehyde at the same temperature, gave the condensation product (**5a**). Without the isolation of **5a**, the mixture was treated with trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature to afford **3a** as a mixture of the two diastereomers[8] in 77% yield from **4** (Scheme 1). The other *O*-(*t*-butyldimethylsilyl) cyanohydrins (**3b—d**) were prepared in good yields using the same procedures as described above (Table 1).



Scheme 1.

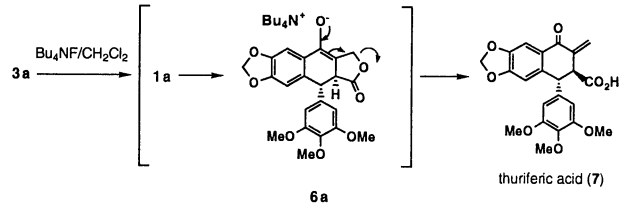
We next examined the conversion of the cyanohydrin moiety of **3a** into the carbonyl group. According to the usual procedure, **3a** was treated with 1.1 molar equivalents of Bu_4NF in CH_2Cl_2 at 0 °C. In this reaction,

Table 1. Yields of Cyanohydrins (**3b—d**) and 1-Aryl 4-Oxotetralin Lignans (**1b—d**, **2b—d**)

Starting material	Yield **3b—d**[a]		Yield of **1b—d** form **3b—d**[a]		Yield of **2b—d** form **3b—d**[a]	
	Compound	Yield/%	Compound	Yield/%	Compound	Yield/%
 **8**	**3b**	69	**1b**	90	**2b**	78
 **4**	**3c**	81	**1c**	92	**2c**	84
 **9**	**3d**	76	**1d**	87	**2d**	80

a) Isolated yield.

however, the desired product (**1a**) was not obtained at all, though the elimination reaction took place to afford (±)-thuriferic acid (**7**) in 91% yield.[9] This was probably formed via the enolate (**6a**) produced by the action of the initially produced Bu_4NCN on **1a** (Scheme 2).



Scheme 2.

In order to suppress the elimination reaction, **3a** was treated with 1.1 molar equivalents of Bu_4NF in CH_2Cl_2 in the presence of 1.5 molar equivalents of acetic acid at 0 °C. On monitering the reaction by TLC analysis ($CHCl_3$: MeOH=100 : 1), the formation of an almost equal amount of two products, the R_f values being 0.41 and 0.45, was observed after 5 min. With the passage of time, the polar one was gradually converted into the less polar one. After 12 h, from the reaction mixture was obtained (±)-picropodophyllone (**2a**) in 87% yield.[4] On the other hand, in order to isolate the other product formed during the early stage of the reaction, the reaction was quenched after 5 min by adding water. Separation of the two products by silica gel column chromatography gave (±)-isopodophyllotoxone (**1a**)[10] and **2a** in 4 and 41% yield, respectively; **1a** gradually decomposed during purification by silica gel chromatography to give **7**. These results clearly indicate that **1a** would isomerize to **2a** under these reaction conditions.

In order to obtain **1a** selectively without the isomerization reaction, we examined the conversion of **3a** into **1a** using a variety of fluorides. We found that the treatment of **3a** with 2 molar equivalents of NH_4F in THF–DMF (10 : 1) containing a small amount of water (ca. 1%) at room temperature for 14 h gave the best result; **1a** was obtained in 92% yield.

This method could be successfully applied to the synthesis of other lignans (**1b—d**, **2b—d**). The results are summarized in Table 1.

This method should find wide applications in the synthesis of a variety of aryltetralin lignans.

Experimental

The *O*-(*t*-butyldimethylsilyl) cyanohydrins (**4**, **8**, and **9**) were prepared according to the Cava's procedure.[11] The physical and spectroscopic properties of **4**, **8**, and **9** are as follows.

α-(*t*-Butyldimethylsilyloxy)-α-(3,4-methylenedioxyphenyl)-acetonitrile (4): Bp 140—146 °C/0.1 mmHg (1 mmHg= 133.322 Pa); IR (film) 2250, 1517 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.12 (s, 3H, $SiCH_3$), 0.22 (s, 3H, $SiCH_3$), 0.93 (s, 9H, *t*-Bu), 5.40 (s, 1H, CHCN), 5.99 (s, 2H, $-OCH_2O-$), 6.80 (d, 2H, *J*=8.0 Hz, ArH), 6.8—7.1 (m, 2H, ArH); MS *m/z* 297 (M^+).

α-(*t*-Butyldimethylsilyloxy)-α-(4-methoxyphenyl)acetonitrile (8): Bp 125—130 °C/2—3 mm Hg; IR (film) 2250, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.02 (s, 3H, $SiCH_3$), 0.22 (s, 3H, $SiCH_3$), 0.93 (s, 9H, *t*-Bu), 3.81 (s, 3H, OCH_3), 5.44 (s, 1H, CHCN), 6.87 (d, 2H, *J*=9.0 Hz, ArH), 7.11 (d, 2H, *J*=9.0 Hz, ArH); MS *m/z* 277 (M^+).

α-(*t*-Butyldimethylsilyloxy)-α-(3,4-dimethoxyphenyl)acetonitrile (9): Mp 54—55 °C; IR (KBr) 2250, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.15 (s, 3H, $SiCH_3$), 0.22 (s, 3H, $SiCH_3$), 0.94 (s, 9H, *t*-Bu), 3.91 (s, 6H, 2×OCH_3), 5.46 (s, 1H, CHCN), 6.8—7.11 (m, 3H, ArH); MS *m/z* 307 (M^+).

(1*R,2*S**,3*S**)-4-(*t*-Butyldimethylsilyioxy)-4-cyano-3-hydroxymethyl-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (3a).** To a solution of LDA in THF [prepared from 2.22 g (22 mmol) of diisopropylamine and 13.8 ml (22 mmol) of butyllithium (1.6 M in hexane, 1 M=1 mol dm^{-3}) in 15 ml of THF] at −78 °C were successively added **4** (5.82 g, 20 mmol) in THF (20 ml), 2-butenolide (1.68 g, 20 mmol) in THF (20 ml) and 3,4,5-trimethoxybenzaldehyde (3.92 g, 20 mmol) in THF (10 ml) under vigorous stirring. After 10 min AcOH (20 ml) was added and the reaction mixture was poured into a mixture of H_2O (100 ml) and AcOEt (200 ml). The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness in vucuo. Purification of the residue by silica gel column chromatography using hexane/AcOEt (2 : 1) as an eluent provided a mixture of the four diastereoisomers (**5a**). Compound **5a** (10.0 g, 17.5 mmol) was dissolved in a mixture of 40 ml of CH_2Cl_2 and 40 ml of TFA. After stirring for 8 h at room temperature, the reaction mixture was poured into water (100 ml). The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness in vacuo. The residue was crystallized from MeOH to furnish a mixture of the two diastereomers (**3a**) (7.47 g, 77%). Chromatography of the mixture (2 g) on silica gel with hexane/AcOEt (4 : 1) as the eluent provided 0.77 g of **3a′** and 0.70 g of **3a″**.

3a′: Mp 176—178 °C (MeOH); IR (KBr) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.48 (s, 3H, $SiCH_3$), 0.57 (s, 3H, $SiCH_3$), 0.96 (s, 9H, *t*-Bu), 2.8—3.1 (m, 1H, $CHCH_2OCO$), 3.16 (dd, 1H, *J*=10.2, 11.2 Hz, CHCOO), 3.65, (s, 6H, 2×OCH_3), 3.69 (s, 3H, OCH_3), 4.08 (d, 1H, *J*=10.2 Hz, Ar_2CH), 4.2—4.8 (m, 2H, CH_2OCO), 5.95 (dd, 2H, *J*=1.6, 1.8 Hz, $-OCH_2O-$), 6.26 (s, 2H, ArH), 6.51 (s, 1H, ArH), 7.51 (s, 1H, ArH); MS *m/z* 553 (M^+), 496 ($M^+-C_4H_9$). Anal. Calcd for $C_{29}H_{35}NO_8Si$: C, 62.90; H, 6.37; N, 2.53%. Found: C, 62.96; H, 6.33; N, 2.46%.

3a″: Mp 206—208 °C (MeOH); IR (KBr) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.44, (s, 3H, $SiCH_3$), 0.53 (s, 3H, $SiCH_3$), 0.99 (s, 9H, *t*-Bu), 2.8—3.1 (m, 1H, $CHCH_2OCO$), 3.16 (dd, 1H, *J*=10.5 11.2 Hz, CHCOO), 3.65 (s, 6H, 2×OCH_3), 3.66 (s, 3H, OCH_3), 4.3—4.8 (m, 2H, CH_2OCO), 4.10 (d, 1H, *J*=11.2 Hz, Ar_2CH), 4.62 (dd, 1H, *J*=6.2, 8.8 Hz, CH_2OCO), 6.01 (dd, 2H, *J*=1.6, 1.8 Hz, $-OCH_2O-$), 6.27 (s, 2H, ArH), 6.58 (s, 1H, ArH), 7.55 (s, 1H, ArH); MS *m/z* 553 (M^+), 496 ($M^+-C_4H_9$). Anal. Calcd for $C_{29}H_{35}NO_8Si$: C, 62.90; H, 6.37; N, 2.53%. Found: C, 63.06; H, 6.43; N, 2.46%.

The cyclized compounds (**3b—d**) were prepared in the same manner as described above and used in the next steps without separation of their diastereomers. The physical and spectroscopic properties of **3b—d** are as follows.

(1*R,2*S**,3*S**)-4-(*t*-Butyldimethylsilyloxy)-4-cyano-1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (3b).** Mp 103—114 °C (MeOH); IR (KBr) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.45, 0.47, 0.55, 0.57 (s, 6H, $SiCH_3$), 0.96, 0.99 (s, 9H, *t*-Bu), 2.8—3.1 (m, 1H, $CHCH_2OCO$), 3.1—3.3 (m, 1H, CHCOO), 3.6—3.9 (m, 9H, OCH_3), 4.1—4.7 (m, 3H, Ar_2CH and CH_2OCO), 6.2—6.5 (m, 4H, ArH), 7.53, 7.56 (s, 1H, ArH); MS *m/z* 509 (M^+), 452 ($M^+-C_4H_9$).

(1*R,2*S**,3*S**)-4-(*t*-Butyldimethylsilyloxy)-4-cyano-1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (3c):** Mp 101—107 °C (MeOH); IR (KBr) 1787 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.45, 0.47, 0.55, 0.57 (s, 6H, $SiCH_3$), 0.96, 0.99 (s, 9H, *t*-Bu),

2.8—3.1 (m, 1H, CHCH$_2$OCO), 3.1—3.3 (m, 1H, CHCOO), 3.6—3.9 (m, 6H, OCH$_3$), 4.1—4.7 (m, 3H, Ar$_2$CH and CH$_2$OCO), 5.9—6.0 (m, 2H, OCH$_2$O), 6.2—6.5 (m, 4H, ArH), 7.53, 7.56 (s, 1H, ArH); MS *m/z* 523 (M^+), 466 ($M^+-C_4H_9$).

(1*R,2*S**,3*S**)-4-(*t*-Butyldimethylsilyloxy)-4-cyano-3-hydroxymethyl-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (3d).** Mp 100—111 °C (MeOH); IR (KBr) 1785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.43, 0.46, 0.55, 0.56 (s, 6H, SiCH$_3$), 0.98, 0.99 (s, 9H, *t*-Bu), 2.8—3.1 (m, 1H, CHCH$_2$OCO), 3.1—3.3 (m, 1H, CHCOO), 3.6—3.9 (m, 15H, OCH$_3$), 4.1—4.7 (m, 3H, Ar$_2$CH and CH$_2$OCO), 6.2—6.5 (m, 3H, ArH), 7.53 (s, 1H, ArH); MS *m/z* 569 (M^+), 512 ($M^+-C_4H_9$).

(±)-Isopodophyllotoxone (1a). To a solution of **3a** (4 g, 7.23 mmol) in THF–DMF (10 : 1, 110 ml) was added NH_4F (535 mg, 14.5 mmol) in water (1 ml) at room temperature. The reaction mixture was stirred for 14 h. The mixture was poured into water (200 ml). The precipitates were collected by filtration, washed with water, and dried. Recrystallization from $CHCl_3$–AcOEt gave pure **1a** (2.74 g 92%) as fine colorless crystals: Mp 225—227 °C [lit,[10] mp 223—225 °C].

1b—**d** were prepared in the same manner as described above. The physical and spectroscopic properties of **1b**—**d** are as follows.

(1*R,2*S**,3*S**)-1-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (1b):** Mp 205—207 °C; IR (KBr) 1785, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.06 (dd, 1H, *J*=11, 14 Hz, CHCOO), 3.45 (m, 1H, COCH), 3.84 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.25 (d, 1H, *J*=11 Hz, CHAr$_2$), 4.47 (*t*, 1H, *J*=10 Hz, CH$_2$OCO), 4.65 (dd, 1H, *J*=9.2, 10 Hz, CH$_2$OCO), 6.3—6.9 (m, 6H, ArH), 7.44 (s, 1H, ArH); MS *m/z* 368 (M^+). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47%. Found: C, 68.51; H, 5.40%.

(1*R,2*S**,3*S**)-1-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-6,7-methylenedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (1c):** Mp 205—208 °C; IR (KBr) 1780, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.08 (dd, 1H, *J*=12, 16 Hz, CHCOO), 3.43 (m, 1H, COCH), 3.83 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.25 (d, 1H, *J*=12 Hz, CHAr$_2$), 4.48 (t, 1H, *J*=10 Hz, CH$_2$OCO), 4.65 (dd, 1H, *J*=9.3, 10 Hz, CH$_2$OCO), 6.00 (s, 2H, OCH$_2$O), 6.3—6.3 (m, 4H, ArH), 7.50 (s, 1H, ArH); MS *m/z* 382 (M^+). Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.97; H, 4.74%. Found: C, 66.11; H, 4.77%.

(1*R,2*S**,3*S**)-3-Hydroxymethyl-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (1d):** Mp 235 °C (decomp); IR (KBr) 1780, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.04 (dd, 1H, *J*=11, 15 Hz, CHCOO), 3.44 (m, 1H, COCH), 3.81 (s, 6H, 2×OMe), 3.88 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.27 (d, 1H, *J*=11 Hz, CHAr$_2$), 4.46 (*t*, 1H, *J*=10 Hz, 4.65 (dd, 1H, *J*=9.0, 10 Hz, CH$_2$OCO), 6.38 (s, 2H, ArH), 6.39 (s, 1H, ArH),7.50 (s, 1H, ArH); MS *m/z* 428 (M^+). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65%. Found: C, 64.11; H, 5.78%.

(±)-Picropodophyllone (2a). To a solution of **3a** (1.8 g 3.25 mmol) in CH_2Cl_2 (20 ml) were added AcOH (0.35 ml, 4.88 mmol) and Bu_4NF (1.0 M in THF, 3.9 ml, 3.9 mmol) at 0 °C. The mixture was stirred for 30 min at the same temperature and then for 12 h at room temperature. After diluting with 20 ml of CH_2Cl_2, the mixture was poured into water (20 ml). The organic layer was washed with 1 M HCl (10 ml), water, saturated aqueous $NaHCO_3$, and brine. The CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated. Recrystallization of the residue from AcOEt gave **2a** as colorless prisms: Mp 201—202 °C [lit,[4] mp 198—199.5 °C].

The compounds (**2b**—**d**) were prepared in the same manner as described above.

(1*R,2*S**,3*S**)-1-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (2b).** Mp 105—107 °C (AcOEt); IR (KBr) 1770, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.3—3.6 (m, 2H, CHCO and CHCOO), 3.78 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.30 (dd, 1H, *J*=4.3, 9.0 Hz, CH$_2$OCO), 4.61 (s, 1H, CHAr$_2$), 4.70 (d, 1H, *J*=9.0 Hz, CH$_2$OCO–), 6.2—6.6 (s, 5H, ArH), 7.52 (s, 1H, ArH); MS *m/z* 368 (M^+). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47%. Found: C, 68.51; N, 5.41%.

(1*R,2*S**,3*S**)-1-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-6,7-methylenedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (2c).** Mp 105—107 °C (AcOEt); IR (KBr) 1770, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.3—3.6 (m, 2H, CHCO and CHCOO), 3.77 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.23 (dd, 1H, *J*=4.3, 9.0 Hz, CH$_2$OCO), 4.63 (s, 1H, CHAr$_2$), 4.77 (d, 1H, *J*=9.0 Hz, CH$_2$OCO), 6.00 (s, 2H, OCH$_2$O), 6.2—6.9 (s, 4H, ArH), 7.50 (s, 1H, ArH); MS *m/z* 382 (M^+). Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.97; H, 4.74%. Found: C, 66.00; H, 4.80%.

(1*R,2*S**,3*S**)-3-Hydroxymethyl-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (2d).** Mp 118—121 °C (AcOEt); IR (KBr) 1780, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.3—3.6 (m, 2H, CHCO and CNCOO), 3.76 (s, 6H, 2×OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.23 (dd, 1H, *J*=4.3, 9.0 Hz, CH$_2$OCO), 4.66 (s, 1H, CHAr$_2$), 4.75 (d, 1H, *J*=9.0 Hz, CH$_2$OCO–), 6.28 (s, 2H, ArH), 6.69 (s, 1H, ArH), 7.52 (s, 1H, ArH); MS *m/z* 428 (M^+). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65%. Found: C, 64.70; H, 5.73%.

Treatment of 3a with Bu_4NF: Thuriferic Acid (7). To a solution of **3a** (1 g, 1.81 mmol) in CH_2Cl_2 (20 ml) at room temperature was added Bu_4NF (1 M in THF, 2 ml, 2 mmol). The reaction mixture was stirred for 6 h, and was then acidified with 1 M HCl (10 ml). The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvent was evaporated to dryness in vacuo to give 708 mg (95%) of **7** as a colorless oil.

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