Photochemical Route to a Representative 1,8-Annulated 7-Methylene-1,3,5-cyclooctatriene

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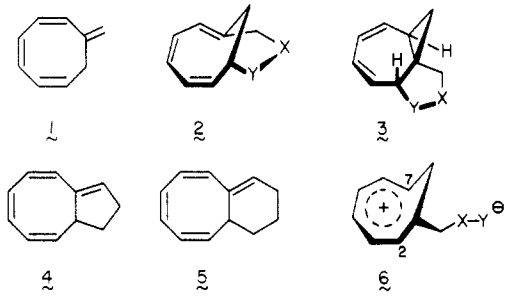
The bifunctional 2-cyclohexenone that is produced by addition of the Grignard reagent derived from 6-chloro-2-hexyne to 3-ethoxycyclohexenone was irradiated. [2+2] Cycloaddition occurred to produce a highly sensitive tricyclic cyclobutene (**14**), which underwent ready double-bond migration in the presence of palladium(II) acetate. With the exocyclic π bond in position, the α,β-unsaturated ketone functionality was next elaborated. Although oxidation of **15** via organoselenium methodology did give **16**, the yield was only modest. A more expedient approach involved initial conversion of **14** to its silyl enol ether and concurrent oxidation–olefin isomerization with Pd(II). Hydride reduction of the resulting dienone proceeded stereospecifically to deliver an allylic alcohol that underwent smooth dehydration to give the target hydrocarbon **11** when treated with 2,4-dinitrobenzenesulfenyl chloride and triethylamine. The available evidence suggests that disrotatory ring opening within intermediate **18** occurs readily.

Although studies of the chemical reactivity of 7-methylene-1,3,5-cyclooctatrienes are sparse, it is already clear that this class of polyolefins offers the potential for inspiring considerable physical–organic and synthetic research. Gream has demonstrated, for example, that **1**, the

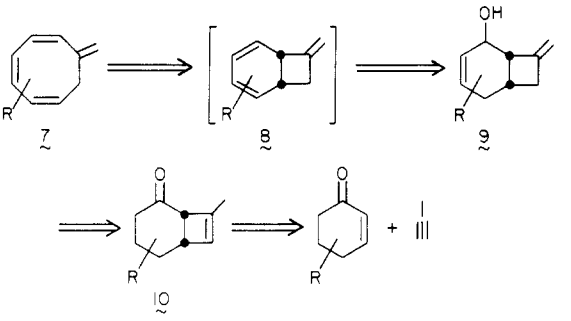


parent member of the series, enters into reaction with highly reactive dienophiles (e.g., tetracyanoethylene) and uniparticulate electrophiles[1] (e.g., chlorosulfonyl isocyanate) to give structurally novel adducts of type **2** and/or **3**.[2] This behavior, which is shared by **4** and **5**, is construed to be indirect evidence for the intervention of functionalized homotropylium zwitterions typified by **6**. Whereas charge annihilation at C-7 yields [8+2] adducts **2**, covalent bond formation at C-2 leads to cyclopropyl products structurally akin to **3**.

Progress in this area has been limited by the synthetic accessibility of 7-methylene-1,3,5-cyclooctatriene derivatives. Tetraene **1**, which is available by appropriate Wittig condensation of cycloocta-2,4,6-trienone with methylenetriphenylphosphorane,[3] may be classified as readily available. However, neither position-specific derivatives of **1** nor annulated homologues of this ring system are as easily acquired. To illustrate, hydrocarbons **4** and **5** are produced (in varying yields and purity depending on solvent) during solvolysis of ω-cyclooctatetraenylalkanesulfonate esters.[4,5] No other synthetic entry is presently available.

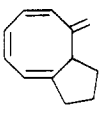
In connection with another research objective, we considered the retrosynthetic analysis summarized in Scheme

Scheme I



I. Thus, [2+2] photocycloaddition of a 2-cyclohexenone to a 2-propyne derivative, on either an intermolecular[6,7] or intramolecular basis,[8,9] can be expected to give rise to **10**. For our purposes, the cyclobutenyl methyl substituent need not be positioned proximal to the carbonyl group, since the location of R can be properly adjusted in the starting cyclohexenone. Migration of the cyclobutene double bond to the external site as in **9** should be thermodynamically driven and consequently accomplished readily. Suitable dehydration of **9** would then give **8**, disrotatory electrocyclic ring opening of which should occur spontaneously[10] to deliver target molecule **7**.

In this paper, we present a detailed account of our successful acquisition of **11** by an intramolecular variant



of the protocol outlined in Scheme I. For convenience, the length of the tether linking the cycloalkenone to the alkyne has been regulated to avoid possible problems with the regioselectivity of the [2+2] cycloaddition.[11]

(1) Paquette, L. A.; Allen, G. R., Jr.; Broadhurst, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 4503.
(2) Ferber, P. H.; Gream, G. E.; Kirkbride, P. K. *Tetrahedron Lett.* **1980**, 2447.
(3) See footnote 1 of ref 2.
(4) (a) Gream, G. E.; Mular, M. *Aust. J. Chem.* **1975**, *28*, 2227. (b) Ferber, P. H.; Gream, G. E.; Wagner, R. D. *Ibid.* **1980**, *33*, 1569.
(5) (a) Kitching, W.; Henzel, K. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1975**, *97*, 4643. (b) Paquette, L. A.; Henzel, K. A. *Ibid.* **1975**, *97*, 4649.
(6) Review: Baldwin, S. W. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 123.
(7) (a) Serebryakov, E. P.; Burstein, K. Y. *Tetrahedron* **1978**, *34*, 3233. (b) Serebryakov, E. P.; Kulomzina-Pletneva, S. D.; Margaryan, A. K. *Ibid.* **1979**, *35*, 77.
(8) Review: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.
(9) (a) Koft, E. R.; Smith, A. B., III *J. Org. Chem.* **1984**, *49*, 832. (b) Koft, E. R.; Smith, A. B., III *J. Am. Chem. Soc.* **1984**, *106*, 2115.
(10) Compare: Paquette, L. A.; Hefferon, G. J.; Samodral, R.; Hanzawa, Y. *J. Org. Chem.* **1983**, *48*, 1262 and relevant references cited therein.

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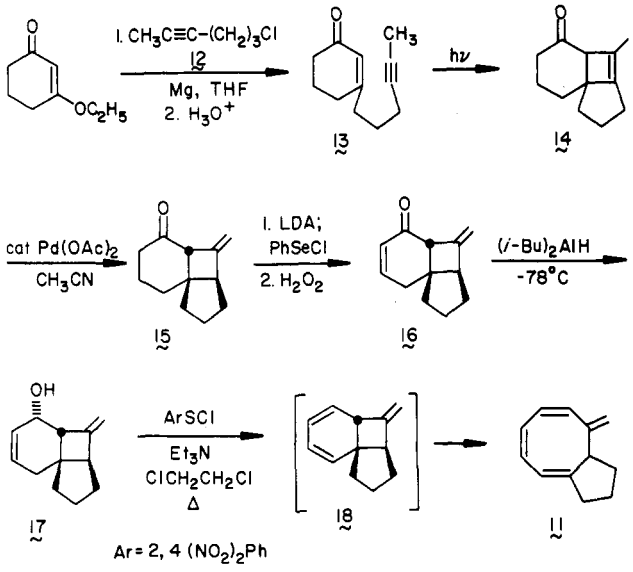
Scheme II



Results and Discussion

The obvious route to photochemical substrate **13** appeared to be addition of the Grignard reagent derived from 6-chloro-2-hexyne (**12**) to 3-ethoxy-2-cyclohexenone followed by hydrolysis. In our hands, direct metalation of commercially available 5-chloro-1-pentyne with *n*-butyllithium and ensuing HMPA-promoted methylation proved to be a particularly direct source of the previously described[11] chloride **12**. The Grignard condensation involving **12** provided **13** in 74% yield (Scheme II), thereby signaling that simple enolization was not a serious competing side reaction.

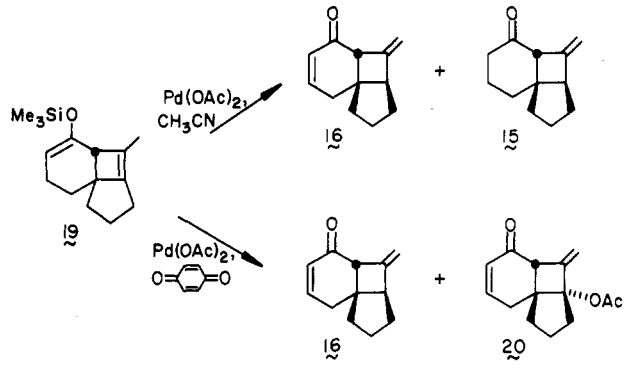
Irradiation of hexane solutions of **13** through Pyrex with a 450-W Hanovia lamp housed in a uranium filter resulted in substantial disappearance of starting material within 7 h. If reaction was arrested at this point, chromatographic purification of the resulting mixture on silica gel afforded **14** in 64% yield and returned 17% of uncyclized **13**. This 77% overall efficiency could be surpassed simply by extending the reaction time to 17 h (see below). Somewhat unexpectedly, the tricyclic enone proved to be highly labile. Although this sensitivity could easily be dealt with by the immediate utilization of **14** in the next step, the acquisition of spectral and analytical data, with the exception of a ^{1}H NMR spectrum, was precluded.

The stage was now set for exploration of the olefinic isomerization strategy. Overnight stirring with a catalytic quantity of palladium acetate in acetonitrile solution proved particularly efficacious. Routinely, **13** was irradiated for 17 h in the manner described above, and the reaction mixture was treated directly with small quantities of $Pd(OAc)_2$. Chromatography subsequently made possible isolation of the more stable exocyclic enone **15** in 83% overall yield. Comparison of the 300-MHz ^{1}H NMR spectra of **14** and **15** clearly revealed that the singlet methyl absorption in the original photoadduct was now supplanted by a pair of olefinic multiplets centered at δ 4.96 and 4.86.

At this point, we faced the task of introducing an added site of unsaturation in the six-membered ring of **15**. Toward this end, it was observed that **16** could be obtained in a single operation by selenenylation of the enolate anion of **15** and in situ oxidative elimination of the phenyl selenide substituent so incorporated. Product dienone was

(11) Compare: (a) Koft, E. R.; Smith, A. B., III *J. Org. Chem.* **1984**, *49*, 832. (b) Pirrung, M. C.; Thomson, S. A. *Tetrahedron Lett.* **1986**, 2703.

Scheme III



easily separated; unfortunately, the yield was very modest (20%). For this reason, attention was directed to the option of preparing silyl enol ether **19** and implementing its Pd(II)-catalyzed oxidation. Usefully, migration of the cyclobutene double bond occurred concurrently to produce **16**.

Despite the lability of **14**, conversion to **19** proceeded acceptably well. The reaction mixture was concentrated and treated directly with palladium(II) acetate in acetonitrile.[12] This protocol delivered **16** in 37% isolated yield (Scheme III). Accompanying **16** was a small amount of **15**. Although no attempt has been made to optimize this conversion, it is our opinion that this route to **16** holds considerable promise for improved efficiency.

An interesting observation was made when *p*-benzoquinone was introduced as cooxidant in the manner recommended by Saegusa.[13] Under these conditions, equal amounts of **16** and keto acetate **20** (combined yield 21%) were produced. The 300-MHz ^{1}H NMR spectrum of **20** bears a striking resemblance to that of **16** in those regions where the olefinic and α-carbonyl protons resonate. On this bases, the acetoxyl group can be reliably considered to be bonded to the more distal allylic cyclobutyl site as shown.

DIBAL-H reduction of **16** proceeded stereospecifically to deliver allylic alcohol **17**. The stereochemical assignment of the α-hydroxy group has not been established but is being assigned on the basis of steric approach control. Treatment of **17** with 2,4-dinitrobenzenesulfenyl chloride and triethylamine according to Reich and Wollonitz[14] resulted in smooth dehydration to give **11** in 49% yield after purification. Evidently, [2,3] sigmatropic rearrangement of the initially formed sulfenate ester and thermal extrusion of the resulting allylic sulfoxide proceed without complication from steric hindrance. No spectral evidence has been garnered to suggest that traces of triene **18** persist. The implication is that electrocyclic ring expansion does indeed occur readily in this instance. The spectral data for **11** (see the Experimental Section) conform fully to expectations based on the assigned structure.

In summary, a new and presumably general approach to 7-methylene-1,3,5-cyclooctatrienes has been developed. Central to the synthetic strategy are a [2+2] photocycloaddition involving a 2-cyclohexenone and a methylacetylene derivative and Pd(II)-catalyzed double-bond isomerization in the adduct to install the requisite exocyclic methylene group. It should prove possible to adjust the

(12) Peterson, P. E.; Dunham, M. *Org. Synth.* **1977**, *57*, 26.
(13) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(14) Reich, H. J.; Wollowtiz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051.
(15) Additional examples of the successful application of this methodology can be found in: (a) Yin, T.-K.; Lee, J. G.; Borden, W. T. *J. Org. Chem.* **1985**, *50*, 531. (b) Coxon, J. M.; Hydes, G. J.; Steel, P. J. *Tetrahedron* **1985**, *41*, 5213.

substitution plan of either photocycloaddition partner to take proper advantage of the locus of this latent $=CH_2$ functionality.

Experimental Section

6-Chloro-2-hexyne (12). A cold (0 °C), magnetically stirred solution of 5-chloro-1-pentyne (1.15 g, 11.2 mmol) in anhydrous tetrahydrofuran (6 mL) was treated with *n*-butyllithium (8 mL of 1.55 M in hexanes, 12.4 mmol). The mixture was stirred for 10 min, cooled to −78 °C, and treated with a solution of methyl iodide (4.56 g, 32.1 mmol) in dry hexamethylphosphoramide (6 mL). Once addition was complete, the contents were allowed to warm to room temperature while being stirred (2 h), diluted with water, and shaken with pentane. The pentane layer was washed with water, dried, and carefully concentrated. Distillation of the residue gave 680 mg (52.3%) of **12** as a colorless liquid, the spectra of which were identical with those earlier reported.[11]

3-(4-Hexynyl)-2-cyclohexenone (13). A magnetically stirred mixture of magnesium turnings (1.15 g, 47.3 mmol) and anhydrous tetrahydrofuran (10 mL) was heated to the reflux temperature. Following the injection of a small amount (ca. 50 μL) of 1,2-dibromoethane, a solution of **12** (5.12 g, 43.9 mmol) in 10 mL of the same solvent was introduced over 25 min. Subsequent to an additional reflux period of 35 min, more dry tetrahydrofuran (10 mL) was added and the Grignard solution was cooled to 0 °C. 3-Ethoxy-2-cyclohexenone (4.9 g, 35.0 mmol) was added, and the reaction mixture was brought to room temperature where stirring was continued for 1.5 h. Ice chips were added, and the solution was acidified with 5% hydrochloric acid to pH 2 (ca. 30 mL). The product was extracted into ether, and the combined ethereal layers were washed with water and dried. After concentration, the residue was chromatographed on silica gel (elution with 30% ethyl acetate in petroleum ether). There was isolated 5.73 g (74.1%) of **13** as a colorless liquid: IR (CH_2Cl_2, cm^{-1}) 2940, 1655, 1260, 895; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1 H), 2.38–2.27 (m, 6 H), 2.19–2.12 (m, 2 H), 2.03–1.96 (m, 2 H), 1.77 (t, J = 2.5 Hz, 3 H), 1.72–1.63 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 199.29, 165.15, 126.11, 78.10, 76.43, 37.39, 37.02, 29.61, 26.44, 22.80, 18.47, 3.32; MS, m/z (M^+) calcd 176.1154, obsd 176.1194.

Photocyclization of 13. A solution of **13** (42 mg) in 10 mL of hexanes was placed in a Pyrex tube, deoxygenated by bubbling argon through for 15 min, and irradiated for 7 h with a uranium-filtered 450-W Hanovia lamp housed in a quartz cold finger. Following solvent evaporation, the residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 27 mg (64.3%) of **14** and 7 mg (16.7%) of unreacted enone **13**. Tricyclic ketone **14** proved to be a very unstable substance: ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (br s, 1 H), 2.54–2.46 (m, 1 H), 2.21–1.91 (series of m, 5 H), 1.88–1.61 (m, 4 H), 1.65 (s, 3 H), 1.48–1.25 (m, 2 H).

Isomerization of 14. A 1.2-g (6.8 mmol) sample of **13** was dissolved in hexanes (500 mL) and irradiated as described above for 17 h. Rapid concentration of the photolysate was followed by dissolution of the residual oil in 30 mL of acetonitrile under nitrogen. Palladium acetate (80 mg, 0.35 mmol) was introduced at once, and the reaction mixture was stirred overnight. The solvent was evaporated under reduced pressure, and the residue was taken up in dichloromethane, washed with water, dried, and again concentrated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in petroleum ether) furnished 1.0 g (83%) of pure **15** as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 2940, 1686, 1340, 1164, 893; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (m, 1 H), 4.86 (m, 1 H), 3.11 (m, 1 H), 3.00 (m, 1 H), 2.60–2.51 (m, 1 H), 2.18–1.37 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 209.45, 146.52, 108.60, 57.75, 50.09, 46.82, 39.67, 39.91, 33.03, 32.23, 25.01, 20.32; MS, m/z (M^+) calcd 176.1201, obsd 176.1199.

Conversion to Dienone 16. A magnetically stirred solution of diisopropylamine (88 μL, 0.63 mmol) in dry tetrahydrofuran (3 mL) was cooled to −78 °C, treated with *n*-butyllithium (0.38 mL of 1.6 M in hexanes), and stirred for 10 min. A solution of **15** (101 mg, 0.57 mmol) in the same solvent (2 mL) was added dropwise. After 30 min, benzeneselenenyl chloride (120 mg, 0.63 mmol) in dry tetrahydrofuran (1 mL) was introduced in one portion. The reaction mixture was stirred for 5 min, warmed to 0 °C, and treated in turn with 1 mL of water, 55 μL of acetic acid, and 0.3 mL of 30% hydrogen peroxide. Stirring was continued for an additional 40 min at room temperature, water was added, and the product was taken up in dichloromethane. The combined organic layers were washed with water, dried, and concentrated. Purification by MPLC on silica gel yielded 20 mg (20%) of **16** along with 10 mg of unoxidized starting material. For **16**: colorless oil; IR (CH_2Cl_2, cm^{-1}) 2940, 1660, 1388, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (m, 1 H), 6.10 (m, 1 H), 4.98 (m, 1 H), 4.82 (m, 1 H), 3.19 (m, 1 H), 3.03 (m, 1 H), 2.48–2.28 (m, 2 H), 1.89–1.42 (m, 6 H); MS, m/z (M^+) calcd 174.1045, obsd 174.1041.

Preparation and Oxidation of Silyl Enol Ether 19. A. Palladium Acetate Alone. A cold (−78 °C), magnetically stirred solution of diisopropylamine (470 mg, 4.71 mmol) in anhydrous tetrahydrofuran (25 mL) was treated with *n*-butyllithium (2.95 mL of 1.6 M in hexanes). After 15 min, a solution of **14** (750 mg, 4.26 mmol) in the same solvent (10 mL) was introduced dropwise. The reaction mixture was stirred at −78 °C for 45 min, trimethylsilyl chloride (480 mg, 4.4 mmol) was added, and warming to room temperature was allowed to occur. Following the evaporation of solvent in vacuo, the residue was taken up in pentane (150 mL), filtered, and reevaporated. The resulting oil (1.0 g) was dissolved in acetonitrile (10 mL) and added at room temperature to a clear solution of palladium acetate (900 mg, 4.0 mmol) in 30 mL of acetonitrile. The reaction mixture was stirred at room temperature under nitrogen for 11 h, diluted with dichloromethane, filtered, and concentrated. The remaining oil was taken up in dichloromethane, washed with water, dried, and reconcentrated. Chromatography of the dark red oil on silica gel (elution with 15% ethyl acetate in petroleum ether) gave 280 mg (37%) of **16** and 30 mg of **15**.

B. The Palladium Acetate–Benzoquinone Combination. A solution containing *p*-benzoquinone (180 mg, 1.66 mmol) and palladium acetate (370 mg, 1.65 mmol) in acetonitrile (25 mL) was treated with a sample of **19** prepared as described above from 600 mg (3.4 mmol) of **14** and dissolved in 10 mL of the same solvent. The reaction mixture was stirred at room temperature for 20 h and worked up as outlined previously. MPLC purification on silica gel (elution with 20% ethyl acetate in petroleum ether) furnished 73 mg (12%) of **16** and 71 mg (9%) of **20**: IR (CH_2Cl_2, cm^{-1}) 2940, 1732, 1656, 1250, 896; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93–6.87 (m, 1 H), 6.06–6.01 (m, 1 H), 5.47 (d, J = 3.0 Hz, 1 H), 5.15 (d, J = 2.4 Hz, 1 H), 3.09 (m, 1 H), 2.65 (m, 2 H), 2.33–2.25 (m, 1 H), 2.01 (s, 3 H), 1.94–1.57 (series of m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 194.23, 169.82, 148.22, 146.94, 128.23, 113.31, 90.70, 53.13, 47.72, 39.27, 37.63, 28.17, 22.89, 21.29; MS, m/z ($M^+ - C_2H_2O$) calcd 190.0994, obsd 190.0990.

Reduction of 16. A cold (−78 °C), magnetically stirred solution of **16** (89.5 mg, 0.51 mmol) in dry dichloromethane (3 mL) was treated slowly with DIBAL-H (0.6 mL of 1 M in hexanes). The reaction mixture was allowed to warm slowly to room temperature, quenched with methanol, acidified with 3 mL of 1 N hydrochloric acid, and extracted with dichloromethane. The combined organic extracts were washed with water, dried, and evaporated to yield a single diastereomer of **17**: 82 mg (91%); ^1H NMR (300 MHz, $CDCl_3$) δ 5.93–5.81 (m, 2 H), 4.97 (t, J = 2.3 Hz, 1 H), 4.85 (t, J = 2.3 Hz, 1 H), 4.26 (br d, J = 7.6 Hz, 1 H), 2.93 (m, 1 H), 2.52 (m, 1 H), 2.05–1.25 (series of m, 6 H).

7-Methylenebicyclo[6.3.0]undeca-1,3,5-triene (11). A cold (0 °C), magnetically stirred solution of unpurified **17** (82 mg, 0.47 mmol) in 5 mL of 1,2-dichloroethane was treated with triethylamine (145 mg, 1.43 mmol) and 2,4-dinitrobenzenesulfenyl chloride (330 mg, 1.4 mmol). The reaction mixture was stirred at room temperature for 10 min and at the reflux temperature for 7 h. Following dilution with pentane (3 mL), the precipitated solid was separated by filtration and the filtrate was passed down a column of silica gel (elution with pentane). There was isolated 36 mg (48.9%) of **11** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, J = 12.5 Hz, 1 H), 5.92–5.65 (m, 6 H), 4.05 (d, J = 8.7 Hz, 1 H), 2.48–1.61 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 149.99, 144.80, 129.64, 129.17, 128.51, 126.96, 124.14, 123.26, 47.53, 31.95, 26.52, 19.27; MS, m/z (M^+) calcd 158.1096, obsd 158.1076.

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