Synthesis of Polyfunctionalized Bicyclo[5.3.1]undecadiene Ring Systems Using a Two-Carbon Ring-Expansion of Cyclobutene Intermediates

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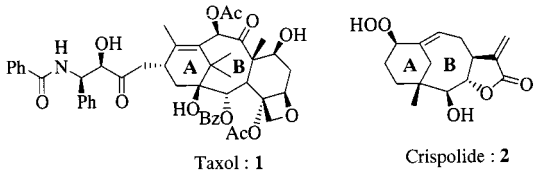
The $ZrCl_4$-catalyzed [2+2] cycloaddition of the silyl enol ether derived from monoprotected bicyclo[3.3.1]nonane-2,6-dione **7** with ethyl propynoate led after acidic treatment to the cyclobutene derivative **12**. Treatment of the latter with HBF_4 in refluxing ethanol smoothly afforded the two-carbon ring-expansion product **13**. On the other hand, the enolate of the β-oxobicyclo[3.3.1]nonane ester **14** has been found to react with electrophilic acetylenes [ethyl propynoate, dimethyl acetylenedicarboxylate (DMAD)] to afford bicyclo[5.3.1]undecadiene derivatives **15**, **16**, most probably through the intermediacy of a tricyclo[5.3.1.$0^{2,5}$]undecene ring system.

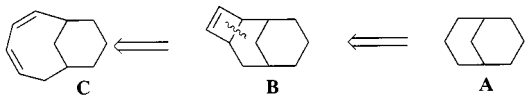
Introduction

Bicyclo[5.3.1]undecane ring systems are widely occurring substructures in numerous natural products, such as taxol[1] (**1**) and crispolide[2] (**2**). Owing to the potent bioactivity of the taxoid family and related compounds, there has been intense effort in the development of new and efficient methodologies leading to the AB bicyclic framework during the last twenty years[3] (Scheme 1).



Scheme 1

Among the many strategies developed, only a few led to the desired bicyclic **AB** system by a two-carbon ring-enlargement induced by the fragmentation of small-ring intermediates.[4] Our interest in the reactivity of electrophilic cyclobutenes[5,6] has led us to the results reported herein concerning the preparation of polyfunctionalized bicyclo[5.3.1]undecane ring systems **C** starting from bicyclo[3.3.1]nonane derivatives **A**. A key step in this transformation is a two-carbon ring-expansion reaction of condensed cyclobutene derivatives **B**[6a] (Scheme 2).



Scheme 2

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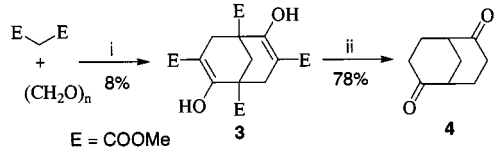
Results and Discussion

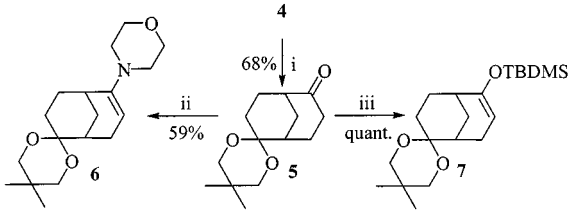
Bicyclo[3.3.1]nonane-2,6-dione (**4**) was chosen as the starting material. Diketone **4** was found to be readily available in two steps, specifically a condensation reaction between dimethyl malonate and paraformaldehyde leading to Meerwein's ester **3**[7] followed by an acidic dealkyloxycarbonylation reaction[8] (HCl/H_2O/AcOH, 1:1:3; reflux). The modest overall yield (ca. 6%) is compensated by the fact that this synthesis could be performed on a molar scale starting from inexpensive commercially available compounds (Scheme 3).



i : 1. piperidine, benzene, reflux. 2. MeONa/MeOH, 20°C to reflux.
ii : HCl/H_2O/AcOH : 1/1/3, reflux.

Scheme 3

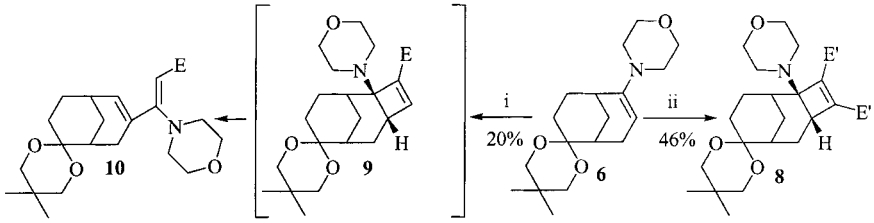
After monoprotection of bicyclo[3.3.1]nonane-2,6-dione (**4**) (with 2,2-dimethylpropane-1,3-diol, PTSA, Dean−Stark apparatus, benzene; 68% yield), the ketone **5** was transformed either into the morpholino enamine **6** by using the procedure of Stork et al.[9] (morpholine, PTSA, Dean−Stark apparatus, benzene; 59% yield) or into the *tert*-butyldimethylsilyl enol ether **7** using the procedure of



i : PTSA, 2,2-dimethylpropane-1,3-diol, Dean-Stark, benzene, reflux.
ii : PTSA, Morpholine, Dean-Stark, toluene, reflux.
iii: TBDMSOTf, NEt_3, CH_2Cl_2, 20°C.

Scheme 4

  1434−193X/01/0509−1753 $ 17.50+.50/0



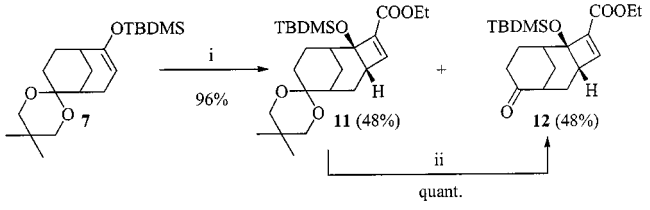
E = CO_2Et; E' = CO_2Me i : ethyl propynoate, toluene, 50°C ii : 50°C,DMAD, dioxane reflux

Scheme 5

Simchen et al.[10] (TBDMSOTf, NEt_3, CH_2Cl_2, 20 °C; quantitative yield) (Scheme 4). At this point, it should be noted that neither the pyrrolidinoenamine nor the trimethylsilyl enol ether of ketone **5** could be efficiently prepared under the same reaction conditions.

The addition of enamine **6** to dimethyl acetylenedicarboxylate (DMAD) afforded the expected aminocyclobutene diester **8** in 46% yield. However, when ethyl propynoate was used as the electrophilic acetylenic derivative, only a 20% yield of the aminodiene **10** could be isolated from a complex crude reaction mixture. Similar observations have previously been reported by Brannock et al.[11] and Reinhoudt et al.[12] in relation to the addition of 1-morpholino-1-cyclohexene to ethyl propynoate (Scheme 5).

On the other hand, the $ZrCl_4$-catalysed [2+2] cycloaddition[5a] of ethyl propynoate to the *tert*-butyldimethylsilyl enol ether **7** furnished both the protected and unprotected cyclobutene esters **11** and **12**. When DMAD was used as the electrophile, no cyclobutene compound was formed. To avoid further complication, ketal **11** was quantitatively converted into ketone **12** by treatment with dilute hydrochloric acid without cleavage of the TBDMS protecting group ($HCl/H_2O/THF$, 1:10:60) (Scheme 6).



i : ethyl propynoate, $ZrCl_4$, CH_2Cl_2/Et_2O, -78°C; ii: HCl /H_2O/THF : 1/10/60, 20°C

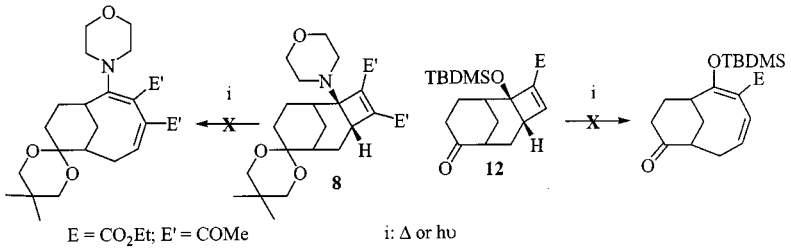
Scheme 6

In order to promote a ring-enlargement reaction, we first explored the use of the thermal reaction conditions previously described by Brannock and co-workers.[13] Unfortunately, in our hands, heating of the cyclobutenes **8** and **12** in various high boiling point solvents (xylene or mesitylene) did not generate the expected bicyclo[5.3.1]undecane ring systems. In each case, a small amount of starting material (less than 10%) was the sole identifiable material that could be isolated from the complex crude reaction mixture. Furthermore, when cyclobutene **12** was refluxed in a mixture of $AcOH/H_2O/THF$,[14] no bicyclo[5.3.1]undecane ring system was obtained and only unchanged starting material was recovered.

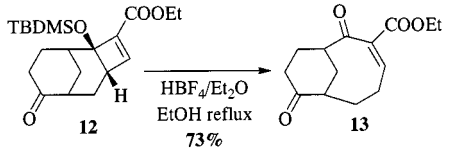
Another means of promoting the desired ring-enlargement reaction might have been a photoinduced ring-enlargement of stable cyclobutene intermediates. Surprisingly, using our previously reported reaction conditions[6b] (irradiation with an HPK-125 medium-pressure Hg lamp; pyrex or quartz photolysis apparatus; various solvents) the cyclobutene compounds **8** and **12** did not give the expected bicyclo[5.3.1]undecane ring systems and the unchanged starting materials were recovered quantitatively (Scheme 7).

To overcome this lack of reactivity, various reaction conditions were tested. It was found that the ring-enlargement reaction proceeded smoothly when cyclobutene **12** was treated with HBF_4 in refluxing EtOH, affording the bicyclo[5.3.1]undecane ring system **13** in 73% yield (Scheme 8).

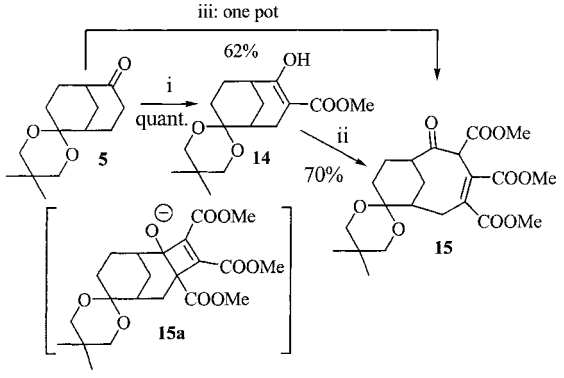
We also decided to study two-carbon ring-enlargement reactions induced by the reaction of an acetylenic ester (DMAD or ethyl propynoate) with enolates of cyclanones bearing an electron-withdrawing group in the β-position. Some examples of this have been reported previously, starting from β-oxo phosphonates,[15] β-oxo sulfonium ylides,[16] or β-oxo esters.[17] These transformations apparently involve an initial Michael-initiated ring-closure (MIRC)[18] reaction; the bridgehead electron-withdrawing group (e.g. phosphonate, sulfonium ylide, or ester) then promotes the fragmentation of the cyclobutene intermediate with generation of the corresponding two-carbon ring-enlargement compound. To the best of our knowledge, the cyclobutene intermediates have never been isolated. In order to obtain a bicyclo[5.3.1]undecadiene ring system, we studied the reactivity of acetylenic esters towards the enolate of the β-oxo ester derived from bicyclo[3.3.1]nonane-2,6-dione (**4**). Thus, the oxo ester **14** was quantitatively prepared by treating the ketone **5** with sodium hydride in neat dimethyl carbonate in the presence of a catalytic amount of methanol. Addition of compound **14** to a suspension of NaH in toluene generated the corresponding sodium enolate, which reacted at room temperature with DMAD to give the desired bicyclo[5.3.1]undecane ring system **15** in 70% yield. Compound **15** could also be prepared in a one-pot procedure, in which the sodium enolate of ketone **5** was successively treated with dimethyl carbonate and DMAD. Under these conditions, the triester **15** was readily isolated in 62% yield (Scheme 9). The structural assignment of compound **15** was



Scheme 7



Scheme 8



i : $(MeO)_2CO$, NaH, MeOH cat.,60°C; ii : a. NaH, toluene, 20°C. b. DMAD, 20°C;
iii: a: $(MeO)_2CO$, NaH, MeOH cat.,60°C; b: NaH, toluene, 20°C; c: DMAD, 20°C

Scheme 9

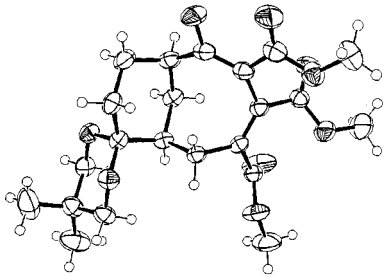
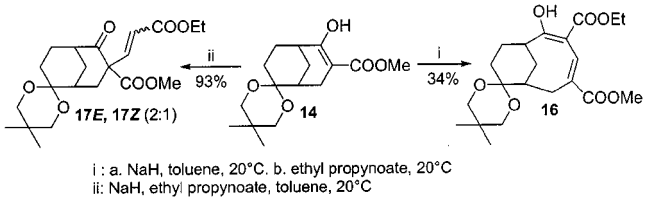


Figure 1. X-ray structure of compound **15**

confirmed by an X-ray crystal structure determination (Figure 1). It also seems reasonable to postulate the tricyclo[5.3.1.$0^{2,5}$]undecene ring system **15a** as the probable intermediate of the reaction.

When ethyl propynoate was used as the acetylenic ester instead of DMAD, the expected ring-enlargement product **16** was isolated in 34% yield. On the other hand, when β-oxo ester **14** was added to a suspension of sodium hydride in a mixture of ethyl propynoate and toluene, the ring-enlargement reaction did not take place, but instead the two Michael-type adducts (*E*)-**17** and (*Z*)-**17** [(*E*)/(*Z*) = 2:1; 93% yield] were generated very cleanly (Scheme 10). Besides ethyl propynoate and DMAD, other electrophilic acetylenes, e.g. ethynyl methyl ketone and ethyl phenylpropynoate, were also tested. However, in these cases, only uncharacterizable reaction mixtures were obtained.



i : a. NaH, toluene, 20°C. b. ethyl propynoate, 20°C
ii: NaH, ethyl propynoate, toluene, 20°C

Scheme 10

Conclusion

The results reported in this article shown that the "cyclobutene pathway" to bicyclo[5.3.1]undecane ring systems represents an interesting and useful synthetic strategy that complements other previously described methods. Our methodologies will be tested in the hope of finding new routes to bioactive analogues of the taxoid family. For example, work is in progress aimed at synthesizing the complete **ABC** tricyclic taxoid framework starting from the polyfunctionalized bicyclo[5.3.1]undecane ring systems described herein.

Experimental Section

General Remarks: Reactions were carried out under argon with magnetic stirring in degassed solvents. Diethyl ether and THF were distilled from sodium/benzophenone under nitrogen prior to use. CH_2Cl_2 was dried with P_2O_5 and distilled. − Thin-layer chromatography (TLC) was carried out on silica gel plates (Merck silica gel 60 F_{254}) and the spots were visualized under a UV lamp (254 nm or 360 nm) or by spraying with a solution of vanillin (25 g) in EtOH/H_2SO_4 (98:2; 1 L) followed by heating on a hot plate. For column chromatography, Merck silica gel 60 (40−60 μm) was used. − Melting points were measured with a Reichert hot stage. − IR spectra were recorded from samples in CCl_4 solution with a Perkin−Elmer IR 881 spectrophotometer. − UV/Vis spectra were recorded with samples in CH_3CN solution with a Perkin−Elmer UV-550 spectrophotometer. − ^1H NMR spectra were recorded with Bruker WP-200 and AC-200 (200 MHz) spectrometers; ^{13}C NMR spectra were recorded with the Bruker AC-200 instrument (50 MHz); the signal of the residual nondeuterated solvent was used as an internal reference (^1H NMR spectra: δ = 7.26 for $CDCl_3$ or δ = 7.16 for C_6D_6; ^{13}C NMR spectra: δ = 77.00 for $CDCl_3$ and δ = 128.02 for C_6D_6). Significant ^1H NMR spectroscopic data are listed in the order: chemical shift (δ) expressed in ppm downfield

from residual $CHCl_3$ in $CDCl_3$, multiplicity (s singlet, d doublet, t triplet, q quadruplet, m multiplet), number of protons, and coupling constants in Hz. Unless otherwise stated, products were recrystallized from diethyl ether/hexane mixtures. − Elemental analyses (C,H ±0.3%) were performed by the Laboratoire de Microanalyses of the Université Louis Pasteur in Strasbourg.

Meerwein's Ester 3: In a 1-L flask fitted with a Dean−Stark head, dimethyl malonate (200 g, 1.51 mol), paraformaldehyde (38 g, 1.19 mol), and piperidine (4 mL) were dissolved in benzene (350 mL). The reaction mixture was refluxed for 6 h. At room temperature, the benzene was slowly removed by distillation under reduced pressure (15 Torr/25 °C, then 0.1 Torr/25 °C when the crude product became too viscous). The sticky residue was redissolved in methanol (100 mL) and a freshly prepared solution of sodium methylate [Na (25 g, 1.10 mol) and MeOH (370 mL)] was quickly added. After a few minutes, the reaction mixture became increasingly pasty; MeOH (100 mL) was then added and the mixture was refluxed for 16 h. After cooling to room temperature, the solvents were removed under reduced pressure (0.1 Torr/25 °C). The residue was then poured into iced water (1500 mL) and extracted with Et_2O (3 × 200 mL). The aqueous layer was conserved and CO_2 was bubbled through it for 2 h. A pale-yellow precipitate was produced, which was collected by filtration, dried in vacuo, and recrystallized from methanol to afford the pure Meerwein tetraester **3** (33 g, 0.09 mol, 8%); colorless crystals, m.p. 174−175 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 2 H, CH_2), 2.87 (s, 4 H, CH_2), 3.77 (s, 6 H, $COOCH_3$), 3.78 (s, 6 H, $COOCH_3$), 12.17 (s, 2 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7 (2 C, CH_2), 35.3 (2 C, CH_2), 47.8 (2 C, −C−), 51.9 (2 C, $COOCH_3$), 52.7 (2 C, $COOCH_3$), 96.9 [2 C, (*E*)-*C*=COH], 168.2 [2 C, (*E*)-C=*C*OH], 172.0 (2 C, *C*$OOCH_3$), 172.5 (2 C, *C*$OOCH_3$). − UV (CH_3CN): λ_{max} = 252 (ε = 17300). − $C_{17}H_{20}O_{10}$ (384.34): calcd. C 53.13, H 5.25; found C 53.21, H 5.40.

Bicyclo[3.3.1]nonane-2,6-dione (4): Meerwein tetraester **3** (23.50 g, 61 mmol) was dissolved in a mixture of acetic acid (70 mL), 37% aq. HCl (23 mL), and water (23 mL) and the resulting solution was heated to reflux for 18 h. After cooling to room temperature, the reaction mixture was neutralized by the slow addition of saturated aqueous $NaHCO_3$ solution (300 mL) and then extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were dried with $MgSO_4$ and then the solvents were removed under reduced pressure (15 Torr/35 °C). Recrystallization of the crude material (8.50 g) from THF afforded the diketone **4** (7.22 g, 48 mmol, 78%) as white crystals, m.p. 134−135 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.01−2.15 (m, 4 H, CH_2), 2.20 (t, *J* = 2.7 Hz, 2 H, CH_2), 2.43 (m, 2 H, CH_2), 2.58 (dt, J_1 = 5.5 Hz, J_2 = 17.3 Hz, 2 H, CH_2), 2.73 (m, 2 H, CHCO). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.7 (2 C, CH_2), 31.5 (2 C, CH_2), 37.1 (2 C, CH_2), 43.6 (2 C, *C*HCO), 213.0 (2 C, C=O). − IR (CCl_4): $\tilde{\nu}$ = 1712 cm^{-1} (C=O). − $C_9H_{12}O_2$ (152.19): calcd. C 71.03, H 7.95; found C 70.97, H 8.03.

Monoprotected Bicyclo[5.3.1]nonane-2,6-dione (5): Diketone **4** (1.65 g, 10.80 mmol), 2,2-dimethylpropane-1,3-diol (1.12 g, 10.80 mmol), and *p*-TsOH (5 mg) were dissolved in benzene (220 mL). The resulting mixture was refluxed for 17 h in a 500-mL flask fitted with a Dean−Stark head. It was then cooled to 0 °C, diluted with Et_2O (30 mL), and then 10% aq. NaOH solution (17 mL) was added. After extraction with Et_2O (2 × 150 mL), the organic layers were collected, washed with saturated aqueous NaCl solution (150 mL), and dried with $MgSO_4$. Volatile components were then removed under reduced pressure (15 Torr/30 °C). The crude material (2.20 g) was purified by chromatography on a silica gel column (60 g of SiO_2; AcOEt/hexane, 5:95). The monoprotected diketone **5** was isolated (1.74 g, 7.29 mmol, 68%) along with a small amount of the starting material **4** (280 mg, 1.84 mmol, 17%). White crystals, m.p. 53−54 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.26−1.50 (m, 1 H), 1.73−2.56 (m, 11 H), 3.49 (s, 2 H, CH_2O), 3.51 (s, 2 H, CH_2O). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 (CH_2), 22.8 (2 C, CH_3), 26.1 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 30.1 [*C*$(CH_3)_2$], 31.5 (CH), 37.6 (*C*H_2CO), 44.2 (CH), 69.7 (CH_2O), 69.9 (CH_2O), 99.0 (OCO), 210.0 (C=O). − IR (CCl_4): $\tilde{\nu}$ = 1705 cm^{-1} (C=O). − $C_{14}H_{22}O_3$ (238.33): calcd. C 70.50, H 9.30; found C 70.60, H 9.10.

Tricyclo[5.3.1.0^{2,5}]undecanoic Derivative 8: The monoprotected diketone **5** (2.17 g, 9.13 mmol) was dissolved in toluene (30 mL) and refluxed with morpholine (10 mL, 10.00 g, 114.78 mmol) and *p*-TsOH (5 mg) in a Dean−Stark apparatus for 5 h. The toluene was then distilled off and the mixture was cooled to room temperature. Residual solvent was removed under reduced pressure (0.2 Torr/30 °C) and the oily residue was dissolved in dioxane (20 mL). To this solution, DMAD (2.00 mL, 2.31 g, 16.28 mmol) was added dropwise at room temperature. After stirring for 15 h at 20 °C, residual DMAD and dioxane were removed under reduced pressure (0.2 Torr/20 °C). The crude material was purified by chromatography on a silica gel column (30 g of SiO_2; AcOEt/hexane, 15:85) to give the cyclobutenic aminoester **8** (2.13 g, 4.75 mmol, 52%) as yellow crystals, m.p. 60−62 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.17−2.05 (m, 8 H), 2.35−2.50 (m, 2 H), 2.56−2.77 (m, 4 H, CH_2NCH_2), 3.21 [dd, J_1 = 3.4 Hz, J_2 = 9.1 Hz, 1 H, (*E*)-CHC=C], 3.37−3.53 (m, 4 H, CH_2OCH_2), 3.69 (t, *J* = 4.6 Hz, 4 H, CH_2OCH_2), 3.78 (s, 6 H, $COOCH_3$). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (CH_2), 22.7 (CH_3), 22.9 (CH_3), 23.2 (CH_2), 23.5 (CH_2), 26.3 (CH_2), 28.7 [*C*$(CH_3)_2$], 30.0 (CH), 30.2 (CH), 38.5 [(*E*)-*C*HC=C], 48.0 (2 C, *C*H_2N*C*H_2), 51.8 ($COOCH_3$), 52.0 ($COOCH_3$), 67.5 (2 C, *C*H_2OCH_2), 69.5 (CH_2OCH_2), 69.8 (*C*H_2OCH_2), 71.2 [(*E*)-C=C*C*N], 99.5 (OCO), 143.6 [(*E*)-*C*=C], 145.4 [(*E*)-C=*C*], 161.3 (*C*$OOCH_3$), 163.7 (*C*$OOCH_3$). − IR (CCl_4): $\tilde{\nu}$ = 1718 cm^{-1} (C=O). − UV (CH_3CN): λ_{max} = 211 nm (ε = 8100), 325 (ε = 1500). − $C_{24}H_{35}O_7N$ (449.55): calcd. C 64.12, H 7.85; found C 64.00, H 8.10.

Bicyclo[3.3.1]nonane Derivative 7: To a solution of the monoprotected diketone **5** (2.00 g, 8.45 mmol) in CH_2Cl_2 (80 mL), TBDMSOTf (2.00 mL, 2.33 g, 8.88 mmol) followed by NEt_3 (2.90 mL, 2.12 g, 21.13 mmol) were added dropwise at room temperature. After stirring for 10 min at room temperature, the mixture was hydrolyzed with water (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure (15 Torr/25 °C). The crude product (3.77 g) was purified by chromatography on a silica gel column (40 g SiO_2; hexane) to give the silylated enol ether **7** (2.97 g, 8.45 mmol, quantitative yield) as a white powder, m.p. 58−60 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.07 [s, 3 H, Si(CH_3)$_2$C$(CH_3)_3$], 0.11 [s, 3 H, Si(CH_3)$_2$C$(CH_3)_3$], 0.87 [s, 9 H, Si$(CH_3)_2$C(CH_3)$_3$], 0.89 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.47−1.59 (m, 4 H), 1.84 (dt, J_1 = 3.0 Hz, J_2 = 12.5 Hz, 1 H), 1.94 (m, 1 H), 2.06−2.13 (m, 3 H), 2.39 (m, 1 H), 3.43 (s, 4 H, CH_2OCH_2), 4.74 (t, *J* = 3.73 Hz, 1 H, CH=COSi). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.7 [Si(*C*H_3)$_2$C$(CH_3)_3$], −4.0 [Si(*C*H_3)$_2$C$(CH_3)_3$], 18.0 [3 C, Si$(CH_3)_2$C(*C*H_3)$_3$], 22.8 (CH_3), 23.0 (CH_3), 24.3 (CH_2), 25.5 (CH_2), 25.8 [Si$(CH_3)_2$*C*$(CH_3)_3$], 26.6 (CH_2), 28.4 (CH_2), 30.1 [*C*$(CH_3)_2$], 31.1 (CH), 34.6 (CH), 69.5 (CH_2O), 69.8 (CH_2O), 100.0 (*C*H=COSi), 102.2 (OCO), 151.9 (CH=*C*OSi). − IR (CCl_4): $\tilde{\nu}$ = 1666 cm^{-1} (C=C enol). − $C_{20}H_{36}O_3Si$ (352.59): calcd. C 68.12, H 10.32; found C 67.95, H 10.44.

Tricyclo[5.3.1.0^{2,5}]undecane Derivative 11: $ZrCl_4$ (1450 mg, 6.22 mmol) was suspended in CH_2Cl_2 (50 mL) and Et_2O (1.50 mL) and then ethyl propynoate (0.70 mL, 678 mg, 6.91 mmol) was added. The resulting mixture was cooled to −78 °C, whereupon a solution of enol ether **7** (1.52 g, 4.30 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After stirring for 10 min at −78 °C and for 10 min at room temperature, the deep-red mixture was hydrolyzed by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). After extraction with Et_2O (3 × 30 mL), the combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure (1 Torr/30 °C). The dark crude product was chromatographed on a silica gel column (15 g of SiO_2; AcOEt/hexane, 3:97) to give the oxo-cyclobutene ester **12** (798 mg, 2.26 mmol, 48%) along with the cyclobutene ketal **11** (943 mg, 2.09 mmol, 48%) (overall yield: 96%). − **Cyclobutene Ketal 11:** White crystals, m.p. 64−65 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 [s, 3 H, $Si(CH_3)_2C(CH_3)_3$], 0.02 [s, 3 H, $Si(CH_3)_2C(CH_3)_3$], 0.87 [s, 9 H, $Si(CH_3)_2C(CH_3)_3$], 0.93 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 1.47−1.59 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.35−1.77 (m, 4 H), 1.92−2.06 (m, 2 H), 2.13−2.30 (m, 2 H), 2.69 [br. d, J = 10.0 Hz, 1 H, (*E*)-C*H*CH=C], $δ_A$ = 3.4, $δ_B$ = 3.5 (AB, J_{AB} = 11.5 Hz, Δν = 16.5 Hz, 2 H, CH_2O), 3.46 (s, 2 H, CH_2O), 4.16 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 6.97 [d, J = 1.3 Hz, 1 H, (*E*)-CH=C]. − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −3.4 [$Si(CH_3)_2C(CH_3)_3$], −3.0 [$Si(CH_3)_2C(CH_3)_3$], 14.3 ($COOCH_2CH_3$), 18.4 [$Si(CH_3)_2C(CH_3)_3$], 22.9 (2 C, CH_3), 23.0 (CH_2), 23.5 (CH_2), 24.4 (CH_2), 25.4 (CH_2), 25.7 [3 C, $Si(CH_3)_2C(CH_3)_3$], 30.0 [$C(CH_3)_2$], 32.0 (CH), 32.6 (CH), 47.2 [(*E*)-*C*HCH=C], 60.0 ($COCH_2CH_3$), 69.6 (CH_2O), 69.8 (CH_2O), 80.1 (COSi), 99.7 (OCO), 140.3 [(*E*)-CH=*C*], 153.1 [(*E*)-*C*H=C], 161.1 (C=O). − IR (CCl_4): $\tilde{\nu}$ = 1614 cm^{-1} (C=C), 1717 (C=O). − UV (CH_3CN): $λ_{max}$ = 217 nm (ε = 7000). − $C_{25}H_{42}O_5Si$ (450.70): calcd. C 66.63, H 9.35; found C 66.83, H 9.14.

Tricyclo[5.3.1.0^{2,5}]undecane Derivative 12: The cyclobutene ketal **11** (943 mg, 2.09 mmols) was dissolved in a mixture of THF (30 mL) and 10% aq. HCl (5 mL). After stirring for 24 h at room temperature, the mixture was neutralized with saturated aq. $NaHCO_3$ solution (50 mL). After extraction with Et_2O (3 × 25 mL), the combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure (1 Torr/30 °C). Filtration of the crude product through a silica gel pad (15 g of SiO_2; AcOEt/hexane, 15:85) gave the oxo-cyclobutene ester **12** (736 mg, 2.09 mmol, quantitative yield) as white crystals, m.p. 72−74 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.01 [s, 3 H, $Si(CH_3)_2C(CH_3)_3$], 0.02 [s, 3 H, $Si(CH_3)_2C(CH_3)_3$], 0.84 [s, 9 H, $Si(CH_3)_2C(CH_3)_3$], 1.26 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.57−1.99 (m, 5 H), 2.12−2.25 [m, 1 H, (*E*)-C*H*CH=C], 2.50−2.67 (m, 4 H), 2.78 (dd, J_1 = 9.9 Hz, J_2 = 2.3 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 6.98 [d, J = 1.3 Hz, 1 H, (*E*)-CH=C]. − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −3.4 [$Si(CH_3)_2C(CH_3)_3$], −3.0 [$Si(CH_3)_2C(CH_3)_3$], 14.3 ($COCH_2CH_3$), 18.3 [$Si(CH_3)_2C(CH_3)_3$], 25.7 [3 C, $Si(CH_3)_2C(CH_3)_3$], 26.4 (CH_2), 28.4 (CH_2), 28.9 (CH_2), 32.7 (CH), 36.3 (CH_2CO), 44.0 (CH), 46.5 [(*E*)-*C*HCH=C], 60.2 ($COOCH_2CH_3$), 79.9 (COSi), 140.5 [(*E*)-CH=*C*], 152.6 [(*E*)-CH=*C*], 161.1 ($COOCH_2CH_3$), 215.0 (C=O). − IR (CCl_4): $\tilde{\nu}$ = 1618 cm^{-1} (C=C), 1716 (C=O), 1719 (C=O). − UV (CH_3CN): $λ_{max}$ = 217 nm (ε = 6100). − $C_{20}H_{32}O_4Si$ (364.21): calcd. C 65.89, H 8.85; found C 66.10, H 9.00.

Bicyclo[5.3.1]undecane Derivative 13: A solution of the cyclobutene compound **12** (200 mg, 0.56 mmol) in a mixture of acetic acid (6 mL), 34% HBF_4·Et_2O (1 mL), water (0.3 mL), and Et_2O (10 mL) was refluxed for 8 h. At room temperature, the reaction mixture was neutralized with saturated aq. $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure (1 Torr/35 °C). The crude product (213 mg) was chromatographed on a silica gel column (15 g of SiO_2; AcOEt/hexane, 5:95) to give the diketone **13** (100 mg, 0.40 mmol, 73%) as colorless crystals, m.p. 70−71 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.62−1.78 (m, 3 H), 2.02 (dt, J_1 = 14.1 Hz, J_2 = 4.3 Hz, 1 H), 2.16−2.36 (m, 2 H), 2.42−2.78 (m, 6 H), 4.16 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 7.21 [t, J = 3.9 Hz, 1 H, (*E*)-CH=C]. − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1 ($COOCH_2CH_3$), 24.2 (CH_2), 25.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 34.4 (CH_2CO), 44.6 (*C*HCO), 50.7 (*C*HCO), 61.5 ($COCH_2CH_3$), 131.8 [(*E*)-CH=*C*], 146.1 [(*E*)-*C*H=C], 164.3 ($COCH_2CH_3$), 207.1 (C=O), 213.0 (C=O). − IR (CCl_4): $\tilde{\nu}$ = 1640 cm^{-1} (C=C), 1700 (C=O), 1721 (C=O), 1741 (C=O). − UV (CH_3CN): $λ_{max}$ = 221 nm (ε = 4000). − $C_{14}H_{18}O_4$ (250.30): calcd. C 67.18, H 7.25; found C 67.18, H 7.11.

Bicyclo[3.3.1]nonane Derivative 14: A solution of the monoprotected diketone **5** (786 mg, 3.30 mmol) in dry methyl carbonate (5 mL) was added dropwise to a suspension of NaH (158 mg, 6.60 mmols) in dry methyl carbonate (10 mL) preheated to 60 °C. The reaction was initiated by adding MeOH (5 drops, ca. 0.1 mL) and terminated when the evolution of hydrogen had ceased (V_{exp} = 156 mL, V_{th} = 148 mL; 20 min). At room temperature, the reaction mixture was carefully hydrolyzed by the addition of saturated aq. NH_4Cl solution (15 mL). After dilution with water (10 mL), the mixture was extracted with Et_2O (2 × 30 mL), the combined organic layers were dried with $MgSO_4$, and the solvents were removed under reduced pressure (15 Torr/30 °C, then 0.2 Torr/25 °C) to give the pure β-oxo ester **14** (969 mg, 3.30 mmol, quantitative yield) as colorless crystals, m.p. 106−108 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 1.13−1.44 (m, 1 H), 1.57 (dt, J_1 = 3.0 Hz, J_2 = 12.3 Hz, 1 H), 1.71 (dt, J_1 = 3.4 Hz, J_2 = 9.9 Hz, 1 H), 1.87−2.05 (m, 2 H), 2.19−2.41 (m, 3 H), 2.45−2.55 (m, 1 H), 3.44 (s, 2 H, CH_2O), 3.46 (s, 2 H, CH_2O), 3.71 (s, 3 H, $COOCH_3$), 11.95 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8 (2 C, CH_3), 26.2 (CH_2), 26.9 (CH_2), 30.1 [$C(CH_3)_2$], 31.8 (CH), 33.9 (CH), 51.3 ($COOCH_3$), 69.6 (CH_2O), 69.8 (CH_2O), 96.9 (OCO), 99.4 [(*E*)-*C*=COH], 172.7 [(*E*)-C=*C*OH], 173.6 ($COOCH_3$). − IR (CCl_4): $\tilde{\nu}$ = 1661 cm^{-1} (C=C enol). − UV (CH_3CN): $λ_{max}$ = 255 nm (ε = 10200). − $C_{16}H_{24}O_5$ (296.37): calcd. C 64.84, H 8.16; found C 65.00, H 7.93.

Bicyclo[5.3.1]undecane Derivative 15: A solution of the β-oxo ester **14** (500 mg, 1.70 mmols) in toluene (5 mL) was added dropwise to a suspension of NaH (50 mg, 2.04 mmol) in toluene (10 mL) at 0 °C. When the evolution of hydrogen had ceased (V_{exp} = 44 mL, V_{th} = 38 mL), DMAD (0.20 mL, 250 mg, 1.71 mmol) was added dropwise. After stirring for 2 h, the mixture was carefully hydrolyzed at room temperature with saturated aq. NH_4Cl solution (5 mL). After extraction with CH_2Cl_2 (3 × 25 mL), the combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure (15 Torr/30 °C). The crude product was purified by chromatography on a silica gel column (30 g of SiO_2; AcOEt/hexane, 10:90) to give the ring-expanded compound **15** (521 mg, 1.19 mmol, 70%).

One-Pot Procedure for the Synthesis of Compound 15 Starting from Ketone 5: The monoprotected diketone **5** (150 mg, 0.63 mmol) was added (as a solid) to a suspension of NaH (34 mg, 1.41 mmol) in toluene (4 mL) preheated to 60 °C. The reaction was initiated by the addition of MeOH (3 drops). When the evolution of hydrogen had ceased (V_{exp} = 30 mL, V_{th} = 28 mL), the solvents were re-

moved under reduced pressure (0.2 Torr/30 °C). The residual white solid was redissolved in toluene (10 mL) at room temperature. After stirring for 2 h at room temperature, ACDM (0.24 mL, 277 mg, 1.95 mmol) was added dropwise over a period of 20 min. The progress of the reaction was monitored by TLC and on completion the reaction mixture was carefully hydrolyzed at room temperature with saturated aq. NH_4Cl solution (5 mL). After extraction with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure (15 Torr/30 °C). The ring-expanded triester **15** (171 mg, 0.39 mmol, 62%) was isolated by chromatography of the crude product on a silica gel column (15 g of SiO_2; Et_2O/hexane, 15:85) as white crystals, m.p. 174−175 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.93 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.45−1.80 (m, 3 H), 1.90−2.65 (m, 6 H), 2.70−2.80 (m, 1 H), δ_A = 3.38, δ_B = 3.47 (AB, J_{AB} = 11.0 Hz, Δν = 41.0 Hz, 2 H, CH_2O), 3.50 (s, 2 H, CH_2O), 3.72 (s, 6 H, $COOCH_3$), 3.82 (s, 3 H, $COOCH_3$), 13.95 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7 (2 C, CH_3), 25.0 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 30.1 [*C*(CH_3)$_2$], 31.9 (CH_2), 33.1 (CH), 38.8 (CH), 52.3 (2 C, COO*C*H_3), 52.4 (COO*C*H_3), 69.7 (CH_2O), 69.9 (CH_2O), 98.5 (OCO), 99.4 [(*E*)-*C*=COH], 129.0 [(*E*)-C=*C*], 141.0 [(*E*)-*C*=C], 167.4 (*C*$OOCH_3$), 170.1 (*C*$OOCH_3$), 173.0 (*C*$OOCH_3$), 180.0 [(*E*)-C=*C*OH]. − IR (CCl_4): ν̃ = 1583 cm^{-1} (C=C), 1650 (C=C enol), 1730 (C=O), 1735 (C=O). − UV (CH_3CN): λ_{max} = 205 nm (ε = 5700), 260 (ε = 7700). − $C_{22}H_{30}O_9$ (438.48): calcd. C 60.26, H 6.89; found C 60.28, H 6.64.

Bicyclo[5.3.1]undecane Derivative 16: A solution of β-oxo ester **14** (296 mg, 1.00 mmol) in toluene (5 mL) was added to a suspension of NaH (30 mg, 1.25 mmol) in toluene (10 mL) at room temperature. When the evolution of hydrogen had ceased (V_{exp} = 27 mL, V_{th} = 23 mL), ethyl propynoate (0.11 mL, 106 mg, 1.08 mmol) was added dropwise. After stirring for 40 min at room temperature, the mixture was hydrolyzed with saturated aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were removed under reduced pressure (15 Torr/30 °C). The crude product was chromatographed on a silica gel column (15 g of SiO_2; hexane) to afford the unchanged starting material **14** (18 mg, 0.06 mmol) along with the ring-expanded compound **16** (134 mg, 0.34 mmol, 34%; 42% based on recovered starting material) as a colorless oil. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.34 (t, *J* = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.63−2.10 (m, 6 H), 2.40−2.55 (m, 2 H), 2.69 (m, 2 H), δ_A = 3.43, δ_B = 3.64 (AB, J_{AB} = 11.6 Hz, Δν = 41.0 Hz, 2 H, CH_2O), δ_A = 3.41, δ_B = 3.65 (AB, J_{AB} = 11.6 Hz, Δν = 48.4 Hz, 2 H, CH_2O), 3.79 (s, 3 H, $COOCH_3$), 4.28 (q, *J* = 7.1 Hz, 2 H, $COOCH_2CH_3$), 7.58 [s, 1 H, (*E*)-CH=C], 14.23 (s, 1 H, OH). − IR (CCl_4): ν̃ = 1575 cm^{-1} (C=C enol), 1635 (C=C), 1709 (C=O). − UV (CH_3CN): λ_{max} = 215 nm (ε = 7300), 264 (ε = 7800), 287 (ε = 7200). − $C_{21}H_{30}O_7$ (394.47): calcd. C 63.94, H 7.67; found C 64.11, H 7.62.

Bicyclo[3.3.1]nonane Derivative (*E*)/(*Z*)-17: Ethyl propynoate (3 mL) was added to a suspension of NaH (30 mg, 1.25 mmol) in toluene (10 mL). After stirring for 15 min at room temperature, a solution of β-oxo ester **14** (280 mg, 0.95 mmol) in toluene (5 mL) was added dropwise. After stirring for 2 h, the mixture was carefully hydrolyzed with saturated aq. NH_4Cl solution (30 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and then the solvents were removed under reduced pressure (15 Torr/30 °C). The crude product (610 mg) was chromatographed on a silica gel column (30 g of SiO_2; hexane) to give the isomeric oxo diesters **(*E*)-17** (230 mg, 0.59 mmol, 61%) and **(*Z*)-17** (118 mg, 0.30 mmol, 32%) (overall yield: 93%) as white crystals, m.p. 104−105 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): **(*E*)-17:** δ = 0.97 (s, 6 H, CH_3), 1.27−1.34 (t, *J* = 7.1 Hz, 3 H, CO-OCH_2CH_3), 1.57 (dt, J_1 = 13.5 Hz, J_2 = 4.0 Hz, 1 H), 1.75 (tt, J_1 = 13.2 Hz, J_2 = 4.0 Hz, 1 H), 1.90−2.20 (m, 4 H), 2.34 (dd, J_1 = 10.9 Hz, J_2 = 16.0 Hz, 1 H), 2.46 (m, 1 H), 2.65−2.73 (m, 2 H), 3.49 (m, 4 H, CH_2OCH_2), 3.81 (s, 3 H, $COOCH_3$), 4.21 (q, *J* = 7.1 Hz, 2 H, $COOCH_2CH_3$), 5.85 [d, *J* = 16.1 Hz, 1 H, (*E*)-C*H*=CH], 6.99 [d, *J* = 16.1 Hz, 1 H, (*E*)-CH=C*H*]; **(*Z*)-17:** δ = 0.90 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 1.32 (t, *J* = 7.1 Hz, 3 H, CO-OCH_2CH_3), 1.43−1.82 (m, 2 H), 1.99−2.21 (m, 4 H), 2.54−2.66 (m, 3 H), 2.98−3.05 (m, 1 H), 5.45−5.48 (m, 4 H, CH_2OCH_2), 3.77 (s, 3 H, $COOCH_3$), 4.19 (q, *J* = 7.1 Hz, 2 H, $COOCH_2CH_3$), 6.02 [d, *J* = 11.9 Hz, 1 H, (*E*)-C*H*=CH], 6.23 [d, *J* = 11.9 Hz, 1 H, (*E*)-CH=C*H*]. − ^{13}C NMR (50 MHz, $CDCl_3$): **(*E*)-17:** δ = 14.2 ($COOCH_2CH_3$), 22.8 (2 C, CH_3), 25.7 (CH_2), 26.1 (CH_2), 27.8 (CH_2), 30.0 [*C*(CH_3)$_2$], 30.4 (CH), 32.4 (CH_2), 41.8 (CH), 52.7 (COO*C*H_3), 60.7 ($COOCH_2CH_3$), 61.5 (*C*$OOCH_3$), 69.7 (CH_2O), 70.1 (CH_2O), 99.0 (OCO), 122.3 [(*E*)-CH=*C*H], 144.3 [(*E*)-*C*H=CH], 165.0 (COO), 170.2 (COO), 212.0 (C=O); **(*Z*)-17:** δ = 14.2 ($COOCH_2CH_3$), 22.7 (2 C, CH_3), 24.5 (CH_2), 25.6 (CH_2), 27.6 (CH_2), 29.0 (CH_2), 30.0 [*C*(CH_3)$_2$], 30.4 (CH), 42.1 (CH), 53.1 (COO*C*H_3), 60.9 ($COOCH_2CH_3$), 62.0 (*C*$OOCH_3$), 69.8 (CH_2O), 70.0 (CH_2O), 99.0 (OCO), 123.9 [(*E*)-CH=*C*H], 146.5 [(*E*)-*C*H=CH], 165.6 (COO), 171.1 (COO), 211.1 (C=O). − IR (CCl_4): ν̃ = 1644 cm^{-1} (C=C), 1716 (C=O), 1720 (C=O), 1746 (C=O). − UV (CH_3CN): λ_{max} = 220 nm (ε = 6500). − $C_{21}H_{30}O_7$ (394.4): **(*E*)-17:** calcd. C 63.94, H 7.67; found C 64.00, H 7.51; **(*Z*)-17:** calcd. C 63.94, H 7.67; found C 64.20, H 7.62.

Table 1. Crystallographic details for compound **15**

Empirical formula	$C_{22}H_{30}O_9$
Molecular mass	438.48
Crystal system	monoclinic
Space group	*P*21/*a*
a [Å]	8.6966(6)
b [Å]	21.832(4)
c [Å]	12.3248(9)
β [°]	108.592(6)
V [Å^3]	2217.9(8)
Z	4
Color	colorless
Crystal dimensions [mm]	0.45 × 0.30 × 0.25
$D_{calcd.}$ [gcm^{-3}]	1.31
F(000)	936
μ [mm^{-1}]	0.095
Trans., min./max.	0.9579/1.0000
Temperature [K]	294
Wavelength [Å]	0.71073
Radiation	Mo-K_α graphite-monochromated
Diffractometer	Enraf−Nonius CAD4
Scan mode	θ/2θ
hkl limits	−10,0/0,27/−14,15
θ limits [°]	2.5/26.29
Number of data collected	4944
Number of data with $I > 3\,\sigma(I)$	2220
Weighting scheme	$4F_o^2/[\alpha 2(F_o^2) + 0.0064F_o^4]$
Number of variables	280
R	0.042
Rw	0.057
GoF	1.079
Largest peak in final difference [eÅ^{-3}]	0.726

X-ray Crystallographic Study: Crystal data, data collection parameters, and salient results for **15** are summarized in Table 1. Data were collected at room temperature and corrected for Lorentz and polarization effects. Absorption corrections were included in the

scaling procedure for data collected using the KappaCCD. The structures were solved by direct methods and refined against |*F*| using the OpenMoleN package and a DEC Alpha workstation. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC-151214). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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