Preparation and Reactions of 2,2-Dimethyl-1,3-dioxan-5-one-SAMP-Hydrazone: A Versatile Chiral Dihydroxyacetone Equivalent

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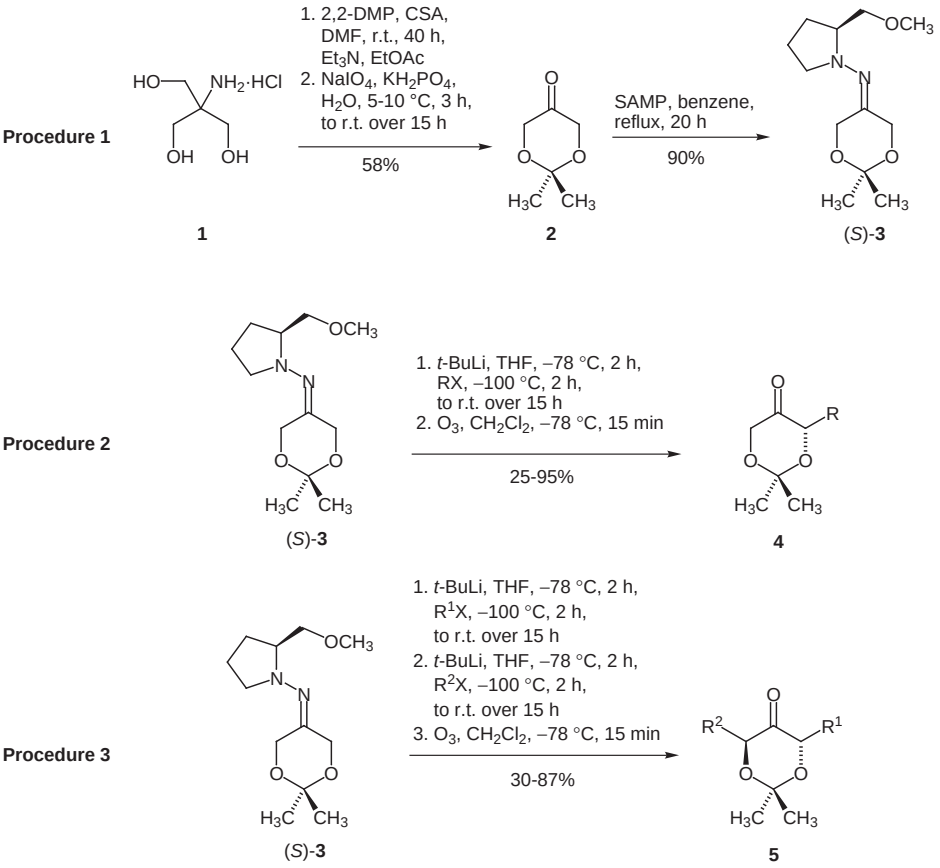
Abstract: The SAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one represents a valuable chiral dihydroxyacetone equivalent. Asymmetric mono- or α,α′-bisalkylations followed by auxiliary cleavage leads to the corresponding mono- or α,α′-disubstituted, acetonide protected ketodiols in excellent diastereo- and enantiomeric excesses.

Key words: asymmetric synthesis, ketodiols, alkylations, hydrazones, chiral dihydroxyacetone equivalent



Scheme 1

Introduction

Nature employs dihydroxyacetone phosphate (DHAP) as a C_3-building block for carbohydrate synthesis via asymmetric enzyme-catalyzed aldol reactions. Consequently many groups have focused on broadening the scope of these enzyme-catalyzed aldol reactions.[1] On the other hand, the development of a chiral DHAP equivalent for chemical asymmetric synthesis would open up not just the possibility of asymmetric aldol reactions but also of other electrophilic substitutions in α-position such as asymmetric alkylations as well, drastically increasing the scope and utility. Whilst a chiral 4-subsituted 2,2-dimethyl-1,3-dioxan-5-one derivative, prepared from D-glucose, has

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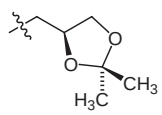
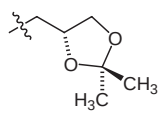
been employed in an asymmetric aldol reaction,[2] the development of a chiral dihydroxyacetone equivalent for general asymmetric synthesis has not been realized. In 1989 we reported that conversion of 2,2-dimethyl-1,3-dioxan-5-one (**2**) to the corresponding SAMP-hydrazone (*S*)-**3** proved an excellent platform for asymmetric alkylations.[3] In this 'Practical Synthetic Procedure' we will show that the broad tolerance of a variety of electrophiles in electrophilic α-substitution reactions and the ease of auxiliary cleavage under a range of conditions make this chiral DHAP equivalent a valuable C_3-building block for a broad range of asymmetric syntheses.

Scope and Limitations

The preparation of 2,2-dimethyl-1,3-dioxan-5-one-SAMP-hydrazone [(*S*)-**3**] is detailed in Procedure 1 (Scheme 1). The preparation of the parent 2,2-dimethyl-1,3-dioxan-5-one (**2**) starting from the aminotriol **1**, both of which are commercially available, was accomplished by a modification of the method of Woodward and Vorbrüggen reported by Hoppe et al.[4] As shown in Table 1 a large range of electrophiles are compatible with the asymmetric alkylation of the SAMP-hydrazone of dioxanone (*S*)-**3** (Procedure 2, Scheme). Smooth reaction of the azaenolate, generated by deprotonation with *tert*-butyllithium at low temperature, occurred with aziridines[5] (Entry 1), Michael acceptors[6] (Entry 2), a range of alkyl halides[3,7–10] (Entries 3–13) and a silyl triflate[11] (Entry 14). Auxiliary cleavage was achieved with either ozone, aqueous oxalic acid, or aqueous copper(II) chloride to give the α-substituted ketones **4** in excellent enantiomeric excesses (ee = 89 to ≥98%). The yield over two steps was 25–95%. Of all the alkyl halides examined, the worst cases were methyl (Entry 3) and allyl (Entry 9) yielding the ketones in 45% and 25% yield, respectively, after ozonolytic cleavage. These relatively low yields may be explained by the high volatility of the ketones and competitive cleavage of the double bond in the allyl case. To avoid ozonolytic cleavage of double bond containing substituents, cleavage conditions can be switched to aqueous copper (II) chloride (Entries 10 and 11).[8] Moreover the reaction was tolerant to *O*-protected α-hydroxy[7] (Entry 6), β-hydroxy[9,10] (Entries 7,12, and 13) and γ-hydroxy alkyl halides[8] (Entry 8), an α-bromo ester[3] (Entry 15), as well as the secondary isopropyl iodide[3] (Entry 4).

Table 1 Examples for Asymmetric Synthesis of 4-Subtituted 2,2-Dimethyl-1,3-dioxan-5-ones **4**

Entry	R	Yield[a] (%)	de (%)	ee (%)
1	$(CH_2)_2NHTs$	70[b]	–	≥98
2	$CH(Me)CH_2CO_2Bu$-*t*	79[c]	96	96
3	Me	45[c]	–	93
4	*i*-Pr	60[c]	–	≥95
5	$(CH_2)_2Ph$	71[c]	–	94
6	CH_2OBn	84[d,e]	–	94
7	$(CH_2)_2OTBS$	95[d]	–	≥96
8	$(CH_2)_3OTBS$	52[b,e]	–	96
9	$CH_2CH=CH_2$	25[c]	–	≥95
10	$(CH_2)_2CH=CH_2$	62[b,e]	–	96
11	$(CH_2)_3CH=CH_2$	90[b,e]	–	96
12		59[c]	89	≥98
13		61[c]	87	≥98
14	$SiMe_2Hex$-*t*	80[c]	–	96
15	$CH_2CO_2CH_3$	45[c]	–	89

[a] Overall yield starting from (*S*)-**3**.
[b] Auxiliary cleavage utilizing aq $CuCl_2$.
[c] Ozonolytic cleavage.
[d] Auxiliary cleavage utilizing aq oxalic acid.
[e] Yield of the auxiliary cleavage step.

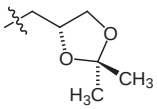
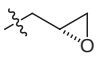
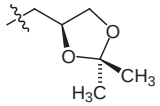
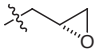
The methodology was further extended to α,α′-bisalkylations (Procedure 3). When the same electrophile is used twice, then after cleavage, C_2-symmetric bisalkylated ketones **5** ($R^1 = R^2$) result (Table 2).[12–14] The exclusively 1,3-*trans* substituted products were isolated in 58–83% yield and enantiomeric excesses greater than 98%. In the unsymmetrical series (Table 3),[10,15,16] yields over three steps were 30–87% with enantiomeric excesses greater than 96% in all cases. Once again, only the 1,3-*trans* substituted products were observed. The functional group tolerance was broadened to alkyl halides containing epoxy functionality[10] (Entries 5 and 10) and three further secondary alkyl halides, α-methylbenzyl[15] (entry 7), cyclopentyl[15] (Entry 8) and cyclohexyl[15] (Entry 9). Cleavage of the auxiliary was accomplished either using ozone or aqueous oxalic acid.

Table 2 Examples for Asymmetric Synthesis of C_2-Symmetric, 4,6-Disubtituted 2,2-Dimethyl-1,3-dioxan-5-ones **5**

Entry	R[a]	X	Yield[b] (%)	de (%)	ee (%)
1	Pr	I	68	≥96	>99
2	*i*-Pr	I	83	≥96	≥98
3	Bn	Br	68	≥96	≥98
4	Et	I	58	≥96	>98
5	$(CH_2)_2Ph$	I	64	≥96	>99

[a] $R = R^1 = R^2$.
[b] Overall yield starting from (*S*)-**3**.

Table 3 Examples for Asymmetric Synthesis of 4,6-Disubtituted 2,2-Dimethyl-1,3-dioxan-5-ones **5**

Entry	R^1	R^2	Yield[a] (%)	de (%)	ee (%)
1	Me	*i*-Pr	76	≥96	>99
2	Me	CH_2OBn	83	≥96	>99
3	Me	$CH_2CO_2CH_3$	70	≥96	>99
4	Me		43	81	≥98
5	Me		51	98	≥98
6	Me	Bn	86	≥96	>99
7	Me	CH(Me)Ph	70[b]	≥96	>99
8	Me	*cy*-Pent	71	≥96	>99
9	Me	*cy*-Hex	40	≥96	>99
10			30	91	≥98
11	Bn	CH_2OBn	87[c]	≥96	≥96

[a] Overall yield starting from (*S*)-**3** utilizing ozone for auxiliary cleavage.
[b] All diastereoisomers.
[c] Auxiliary cleavage utilizing aq oxalic acid.

A limitation of the methodology appears to be the reaction of the azaenolates of the SAMP-dioxanone with aldehydes.[17] A solution to this problem has been to employ the α-silyldioxanone (Entry 14, Table 1) as an alternative chiral DHAP equivalent for aldol reactions.[11]

The utility of this methodology has been further demonstrated in target oriented synthesis. The applications are varied and include such topics as piperidine synthesis (via reductive amination),[18] C_5- to C_9-deoxy sugar synthesis (via diastereoselective reduction)[10] and the synthesis of HIV-1 protease inhibitors.[13] Furthermore, the total synthesis of the natural products (+)-aspicillin (via the corresponding RAMP hydrazone),[19] L-threosphingosine,[20] as well as both enantiomers of streptenol A[9] have also been accomplished. Majeswki et al. have also used the SAMP-dioxanone (*S*)-**3** in a total synthesis of (+)-frontalin.[21]

In summary, 2,2-dimethyl-1,3-dioxan-5-one-SAMP-hydrazone [(*S*)-**3**] has proven to be a very versatile chiral DHAP equivalent for asymmetric synthesis. We are continuing to examine new electrophiles in the alkylation reactions (such as epoxides for example), as well as new ways of functionalising the final products (such as methylenation and hydrogenation)[14] and new applications (such as quaternary centre construction).[22]

Procedures

Herein we describe the synthesis of SAMP-hydrazone (*S*)-**3** and two typical procedures for monosubstituted as well as for α,α′-disubstituted dioxanones **4** and **5**. In the first procedure (Procedure 1) the two step synthesis of 2,2-dimethyl-1,3-dioxan-5-one (**2**) starting from the commercially available aminotriol **1** followed by condensation with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) to afford the title compound (*S*)-**3** in an overall yield of 52% is described. Procedures 2 and 3 show the mono- and α,α′-bisalkylation of SAMP-hydrazone (*S*)-**3** and the oxidative cleavage to give the monsubstituted dioxanone **4** (71%, 2 steps) or the α,α′-disubstituted dioxanone **5** (86%, 3 steps), respectively.

2,2-Dimethyl-1,3-dioxan-5-one (2)

A 2 L round-bottom flask, equipped with a magnetic stirring bar, was filled with 2-amino-2-hydroxymethyl-1,3-propandiol hydrochloride (**1**; 78.0 g, 500 mmol), DMF (160 mL), 2,2-dimethoxypropane (2,2-DMP, 63.8 g, 600 mmol) and camphorsulfonic acid (CSA, 4.18 g, 25 mmol). The mixture was stirred at r.t. for 40 h. Et_3N (4.2 mL) was added followed by removal of the solvent under reduced pressure. The residue was dissolved in EtOAc (1.2 L) and Et_3N (67 mL) and stirred at r.t. for 10 min. The precipitate was filtered and the solvent was removed under reduced pressure. The crude β-amino alcohol (50.0 g, 310 mmol) was then transferred to a 2 L three necked round-bottom flask, equipped with an overhead stirrer, dropping funnel and thermometer and was dissolved in H_2O (450 mL). KH_2PO_4 (42.4 g, 310 mmol) was added and the solution was cooled to 5 °C. Then, an aq $NaIO_4$ solution (924 mL, 0.5 M) was added dropwise over 3 h while the temperature was maintained at 5–10 °C. The cooling bath was removed and the mixture was stirred at r.t. for 15 h. The aqueous solution was extracted with CH_2Cl_2 (15 × 70 mL). The combined organic layers were washed with brine (70 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by distillation using a Vigreux column to afford 2,2-dimethyl-1,3-dioxan-5-one (**2**) as a colorless oil (25.3 g, 58%; 2 steps); bp 50–54 °C/11 Torr.

IR ($CHCl_3$): 3472, 2991, 2941, 2893, 2538, 1801, 1753, 1445, 1425, 1378, 1338, 1270, 1222, 1153, 1121, 1093, 1052, 1029, 1007, 975, 918, 849, 832, 733, 715, 664, 624, 572, 559, 515, 477 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.16 (s, 4 H, CH_2), 1.45 (s, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 208.0 (CO), 100.1 (CCH_3), 66.8 (2 C, CH_2), 23.5 (2 C, CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 130 (M^+, 63), 115 (65), 10 (67), 73 (5), 72 (100), 59 (17), 58 (18), 57 (6).

Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.14; H, 7.71.

(*S*)-(+)-1-(2,2-Dimethyl-1,3-dioxan-5-ylidenamino)-2-methoxymethylpyrrolidine [(*S*)-3]

In a flask equipped with a Dean–Stark trap (for azeotropic removal of H_2O) and a reflux condenser, dioxanone **2** (8.45 g, 65 mmol) and (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) (8.46 g, 65 mmol) in benzene (80 mL) were refluxed for 20 h. After cooling, Et_2O (200 mL) was added and the mixture was washed with H_2O (2 × 10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude hydrazone was purified by distillation under reduced pressure to give (*S*)-**3** as a pale yellow oil (14.2 g, 90%); bp 82–88 °C/0.05 Torr; α_D^{23} +230° (neat).

IR ($CHCl_3$): 1460, 1450, 1380, 1370, 1340, 1220, 1155–1040, 835 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.21–4.58 (m, 4 H, $CNCOCH_2$), 3.35 (s, 3 H, OCH_3), 3.04–3.46 (m, 4 H, C*H*HN, CH, C*H*$_2$OCH$_3$), 2.50 (q, *J* = 8.3 Hz, 1 H, CH*H*N), 1.95–2.06 (m, 1 H, CHC*H*H), 1.80–1.89 (m, 2 H, NCH_2CHH, CHCH*H*), 1.60–1.71 (m, 1 H, NCH_2CHH), 1.43 (s, 3 H, CCH_3), 1.40 (s, 3 H, CCH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.0 (C=N), 99.9 [*C*$(CH_3)_2$], 75.4 (*C*H_2OCH_3), 66.6 (CH), 62.6, 60.3 (2 C, CN*C*H_2), 59.2 (OCH_3), 55.4 (NCH_2), 24.5 (C*C*H_3), 23.2 (C*C*H_3), 22.7 (NCH_2CH_2).

MS (EI, 70 eV): *m*/*z* (%) = 242 (M^+, 1.5), 139 (43), 98 (60), 70 (100), 43 (30).

Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.47; H, 9.36; N, 11.34.

(*S*)-(–)-2,2-Dimethyl-4-phenethyl-1,3-dioxan-5-one [(S)-4] [R = $(CH_2)_2$Ph]

A dry, argon flushed, 100 mL Schlenk round-bottom flask, equipped with a magnetic stirring bar, was filled with SAMP-hydrazone (*S*)-**3** (2.42 g, 10 mmol) and anhyd THF (40 mL). Then, *t*-BuLi (7.5 mL, 15% in *n*-pentane, 11 mmol) was added dropwise by syringe at –78 °C. After stirring for 2 h at this temperature, the mixture was cooled to –100 °C and 2-phenylethyl iodide (1.59 mL, 11 mmol), dissolved in anhyd THF (2 mL) was added slowly. After further stirring for 2 h at –100 °C, the mixture was allowed to warm to r.t. over 15 h. The mixture was quenched with pH 7 buffer solution (2 mL) and diluted with Et_2O (80 mL). The organic layer was washed with pH 7 buffer solution (10 mL) and brine (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The obtained monoalkylated SAMP-hydrazone was dissolved in CH_2Cl_2 (50 mL) and flushed with ozone (60 Lh^{-1}) at –78 °C for 15 min. The reaction mixture was allowed to warm to r.t. and flushed with argon. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel, *n*-pentane–Et_2O; 30:1) to afford (*S*)-**4** as a colorless oil (1.66 g, 71%); $[\alpha]_D^{27}$ –189.0 (*c* = 1.02, $CHCl_3$).

IR ($CHCl_3$): 3473, 3086, 3063, 3028, 2989, 2936, 2865, 2633, 2157, 1951, 1875, 1801, 1746, 1604, 1585, 1497, 1455, 1432, 1379, 1323, 1250, 1225, 1173, 1105, 1071, 1036, 991, 974, 918, 867, 853, 774, 750, 701, 623, 605, 582, 538, 517, 490 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.16–7.29 (m, 5 H, C_6H_5), 4.24 (dd, *J* = 1.5, 16.9 Hz, 1 H, COC*H*H), 4.15 (ddd, *J* = 1.5, 3.6, 9.1 Hz, 1 H, COCH), 3.95 (d, *J* = 17.0 Hz, 1 H, COCH*H*), 2.80 (m, 1 H, PhC*H*H), 2.68 (m, 1 H, PhCH*H*), 2.20 (m, 1 H, CHC*H*H), 1.86 (m, 1 H, CHCH*H*), 1.45 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.8 (CO), 141.2 (*C*Ph), 128.3, 128.6 (4 C, OCH, *m*-CH), 126.3 (*p*-CH), 101.1 (*C*CH_3), 73.8 (CHO), 66.7 (CO*C*H_2), 31.2, 30.4 (2 C, CH_2), 24.4, 24.1 (2 C, CH_3).

MS (CI, Isobutane): *m*/*z* (%) = 236 (15), 235 (M^+ + 1, 100), 218 (7), 217 (64), 178 (11), 177 (93), 176 (14), 159 (36), 134 (11), 133 (11), 131 (5), 130 (6).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.50; H, 7.89.

(*S*,*S*)-(–)-4-Benzyl-2,2,6-trimethyl-1,3-dioxan-5-one [(*S*,*S*)-5] [R^1 = CH_3, R^2 = Bn]

A dry, argon flushed, 100 mL Schlenk round-bottom flask, equipped with a magnetic stirring bar, was filled with (*S*)-**3** (2.42 g, 10 mmol) and anhyd THF (40 mL). Then, *t*-BuLi (7.5 mL, 15% in *n*-pentane, 11 mmol) was added dropwise by syringe at –78 °C. After stirring for 2 h, the mixture was cooled to –100 °C and a solution of MeI (0.68 mL, 11 mmol) in anhyd THF (2 mL) was added slowly. After further stirring for 2 h, the mixture was allowed to warm to r.t. over 15 h. The mixture was quenched with pH 7 buffer solution (2 mL) and diluted with Et_2O (80 mL). The organic layer was washed with pH 7 buffer solution (10 mL) and brine (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting monsubstituted SAMP-hydrazone was alkylated again at the α′-position using benzyl bromide as the electrophile following the procedure described above. The obtained 4,6-disubstituted SAMP-hydrazone was dissolved in CH_2Cl_2 (50 mL) and flushed with ozone (60 Lh^{-1}) at –78 °C for 15 min. The reaction mixture was allowed to warm to r.t. and flushed with argon. After removal of the solvent under reduced pressure the crude product was purified by flash chromatography (silica gel, *n*-pentane–Et_2O, 20:1) to afford (*S*,*S*)-**5** as a colorless oil (2.01 g, 86%); $[\alpha]_D^{25}$ –198.3 (*c* = 1.05, $CHCl_3$).

IR ($CHCl_3$): 3016, 2966, 2958, 2927, 2855, 1745, 1497, 1455, 1377, 1217, 1174, 1122, 1076, 1031, 968, 944, 835, 758, 700, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.18–7.30 (m, 5 H, C_6H_5), 4.44 (ddd, *J* = 1.4, 3.3, 8.8 Hz, 1 H, CH_2CH), 4.29 (qd, *J* = 1.4, 6.9 Hz, 1 H, CH_3CH), 3.23 (dd, *J* = 3.2, 15.0 Hz, 1 H, C*H*H), 2.80 (dd, *J* = 9.1, 14.8 Hz, 1 H, CH*H*), 1.43 (d, *J* = 0.6 Hz, 3 H, CCH_3), 1.33 (d, *J* = 0.6 Hz, 3 H, CCH_3), 1.29 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 210.7 (CO), 137.6 (*C*Ph), 129.0, 128.0 (4 C, OCH, *m*-CH), 126.2 (*p*-CH), 101.0 [*C*$(CH_3)_2$], 75.0, 70.6 (2 C, CH), 34.8 (CH_2), 24.0 (CH_3), 23.9 (CH_3), 14.4 (CH*C*H_3).

MS (EI, 70 eV): *m*/*z* (%) = 234 (M^+, 12), 190 (25), 176 (83), 162 (27), 147 (33), 147 (16), 133 (33), 132 (90), 131 (81), 119 (18), 119 (48), 114 (26), 105 (20), 104 (100), 103 (23), 91 (23), 86 (83), 78 (14), 77 (18), 65 (10), 59 (31), 58 (94), 56 (17), 56 (64), 51 (14), 45 (13).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.45; H, 7.74.

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