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Synthesis of Indenone by Self-Condensation of 1-Acetyl-2-methylcyclopentene and Subsequent Unusual Autoxidation

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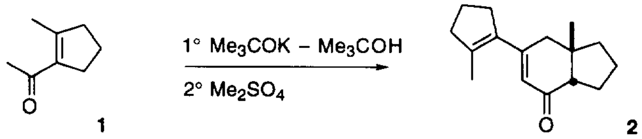
Abstract: Potassium *tert*-butoxide induced self-condensation of 1-acetyl-2-methylcyclopentene leads to 6-methyl-4-(2'-methylcyclopent-1'-enyl)bicyclo[4.3.0]non-3-en-2-one **2** in 35% yield when one equivalent of dimethyl sulfate is added. Dienone **2** undergoes facile autoxidation leading to the corresponding epoxide **12** and triketone **13**.

In the course of studies concerning the acylation reaction of methylcyclopentene derivatives,[1] we expected to prepare methoxydienes by *O*-alkylation of 1-acetyl-2-methylcyclopentene enolate with dimethyl sulfate. Since it is well known that the use of dimethyl sulfate as alkylating reagent favors *O*-alkylation,[2] we added dimethyl sulfate to a premixed solution of potassium *tert*-butoxide and 1-acetyl-2-methylcyclopentene in *tert*-butanol. However, much to our surprise, the only isolated product was a dimeric enone ($C_{16}H_{22}O$) resulting from an aldolisation-dehydration reaction (35% yield). Moreover, in the absence of dimethyl sulfate, the yield of **2** decreased to 15%. When NaH/DMSO was used instead of *t*-BuOK/*t*-BuOH, high-molecular weight products were formed and only *ca* 5% of **2** was isolated.



Tandem enolate addition to α-enone/cyclization is a well-documented process. Thus, substituted cyclohexenones are known to lead to spirocompounds,[3] and in the Robinson annulation, the first step, a Michael addition, is followed by a ketolization.[4] Three dimeric structures, **2**, **3** and **4** (Figure 1), were in accordance with the ^1H and ^{13}C NMR spectra, and 2D-X COR studies (400 MHz), and also compatible with the reaction conditions.

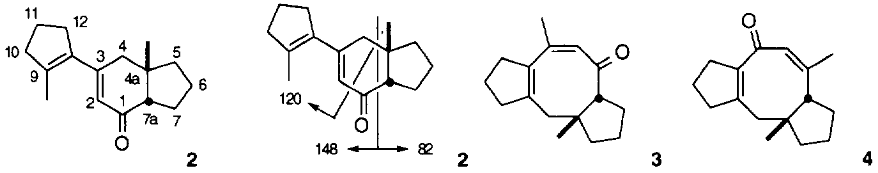
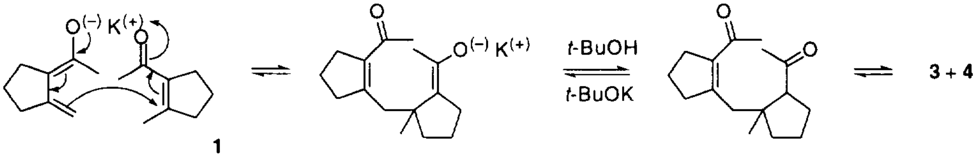


Figure 1

Both the formation of eight-membered cyclic dienones **3** and **4** would result from a Michael addition of the thermodynamic enolate of **1** on a neutral molecule, followed by an aldolisation-dehydration process.



However, considering that enone **1** is a poor Michael acceptor (tetrasubstituted double bond), an aldol condensation of the kinetic enolate of **1** on a neutral molecule is worth considering. Indeed, such a condensation followed by a dehydration giving rise to trienone **5**, a deprotonation leading to trienolate **6** and then a disrotatory cyclization could account for the formation of dienone **2**. Moreover, examples of similar processes are described in the literature.[1c,5]

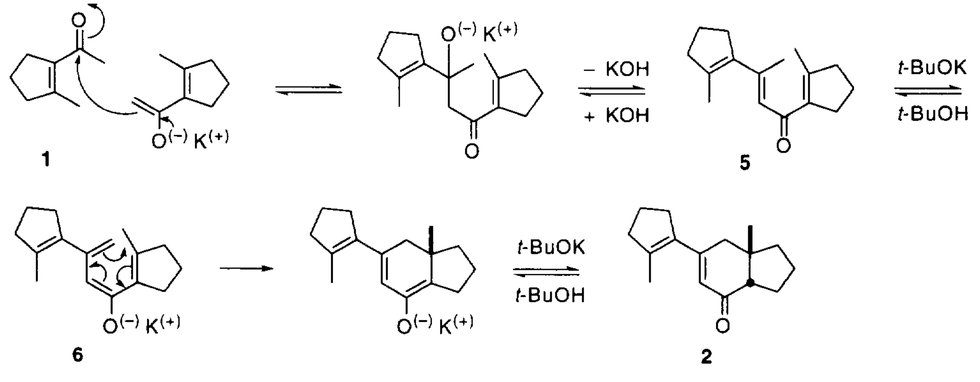
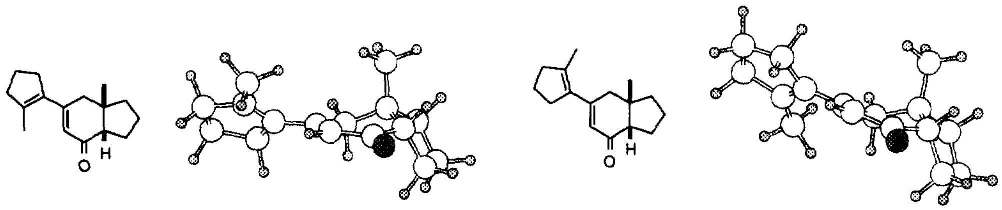


Figure 2

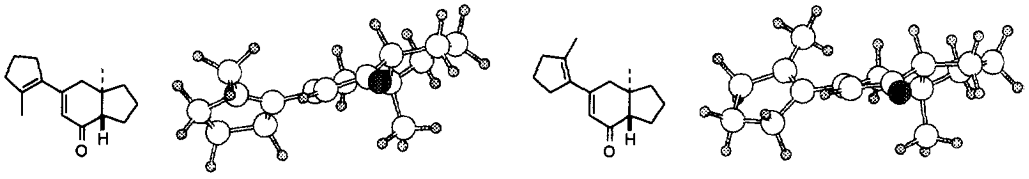
With the molecular formula and carbon functionality, the structural elucidation required an accurate definition of carbon connectivities. Mass spectrum experiments provided very useful information. Thus, MIKE mass spectra of the ions *m/z* 230 (molecular ion) and *m/z* 148 (M – 82) showed that fragment *m/z* 120 (base peak) resulted from the fragmentation of ion *m/z* 148 and not directly from ion *m/z* 230 (Figure 1). These observations are not compatible with structure **4**. Moreover, 2D COSY experiments (400 MHz) showed a lack of coupling between the single ethylenic proton (δ, 5.80 ppm) and the allylic methyl (δ, 1.70 ppm). With structures **3** or **4**, a pattern resulting from a ^4J coupling constant should have occurred. Consequently, structure **2** is the only one in agreement with all experimental data. The structure of **2** was furthermore confirmed by the use of the lanthanide shift reagent Pr(III)tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)(Pr(fod)$_3$). ^{13}C NMR chemical shift differences were determined and plotted *vs.* the ratio [Pr(fod)$_3$]/[**2**] (7.5, 15 and 30 w/w%). Magnitudes of the induced upfield shifts of the carbon atoms were in the order: δC(1) > δC(7a) > δC(2) > δC(7) > δC(4a) > δC(3) and indeed in agreement with structure **2** (Fig. 1). Finally, it appeared from NOESY experiments that, as in the parent 6-methylbicyclo[4.3.0]non-3-en-one,[1d] the ring junction is *cis*.

Molecular mechanics and semi-empirical AM1 calculations[6] showed that *cis*-dienone **2** is, regardless of its conformation, more stable than its *trans*-isomer **2'** (Fig. 3). Moreover, dienone **2** is also more stable than *cis*-dienone **3** (–39.02 kcal/mol)(Fig. 1) and *cis*-dienone **4** (–36.19 kcal/mol)(Fig. 1). Considering the reaction conditions, the formation of the thermodynamic product seems indeed reasonable.



Dienone **2**: cis / *s*-cis:
–45.74 kcal/mol (AM1); 33.65 kcal/mol (MM)

Dienone **2**: cis / *s*-trans:
–45.05 kcal/mol (AM1); 33.46 kcal/mol (MM)



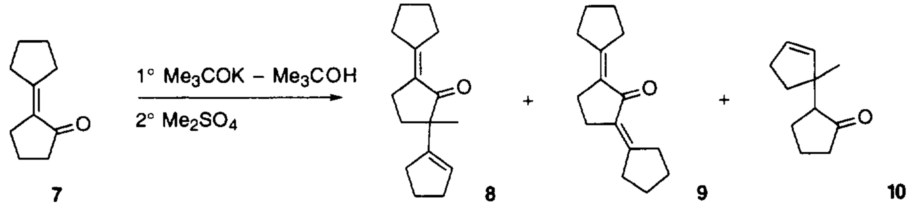
Dienone **2'**: trans / *s*-cis:
–41.70 kcal/mol (AM1); 35.01 kcal/mol (MM)

Dienone **2'**: trans / *s*-trans:
–40.92 kcal/mol (AM1); 35.85 kcal/mol (MM)

Figure 3: Computed structures and related energies of *s-cis* and *s-trans* conformers of *cis*-dienone **2** and its *trans*-isomer **2'**.

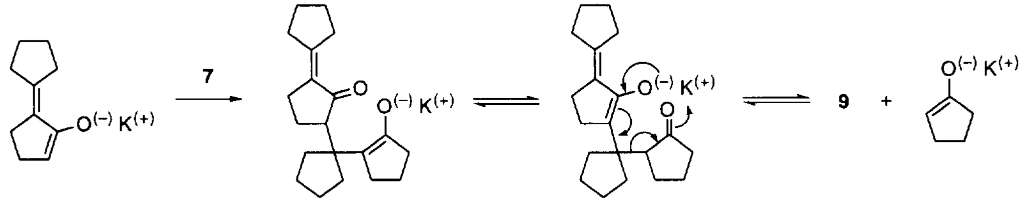
The effect of dimethyl sulfate is both striking and puzzling. Since the self-condensation of enone **1** leads to the formation of trienone **5** and potassium hydroxide as by-product (Cf. Fig. 2), dimethyl sulfate may be of importance in trapping potassium hydroxide and therefore reducing retrograde aldol reaction.

Generally the self-condensation of the α,β-unsaturated ketones leads to a mixture of products and is not a preparative reaction.[7,8] Actually, our efforts to expand the scope of the reaction of self-condensation in the presence of dimethyl sulfate to mesityl oxide or 2-cyclopentylidenecyclopentanone **7** failed. Mesityl oxide led to isophorone in moderate yield (24%) with several side products and enone **7** gave rise to a mixture of dienones **8** and **9**,[9] and enone **10** resulting from methylation and/or transaldolization.

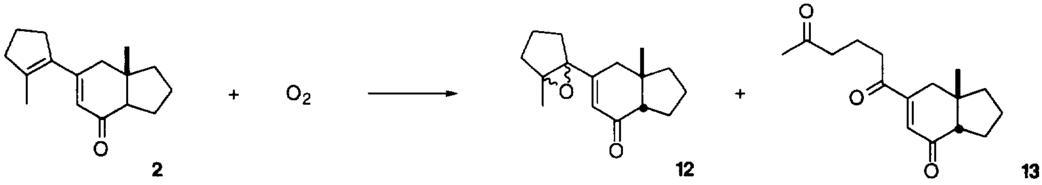


7 **8** **9** **10**

The presence of dienones **8** and **9** shows that cyclopentanone is an intermediate of the reaction. Indeed, the formation of dienones **8** and **9** can only be accounted for by the occurence of a retrograde aldol reaction (promoted by potassium hydroxide). The base-catalyzed *trans*-aldol reaction is believed to proceed by formation of the Michael adduct of two molecules of **7** and subsequent fragmentation.

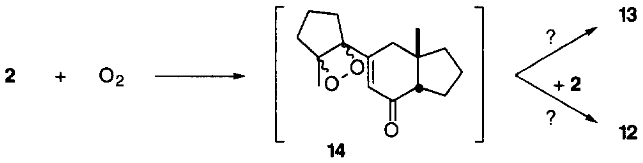


Another interesting feature is the fact that dienone **2** was converted on storage, after several days but even at low temperature (–25 °C) and in the darkness, into several other products, the major ones being epoxide **12** (1:1 mixture of diastereomers)[10] and triketone **13**. Such a result was obtained with better yields when a solution of dienone **2** in MeCN was stirred at room temperature under an atmosphere of molecular oxygen.



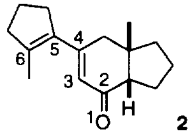
2 **12** **13**

We were able to establish that epoxide **12** was stable under these conditions and therefore that triketone **13** did not result from its further oxidation. Epoxide **12** and triketone **13** could however result from 1,2-dioxetane **14** (formed through the [2+2] cycloaddition of O_2 on the γ,δ-double bond of dienone **2**)[11,12] but, our efforts notwithstanding, we were unable to isolate and characterize such a compound.

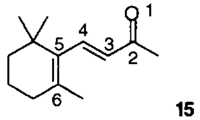


Although not unknown, the autoxidation[13] of olefinic compounds into epoxides or carbonyl derivatives is a seldom observed reaction. Thus, it has been reported to occur on cyclopentene[14] and dihydrofuran[15] derivatives, and on humulene.[16] After a scrupulous work, Bartlett and Banavali concluded that autoxidation of olefins, initiated by direct reaction of triplet oxygen, can be spontaneous and that the ease with which the initiation occurs could be related to the angle strain in the double bond with four bond angles contracted to 108° or less instead of 120°.[14] To the best of our knowledge, enones are not known to undergo autoxidation,[17] but an example of epoxidation, of conjugated dienones on the γ,δ-double bond, with molecular oxygen was reported by Hart.[18] Thus, β-ionone **15** led to the corresponding γ,δ-epoxide with 72% yield when heated for 24h at 120–130 °C in xylene under an atmosphere of molecular oxygen. However, in our hands, β-ionone **15** remained unaffected under the much milder conditions leading to the autoxidation of dienone **2**.

In order to shed some light on the origin of the reactivity of dienone **2**, we have undertaken AM1 calculations of the atomic partial charges and HOMOs of **2** and **15**. As shown in table 1, atomic partial charges are very similar and cannot account for the difference of reactivity observed.



2



15

	2	15	Δ
Charges			
O(1)	−0.301	−0.306	0.005
C(2)	0.264	0.255	0.009
C(3)	−0.231	−0.260	0.029
C(4)	0.011	−0.029	0.040
C(5)	−0.106	−0.102	0.004
C(6)	−0.084	−0.074	0.010

	2	15	$\lvert\Delta\rvert$
HOMO, eV	-8.98276	-9.19167	0.20891
Coeff.			
O(1)–Pz	−0.11449	0.13505	0.021
C(3)–Px	−0.14552	−0.14968	0.004
C(3)–Pz	0.31616	−0.33914	0.023
C(4)–Pz	0.31407	−0.22389	0.090
C(5)–Py	0.19576	−0.21105	0.016
C(5)–Pz	−0.27285	0.45767	0.184
C(6)–Py	0.42165	−0.25416	0.167
C(6)–Pz	−0.48053	0.43501	0.045

Table 1: Atomic partial charges and atomic orbital contributions to the HOMOs of **2** and **15**

Moreover, although some differences exist, especially for atoms C(5) and C(6) in the contribution of the six atoms of the conjugated system in both molecules, that might not be sufficient to explain the particular reactivity of **2**. More interestingly, the HOMO of **2** is less stable than its counterpart in **15** (–8.98276 eV *vs* –9.19167 eV). Either this difference is at the origin of the observed phenomenon, either, more simply, the strain of the cyclopentene moiety is the main factor responsible for it, and electronic ones have only minor roles if any.

In conclusion, we have provided evidence for the self-condensation of 1-acetyl-2-methyl cyclopentene **1** and the unusual role played by dimethyl sulfate, and for the autoxidation of dienone **2**; the latter phenomenon being an unknown process so far. Further theoretical and experimental investigations towards a better understanding of this autoxidation process are currently underway.

Acknowledgments: We would like to thank Dr. Robert Faure for NMR measurements at 400 MHz. We are also grateful to the French "Ministère des Affaires Etrangères" for a Franco-Algerian cooperation grant and to the Centre de Mesures Physiques de l'Ouest (Rennes) for mass spectra.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using Brucker AC 200 or Brucker AMX 400 spectrometers. All two-dimensional experiments were run at 400 MHz (^{1}H). IR spectra were obtained from Perkin-Elmer 298 or FTIR 1605 spectrometers. Mass spectra were recorded on a Varian MAT 311 mass spectrometer. Semi-empirical AM1 calculations[6] were performed on a IBM 3090 200 computer using the AMPAC package.[19] Molecular mechanics calculations were performed on a PC using the HyperChem Package.[20] Computed structures were obtained from AM1 data using EDMOL[21] software.

6-Methyl-4-(2'-methylcyclopent-1'-enyl)-bicyclo[4.3.0]non-3-en-2-one (2): To a premixed solution of potassium *tert*-butoxide (617 mg, 5.5 mmol) in *tert*-butanol (5 mL) was added **1** (620 mg, 5 mmol) in *tert*-butanol (1 mL). After 1 hour of refluxing, dimethyl sulfate (0.6 mL, 6 mmol) was added and the solution was refluxed for 5 hours. After hydrolysis with chilled water and pentane (10 mL of each) and extraction with ether of the aqueous phase, the organic phase was washed with brine and dried. Flash chromatography (ether:pentane 25:75) afforded **2** (200 mg, 35%). **2** (oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1, s), 2.46 (2, m), 2.43 (1, 1/2 AB, m), 2.40 (2, m), 2.21 (1, 1/2 AB, J = 17.7 Hz), 2.18 (1, t, J = 8.8 Hz), 2.00 (1, 1/2 AB, m), 1.85 (1, 1/2 AB, m), 1.80–1.65 (2, m), 1.82 (3, br. s), 1.60 (1, 1/2 AB, m), 1.45 (1, 1/2 AB, m), 1.05 (3, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.1 (s), 155.9 (s), 142.9 (s), 134.8 (s), 123.2 (d), 55.8 (d), 44.3 (s), 40.9 (t), 38.9 (t), 37.1 (t), 35.4 (t), 28.5 (t), 25.9 (q), 22.0 (t), 21.4 (t), 16.4 (q); IR (neat) 1655, 1610 cm^{-1}; HRMS calcd for $C_{16}H_{22}O$ 230.1671, found 230.1662, *m/z* 230 (66), 215 (18), 202 (12), 173 (12), 148 (88), 133 (14), 122 (16), 120 (100), 105 (45), 92 (33), 91 (32).

6-Methyl-4-(2'-methyl-1',2'-oxacyclopentyl)-bicyclo[4.3.0]non-3-en-2-one (12) and 6-Methyl-4-(2',5'-dioxohexyl)-bicyclo[4.3.0]non-3-en-2-one (13). A solution of dienone **2** (0.52 mmol; 120 mg) in MeCN (2 ml) was stirred at room temperature under a positive atmosphere of molecular oxygen. The progress of the oxidation was monitored by TLC and ^{1}H 200 MHz. After 12 days, integration of the 6.6–5 6 ppm section of the NMR spectrum revealed the following ratio: **2**: 13%, **12**: 63%,

13: 11% along with 4% and 9% of two unknown products. A flash chromatography of the reaction mixture led to the isolation of **2** (10 mg; 8%), **12** (58 mg; 45%), and **13** (11 mg; 8%). **12** (oil): (1:1 mixture of 2 isomers): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.01 (1, br. s), 1.26 (3, s), 1.25 (3, s), 1.09 (3, s), 1.05 (3, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.6 and 201.5 (s), 157.0 and 156.9 (s), 124.0 and 123.6 (d), 72.3 and 72.0 (s), 71.7 and 71.5 (s), 56.6 and 56.2 (d), 45.0 and 44.3 (s), 39.6 and 38.7 (t), 36.1 and 35.9 (t), 33.1 (t), 30.2 and 30.1 (t), 28.9 and 28.5 (t), 26.6 and 26.0 (q), 22.4 and 22.1 (t), 19.3 and 19.2 (t), 15.1 and 15.0 (q); IR (neat) 1660, 1100 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_2$ 246.1619, found 246.1614, *m/z* 246 (74), 203 (20), 188 (17), 175 (16), 149 (12), 136 (17), 122 (19), 121 (39), 105 (32), 95 (20), 93 (30), 91 (24), 81 (24), 79 (32), 67 (29), 43 (100). **13** (oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.53 (1, s); 2.77 (2, t, J = 7.1 Hz); 2.51 (2, t, J = 7.0 Hz); 2.39 (2, broad s); 2.14 (3, s); 2.50–2.10 (9, m); 1.09 (3, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.4 (s); 204.3 (s); 202.2 (s); 151.3 (s); 129.6 (d); 56.7 (d); 44.3 (s); 42.4 (t); 39.1 (t); 37.4 (t); 31.7 (t); 30.0 (q); 28.5 (t); 25.8 (q); 22.2 (t); 17.9 (t); IR (neat) 1712, 1672, 1372 cm^{-1}.

2-(1'-Cyclopentenyl)-5-cyclopentylidene-2-methyl cyclopentanone (8), 2,5-bis (cyclopentylidene) cyclopentanone (9) and 2-(1'-cyclopentenyl)-2-methyl cyclopentanone (10): To a premixed solution of potassium *tert*-butoxide (16.3g, 0.145 mol) in *tert*-butanol (100 mL) was added **7** (10 g, 0.158 mol) in *tert*-butanol (50 mL). After 1 hour of refluxing, dimethyl sulfate (15.13 mL, 0.158 mol) was added and the solution was refluxed for 4 hours. After hydrolysis with chilled water and pentane (150 mL of each) and extraction with ether of the aqueous phase, the organic phase was washed with brine and dried. Flash chromatography (ether:pentane 5:95) afforded **8** (1.935 g; 19%) and 1.3:1 mixture of **9**:**10** (1.804 g) (further separation enabled the obtention of pure samples of **9** and **10**): **8** (oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.43 (1, broad s); 2.79 (2, broad s); 2.44 (2, m); 2.35–2.18 (6, m); 1.90–1.60 (8, m); 1.18 (s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.3 (s); 159.6 (s); 145.6 (s); 127.3 (s); 124.8 (d); 52.1 (s); 34.2 (t); 33.4 (t); 32.5 (t); 32.3 (t); 317 (t); 26.8 (t); 25.9 (t); 25.1 (t); 23.2 (t); 21.9 (q); IR (neat) 1740, 1710, 1640, 1250, 1170 cm^{-1}; HRMS calcd for $C_{16}H_{22}O$ 230.1671, found 230.1662, *m/z* 230 (35), 215 (32), 108 (34), 93 (81), 91 (46), 84 (29), 79 (53), 77 (30), 67 (30), 55 (100); Elem. Anal. calcd for $C_{16}H_{22}O$ C: 83.42, H: 9.63; found C: 82.70, H: 9.72. **9** (oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60 (4, m); 2.25 (4, m); 2.00 (4, m); 1.45 (8, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 194.7 (s); 156.5 (s); 130.6 (s); 33.5 (t); 31.6 (t); 26.6 (t); 25.3 (t); 24.8 (t); IR (neat) 1740, 1700, 1650, 1630, 1260 cm^{-1}; HRMS calcd for $C_{15}H_{20}O$ 216.1514, found 216.1519; Elem. Anal. calcd. for $C_{15}H_{20}O$ C: 83.29, H: 9.32, found C: 83.24, H: 9.17. **10** (oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.24 (1, m); 2.18–2.00 (6, m); 1.75–1.55 (6, m); 0.97 (3, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 219.7 (s); 144.3 (s); 125.2 (d); 50.8 (s); 37.0 (t); 36.0 (t); 32.0 (t); 31.2 (t); 23.0 (t); 21.1 (q); 18.6 (t); HRMS calcd for $C_{11}H_{16}O$ 164.1201, found 164.1194.

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