DOI: 10.1002/ejoc.201000986

Anionic Cascade Reaction Followed by Silylative Dieckmann Cyclization: A Straightforward Route to Tricyclic Fused Ring Systems Starting from Alkynyl Esters Tethered to Bicyclo[*n*.2.0]alkanones

Vincent Rietsch,[a] Laurence Miesch,[a] Daisuke Yamashita,[b] and Michel Miesch*[a]

Keywords: Alkynyl esters / Fused ring systems / Domino reactions / Cyclization / Diastereoselectivity

The successive addition of sodium ethoxide and TBSOTf (or TMSOTf) to alkynyl esters tethered to bicyclo[*n*.2.0]alkanones (*n* = 3–5) promoted a domino anionic reaction and a Dieckmann condensation, respectively, which led to 5-6-5, 6-6-5, and 7-6-5 tricyclic fused ring systems. These systems represent relevant substructures of numerous bioactive compounds.

Introduction

The 5-6-5, 6-6-5, and 7-6-5 tricyclic fused carbon frameworks are relevant substructures of numerous bioactive compounds such as Taiwaniasterol,[1] Walsucochin A,[2] Lancifodilactone F,[3] Cyanthiwigin F,[4] Lagaspholone A,[5] Crotofolin[6] A, and Mangicol A[7] (Figure 1).

The synthesis of these tricyclic derivatives remains challenging. Intramolecular Diels–Alder reactions,[8] anionic oxy-Cope rearrangements,[9] transition-metal-catalyzed [2+2+2] cyclizations of α,ω-diyne or (di)eneyne,[10] intramolecular reductive cyclization,[11] and palladium-catalyzed domino reactions[12] were reported to afford the corresponding tricyclic fused ring systems. Nevertheless, the development of an original methodology is important to provide new access to these scaffolds. Toward this end, an alternative methodology, which readily affords tricyclic fused carbon skeletons, is described. Our strategy calls for a base-promoted domino reaction followed by a Lewis acid induced Dieckmann ring closing reaction, starting from alkynyl esters tethered to bicyclo[*n*.2.0]alkanones. This study was motivated by the fact that an unexpected base-promoted domino reaction took place starting from ynoates tethered to mono-cycloalkanones. Furthermore, the bicyclo[*n*.2.0]alkanone skeleton is a very interesting building block for different ring expansion or skeletal isomerization reactions, which are promoted by inherent ring strain.[13]

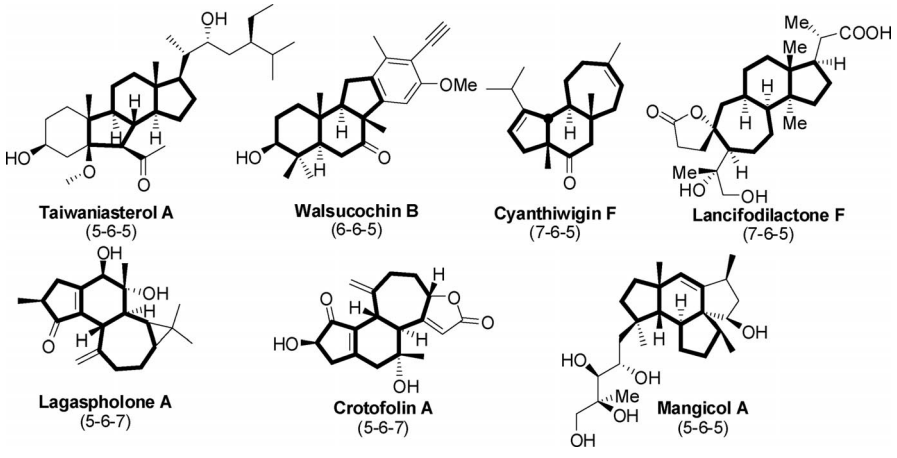


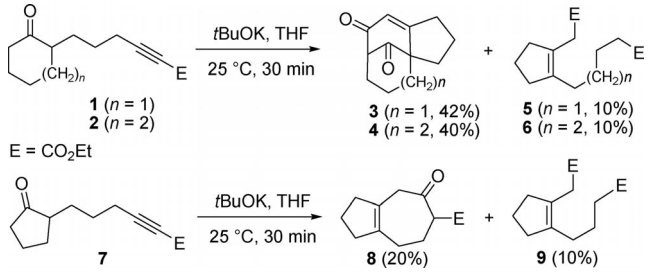
Figure 1. Natural products bearing 5-6-5, 6–6-5, and 7-6-5 fused rings.

[a] Université de Strasbourg, Institut de Chimie, UMR 7177, Laboratoire de Chimie Organique Synthétique,
1 rue Blaise Pascal, BP 296/R8, 67008 Strasbourg, France
Fax: +33-3-68851752
E-mail: m.miesch@unistra.fr
[b] Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI),
2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000986.

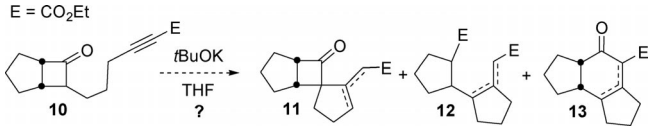
Results and Discussion

We have previously reported that the addition of *t*BuOK to the alkynyl esters **1** and **2** tethered to cyclohexanone or cycloheptanone, respectively, gave the tricyclic diketones **3** and **4** and the α,ω-diesters **5** and **6**, which result from an anionic domino reaction.[14] However, starting from compound **7**, the addition of *t*BuOK yielded the α,ω-diester **9** and the perhydroazulene **8**, which was probably formed by a base-promoted Dieckmann reaction of compound **9** (Scheme 1).



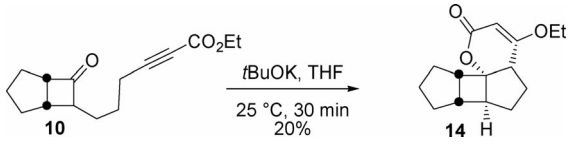
Scheme 1. Addition of *t*BuOK to the acetylenic ω-keto esters **1**, **2**, and **7**.

On the basis of these observations, it was hypothesized that this domino reaction could be extended to the bicyclo[3.2.0]derivative **10** to afford three different types of products: the spiro derivative **11**, the α,ω-diester **12**, and the tricyclic derivative **13**. The latter was the desired product (Scheme 2).



Scheme 2. Possible products resulting from the addition of *t*BuOK to the acetylenic ω-keto ester **10**.

Amazingly, the addition of *t*BuOK to the bicyclo[3.2.0]-derivative **10** did not afford the expected products **11**, **12**, or **13** but gave a complex mixture of compounds, among which the tetracyclic derivative **14** was isolated in 20% yield. The structure of compound **14** was confirmed by X-ray crystallography, which clearly shows the presence of the *cis–anti–cis* configuration of the tricyclic core (Scheme 3, Figure 2).[15]



Scheme 3. Addition of *t*BuOK to the acetylenic ω-keto ester **10**.

This result prompted us to study the influence of the base on the unfolding of this anionic domino reaction by using NaOEt instead of *t*BuOK. When a mixture of NaOEt (obtained by adding Na to EtOH) and bicyclo[3.2.0]derivative **10** was stirred overnight at room temperature, the α,ω-diester **16** was isolated in 58% yield. No trace of the tetracyclic

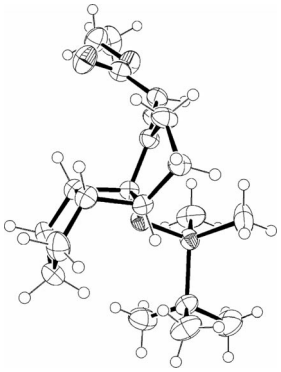
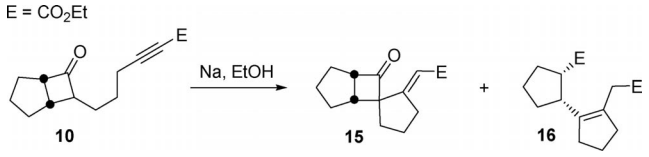


Figure 2. ORTEP depiction of compound **14**, with thermal ellipsoids at the 30% probability level.

derivative **14** was observed. However, when the same reaction was carried out at room temperature for 30 min, a 1:1.4 mixture of α,ω-diester **16** and spiroketo ester **15** was obtained. These compounds were easily separated. This experiment suggests that the spiro keto ester **15** was first generated and then underwent a NaOEt-promoted ring opening reaction to provide the α,ω-diester **16**. To support this hypothesis, the spiroketo ester **15** was treated with NaOEt to give the corresponding α,ω-diester **16** in 75% yield. Finally, when NaOEt was added at 0 °C to the bicyclo[3.2.0] derivative **10**, α,ω-diester **16** was obtained in 75% yield (Scheme 4, Table 1).

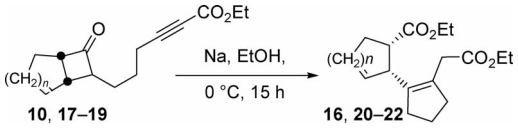


Scheme 4. Addition of NaOEt to the acetylenic ω-keto ester **10**.

Table 1. Formation of compounds **15** and **16**.

Entry	Reaction conditions	Yield **15** [%]	Yield **16** [%]
1	Na (1.5 equiv.), EtOH, 25 °C, 8 h	16	58
2	Na (1.5 equiv.), EtOH, 25 °C, 30 min	26	36
3	Na (4.0 equiv.), EtOH, 0 °C, 15 h	<1	75

No epimerization occurred; compound **16** was isolated as a sole *cis* diastereomer for which the relative configuration was established by extensive NOESY experiments and by further chemical transformation (vide infra). To broaden the scope of this strategy, these optimal reaction conditions were extended to acetylenic ω-keto esters **17**–**19** derived from bicyclo[3.2.0]hept-2-en-6-one, bicyclo[4.2.0]octanone, and bicyclo[5.2.0]nonanone, respectively. A domino anionic reaction took place to afford the corresponding α,ω-diesters **20**–**22** in good yields with a total diastereoselectivity (Scheme 5, Table 2).



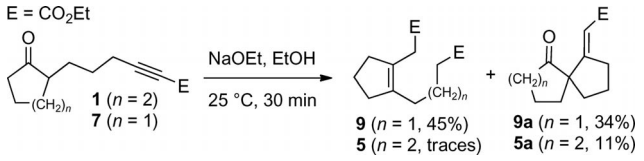
Scheme 5. Addition of NaOEt to the acetylenic ω-keto esters **17**–**19**.

Table 2. Formation of the α,ω-diesters **16** and **20**–**22**.

Starting material	*n*	Compound (yield)
10	1	**16** (75%)
17[a]	1	**20** (77%)
18	2	**21** (74%)
19	3	**22** (76%)

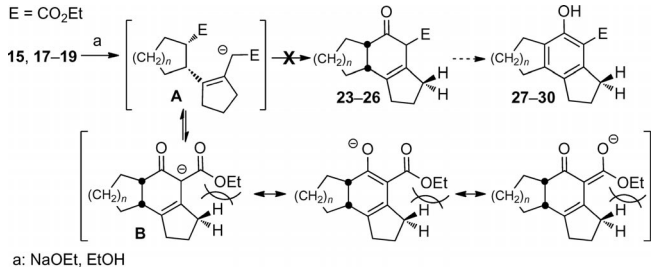
[a] Compound **17** derived from bicyclo[3.2.0]hept-2-en-6-one.

The addition of NaOEt to the acetylenic ω-keto esters **1** and **7** derived from cyclohexanone and cyclopentanone led to a mixture of the α,ω-diesters **9** and **5**, respectively, isolated in moderate yield (45%) and in trace amounts (<1%), along with the corresponding spiro derivatives **9a** (34%) and **5a** (11%). These results sharply contrast the above results. These results are explained by the fact that the strain release energy of a four-membered ring is much higher than that of a five- or six-membered ring. Thus, the four-membered ring opening reaction was highly favored (Scheme 6).[16]



Scheme 6. Addition of NaOEt to the acetylenic ω-keto esters **1** or **7**.

The formation of the α,ω-diesters **16** and **20**–**22** is surprising. Indeed, it was quite reasonable to anticipate that carbanion **A**, the direct precursor of the α,ω-diesters **16** and **20**–**22**, should undergo an in situ Dieckmann condensation to afford the tricyclic derivatives **23**–**26**. These compounds could evolve by an aromatization reaction to yield the final aromatic derivatives **27**–**30**. However, the formation of the latter was never detected. Moreover, the addition of various bases to the α,ω-diesters **16** and **20**–**22** yielded exclusively a complex mixture of compounds. An explanation of this result is that the Dieckmann condensation is a reversible reaction in which the key step is the deprotonation of the β-dicarbonyl system. Thus, the carbanion **A** is in equilibrium with carbanion **B** where an extended conjugated II system may create a 1,3-allylic-type strain. Moreover, rotation of the carboxylate moiety out of the plane will decrease conjugation and delocalization of electron density (Scheme 7).



Scheme 7. Addition of NaOEt to acetylenic ω-keto esters **16**–**19**.

The fact that the Dieckmann condensation product was not observed could also be explained as follows: as indicated in Scheme 1, the formation of the hydroazulene **8** occurred through the generation of an enolate on the 3-(ethoxycarbonyl)propyl side chain and not from the "allylic" enolate. Indeed, the latter is probably too inactive (conjugation with the double bond and with the ester group) to undergo a Dieckmann condensation. This explanation can be extended to carbanion **A** (Scheme 7), which explains its very low reactivity.[18]

Nevertheless, an acidic Dieckmann condensation was considered as a valuable alternative in this case.[17] We were delighted to find that the addition of a mixture of TBSOTf/NEt_3 to α,ω-diester **16** led quantitatively to the tricyclic derivative **31**, with a total diastereoselectivity. This is probably because a unique *Z*-ketene silyl acetal **16a** was formed.[19] The structure of compound **31** was confirmed by X-ray crystallography, which clearly indicates a *cis* ring junction for the AB fused ring system (Figure 3).[20] This result corroborates our previous observation, namely that the α,ω-diester **16** was obtained as a unique *cis* diastereomer. The Dieckmann condensation tolerates a double bond in cycle A as well, which yields the corresponding tricyclic derivative **32** in 80% yield via the *Z*-ketene silyl acetal **17a** (Scheme 8).

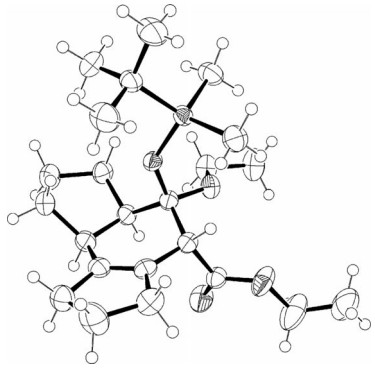
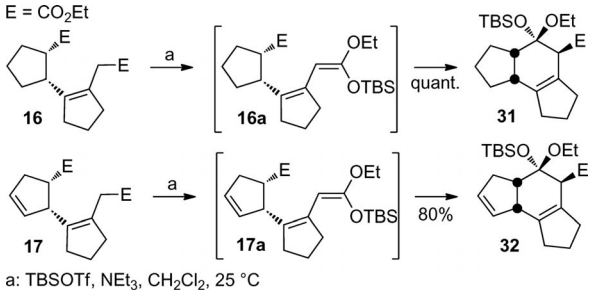


Figure 3. ORTEP depiction of compound **31**, with thermal ellipsoids at the 30% probability level.

Initial attempts to apply this Dieckmann reaction to α,ω-diesters **21** and **22** failed. No Dieckmann cyclization occurred, probably because of steric hindrance and subtle stereoelectronic effects. However, further investigation showed that the Dieckmann condensation took place in the presence of TMSOTf/NEt_3. Thus, starting from the α,ω-

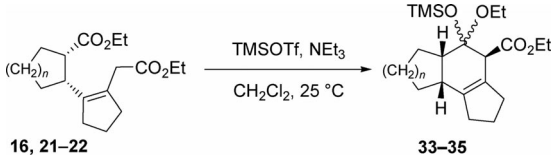


Scheme 8. TBSOTf-promoted Dieckmann condensation starting from α,ω-diesters **16** and **17**.

diesters **21** and **22**, the corresponding tricyclic derivatives **33** and **34** were isolated as a mixture of isomers (ratio: 1:1). Indeed, the TMS group is not as bulky as the TBS group so that a mixture of *E*- and *Z*-ketene silyl acetals was probably formed, which led to the tricyclic derivatives **33**–**35** (Table 3). Of course, when the same reaction conditions were applied to the α,ω-diester **16**, the tricyclic derivative **35** was also readily obtained as a 1:1 mixture of isomers in 80% yield (Scheme 9).

Table 3. Formation of the tricyclic derivatives **33**–**35**.

Starting material	*n*	Compound (yield; ratio)
16	1	**33** (80%; 1:1)
21	2	**34** (90%; 1:1)
22	3	**35** (84%; 1:1)



Scheme 9. TMSOTf-promoted Dieckmann condensation starting from α,ω-diesters **16**, **21** and **22**.

Conclusions

A new methodology employing a base-promoted domino reaction followed by a Lewis acid induced Dieckmann ring closing reaction readily led to 5-6-5, 6-6-5, and 7-6-5 tricyclic fused ring systems (overall yields: 65–75%), which represent important substructures of numerous bioactive natural products. Further extensions of this methodology toward the synthesis of natural products are currently underway.

Experimental Section

General Remarks: Reactions were carried out under a positive pressure of argon with magnetic stirring and by using degassed solvents in oven-dried glassware. Et_2O and THF were distilled from Na/benzophenone. Thin-layer chromatography (TLC) was carried out on silica gel plates Merck $60F_{254}$ and the spots were visualized under a UV lamp (254 or 365 nm) and/or sprayed with a solution of vanillin (25 g) in $EtOH/H_2SO_4$ (98:2; 1 L) or with phosphomolybdic acid followed by heating on a hot plate. For column chromatography, silica gel (Merck, Si60, 40–60 μm) was used. Melting points (m.p.) were measured on a hot plate Stuart Scientific SMP 3 apparatus. IR spectra were recorded as CCl_4 solutions. ^1H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 75 or 125 MHz on a Bruker AC-300 or ARX-500 by using the signal of the residual non-deuterated solvent as internal reference. Significant ^1H NMR spectroscopic data are tabulated in the following order: chemical shift (δ) expressed in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constants *J* in Hz, number of protons. The ratios of compounds indicated below were calculated from the NMR integrations. IR spectra were recorded as CCl_4 solutions on a Perkin–Elmer IR-881 and on a Bruker Alpha spectrometer. Microanalysis were carried out by the Service Commun d'Analyses du CNRS, Institut de Chimie-Strasbourg.

Compound 14: To a solution of acetylenic ω-keto ester **10** (0.213 g, 0.86 mmol, 1 equiv.) in THF (10 mL) was added *t*-BuOK (106 mg, 0.94 mmol, 1.1 equiv.), and the suspension was stirred for 30 min. After hydrolysis with a saturated aqueous NH_4Cl solution (3 mL) and a 10% aqueous solution of HCl (10 mL), the aqueous layer was extracted three times with ether. The combined organic phases were successively washed with aqueous $NaHCO_3$ solution and brine and dried with Na_2SO_4. After filtration and removal of the solvent (25 °C, 15 Torr), the residue was purified by column chromatography (15 g of SiO_2 petroleum ether/AcOEt: 100:0 to 80:20) to yield compound **14** (43 mg, 20%).

Compound 14: ^1H NMR (300 MHz, $CDCl_3$): δ = 5.11 (s, 1 H, OCC*H*=C), 3.89 (ABX_3 system, J_{AB} = 10.4, J_{AX} = 7.1, J_{BX} = 7.1 Hz, $\Delta\upsilon$ = 30 Hz, ∂_A = 3.94 ppm, ∂_B = 3.84 ppm, 2 H, CH_2CH$_3$), 2.64–2.60 (m, 1 H, CH), 2.54 (t, *J* = 7.5 Hz, 1 H, C*H*C=CH), 2.30–2.05 (m, 4 H, CH), 2.00–1.40 (m, 8 H, CH_2), 1.35 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 166.2, 91.4, 85.2, 64.6, 50.4, 47.1, 45.7, 39.1, 32.9, 29.6, 28.4, 27.2, 26.1, 14.0 ppm. IR (CCl_4): $\tilde{\nu}$ = 1716, 1628 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{20}NaO_3$ $[M + Na]^+$: 271.1310; found 271.1312.

General Procedure for the Synthesis of Diesters 16 and 20–22: To a solution of sodium (1.5 equiv.) in ethanol (10 mL) was added dropwise acetylenic ω-keto ester (1.9 mmol, 1 equiv.) in ethanol (10 mL), and the reaction mixture was stirred at 0 °C for 15 h. After hydrolysis with a 2% aqueous solution of HCl (6 mL), the aqueous layer was extracted three times with ether. The combined organic phases were successively washed with aqueous $NaHCO_3$ solution and brine and dried with Na_2SO_4. After filtration and removal of the solvent (25 °C, 15 Torr), the residue was purified by column chromatography (15 g,SiO_2, petroleum ether/AcOEt: 100:0 to 94:6) to give compounds **16** (yield: 75%), **20** (yield: 77%), **21** (yield: 74%), and **22** (yield: 76%).

Compound 16: ^1H NMR (300 MHz, $CDCl_3$): δ = 4.10 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 3.98 (ABX_3 system, J_{AB} = 11.5 Hz, J_{AX} = 6.8 Hz, J_{BX} = 7.3 Hz, $\Delta\upsilon$ = 9 Hz, ∂_A = 4.00 ppm, ∂_B = 3.97 ppm, 2 H, CH_2CH$_3$), 3.19–3.13 (m, 1 H, CH), 3.08 (AB system, J_{AB} = 15.2 Hz, $\Delta\upsilon$ = 66 Hz, ∂_A = 3.19 ppm, ∂_B = 2.97 ppm, 2 H, CH_2CO), 2.93–2.85 (m, 1 H, CH), 2.45–2.15 (m, 4 H, CH_2), 2.01–1.15 (m, 8 H, CH_2), 1.23 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.16 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 171.4, 139.6, 130.3, 60.5, 60.1, 48.4, 41.8, 36.4, 34.9, 34.0, 30.2, 28.7, 25.2, 22.1, 14.3 ppm. IR (CCl_4): $\tilde{\nu}$ = 1733 cm^{-1}. $C_{17}H_{26}O_4$ (294.39): calcd. C 69.36, H 8.90; found C 69.97, H 8.97. HRMS (ESI): calcd. for $C_{17}H_{26}NaO_4$ $[M + Na]^+$: 317.1728; found 317.1710.

Compound 20: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.79–5.83 (m, 1 H, CH_2CH=CH), 5.50–5.47 (m, 1 H, CH_2CH = CH), 4.12 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 4.02 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 3.34–3.22 (m, 1 H, CH), 3.14 (AB system, J_{AB} = 15.3 Hz, $\Delta\upsilon$ = 102 Hz, ∂_A = 2.97 ppm, ∂_B = 3.31 ppm, 2 H, CH_2CO), 2.91–2.80 (m, 1 H, CH), 2.51–2.43 (m, 2 H, CH_2CH=CH), 2.34–2.16 (m, 4 H, CH_2), 1.84–1.61 (m, 2 H, CH_2), 1.25 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.18 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 171.5, 138.8, 131.4, 130.7, 130.5, 60.6, 60.3, 47.3, 46.8, 36.6, 34.8, 34.5, 33.6, 21.9, 14.4 ppm. IR (CCl_4): $\tilde{\nu}$ = 1729 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{24}NaO_4$ [M + Na]$^+$: 315.1572; found 315.1580.

General Procedure for the Synthesis of Tricyclic Fused Rings 31–35: NEt_3 (2.5 equiv.) was added to a solution of the diesters **16**, **20**–**22** (1 equiv.) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 20 min at room temperature. TBSOTf or TMSOTf (1.2 equiv.) was added dropwise, and the reaction mixture was stirred for 4 h at room temperature. NEt_3 (2.5 equiv.) was added again, and the mixture was stirred for a further 20 min. TBSOTf or TMSOTf (1.2 equiv.) was added dropwise, and the mixture was stirred for 1 h at room temperature, hydrolyzed with water (5 mL), and then extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with brine and dried with Na_2SO_4. After filtration and removal of the solvent (25 °C, 15 Torr), the residue was purified by column chromatography (15 g SiO_2, petroleum ether/AcOEt/NEt_3: 95:0:5 to 94:3:3) to give compounds **31** (yield: quant.), **32** (yield: 78%), **33** (yield: 90%), **34** (yield: 84%), and **35** (yield: 80%).

Compound 31: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.16–4.05 (m, 2 H, COOCH_2CH$_3$), 3.53 (ABX$_3$ system, J_{AB} = 14.1 Hz, J_{AX} = 6.9 Hz, J_{BX} = 7.2 Hz, $\Delta\upsilon$ = 24 Hz, ∂_A = 3.49 ppm, ∂_B = 3.57 ppm, 2 H, OCH_2CH$_3$), 3.30 (s, 1 H, CHCOO), 2.91–2.83 (m, 1 H, CH), 2.59–2.47 (m, 1 H, CH), 2.25–1.30 (m, 12 H, CH_2), 1.25 (t, J = 7.2 Hz, 3 H, COOCH$_2$CH_3), 1.07 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 0.83 [s, 9 H, C(CH_3)$_3$], 0.13 [s, 3 H, Si(CH_3)$_2$], 0.11 [s, 3 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 140.1, 128.6, 102.0, 60.3, 58.9, 56.2, 43.4, 41.7, 34.7, 34.4, 31.2, 27.0, 26.5, 26.0, 22.4, 18.4, 15.8, 14.5, –2.7, –2.9 ppm. IR (CCl_4): $\tilde{\nu}$ = 1736 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{40}NaO_4Si$ [M + Na]$^+$: 431.2594; found 431.2589.

Compound 33 (Dia 1): ^{1}H NMR (300 MHz, C_6D_6): δ = 4.15–3.90 (m, 2 H, COOCH_2CH$_3$), 3.52 (s large, 1 H, CHCOO), 3.58–3.37 (m, 2 H, OCH_2CH$_3$), 2.62–1.15 (m, 16 H, CH and CH_2), 1.06 (t, J = 7.1 Hz, 3 H, COOCH$_2$CH_3), 1.05 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 0.30 [s, 9 H, Si(CH$_3$)$_3$] ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 171.1, 103.4, 60.2, 57.1, 55.9, 34.7, 33.0, 28.9, 25.9, 24.7, 23.6, 22.7, 15.7, 14.5, 2.5 ppm. IR (CCl_4): $\tilde{\nu}$ = 1728 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{36}NaO_4Si$ [M + Na]$^+$: 403.2281; found 403.2237.

Compound 33 (Dia 2): ^{1}H NMR (300 MHz, C_6D_6): δ = 4.15–3.90 (m, 2 H, COOCH_2CH$_3$), 3.39 (s large, 1 H, CHCOO), 3.58–3.37 (m, 2 H, OCH_2CH$_3$), 2.62–1.15 (m, 16 H, CH and CH_2), 1.02 (t, J = 7.0 Hz, 3 H, COOCH$_2$CH_3), 1.00 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3), 0.25 [s, 9 H, Si(CH$_3$)$_3$] ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 170.6, 103.3, 60.1, 54.3, 52.0, 34.4, 32.7, 28.8, 25.6, 24.7, 23.4, 22.5, 15.6, 14.5, 2.5 ppm. IR (CCl_4): $\tilde{\nu}$ = 1728 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{36}NaO_4Si$ [M + Na]$^+$: 403.2281; found 403.2237.

Supporting Information (see footnote on the first page of this article): Experimental procedures and analytical data for compounds **14**, **16**, **20**–**22**, and **31**–**35**.

Acknowledgments

Support for this work was provided by the Centre National de la Recherche Scientifique and the Université de Strasbourg. The authors are grateful to Dr. Jennifer Wytko for assistance in preparing this manuscript. V. R. thanks the Ministère de la Recherche et de la Technologie (France) for a research fellowship.

[1] W.-H. Lin, J.-M. Fang, Y.-S. Cheng, *Phytochemistry* **1998**, *48*, 1391–1397.
[2] Z.-W. Zhou, S. Yin, H.-Y. Zhang, Y. Fu, S.-P. Yang, X.-N. Wang, Y. Wu, X.-C. Tang, J.-M. Yue, *Org. Lett.* **2008**, *10*, 465–468.
[3] S. H. Senett, S. A. Pomponi, A. E. Wright, *J. Nat. Prod.* **1992**, *55*, 1421–1429.
[4] Q. Wang, C. Chen, *Org. Lett.* **2008**, *10*, 1223–1226.
[5] N. Duarte, M.-J. U. Ferreira, *Org. Lett.* **2007**, *9*, 489–492.
[6] W. R. Chan, E. C. Prince, P. S. Manchand, J. P. Springer, J. Clardy, *J. Am. Chem. Soc.* **1975**, *97*, 4437–4439.
[7] M. K. Renner, P. R. Jensen, W. Fenical, *J. Org. Chem.* **2000**, *65*, 4843–4852.
[8] a) M. Juhl, D. Tanner, *Chem. Soc. Rev.* **2009**, *38*, 2983–2992; b) K. Takao, R. Munakata, K. Tadano, *Chem. Rev.* **2005**, *105*, 4779–4807.
[9] a) L. A. Paquette, Z. Gao, Z. Ni, G. F. Smith, *J. Am. Chem. Soc.* **1998**, *120*, 2542–2552; b) L. A. Paquette, D. MacDonald, L. G. Anderson, J. Wright, *J. Am. Chem. Soc.* **1989**, *111*, 8037–8039; c) L. A. Paquette, J. L. Romine, H. S. Lin, J. Wright, *J. Am. Chem. Soc.* **1990**, *112*, 9284–9292; d) L. A. Paquette, D. MacDonald, L. G. Anderson, *J. Am. Chem. Soc.* **1990**, *112*, 9292–9299; e) J. K. Whitesell, M. A. Minton, *J. Am. Chem. Soc.* **1987**, *109*, 6403–6408.
[10] Reviews: a) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635–662; b) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834. For some recent examples, see: D. Tanaka, Y. Sato, M. Mori, *J. Am. Chem. Soc.* **2007**, *129*, 7730–7731; T. Shibata, H. Kurokawa, K. Kanda, *J. Org. Chem.* **2007**, *72*, 6521–6525.
[11] S. T. Handy, D. Omune, *Tetrahedron* **2007**, *63*, 1366–1371.
[12] A. de Meijere, P. von Zezschwitz, S. Bräse, *Acc. Chem. Res.* **2005**, *38*, 413–422.
[13] a) N-Y. Fu, S-H. Chan, H. N. C. Wong in *The Chemistry of Cyclobutanes*, (Eds: Z. Rappoport, J. F. Liebman), Wiley-VCH, Weinheim, **2005**, pp. 357–440; b) M. Le Liepvre, J. Ollivier, D. J. Aitken, *Eur. J. Org. Chem.* **2009**, 5953–5962.
[14] A. Klein, M. Miesch, *Tetrahedron Lett.* **2003**, *44*, 4483–4485.
[15] CCDC-705681 contains the supplementary crystallographic data for compound **14**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[16] E. Cossement, R. Binamé, L. Ghosez, *Tetrahedron Lett.* **1974**, *12*, 997–1000.
[17] T. R. Hoye, V. Dvornikos, E. Sizova, *Org. Lett.* **2006**, *8*, 5191–5194.
[18] The authors thank and fully agree with the referee who gave this relevant comment.
[19] C. S. Wilcox, R. E. Baston, *J. Org. Chem.* **1984**, *19*, 1451–1453.
[20] CCDC-705680 contains the supplementary crystallographic data for compound **31**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: July 13, 2010
Published Online: November 12, 2010

