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DIASTEREOSELECTION IN THE $LiAlH_4$ REDUCTION OF SEVERELY HINDERED β-DIKETONES EXAMPLES OF anti-CURTIN-HAMMETT PREEQUILIBRIUM CONDITIONS

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Abstract.- $LiAlH_4$ Reduction of α-adamantyl(and tert-butyl)-β-diketones occur under anti-Curtin-Hammett preequilibrium conditions, each preferred conformer leading to a different stereoisomeric diol, whereas reduction of 3-adamantyl--3-methyl(and ethyl)pentane-2,4-dione occurs with high diastereoselectivity to afford only the (2R,3r,4S) meso diol.

INTRODUCTION

Stereoselective synthesis of 1,3-polyols is a topic of current interest.[1] Synthesis of both syn and anti-1,3-diols can be achieved by diastereoselective reduction of β-hydroxyketones.[1] The popularity of this strategy is in contrast with the lack of information on reductions of β-diketones with hydride donors. Many unsubstituted and α-monosubstituted β-diketones are enols and, on reduction with hydride donors, give products other than diols. Thus, pentane-2,4-dione on treatment with lithium aluminium hydride in refluxing ether affords 3-penten-2-ol as the main product.[2] α-Disubstituted β-diketones do give β-diols on reduction with $LiAlH_4$; thus, 3,3-dimethylpentane-2,4-dione has been reported to yield meso (syn) and d,l (anti) diols in a ratio 30:70.[3]

Cobalt(II) and copper(II) mediated alkylation of β-dicarbonyl compounds permits efficient preparations of severely hindered β-diketones (Scheme and Table 1), bearing bulky substituents (R^3 = 1-adamantyl and tert-butyl) at Cα.[4] These diketones i) present slow rotation around sigma bonds;[4c-d,5] ii) are fully diketonic; and iii) their conformational preferences are known.[4b,5]

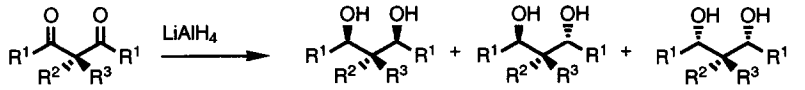
Diketones **1-8** present in solution two families of preferred conformations: one family is made of "Low Dipole Moment Conformers" (LDMC) (< 2.5D units), the angle between dipoles being in the range 158-175º;[4b] the second family is made of "High Dipole Moment Conformations" (HDMC) (> 2.5D units) and the angle between dipoles ranges between 28 and 87º.[4b] Scheme 2 contains graphical representations of LDMC and HDMC and Table 1 shows the conformational preferences in cyclohexane.[4b]

The structural features of compounds **1-8** and the conformational information available renders them suitable models to study the diastereoselectivity of reductions with hydride donors. Reductions of monocarbonyl compounds occur under Curtin-Hammett

preequilibrium conditions,[6,7] which means that the ratio of products depends on the differences in Gibbs free energies between the transition states leading to them, but not on the equilibrium conformational population of the starting carbonyl compound. However, our diketones exhibit slow rotation around C-C bonds, and this renders some of the here reported reductions exceptional in that they do not occur on the preequilibrated conformers.

RESULTS

The results of the reductions of β-diketones **1-8** with excess $LiAlH_4$ in refluxing ether are summarized in Scheme 1 and Table 1. 3-(1-Adamantyl)pentane-2,4-dione, **1**, affords one syn diol, (2R,3r,4S)-3-(1-adamantyl)pentane-2,4-diol, **9a**, and the only possible anti diol: (2RS,4RS)-3-(1-adamantyl)pentane-2,4-diol, **9b**, in a ratio 75:25, coincident with the conformational ratio of diketone **1**. The configuration of **9a** was determined by X-ray diffraction.[8]



1-8 **9a-14a** (R,r,S) **15a** (R,S) **16a** (S,s,R) **9b-15b** (RS,RS) **16b** (SR,SR) **9c-14c** (S,s,R) **16c** (R,r,S)

SCHEME 1

TABLE 1. Reductions of Diketones **1-8** with $LiAlH_4$ in Refluxing Ether[a]

	Diketones				Diols	
	R^1	R^2	R^3	LDMC : HDMC[b]	%	a: b:c
1	Me	H	1-Ada	74:26	**9** (80)	75:25:-
2	Me	Me	1-Ada	65:20	**10** (84)	95: 5:-
3	Me	Et	1-Ada	not determined	**11** (74)	100:—:-
4	Me	H	t-Bu	74:26	**12** (58)	74:26:-
5	Me	H	c-C_6H_{11}	76:10	**13** (73)	75:23:2
6	Me	Me	c-C_6H_{11}	not determined	**14** (79)	63:33:4
7	Me	Me	Me	80:—	**15** (69)	30:70:-
8	t-Bu	H	1-Ada	46:54	**16** (66)	39:61:-

a) Molar ratio diketone:$LiAlH_4$ is 1:2 but for **2** (1:4). b) Ref. 4b. Only conformers populated to an extent larger than 10% are included. For this reason sometimes the sum does not reach 100%.

Also, 3-(tert-butyl)pentane-2,4-dione, **4**, produces the isomers (2R,3r,4S)- and (2RS,4RS)-3-(tert-butyl)pentane-2,4-diol, **12a** and **12b**, in a 74:26 ratio, also coincident with the conformational ratio of diketone **4**.

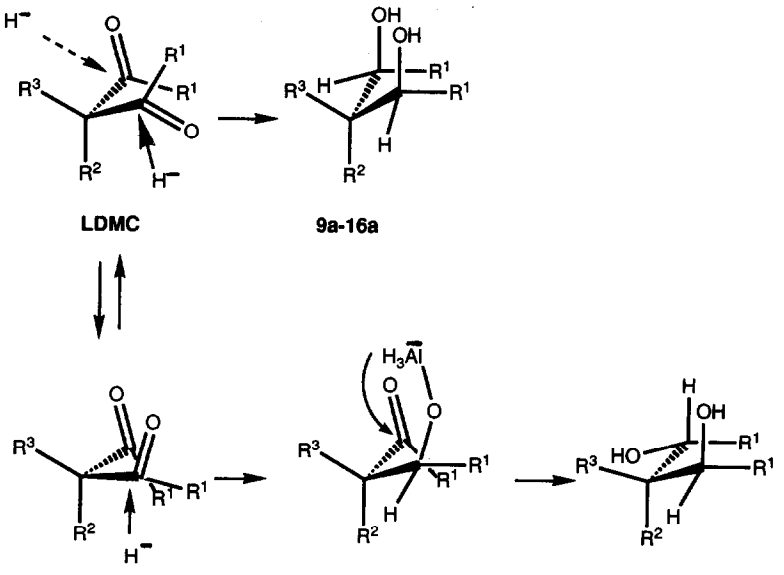
On the other hand, 4-(1-adamantyl)-2,2,6,6-tetramethylheptane-3,5-dione, **8**, affords (3R,4s,5S)-4-(1-adamantyl)-2,2,6,6-tetramethylheptane-3,5-diol, **16a**,[9] and its anti isomer (3RS,5RS), **16b**, in a 39:61 ratio, that reflects the conformational ratio of diketone **8**. Configurations of **12a** and **16a** are assumed by analogy with **9a** and for the reasons discussed below and in the following paper.[8] Configurations of anti isomers of family **b** derive from separate signals (PMR) for methyl (or tert-butyl) and for CHOH protons.

The ratios in which compounds **9**, **12** and **16** are formed are coincident with the ratios of LDMC to HDMC.[4b] This suggests that LDMC give rise to meso isomers **a** and HDMC produce d,l isomers **b**. Thus, the equilibration between the conformational families (LDMC $\rightleftharpoons$ HDMC) is slower than the reactions of each conformer with the hydride donor (Schemes 2 and 3). In other words, these systems are not in the Curtin-Hammett preequilibrium conditions,[6] which means that the ratio of products does not depend on the differences in Gibbs free energies between the transition states leading to them, but on the conformational population of the starting carbonyl compound.

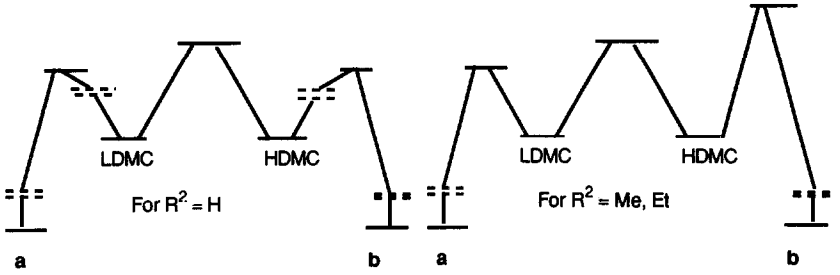
$\Delta H^{\neq}$ and $\Delta S^{\neq}$ values of 41.4 kJ x mol^{-1} (9.9 kcal x mol^{-1}) and -109.6 J x mol^{-1} x K^{-1} (-26.2 cal x mol^{-1} x K^{-1}) have been measured for the reduction of mesityl phenyl ketone with $LiAlH_4$ in THF.[10] The $\Delta H^{\neq}$ value is expected to be lower for more electrophilic aliphatic ketones. In order to have more information on the slow rotation of sigma bonds of our starting diketones,[4c-d,5] we registered low temperature CMR spectra of **1** and **3**, two diketones showing different reduction diastereoselectivities. Thus, **1** presents a signal at δ 32.9 assigned to the methyl groups. This signal splits into four signals clearly separated at 222K. Also, the signal at 77.4 assigned to C-3 splits into two signals. A similar behaviour has been observed for **3**, although this time splitting was only observed for the methyl groups signal at 35.4. The small separation of peaks rendered the exact determination of T_c very difficult. A reasonable estimation could be T_c around 260K.

In summary, we hypothesize that the rotation barriers around the bonds connecting the central carbon atoms of diketones **1** and **3** (and probably others), are lower (or of the same order) than the activation Gibbs free energies for $LiAlH_4$ reductions.

Next, the question arises of why, for **1**, **4** and **8**, LDMC give only syn isomers **a** and HDMC give only anti isomers **b**. Reduction of β-hydroxyketones to afford syn diols occurs by external delivery of hydride to the less hindered face of the carbonyl group,[11] whereas preparation of anti diols requires intramolecular hydride delivery from the alcohol group complexed with the hydride donor.[12] A similar explanation can account for our results. Thus, inspection of models reveals that attack by $LiAlH_4$ on LDMC occurs independently to the less hindered faces of the ketone groups (from below in Scheme 2) affording isomers **9a**, **12a** and **16a**. On the other hand, attack on HDMC occurs from below to the front ketone group to afford intermediate **17** in which proximity between the complexed alcohol and the rear carbonyl group permits intramolecular hydride delivery to



SCHEME 2



The meanings of "a" and "b" are: the species that, after acidic work up, lead to families of diols a and b. For relative LDMC and HDMC levels see Table 1. Relative levels of transition states on the left part are undetermined.

SCHEME3

the top face of the rear ketone group to give **9b**, **12b** and **16b**.

Again, inspection of models shows that nucleophilic attack to the front carbonyl group on HDMC is hindered if R^2 is bulkier than H (for **2** and **3**). In such cases attack to HDMC is slow enough to permit equilibration to LDMC and subsequent reactions on these to afford meso diols **10a** and **11a** with a high degree of diastereoselectivity. Configuration of **10a** was determined by X-ray diffraction[8] and that of **11a** was deduced by comparison of the IR behaviours of **10a** and **11a**.[8]

Diketone **5** still exhibits a diastereoselectivity similar to those of **1**, **4** and **8**. Comparison of the ratio of diols with the ratio LDMC:HDMC for **5** is not so clear since conformations populated to an extent of less than 10% were not included.

When sizes of R^2 and R^3 become closer, the diastereoselectivity decreases as expected (compare results for **2** and **6**). Finally, we have confirmed the literature data[3] for diketone **7**.

Scheme 3 contains in a simplified manner the reaction coordinates for both extreme situations (for **1**, **4** and **8** and perhaps for **5** on one side, and for **2** and **3** on the other side). Attempts to isolate the intermediate β-hydroxyketone in the reduction of **1** failed, thus indicating that the second reduction in faster than the first. Therefore, in order to simplify the diagrams of Scheme 3, only one transition state is represented in the pathways between the reacting conformers and the final products.

EXPERIMENTAL

General.- Routine HMR (and CMR) spectra were registered at 80 (and 20) MHz respectively. Variable temperature HMR (and CMR) spectra and those required for analyses of mixtures were registered at 400 (and 100Mz) respectively. Mass spectra were run at 70 eV.

Diketones **1-8**.- Diketones **1**,[4a] **2**,[4d] **3**,[4d] **4**,[4b] **5**,[4b] **7**,[4b] and **8**,[4a,4d] have been previously described.

3-Cyclohexyl-3-methylpentane-2,4-dione, **6**. A mixture of 3-bromocyclohexene (4.0 g, 24.8 mmole), copper(II) bis(3-methylpentane-2,4-dionato)[4d] (3.6 g, 12.4 mmole) and ethanol-free chloroform (15 mL) was heated in a closed reactor at 50ºC for 17 hours (Glc monitoring). The mixture was partitioned between dichloromethane and 1N HCl. The organic layer was dried and filtered through silica gel. The filtered solution was evaporated to afford 3-(2-cyclohexenyl)-3-methylpentane-2,4-dione (2.7 g, 56%). Bp. 75ºC (oven temp.)/0.05 mmHg. IR(film): 1697 cm^{-1}; HMR($CDCl_3$): δ 1.0-1.1 (m, 1H), 1.17 (s, 3H), 1.35-1.55 (m, 2H), 1.64-1.73 (m, 1H), 1.78-1.92 (m, 2H), 1.98 (s, 3H), 2.05 (s, 3H), 5.13 (d, J = 11 Hz, 1H), 5.60-5.70 (m, 1H); CMR($CDCl_3$): δ 13.7, 22.1, 23.3, 24.8, 26.5, 26.9, 39.2, 70.7, 127.1, 129.8, 206.1, 206.5.

A mixture of 3-(2-cyclohexenyl)-3-methylpentane-2,4-dione (2.0 g, 10 mmole), 0.2 g of 10% Pd-C and ethanol (50 mL) was strongly stirred at room temperature under hydrogen atmosphere. The theoretical amount of hydrogen was consumed in four hours. The mixture was twice filtered through celite and silica gel. The filtrate was evaporated and the

residue was distilled (65ºC (oven temp.)/0.05 mmHg) to afford pure **6** (1.64 g, 81%) that crystallized spontaneously. M.p.: 42-3ºC; IR(KBr): 2930, 2856, 1698 cm^{-1}; HMR($CDCl_3$): δ 0.72-1.96 (m, 11H), 1.29 (s, 3H), 2.09 (s, 6H); CMR($CDCl_3$): δ 13.3, 26.3, 26.7, 28.1, 41.8, 71.5, 206.8.

Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.44; H, 10.29.

General procedure for reduction of diketones with $LiAlH_4$

3-(1-Adamantyl)pentane-2,4-diols, **9a, 9b.** A solution of 3-(1-adamantyl)pentane-2,4-dione, **1**, (7.0 g, 30 mmole) in diethyl ether (20 mL) was dropwise added over lithium aluminium hydride (2.3 g, 60 mmole) in refluxing diethyl ether (100 mL). The mixture was left for 10 minutes (IR monitoring). After that acetone (20 mL) was added and the mixture partitioned between chloroform and 1N HCl. The organic layer was dried and evaporated to afford an oil that was chromatographed through silica gel using mixtures of chloroform-ethyl acetate as eluent. The following products were eluted:

(2RS,4RS)-3-(1-Adamantyl)pentane-2,4-diol, **9b**, 1.45 g (19.6%). Mp. 94-5ºC (petroleum ether-acetone); IR(KBr): 3350 cm^{-1}; HMR($CDCl_3$): δ 0.9 (t, J = 1.9 Hz, 1H), 1.27 (d, J = 6.91 Hz, 3H), 1.43 (d, J = 6.5 Hz, 3H), 1.6-2.1 (m, 15 H), 2.60 (s, 2H), 4.35 (dq, J = 1.98 and 6.50, 1H), 4.42 (dq, J = 1.26 and 6.91, 1H); CMR($CDCl_3$): δ 23.9, 25.1, 28.9, 37.1, 40.6, 41.7, 58.4, 67.4, 68.3. MS: m/e 176(100), 135(51), 119(40), 91(46), 79(29), 43(18).

Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.51; H, 11.15.

(2R,3r,4S)-3-(1-Adamantyl)pentane-2,4-diol, **9a**, 4.34 g (60.6%). Mp. 138-9ºC (hexane); IR(KBr): 3300 (broad) cm^{-1}; HMR($CDCl_3$): δ 1.50(d, J = 6.89 Hz, 6H), 1.64-2.0 (m, 16 H), 2.2 (s, 2H), 4.29 (dq, J = 6.89 and 3.09 Hz, 2H); CMR($CDCl_3$): δ 23.0, 28.8, 34.8, 37.0, 41.3, 59.3, 68.9. MS: m/e 176(51), 135(100), 119(24), 91(38), 79(31), 43(25).

Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.27; H, 11.29.

The following diols were prepared by the same general method:

(2R,3r,4S)-3-(1-Adamantyl)-3-methylpentane-2,4-diol, **10a.** Mp. 115-6ºC; IR(KBr): 3278 cm^{-1}; HMR($CDCl_3$): δ 0.85 (s, 3H), 1.46 (d, J = 6.0 Hz, 6H), 1.62-2.14 (m, 17H), 3.97 (q, J = 6.0 Hz, 2H), CMR($CDCl_3$): δ 15.6, 21.6, 29.0, 36.9, 39.1, 39.2, 48.2, 75.8.

Calcd. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.73; H, 11.47.

The mother liquor of recrystallizing **10a** was evaporated. A HMR spectrum of the residue presented the peaks of **10a** and two quartets centered at 4.19 and 4.09 assigned to the (RS,RS) isomer, **10b.**

(2R,3r,4S)-3-(1-Adamantyl)-3-ethylpentane-2,4-diol, **11a.** Mp. 119-21ºC (hexane); IR(KBr): 3400 cm^{-1}; HMR($CDCl_3$): δ 0.92 (t, J = 7.4 Hz, 3H), 1.40 (d, J = 6.7 Hz, 6H), 1.50-2.12 (m, 17H), 4.20 (q, J = 6.7 Hz, 2H); CMR($CDCl_3$): δ 9.6, 21.0, 21.3, 29.6, 37.2, 39.9, 40.1, 49.4, 73.6.

Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.66; H, 11.40.

(2R,3r,4S)-3-t-Butylpentane-2,4-diol, **12a.** Bp. 75ºC (oven temp.)/0.1 mmHg; IR(film): 3370 cm^{-1}; HMR($CDCl_3$): δ 0.90 (s, 9H), 1.30 (d, J = 6.67 Hz, 6H), 1.85 (t, J = 3.24 Hz,

1H), 3.16 (s, 2H), 4.26 (q, J = 6.67 and 3.24 Hz, 2H); CMR($CDCl_3$): δ 22.3, 29.7, 32.4, 57.7, 69.4; MS: m/e 98(27), 83(100), 57(32), 55(43), 45(42), 43(37), 41(35).

Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 65.53; H, 12.18.

(2RS,4RS)-3-t-Butylpentane-2,4-diol, **12b**. Bp. 65-70ºC (oven temp.)/0.05 mmHg; IR(film): 3370 cm^{-1}; HNM($CDCl_3$): δ 1.09 (s, 9H), 1.23 (d, J = 6.57 Hz, 3H), 1.54 (d, J = 7.14 Hz, 3H), 2.50 (s, 2H), 4.27 (dq, J = 6.57 and 2.89, 1H), 4.31 (dq, J =, 7.14 and 1.80, 2H); CMR($CDCl_3$): δ 22.7, 24.9, 29.9, 33.5, 56.6, 68.2, 68.5; MS: m/e 98(36), 83(100), 55(35), 45(22), 43(26), 41(28).

Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 66.12; H, 12.21.

(2R,3r,4S)-3-cyclohexylpentane-2,4-diol, **13a**. Bp. 125ºC (oven temp.)/0.01 mmHg; IR(film): 3353 cm^{-1}; HMR($CDCl_3$): δ 1.05-1.92 (m, 12H), 1.28 (d, J = 6.55 Hz, 6H), 2.73 (s, 2H), 4.16 (dq, J = 6.55 and 4.07, 2H); CMR($CDCl_3$): δ 21.8, 26.4, 27.0, 32.4, 36.5, 54.7, 69.6.

Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.84; 12.20.

From the column chromatography a fraction was separated that presented two -CH(OH)- absortions of equal intensity centered at 4.27 (dq, J = 2.19 and 6.58) and at 4.22 (apparent quintuplet, J about 6.17), assigned to the (2RS,4RS) isomer, **13b**. This sample also showed an apparent quintuplet centered at 4.02 (J about 6.44) assigned to the (2S,3s,4R) isomer, **13c**.

3-Cyclohexyl-3-methylpentane-2,4-diol, **14** (mixture of isomers). A HMR($CDCl_3$) spectrum of the mixture permitted identification of three isomers:

(2R,3r,4S): 1.0 (s, 3H), 1.29 (d, J = 6.75, 6H), 3.89 (q, J = 6.75 Hz, 2H).

(2RS,4RS): 0.82 (s, 3H), 1.13 (d, J = 6.40 Hz, 3H), 1.25 (d, J = 6.63 Hz, 3H), 3.91 (q, J = 6.63 Hz, 1H), 4.10 (q, J = 6.40 Hz, 1H).

(2S,3s,4R): 0.75 (s, 3H), 1.19 (d, J = 6.51 Hz, 6H), 4.06 (q, J = 6.51 Hz, 2H).

Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found (mixture of isomers): C, 71.90; H, 12.28.

(2RS,4RS)-3,3-Dimethylpentane-2,4-diol, **15b**. Mp. 35-6ºC (hexane); IR(film): 3350 cm^{-1}; HMR($CDCl_3$): δ 0.86 (s, 6H), 1.15 (d, J = 6.5 Hz, 6H), 3.45 (s, 2H), 3.80 (q, J = 6.5 Hz, 2H).

(2R,4S)-3,3-Dimethylpentane-2,4-diol, **15a**. Mp. 79-80ºC (hexane) (Lit.[3] mp. 80ºC); IR(KBr): 3330 cm^{-1}; HMR($CDCl_3$): δ 0.69 (s, 3H), 0.90 (s, 3H), 1.18 (d, J = 6.3 Hz, 6H), 2.90 (s, 2H), 3.85 (q, J = 6.3 Hz, 2H).

(3S,4s,5R)-4-(1-Adamantyl)-2,2,6,6-tetramethylheptane-3,5-diol, **16a**. Mp. 132-3ºC (hexane); IR(KBr): 3610, 3516 cm^{-1}; HMR($CDCl_3$): δ 1.05 (s, 18H), 1.55 (t, J ca. 2.4 Hz, 1H), 1.6-2.1 (m, 15H), 3.96 (d, J = ca. 2.4 Hz, 2H); CMR($CDCl_3$): δ 26.4, 27.6, 34.8, 35.7, 36.4, 40.7, 55.1, 78.8.

Calcd. for $C_{21}H_{38}O_2$: C, 78.20; H, 11.87. Found: C, 78.25; H, 11.90.

(3SR,5SR)-4-(1-Adamantyl)-2,2,6,6-tetramethylheptane-3,5-diol, **16b**. Mp. 196ºC (hexane); IR(KBr): 3484, 3399 cm^{-1}; HMR($CDCl_3$): δ 0.90 (s, 9H), 1.15 (s, 9H), 1.6-2.1 (m, 16H), 3.75 (s, 1H), 4.15 (broad s, 1H); CMR($CDCl_3$): δ 27.3, 29.0, 29.8, 35.4, 36.0, 36.6,

37.2, 42.5, 48.0, 78.3, 79.8.

Calcd. for $C_{21}H_{38}O_2$: C, 78.20; H, 11.87. Found: C, 78.18; H, 11.83.

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