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A three-carbon (n+1+2) ring expansion method for the synthesis of macrocyclic enones. Application to muscone synthesis

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This paper is dedicated to Professor Waldemar Adam on the occasion of his 75th birthday

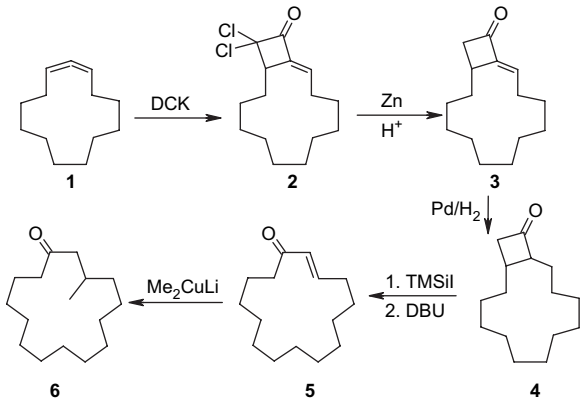
ABSTRACT

The three-carbon ring expansion methodology commences with the preparation of a cyclic allene (C9, C11, C13), readily available from the corresponding cycloalkene via dibromocarbene addition and subsequent treatment with methyllithium. Dichloroketene addition to the cyclic allene regioselectively provides the [2+2] cycloadduct, which is reductively dechlorinated with zinc in methanol. The resulting cyclobutanone is then catalytically hydrogenated; cyclobutanone ring opening is affected with trimethylsilyl iodide; immediate dehydroiodination of the resulting β-iodocycloalkanone with diazabicycloundecane (DBU) provides the corresponding macrocyclic enone. The 15-membered enone was converted to *d*,*l*-muscone with $(CH_3)_2CuLi$.

1. Introduction

Macrocyclic ring synthesis has become increasingly important due to the abundance of large rings in various naturally occurring systems.[1] Muscone and its 3-demethyl analog exaltone (cyclopentadecanone) are prominent members of the class of macrocyclic musk odorants[2] and have been popular targets for demonstrating individually developed synthetic methodologies.[3] In the course of our studies on dichloroketene cycloadditions,[4a–d] we have combined a number of well-known reactions into a straightforward and practical three-carbon ring expansion methodology[5] starting from the readily available cycloalkenes and featuring dichloroketene additions to cyclic allenes.

This paper describes the applicability of this methodology to the synthesis of 11-, 13-, and 15-membered cyclic enones, as well the naturally occurring muscone, the odorous principle of musk.[6] The muscone synthesis commences with the commercially available cyclododecene. The ring expansion sequence utilizes consecutive one- and two-carbon ring homologations (Scheme 1).[7]



Scheme 1.

2. Results and discussion

Cyclotrideca-1,2-diene (**1**), obtained in high yield from cyclododecene via the dibromocarbene adduct and subsequent treatment with methyllithium,[8] was reacted with a slight excess of dichloroketene (DCK),[9] generated in situ from trichloroacetyl chloride and activated zinc in the presence of $POCl_3$ in diethylether at room temperature;[10,11] agitation of the mixture was provided by an ultrasound bath.[12] The ^{1}H NMR spectrum of the cycloadduct showed a 7.5:1 mixture of two stereoisomers (total yield 83% after chromatography on silica gel). The major product turned out to be the expected (*E*)-isomer, whereas the minor isomer was (*Z*), according to its characteristic ^{1}H NMR spectrum. Although their separation was not necessary for the subsequent synthetic protocol, analytical samples of both isomers were obtained by careful column chromatography (the (*Z*)-isomer eluted faster than the (*E*)-isomer) on silica gel and characterized by spectroscopy. The reductive dechlorination of the cycloadduct with simultaneous hydrogenolysis of the double bond with H_2/Pd/C in ethyl acetate solution in a single step was attempted next. Presumably due to catalyst poisoning by HCl, only partial reduction could be realized

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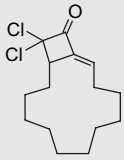
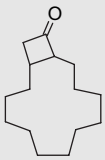
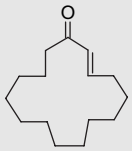
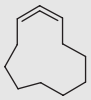
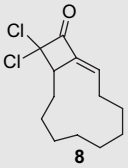
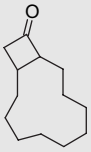
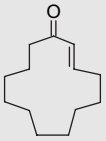
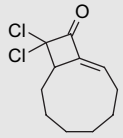
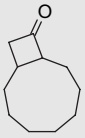
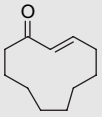
Table 1
Macrocyclic enones from cyclic allenes

Entry	Cyclic allene	DCK-adduct		Cyclobutanone[a]		Macrocyclic enone	
1	 **1**	 **2**	90%	 **4**	78%	 **5**	72%
2	 **7**	 **8**	82%	 **9**	86%	 **10**	75%
3	 **11**	 **12**	77%	 **13**	83%	 **14**	67%

[a] Overall yields of compounds **4**, **9**, and **13** for the two-step reductive dechlorination–catalytic hydrogenation sequence.

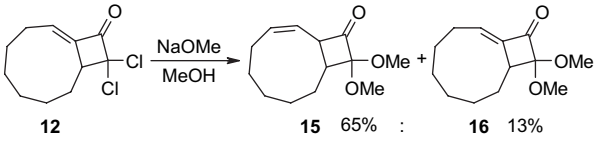
under these conditions leading to the corresponding α-chlorocyclobutanone (two isomers). [13] In an attempt to circumvent this problem the catalytic reduction was repeated in the presence of triethylamine; however, this variation proved unsatisfactory in terms of the isolated yield on the fully reduced cyclobutanone (35%) as well as problems separating **4** from undesired side products. The remaining chlorine atom was, therefore, reduced with zinc in acetic acid at 90 °C in an overall yield of 78% in the two-step reduction sequence. This reduction protocol was abandoned in favor of a much more efficient route described below.

The chlorine atoms in **2** were selectively reduced with zinc in methanol, saturated with NH_4Cl[14] to give the α,β-unsaturated cyclobutanone **3**; catalytic hydrogenation of **3** in ethyl acetate over Pd/C again delivered a mixture of both isomers of **4** (75% cis, 25% trans) in 78% overall yield, starting from **2**. The bicyclo[11.2.0]-pentadecan-13-one (**4**) thus obtained gave a satisfactory elemental analysis for the $C_{15}H_{26}O$ composition. Upon treatment of this mixture with KOH in methanol at room temperature, complete conversion of the cis isomer to the trans isomer took place. The trans stereochemistry in **4** was inferred from the coupling constants[15,16] between the cyclobutanone ring hydrogens, obtained from selective decoupling experiments. Moreover, inspection of Dreiding models of the two isomers suggests that the trans isomer is indeed the less strained, thus thermodynamically more stable isomer. The preference for the trans stereochemistry has also been observed in α,α-dimethylcyclobutanones fused to nine-membered rings.[17,18]

The cyclobutanone cleavage in **4** was realized with trimethylsilyl iodide in CCl_4 in the presence of metallic mercury according to Miller and McKean's method.[19] The resulting 3-iodocyclopentadecanone[20] was treated without further purification with an equimolar amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 solution at room temperature to furnish (*E*)-2-cyclopentadecen-1-one **5**[21] (76% from **4**). Finally, treatment of **5** with lithium dimethylcuprate in diethylether at −25 °C gave an 85% yield of *d*,*l*-muscone (**6**). We have successfully applied the three-carbon ring expansion methodology described above to the synthesis of two other macrocyclic enones, (*E*)-2-cycloundecen-1-one (**14**) and (*E*)-2-cyclotridecen-1-one (**10**), respectively (Table 1).

On an interesting note, the DCK–cylonona-1,2-diene adduct **12**[22] was subjected to reaction with NaOMe in methanol. It was known that α,α-dihalocyclobutanones undergo ring cleavage to γ,γ-dihalocarboxylic acids with base, however, cis-fused α,α,-dichlorocyclobutanones undergo quantitative ring contraction into bifunctional cyclopropanes.[23] On the other hand, Harding et al. found that the cis-fused α,α-dichlorocyclobutanone to cyclohexene gave, upon treatment with NaOMe in a 'Cine' substitution to give the methoxychlorocyclobutanones.[24] The question was, what role the α,β-unsaturation at the cyclobutanone ring of the bicyclic framework would play during the base attack.

Upon treatment of **12** with sodium methoxide at room temperature, the solution immediately turned red. After stirring at room temperature and monitoring the progress of the reaction by TLC, the reaction was stopped, and after work-up and column chromatography on silica gel, two fractions were isolated in a ratio of 5:1, to which the structures **15** and **16** were assigned, respectively, based on spectroscopic data. Compound **16** clearly stems from a double Cine substitution, whereas compound **15** is a secondary product derived from **16** via base-catalyzed double bond isomerization. A few cases of similar double-Cine substitutions in DCK-adducts onto ordinary alkenes have previously been observed (Scheme 2).[25–29]



Scheme 2.

3. Conclusion

In summary, we have developed a convenient and general three-carbon ring expansion methodology starting with readily available cycloalkenes. After a well-documented one-carbon expansion to the corresponding cyclic allene, regioselective dichloroketene addition, followed by reduction of the chlorine

atoms and double bond, the ring opening with TMSI/Hg, and immediate dehydroiodination completes the sequence. In the case of the 15-membered system, the enone was converted to *d*,*l*-muscone by reaction with Me_2CuLi.

4. Experimental

4.1. General

^1H NMR spectra were obtained with a GE-Nicolet QE-Plus 300 MHz and Bruker Avance DRX 300 MHz spectrometers, using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise specified. IR spectra were obtained with a Nicolet 20DBX FT-IR instrument. Non-deuterated solvents were dried and distilled before use. The cyclic allenes **1**, **7**, and **11** can readily be synthesized from the corresponding cycloalkenes by the two-step protocol according to Moore and Ward, as well as Skattebol's method by dibromocarbene addition followed by treatment of the adduct with methyllithium at −20 °C. All three cyclic allenes used in this study were previously reported in literature.[30] For the dibromocarbene additions, we used the Makosza method employing a two-phase system using a phase-transfer catalyst.[31] Full details for the two-step protocol are described below.

4.2. General procedure for the synthesis of allenes

(a) Dibromocarbene additions. To an ice-cold solution of 20 mmol of cycloalkene, bromoform (15 g, 60 mmol), 145 mg of benzyltriethylammonium chloride (TEBA), and 1 mL of ethanol was added dropwise a 50% aqueous KOH solution (from 10 g KOH), with efficient mechanical stirring (Hershberg-stirrer). After stirring the brown mixture for 12 h, 100 mL of H_2O was added, and the product extracted with *n*-hexane (5×30 mL). The combined organic extracts were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and the solvent rotaevaporated. The residue was purified by Kugelrohr distillation. Yields: 9,9-dibromobicyclo[6.1.0]nonane (90%), 11,11-dibromo[8.1.0]undecane (76%), and 13,13-dibromobicyclo[10.1.0]tridecane (84%).

(b) Treatment of the diboromocarbene adducts with MeLi. To a solution of 20 mmol of the diboromocarbene adduct in 40 mL of anhydrous ether was added dropwise 27 mL of MeLi (38 mmol, 1.4 M) at −78 °C under a dry nitrogen atmosphere. After stirring for15 min, the solution was allowed to warm to room temperature (22 °C). Water (40 mL) was added dropwise, and the ether layer was separated, washed once with saturated $NaHCO_3$ solution, twice with brine (each 20 mL), and dried over anhydrous Na_2SO_4. The solvent was rotoevaporated and the product isolated by Kugelrohr distillation.

*4.2.1. 1,2-Cyclononadiene (**11**, 72%)*

^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (m, 2H), 2.20 (m, 4H), 1.2–1.9 (m, 8H) ppm.

*4.2.2. 1,2-Cycloundecadiene (**7**, 68%)*

^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (m, 1H), 1.8–2.2 (m, 4H), 1.2–1.8 (m, 12H) ppm.

*4.2.3. 1,2-Cyclotridecatriene (**1**, 82%)*

^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (m, 2H), 2.1 (m, 4H), 1.0–1.7 (m, 16H) ppm.

4.3. Dichloroketene additions

In a 250 mL two-necked flask equipped with a reflux condenser carrying a drying tube and a 50 mL pressure-equalizing dropping funnel was placed a solution of 0.01 mol of cyclic 1,2-diene in 50 mL dry ether, and 1.71 g of zinc dust was added. The suspension was partially submerged in a Branson B-321 ultrasonic cleaner (50/60 Hz, 117 V) filled 95% with water in a place that produced maximum agitation. To this suspension, 3.05 g (0.017 mol) of freshly distilled trichloroacetyl chloride in 25 mL dry ether was added dropwise within 30 min while sonication continued. Ice was added occasionally to the water bath to maintain the bath temperature between 15 and 20 °C. After the completion of the reaction (ca. 60 min), it was quenched with wet ether (10 mL) and the reaction mixture suction-filtered through Celite. The filtrate was washed successively with water (2×20 mL), saturated aqueous bicarbonate (5×20 mL), and brine solution (2×20 mL). After drying the ether solution over Na_2SO_4, the solvent was evaporated in vacuo, and the product isolated by column chromatography on silica gel, eluting with pet. ether/CH_2Cl_2 (90:10).

*4.3.1. (E)-11,11-Dichlorobicyclo[7.2.0]undec-8-en-10-one (**12**)*

Yield 77%; mp 62–64 °C (from pet. ether). Though this compound had been described by Brady et al., its ^1H NMR was recorded on a lower resolution instrument. Below, high resolution NMR spectra of **12** and its IR data are described: ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (ddd, *J*=2.8, 6.9, 9.6 Hz, 1H), 3.43 (dm, *J*=12.0 Hz, 1H), 2.2–2.5 (m, 3H), 2.1 (m, 1H), 1.7 (m, 2H), 1.3–1.6 (m, 6H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 187.0, 146.2, 141.7, 88.5, 58.8, 31.0, 29.3, 26.5, 25.9, 25.7, 22.6 ppm; FTIR (KBr): 2930, 2860, 1772.5, 1660, 1457, 911, 747 cm^{-1}.

*4.3.2. (E)-13,13-Dichlorobicyclo[9.2.0]tridec-10-en-12-one (**8**)*

Yield 82%; ^1H NMR ($CDCl_3$, TMS): δ 6.8 (m, 1H), 3.5 (m, 1H), 2.1–2.5 (m, 4H), 1.3–1.7 (m, 8H) ppm; FTIR (film): 2928, 2859, 1774, 1658, 1455, 1442, 910, 751 cm^{-1}. Anal. Calcd for $C_{13}H_{18}Cl_2O$: C, 59.78; H, 6.95; Cl, 27.15. Found: C, 59.76; H, 6.94; Cl, 26.96.

*4.3.3. (E)-15,15-Dichlorobicyclo[11.2.0]pentadec-12-en-14-one (**2a**)*

Yield 79%; ^1H NMR (300 MHz, $CDCl_3$) δ 6.8 (ddd, *J*=2.9, 6.1, 10.3 Hz, 1H), 3.57 (m, 1H), 2.22 (m, 2H), 1.97 (m, 1H), 1.8 (m, 1H), 1.2–1.7 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 143.5, 142.4, 87.7, 55.9, 29.9, 27.9, 26.4, 26.1, 25.9, 25.83, 25.81, 24.6, 24.5, 24.2 ppm; FTIR (film): 2932, 2860, 1774, 1655, 1463, and 1446 cm^{-1}. Anal. Calcd for $C_{15}H_2H_2Cl_2O$: C, 62.29; H, 7.67; Cl, 24.51. Found: C, 62.26; H, 7.66; Cl, 24.46.

*4.3.4. (Z)-15,15-Dichlorobicyclo[11.2.0]pentadec-12-en-14-one (**2b**)*

Yield 11%; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (ddd, *J*=2.1, 5.1, 11.6 Hz), 3.15 (m, 1H), 3.0 (m, 1H), 2.1 (m, 2H), 1.95 (m, 1H), 1.2–1.75 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 146.5, 143.5, 86.8, 55.8, 31.0, 30.5, 27.1, 26.8, 26.2, 25.3, 25.1, 24.8, 23.7, 23.0 ppm. Anal. Calcd for $C_{15}H_2H_{22}Cl_2O$: C, 62.29; H, 7.67; Cl, 24.51. Found: C, 62.28; H, 7.64; Cl, 24.58.

4.4. Reductive dechlorination of allene–DCK cycloadducts

To a solution of 0.1 mol of the DCK–allene cycloadduct in 100 mL of methanol (previously saturated with NH_4Cl) 2 g of zinc dust was added, and the mixture was stirred at room temperature overnight. The solid was removed by suction filtration, the filter cake washed with 50 mL of ether. To the filtrate, another 150 mL of ether was added, and the solution transferred to a separatory funnel and extracted sequentially with each 200 mL of water, 200 mL of brine, and 100 mL of saturated aqueous $NaHCO_3$ solution, respectively. The ethereal solution was then dried over $MgSO_4$, and the solvent rotaevaporated to give a yellowish oil that was purified by flash chromatography (20% EtOAc/pet. ether) on silica gel.

4.4.1. (E)-Bicyclo[7.2.0]undec-8-en-10-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.3 (m, 1H), 3.1 (dd, J=9.0, 17.1 Hz, 1H), 2.95 (m, 1H), 2.48 (dd, 4.8, 17.1 Hz, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.3–1.7 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6, 153.4, 130.3, 51.6, 37.1, 33.25, 29.8, 28.9, 27.2, 26.2, 22.9 ppm; FTIR (neat): 2923, 2861, 1750, 1669, 1450, 1120.4, 1049 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.48; H, 9.86.

4.4.2. (E)-Bicyclo[9.2.0]tridec-10-en-12-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25 (ddd, J=2.47, 3.48, 12 Hz, 1H), 3.15 (m, 1H), 3.0 (dd, J=8.9, 16.9 Hz, 1H), 2.56 (dd, 4.72, J=16.9 Hz, 1H), 2.35 (m, 1H), 2.1 (m, 1H), 1.2–1.7 (m, 14H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 199.3, 151.4, 131.7, 49.1, 35.1, 32.4, 26.9, 26.7, 26.1, 26.0, 24.5, 23.6 ppm; FTIR (neat): 2925, 2860, 1751, 1656, 1469, 1445, 1122 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.24; H, 10.45.

*4.4.3. (E)-Bicyclo[11.2.0]pentadec-12-ene-14-one (**3**)*

Mp 39–40 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25 (ddd, J=2.5, 5.4, 9.4 Hz, 1H), 3.2 (m, 1H), 3.0 (dd, J=9.4, 17.4 Hz, 1H), 2.7 (dd, J=5.4, 17.4 Hz, 1H), 2.15 (m, 2H), 1.9 (m, 1H), 1.2–1.7 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.2, 150.8, 132.1, 48.6, 33.8, 31.3, 26.8, 26.7, 26.5, 26.0, 24.7, 24.6, 24.4, 23.0 ppm; FTIR: 2927, 2856, 1749, 1663 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.73; H, 10.94.

4.5. General procedure for the catalytic hydrogenations of the α,β-unsaturated cyclobutanones

A solution of 0.1 mol of unsaturated compound obtained by reductive dechlorination of the DCK-adduct was dissolved in 25 mL of ethyl acetate, and hydrogenated over 0.1 g of Pd/C. The progress of hydrogen uptake was monitored by means of a burette. After filtration of the catalyst, the solvent was rotaevaporated to give the fully saturated bicyclic cyclobutanone as a mixture of cis–trans isomers. Though for the TMSI-promoted cyclobutanone ring opening it was not necessary to isomerize the cis–trans mixtures to the more stable trans isomers, small amounts were subjected to base-catalyzed isomerization for characterization purposes.

4.6. General procedure for the base-catalyzed isomerization of the cis–trans mixtures to the trans isomers

Bicyclic cyclobutanone (0.01 mol) dissolved in 5 mL of methanol was added dropwise to a solution of 0.5 g of KOH in 10 mL of methanol at 0 °C. The solution was stirred at room temperature for 30 min, then 50 mL water and 20 mL of ether were added, the layers separated, the aqueous layer extracted with two 20 mL portions of ether, the combined ether extracts dried over $MgSO_4$, and the solvent rotaevaporated. The residue was purified by preparative TLC, eluting with 15% EtOAc/hexane.

*4.6.1. trans-Bicyclo[7.2.0]undecan-10-one (**13**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.0 (ddd, J=2.1, 8.1, 16.8 Hz, 1H), 2.95 (m, 1H), 2.65 (ddd, J=2.1, 9.3, 16.8 Hz, 1H), 2.15 (m, 1H), 2.08 (m, 1H), 1.85 (m, 1H), 1.25–1.7 (m, 12H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 199.6, 68.5, 52.6, 37.4, 35.3, 28.4, 27.9, 26.7, 26.6, 26.0 ppm; FTIR (film): 2919, 2860, 1784, 1476, 1448, 1136 cm^{-1}. This compound has previously been prepared by Ghosez et al.[18]

*4.6.2. trans-Bicyclo[9.2.0]tridecan-12-one (**9**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.1 (ddd, J=2.6, 8.8, 17.5 Hz, 1H), 2.9 (m, 1H), 2.65 (ddd, J=2.8, 7.2, 17.5 Hz, 1H), 2.18 (m, 1H), 1.9 (2H), 1.2–1.65 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212, 66.2, 51.4, 35.3, 32.5, 27.1, 26.6, 26.2, 25.9, 25.7, 24.9, 22.9 ppm; FTIR (film): 2929, 2859, 1778, 1459, 1445, 1160 cm^{-1}. A cis–trans mixture of this compound has previously been reported by an alternate route, see Ref. 32.

*4.6.3. trans-Bicyclo[11.2.0]pentadecan-14-one (**4**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (ddd, J=2.8, 8.7, 17.6 Hz, 1H), 2.85 (m, 1H), 2.6 (ddd, J=3.3, 7.2, 17.6 Hz, 1H), 2.0 (m, 1H), 1.8 (m, 2H), 1.1–1.7 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.3, 50.3, 36.5, 31.3, 28.2, 27.2, 26.1, 25.8, 25.7, 25.5, 25.4, 25.1, 23.9 ppm; FTIR (film): 2930, 2861, 1779, 1462, 1450, 1150 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.06; H, 11.77.

4.7. General procedure for the synthesis of the cyclic enones

Cyclobutanone (1 mmol) was dissolved in 2 mL of CCl_4 and 150 mg of Hg was added. The mixture was kept under an argon atmosphere while freshly distilled TMSiI (0.6 g, 3 mmol) was added, and the mixture stirred for 2 h. The mixture was then diluted with 25 mL of ether, and washed with 5% Na_2SO_3, followed by 5 mL of $NaHCO_3$, dried, and the solvent rotaevaporated. The β-iodocycloalkanone was dissolved in 10 mL of dry CH_2Cl_2 and 1 mmol of DBU was added dropwise at 0 °C. The solution was stirred for 30 min at room temperature, then 10 mL of H_2O was added, the organic layer washed successively with 5% HCl and $NaHCO_3$, the solution dried over $MgSO_4$, the filtrate rotaevaporated, and the residue purified by column chromatography on silica gel (15% EtOAc/hexane) to give the macrocyclic enone. During the TMSI-promoted ring opening reaction of **9**, a small aliquot was isolated and analyzed by ^{1}H NMR spectrum. The β-iodocyclotridecanone derivative was clearly discernible in the spectrum due to the characteristic 3° β-hydrogen at 4.3 ppm (m, 1H), and the α-CH_2 group exhibiting an AB system at 2.7 (dd, J=9.2, 17.2 Hz, 1H) and 2.15 (dd, J=7.0, 17.2 Hz, 1H).

*4.7.1. (E)-Cycloundec-2-enone (**14**)*

Yield 67%; ^{1}H NMR δ 6.8 (dt, J=7.8, 16.5 Hz, 1H), 6.15 (dt, J=1.2, 16.5 Hz), 2.6 (t, J=6.6 Hz, 2H), 2.25 (m, 2H), 1.66 (m, 4H), 1.3 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 149.1, 134.3, 37.3, 33.9, 28.1, 26.4, 26.1, 23.9, 23.0, 22.4 ppm; FTIR (film): 2931, 2859, 1690, 1668, 1165, 1463, 1445, 1212, 985 cm^{-1}; see Ref. 33.

*4.7.2. (E)-Cyclotridec-2-one (**10**)*

Yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.8 (dt, J=7.5, 15.3 Hz, 1H), 6.15 (dt, J=1.2, 15.3 Hz, 1H), 2.45 (m, 2H), 2.2 (m, 2H), 1.67 (m, 2H), 1.53 (m, 2H) 1.2–1.3 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 149.3, 132.8, 39.2, 33.4, 27.4, 27.3, 26.9, 26.7, 26.6, 26.1, 25.9, 25.8 ppm; FTIR (film): 2972, 2924, 2865, 1689, 1659, 1622, 1464, 1442, 1387, 1350, 1119, 912.6, 740 cm^{-1}; see Ref. 34.

*4.7.3. (E)-Cyclopentadec-2-one (**5**)*

Yield 73%. All spectral data were identical to those reported in literature, see Refs. 3 and 35.

*4.7.4. d,l-Muscone (**6**)*

Dried CuI (2.8 g, 14.7 mmol) was placed in a 50 mL two-necked round-bottomed flask, equipped with a magnetic stir bar and a rubber septum. Dry ether (25 mL) was added to the flask and the mixture was cooled to ca. −25 °C under an argon atmosphere. To the stirred suspension was added MeLi (23 mL of a 1.18 M ethereal solution, 26.7 mmol) with stirring. The mixture was stirred for 30 min, a solution of enone 5 (1 g, 45 mmol) in 10 mL of ether was added over a period of 25 min. The mixture was stirred for 1 h at −25 °C, and 25 mL of H_2O and 3 N HCl were added. The mixture was extracted with 3×25 mL of ether, the combined extracts were washed with $NaHCO_3$ solution, then Na_2SO_3 solution, and finally with brine. After drying over $MgSO_4$, the solvent was rotaevaporated. The resulting yellowish oil was purified by column

chromatography on silica gel, eluting with 15% EtOAc/pet. ether to give 1.1 g of *d,l*-muscone (85%), identical in all respects to an authentic sample.

4.8. Reaction of 12 with NaOMe

(*E*)-11,11-Dichlorobicyclo[7.2.0]undec-8-en-10-one (1 g, 4.3 mmol) was dissolved in 20 mL of MeOH. This solution was added dropwise to a NaOMe solution (preformed from 0.2 g, 8.3 mmol of Na and 20 mL of MeOH) at 0 °C. Upon addition, the color of solution immediately turned red. The mixture was stirred at 0 °C for 30 min, then heated to 50 °C for 1 h. It was poured onto 100 mL of ice-water, acidified with 10% HCl, extracted with 3×50 mL of ether. The combined ether extracts were dried over $MgSO_4$, the solvent rotaevaporated, and the yellowish waxy material was purified by column chromatography on silica gel (15% EtOAc/pet. ether) to give two products.

*4.8.1. (E)-11,11-Dimethoxybicyclo[7.2.0]undec-8-en-10-one (**16**)*

Yield 13%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.6 (ddd, J=2.9, 7.4, 9.6 Hz, 1H), 3.5 (s, 3H), 3.3 (s, 3H), 3.0 (m, 1H), 2.35 (m, 2H), 2.0 (m, 2H), 1.4–1.7 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 147.8, 138.3, 121.9, 52.9, 51.6, 51.2, 30.4, 29.6, 26.7, 26.5, 26.4, 22.5 ppm. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.60; H, 9.95.

*4.8.2. (Z)-11,11-Dimethoxybicyclo[7.2.0]undec-7-en-10-one (**15**)*

Yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (dd, J=6.8, 10.5 Hz, 1H), 5.56 (ddt, J=1.7, 6.2, 10.5 Hz, 1H), 3.85 (dd, J=6.8, 10.8 Hz, 1H), 3.4 (s, 3H), 3.3 (s, 3H), 2.2 (m, 2H), 2.1 (m, 2H), 1.85 (5, 1H), 1.2–1.7 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 133.1, 125.3, 58.5, 53.5, 50.4, 46.7, 27.5, 27.1, 26.6, 26.0, 21.8 ppm; FTIR (film): 3012, 2931, 2861, 2834, 1785, 1445, 1256, 1210, 1125, 1078, 1044, 997, 909, 797, 727 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.65; H, 9.96.

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