# Cascade Reactions of Methyl 2-Chloro-2-cyclopropylideneacetate with Five- and Seven-Membered Cyclic Dienolates: A Novel Approach to the Bicyclo[4.2.1]nonane Segment of the Skeleton of Mediterraneols[1]

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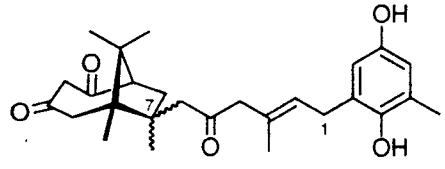
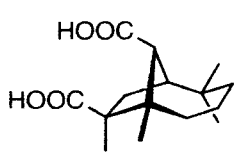
The MIMIRC (Michael–Michael–Ring Closure) reaction of methyl 2-chloro-2-cyclopropylideneacetate (**5**) with the cyclic dienolates **6a, 6c**, and the one derived from **11-R** under aprotic conditions gave the tricyclic adducts **7a**, **7c**, and **10-R**, respectively, in moderate to good yield. Compound **10-R** is conceived as a potential intermediate for the synthesis of the biologically active marine diterpenes mediterraneol **1**.

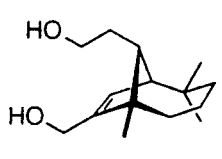
The enhanced Michael reactivity of methyl 2-chloro-2-cyclopropylideneacetate (**5**)[2] and ethyl cyclopropylideneacetate[3] towards lithium cyclohexadienolates **6b** generated under kinetic control, has been described and used for the efficient assembly of bicyclo[2.2.2]- as well as bicyclo[3.2.1]octane skeletons[4] and highly functionalized bicyclic and tricyclic precursors for terpenoid natural products.[5] We have now extended this versatile method to smaller and larger ring systems in order to prepare suitably functionalized potential building blocks for other terpenoid skeletons. The possible "one-pot" approach to bicyclo[4.2.1]nonane derivatives from cycloheptadienolates is of particular interest for the synthesis of the biologically active mediterraneols (**1**), isolated from the mediterranean alga *Cystoseira mediterranea* (Phaeophyta).[6] These uniquely composed diterpenes contain a highly substituted bicyclo[4.2.1]nonane skeleton, which has also been found in several other natural terpenoids and their metabolites such as longicamphoric acid (**2**), and secolongifolenediol (**3**).



α-7-Me: Mediterraneol A (**1a**)
β-7-Me: Mediterraneol B (**1b**)



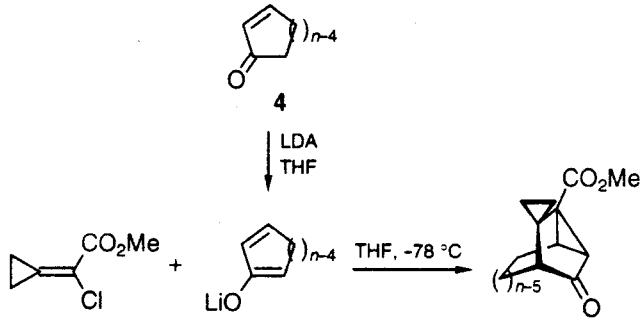
Longicamphoric acid (**2**)



Secolongifolenediol (**3**)

A tetramethylated derivative of *rac*-**1b** has recently been synthesized, and it appears that the structure proposed by Francisco et al. must be corrected to some extent.[7] Most probably, however, this correction does not influence the basic bicyclo[4.2.1]nonane skeleton. Although previously developed routes for the construction of such a skeleton, namely an anionic [1,3] rearrangement of an *exo*-alkenylbicyclo[2.2.1]hept-5-en-2-ol,[8] Cope rearrangement of vinylbicyclo[3.2.0]heptenes,[9] the trapping of cyclooctatetraene dianion with dimethylcarbamoyl chloride,[10] the [6 + 2] cycloadditions with cycloheptatriene,[11] the rearrangement of 7-bromobicyclo[4.3.0]nona-2,4-dien-8-ones under strongly basic conditions,[12] and the Pd-catalyzed allylation of 1-piperidinocyclopentene,[13] all yield unsaturated derivatives, they do not easily permit the preparation of an appropriately substituted skeleton with a complete set of functionalities with defined stereochemistry for necessary further synthetic manipulations in a convergent manner.[14]

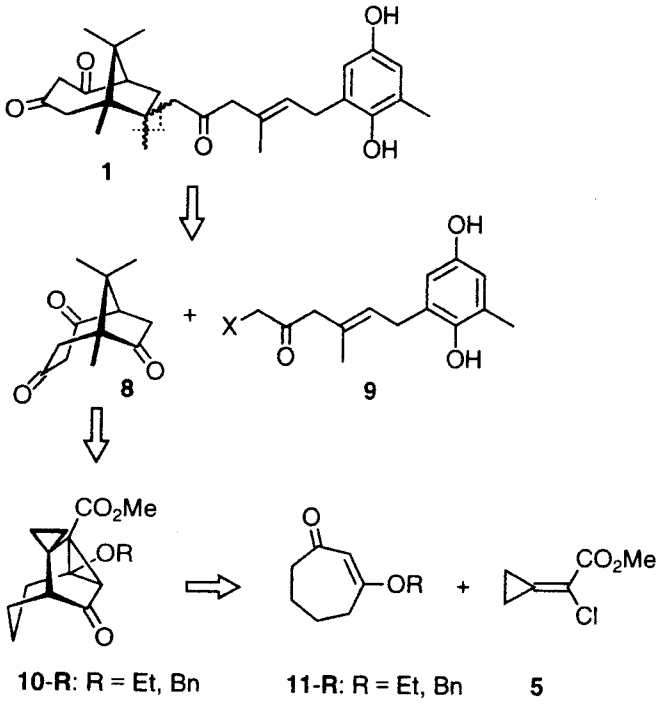
However, the unique properties of the α-chloroacrylate **5** offers such versatility, and we have now found that it is not only an excellent Michael acceptor for six-membered[5] but also for smaller and larger cyclic dienolates. Even the enolate of cyclopent-2-enone **4a** reacts with the α-chloroacrylate **5** under standard conditions,[5] giving methyl 5′-oxospiro[cyclopropane-1,3′-tricyclo[2.2.1.0$^{2,6}$]heptane]-2′-carboxylate (**7a**) in 40% yield. The enolate **6c** of cyclohept-2-enone (**4c**) reacts with **5** to afford methyl 9′-oxospiro[cyclopropane-1,7′-tricyclo[4.2.1.0$^{2,8}$]nonane]-8′-carboxylate (**7c**) in 78% yield. In the latter case, three C–C bonds are formed consecutively with an efficiency of > 90% for each bond in an anionically induced cascade of reactions.[15]



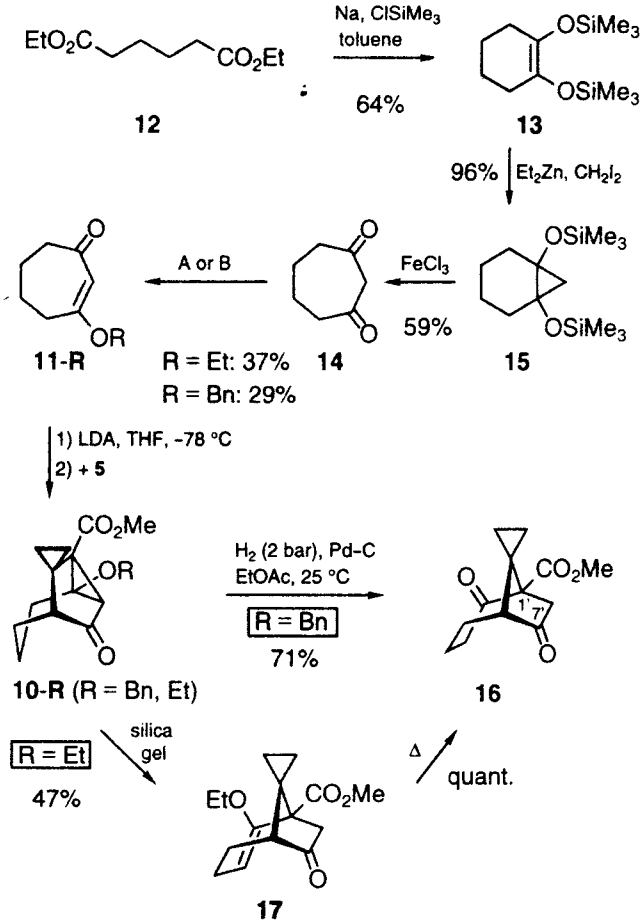

Scheme 1

The easy access to tricycles of type **7c** is of great interest because the key structure of mediterraneols **1** is a bicyclo[4.2.1]nonane skeleton. By applying the previously ex-

ercised retrograde aldol reaction[5] to a bridgehead alkoxy derivative like **10-R** of the tricycle **7c**, one would obtain a bicyclo[4.2.1]nonane-2,7-dione derivative, a potential precursor to the corresponding trione **8** and thus mediterraneol **1** itself (Scheme 2).




Scheme 2




A: EtOH, *p*-TsOH, Δ, 90 min. B: $CF_3SO_3H$, $CH_2Cl_2$, 25 °C, 12 h.

Scheme 3

The bicyclo[4.2.1]nonane-2,7-dione derivatives should thus be accessible from the cycloadducts of the enolate derived from cycloheptenone **11-R** and the α-chloroacrylate **5** by subsequent hydrolysis.

The acyloin condensation[16] of diethyl adipate (**12**) afforded 1,2-bis(trimethylsilyloxy)cyclohexene (**13**). Cyclopropanation ($Et_2Zn/CH_2I_2$) of **13** gave the bicycle **15**, and its treatment with $FeCl_3$[17] afforded cycloheptane-1,3-dione (**14**).[18] The ethyl enol ether **11-Et** was formed from **14** by treatment with ethanol in the presence of 4-toluenesulfonic acid. The benzyl trichloroacetimidate method[19] was used to prepare the corresponding 3-benzyloxycycloheptenone **11-Bn**. Deprotonation with LDA and subsequent addition of α-chloroacrylate **5** afforded the tricyclic oxo ester **10-Bn** (61 % yield). The corresponding ethoxy derivative **10-Et** could not be purified by chromatography, as it rearranged on silica gel to give the bicyclo[4.2.1]non-2'-enol ether **17**. An attempted purification of **17** by distillation under reduced pressure yielded 2',7'-dioxobicyclo[4.2.1]nonane-1'-carboxylate **16**. The dioxo ester **16** was also obtained in good yield (71 %) by hydrogenation of the benzyloxy oxo ester **10-Bn**.

Mp were measured on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS (FT) spectrophotometer. $^1H$ and $^{13}C$ NMR were obtained on a Bruker AM 250 spectrometer. For $^1H$ NMR spectra, chemical shifts are reported in ppm relative to TMS ($CDCl_3$). $^{13}C$ NMR spectra were referenced to the center peak of $CDCl_3$ ($\delta = 77.0$). MS were recorded on a Finnigan MAT CH 7. Elemental analyses were done by the Mikroanalytisches Laboratorium der Universität Göttingen.

Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl or $CaH_2$. All moisture- and air-sensitive reactions were performed in flame-dried glassware under a positive pressure of $N_2$. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated using a Büchi rotary evaporator at ca. 20 Torr.

**Methyl 5'-Oxospiro[cyclopropane-1,3'-tricyclo[2.2.1.0$^{2,6}$]heptane]-2'-carboxylate (7a):**

3.03 M BuLi in cyclohexane (3.30 mL, 10 mmol) was slowly added to a cooled (5 °C) and stirred solution of dry *i*-$Pr_2NH$ (1.41 mL, 9.97 mmol) in anhyd THF (10 mL) under $N_2$. The resulting yellow solution was stirred at 5 °C for 15 min, cooled to − 78 °C and a solution of cyclopent-2-enone (**4a**, 0.82 g, 10 mmol) in anhyd THF (10 mL) was added over 15 min. The resulting yellow solution was stirred at − 78 °C for 45 min, and a solution of methyl 2-chloro-2-cyclopropylideneacetate (**5**, 1.46 mg, 10 mmol) in anhyd THF (10 mL) was added over 15 min. The resulting solution was stirred overnight. Water (20 mL) was added, the organic layer was separated, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel ($CH_2Cl_2$) to afford **7a**; yield: 770 mg (40 %); colorless oil; bp 115 °C/0.03 Torr (Kugelrohr).

IR (neat): $\nu$ = 2955, 1767, 1729, 1440, 1300, 1227, 1164, 1105 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): $\delta$ = 0.38–0.43 (m, 1 H), 0.57–0.63 (m, 1 H), 1.12–1.17 (m, 1 H), 1.14 (s, 1 H), 1.39 (t, $J$ = 1.4 Hz, 1 H), 2.06–2.08 (m, 3 H), 2.75 (ddd, $J$ = 5.5, 2.8, 1.4 Hz, 1 H), 3.62 (s, 3 H).

$^{13}C$ NMR ($CDCl_3$): $\delta$ = 3.6, 4.8, 29.0, 29.2, 29.8, 30.8, 34.3, 47.9, 51.5, 169.3, 209.1.

MS (EI): $m/z$ (%) = 192 ($M^+$, 33), 163 (16), 161 (18), 150 (33), 133 (85), 105 (100), 91 (45), 77 (34).

**Methyl 9′-Oxospiro[cyclopropane-1,7′-tricyclo[4.2.1.0$^{2,8}$]nonane]-8′-carboxylate (7c):**

3.03 M BuLi in cyclohexane (3.30 mL, 10.00 mmol) was slowly added to a cooled (5 °C), stirred solution of dry $i$-$Pr_2NH$ (1.41 mL, 9.97 mmol) in anhyd THF (10 mL) under $N_2$. The resulting yellow solution was stirred at 5 °C for 15 min, cooled to − 78 °C, and a solution of cyclohept-2-enone (**4c**, 1.10 g, 10.00 mmol) in anhyd THF (10 mL) was added over 15 min. The resulting yellow solution was stirred at − 78 °C for 60 min and a solution of methyl 2-chloro-2-cyclopropylideneacetate (**5**, 1.46 g, 10 mmol) in anhyd THF (10 mL) was added over 15 min. The resulting solution was stirred overnight. Sat. aq $NH_4Cl$ (20 mL) was added, the organic layer was separated, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (eluent: $CH_2Cl_2$) to afford **7c**; yield: 1.78 g (78%); colorless oil; bp 130 °C/0.01 Torr (Kugelrohr).

IR (neat) $\nu$ = 2935, 1719, 1438, 1228, 1182, 1151, 1076 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): $\delta$ = 0.25–0.33 (m, 1 H), 0.61–0.70 (m, 1 H), 1.02–1.11 (m, 1 H), 1.22–1.31 (m, 2 H), 1.42–1.50 (m, 1 H), 1.58–1.64 (m, 1 H), 1.72–1.76 (m, 1 H), 1.98–2.01 (m, 1 H), 2.09–2.27 (m, 3 H), 2.53 (dd, $J$ = 9.4, 1.8 Hz, 1 H), 3.58 (s, 3 H).

$^{13}C$ NMR ($CDCl_3$): $\delta$ = 6.7, 11.9, 22.6, 22.7, 23.0, 25.5, 32.6, 40.2, 40.8, 51.5, 53.8, 170.3, 220.4.

MS (EI): $m/z$ (%) = 220 ($M^+$, 70), 205 (31), 192 (48), 188 (33), 161 (49), 160 (55), 133 (100), 117 (45), 105 (81), 91 (78), 77 (34).

**1,6-Bis(trimethylsilyloxy)bicyclo[4.1.0]heptane (15):**[20]

To a suspension of sodium (22.5 g, 0.935 mol) in toluene (350 mL) was added TMSCl (100 mL, 0.785 mol). The resulting mixture was stirred at 40 °C, while a solution of diethyl adipate (**12**, 37.8 g, 0.187 mol) in toluene (60 mL) was added over a period of 16 h. The reaction mixture was then heated under reflux for 4 d. After cooling to r.t., the mixture was filtered, the residue was washed with toluene (2 × 100 mL). The combined organic extracts were evaporated, and the residual oil was fractionally distilled to afford 1,2-bis(trimethylsilyloxy)cyclohexane (**13**);[16] yield: 31.0 g (64%); colorless oil; bp 110–115 °C/25 Torr.

A solution of $Et_2Zn$ (24 mL, 161.9 mmol) in dry toluene (80 mL) was slowly added to a cooled (0 °C) solution of **13** (22.0 g, 81.4 mmol), and $CH_2I_2$ (24 mL) in dry toluene (100 mL). Stirring was continued at 0 °C for an additional 1 h and then at r.t. for 16 h. Sat. aq $NH_4Cl$ (400 mL) was added, the organic layer separated and the aqueous layer extracted with toluene (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried ($MgSO_4$). The solvent was evaporated to afford practically pure 1,6-bis(trimethylsilyloxy)bicyclo[4.1.0]heptane (**15**); yield: 20.2 g (96%); light yellow oil; bp 67–70 °C/0.4 Torr.

**Cycloheptane-1,3-dione (14):**[17]

A solution of **15** (13.7 g, 50.0 mmol) in dry toluene (20 mL) was added over 30 min to a cooled solution of anhyd $FeCl_3$ (25.0 g, 0.154 mol) in dry toluene (100 mL). The resulting mixture was heated at 60 °C for 14 h. After cooling, the reaction was quenched with 10% aq HCl (200 mL), and the mixture extracted with $CHCl_3$ (4 × 50 mL). The combined organic layers were washed with 10% aq HCl (5 × 100 mL) and brine (2 × 100 mL), and then dried ($MgSO_4$). The solvent was evaporated and the residue distilled (Kugelrohr) under reduced pressure to afford cycloheptane-1,3-dione (**14**); yield: 3.70 g (59%); colorless oil; bp 60–70 °C/0.1 Torr.

**3-Ethoxycyclohept-2-en-1-one (11-Et):**

A mixture of cycloheptane-1,3-dione (**14**, 1.0 g, 7.94 mmol), dry EtOH (2 mL), and a catalytic amount (20 mg) of $p$-TsOH in dry benzene (50 mL) was heated under reflux for 90 min. The solvent was evaporated, and the residue was chromatographed on flash silica gel to afford **11-Et**; yield: 668 mg (55% at 68% conversion); yellow oil.

$^1H$ NMR ($CDCl_3$): $\delta$ = 1.28 (t, $J$ = 7.0 Hz, 3 H), 1.74–1.80 (m, 4 H), 2.49–2.55 (m, 4 H), 3.74 (q, $J$ = 7.0 Hz, 2 H), 5.33 (s, 1 H).

$^{13}C$ NMR ($CDCl_3$): $\delta$ = 14.1, 22.2, 23.4, 32.9, 41.5, 64.0, 105.6, 176.3, 202.5.

**3-Benzyloxycyclohept-2-enone (11-Bn):**

A mixture of benzyl trichloroacetimidate (5.20 g, 20.4 mmol), and cycloheptane-1,3-dione (**14**, 1.40 g, 11.1 mmol) in anhyd $CH_2Cl_2$ (50 mL) was treated with $CF_3SO_3H$ (1.67 g, 11.1 mmol) at r.t. for 12 h. The reaction mixture was quenched with aq $NaHCO_3$, extracted with $CH_2Cl_2$ (3 × 75 mL) and chromatographed on silica gel (75 g) with petrol ether/$Et_2O$ (1:1) as eluent; yield: 0.69 g (29%); yellow oil.

$^1H$ NMR ($CDCl_3$): $\delta$ = 7.3–7.4 (m, 5 H, arene-H), 5.52 (s, 1 H, H-2), 4.79 (s, 2 H, $OCH_2$), 2.6–2.7 (m, 4 H), 1.75–2.0 (m, 4 H).

$^{13}C$ NMR ($CDCl_3$): $\delta$ = 202.5 (s), 179.0 (s), 135.4 (s), 128.7 (d), 128.4 (d), 127.8 (d), 106.5 (d), 70.4 (t), 41.6 (t), 32.8 (t), 23.4 (t), 21.1 (t).

**Methyl 2′-Ethoxy-7′-oxospiro[cyclopropane-1,9′-bicyclo[4.2.1]non-2′-ene]-1′-carboxylate (17):**

2.85 M BuLi in cyclohexane (1.75 mL, 4.99 mmol) was slowly added to a cooled (5 °C) and stirred solution of dry $i$-$Pr_2NH$ (0.70 mL, 4.95 mmol) in anhyd THF (10 mL) under $N_2$. The resulting yellow solution was stirred at − 5 °C for 30 min, cooled to − 78 °C, and a solution of 3-ethoxycyclohept-2-enone (**11-Et**, 750 mg, 4.87 mmol) in anhyd THF (10 mL) was added over 10 min. The resulting yellow solution was stirred at − 78 °C for 40 min and a solution of **5** (715 mg, 4.88 mmol) in anhyd THF (10 mL) was added over 10 min. The resulting solution was stirred overnight. Sat. aq $NH_4Cl$ (20 mL) was added, the organic layer separated, the aqueous layer extracted with $CH_2Cl_2$ (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed on silica gel ($CH_2Cl_2$) to afford **17**; yield: 610 mg (47%); colorless oil.

$^1H$ NMR ($CDCl_3$): $\delta$ = 0.31–0.45 (m, 1 H), 0.75–0.83 (m, 1 H), 0.97–1.00 (m, 1 H), 1.10 (t, $J$ = 7.0 Hz, 1 H), 1.32–1.41 (m, 1 H), 1.80–2.04 (m, 4 H), 2.50–2.55 (m, 1 H), 2.62 (d, $J$ = 17.2 Hz, 1 H), 3.15 (d, $J$ = 17.2 Hz, 1 H), 3.50–3.57 (m, 1 H), 3.62 (s, 3 H), 3.70–3.76 (m, 1 H), 4.78 (dd, $J$ = 9.8, 3.6 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): $\delta$ = 8.0, 11.9, 14.3, 20.2, 25.3, 32.1, 50.5, 51.9, 53.0, 61.0, 62.5, 98.5, 156.1, 170.5, 218.6.

**Methyl 2′,7′-Dioxospiro[cyclopropane-1,9′-bicyclo[4.2.1]nonane]-1′-carboxylate (16):**

Distillation (110 °C/0.01 Torr) of **17** (610 mg, 2.16 mmol) afforded **16**; yield: 510 mg (quant); colorless crystals; mp 88–89 °C ($CHCl_3$/hexane).

IR (KBr): $\nu$ = 3082, 2953, 2939, 1743, 1696, 1448, 1442, 1295, 1249, 1234, 1178, 949, 864, 784 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): $\delta$ = 0.48–0.60 (m, 2 H), 0.89–0.97 (m, 1 H), 1.15–1.23 (m, 4 H), 1.38–1.50 (m, 1 H), 1.75–1.91 (m, 2 H), 2.07–2.13 (m, 2 H), 2.50–2.57 (m, 1 H), 2.51 (d, $J$ = 19.4 Hz, 1 H), 3.16 (dt, $J$ = 13.3, 1.9 Hz, 1 H), 3.47 (d, $J$ = 19.4 Hz, 1 H), 3.65 (s, 3 H).

$^{13}C$ NMR ($CDCl_3$): $\delta$ = 7.1, 14.9, 20.7, 26.9, 30.7, 43.1, 50.0, 52.5, 56.5, 66.2, 169.4, 221.7, 226.3.

MS (EI): $m/z$ (%) = 236 ($M^+$, 24), 204 (100), 190 (24), 176 (58), 162 (15), 149 (43), 148 (52), 131 (22), 122 (35), 107 (23), 104 (34), 91 (77), 76 (48).

Anal. calc. for $C_{13}H_{16}O_4$ (236.27): C, 66.09; H, 6.83. found: C, 65.96; H, 6.74.

**Methyl 2′-Benzyloxy-9′-oxospiro[cyclopropane-1,7′-tricyclo[4.2.1.0$^{2,8}$]nonane]-7′carboxylate (10-Bn):**
Enone **11-Bn** (0.432 g, 2.0 mmol) in anhyd THF (10 mL) was deprotonated under Ar with LDA (2.2 mmol) in THF (20 mL) at −78 °C. After 30 min a solution of α-chloro ester **5** (0.351 g, 2.4 mmol) in anhyd THF (10 mL) was added. The reaction mixture was allowed to warm up to r.t. and quenched with aq $NH_4Cl$ (50 mL). The whole mixture was extracted with $Et_2O$ (5 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated to give an oil, which was purified by preparative TLC (silica gel, petrol ether/$Et_2O$, 1:1 as eluent); yield: 0.40 g (61 %); mp 93–95 °C. The compound decomposes on standing to yield **16**.

$^1$H NMR ($CDCl_3$): $\delta$ = 7.15–7.35 (m, 5H), 4.60 (*AB*, $J_{AB}$ = 11.3 Hz, 1H), 4.41 (*AB*, $J_{AB}$ = 11.3 Hz, 1H), 3.60 (s, 3H, ester), 2.66 (d, 1H), 2.6–2.4 (m, 2H), 2.1–1.7 (m, 3H), 1.6–1.3 (m, 2H), 1.3–1.2 (m, 1H, cyclopropyl-H), 0.9–0.7 (m, 2H, cyclopropyl-H), 0.5–0.4 (m, 1H, cyclopropyl-H).

$^{13}$C NMR ($CDCl_3$): $\delta$ = 209.1 (s), 166.8 (s), 137.0 (s), 128.2 (d), 127.6 (d), 127.1 (d), 74.5 (s), 69.3 (t), 53.0 (d), 51.7 (q), 49.0 (s), 44.0 (d), 27.4 (t), 27.3 (t), 23.9 (s), 21.6 (t), 12.7 (t), 6.4 (t).

**Hydrogenolysis of 10-Bn:**
A solution of the ester **10-Bn** (150 mg, 0.46 mmol) in EtOAc (50 mL) was hydrogenated (2 bar, 20 °C, 48 h) in the presence of 20 mg Pd/C (10 %). Filtration and evaporation gave pure **16**; yield: 77 mg (71 %).

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