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The six-membered annulation reaction involving sequential palladium-catalyzed allylic alkylation and Michael addition: scope and limitations

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Abstract—The palladium-catalyzed condensation of a variety of active methylene compounds with methyl 6-acetoxymethyl-hepta-2,6-dienoate was investigated. The six-membered adducts resulting from a η^3 palladium complex alkylation–Michael addition sequence were obtained with moderate to good yields. In some cases, further evolution of the primary adduct was observed. The process has been expanded to access nitrogen heterocycles by using sodium *p*-toluenesulfonamide as the nucleophilic partner.

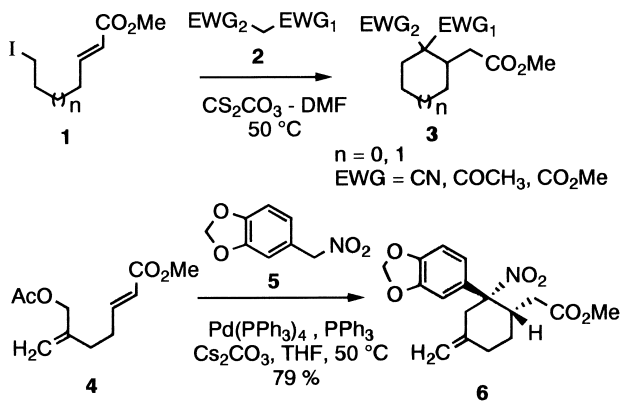
1. Introduction

The ability to sequence carbon–carbon bond forming reactions provides obvious efficiencies in selective organic synthesis. Sequential methods are attractive because elaborate products may be accessed in a single, one-pot process from relatively simple precursors. Many sequential reactions have been designed and a classification has been proposed.[1] Among the tandem processes, anionic sequences in which the first step is a carbon–carbon bond formation through nucleophilic substitution reaction are relatively rare despite their evident synthetic potential.[2] In this respect, we have disclosed an efficient six-membered annulation reaction of compounds possessing an acidic methylene group involving a tandem alkylation–Michael addition sequence.[3]

Thus, the condensation of a methylene active compound **2** with ω-iodo-unsaturated ester **1** in presence of cesium carbonate provided the annulated esters **3** in moderate to good yields. Likewise, when the methylene group is included in a cyclic structure, the reaction can be exploited to provide entry into spirocyclic rings systems.[3]

However this process suffers from a severe drawback, namely the lack of reactivity of substrates possessing a relatively acidic methylene group ($pK_a \leq 9-10$) such as arylnitromethanes. Furthermore cyclic 1,3-diones afford mainly products arising from *O*-alkylation instead of the expected spirocyclic derivatives. Since in both cases the limiting step of this process is the initial S_N2 type alkylation reaction, we recently introduced a variant involving a new η^3 palladium complex alkylation–Michael addition sequence to solve this problem.[4] This reaction was designed at first to prepare the nitro ester **6**, an intermediate in the synthesis of an *Erythrina* alkaloid, from arylnitromethane derivative **5**.[5] Thus reaction of **5** with acetate **4** in presence of 3 mol% of $Pd(PPh_3)_4$ and cesium carbonate as base afforded **6** with a 79% yield.[4] (Scheme 1).

As a development of this promising sequential reaction we wish to report herein the results obtained with others methylene active compounds [**2**+**4**→**7**], thus making this procedure of quite general applicability (Scheme 2).



Scheme 1.

Keywords: annulation; sequential reaction; Michael reaction; palladium and compounds; polycyclic aliphatic compounds.

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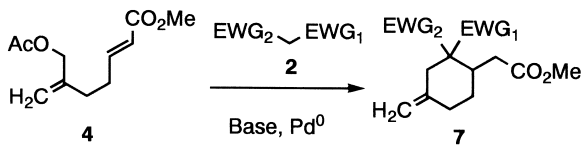
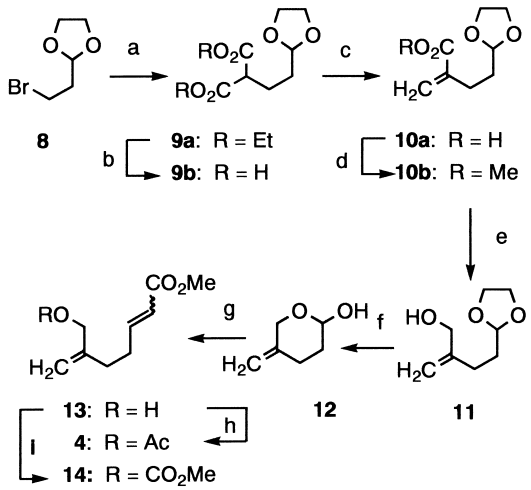


Scheme 2.

2. Results and discussion

The requisite acetoxy-ester **4** was prepared by a variant of our initial procedure[4] allowing a more effective synthetic route on multigram scales.[5a] Commercially available bromo-ketal **8** was reacted with diethyl malonate in presence of sodium ethoxide according to the procedure of Sakai[6] to afford adduct **9a** in 71% yield. Saponification of both ester groups of compound **9a** with potassium hydroxide gave diacid **9b** in 93% yield. Upon decarboxylative Mannich reaction using formalin and dimethylamine,[7] followed by esterification with *N*,*N*-dimethylformamide dimethyl acetal, diacid **9b** provided the unsaturated ester **10b** in 61% overall yield. Attempts to reduce the ester function by using LAH as described,[7] gave an inseparable mixture of **11** and the corresponding saturated alcohol.



Scheme 3. Synthetic route to the allylic acetate **4**. *Reagents and conditions*: (a) $EtO_2CCH_2CO_2Et$, EtONa, EtOH, 80°C, 3 h (71%); (b) KOH, EtOH, 20°C, 12 h (93%); (c) Formalin 40%, Me_2NH, DMSO, 100°C, 2 h (70%); (d) $Me_2NCH(OMe)_2$, toluene, 110°C, 1 h (87%); (e) DIBAL-H, CH_2Cl_2, −78°C; 1 h (72%); (f) HCl 2N, THF, 20°C, 6 h; (g) 2 equiv. $Ph_3P{=}CHCO_2Me$, THF, 20°C, 24 h (77% from **11**); (h) Ac_2O, CH_2Cl_2, Et_3N, DMAP, 20°C, 30 min (97%); (i) MeOCOCl, CH_2Cl_2, py, 20°C, 8 h (90%).

Selective 1,2-reduction of the unsaturated ester group in **10b** was achieved using DIBAL-H. Hydrolysis of the ketal group of **11** afforded the sensitive hemiketal **12**, which was then reacted with methyl (triphenylphosphoranylidene)acetate and acetylated to provide the desired unsaturated ester **4** as a 4:1 mixture of *E*/*Z* isomers in 74% overall yield from **11** (Scheme 3). Alternatively, treatment of alcohol **13** with methyl chloroformate provided carbonate **14** in 90% yield.

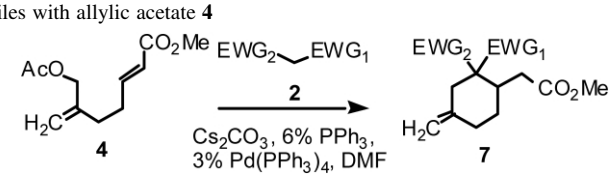
The generality of the annulation reaction was next investigated on simple systems, and the results of this study are summarised in Table 1. Typically, when a DMF solution of 1 equiv. of acetate **4** (as a 4:1 *E*/*Z* mixture) and 3 equiv. of the methylene active compound **2** was heated with 3 equiv. of cesium carbonate in the presence of 3 mol% of $Pd(PPh_3)_4$ and 6 mol% of triphenylphosphine, a smooth reaction occurred to afford annulated esters **7** as a mixture of diastereomers in reasonable yields.

Allylic carbonate **14** could equally be used as the electrophilic partner, provide that cesium carbonate was added to the reaction mixture. Since neither the yield nor the selectivity was improved, this method was not pursued.

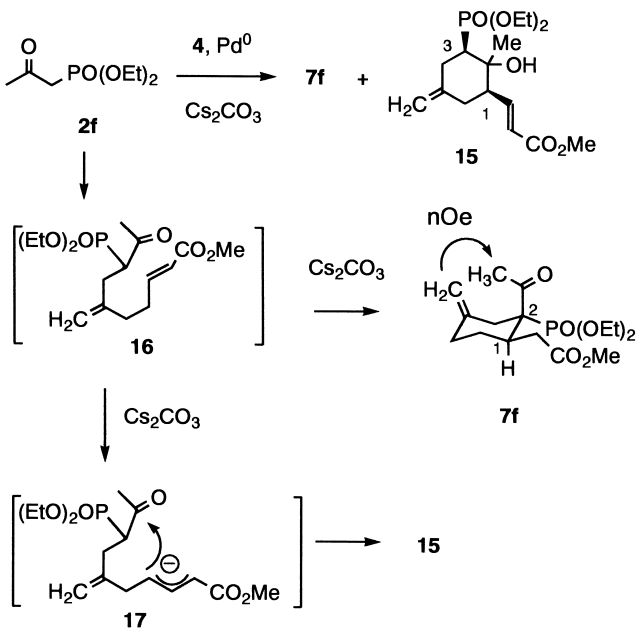
Interestingly, when diethyl (2-oxopropyl)phosphonate **2f** was used as the substrate, the expected adduct **7f** was obtained in 40% as a single diastereomer, along with compound **15** (25%). The stereostructure of phosphonate **7f** was deduced from 2D NMR and NOESY spectra. Unfortunately we were unable to specify the relative stereochemistry of the tertiary alcohol moiety at C-2. The formation of the hydroxy phosphonate **15** could be tentatively explained as follows. Initially, the unsaturated ester **16** was generated by alkylation reaction of the η^3-allylpalladium complex. Cyclization through Michael addition reaction afforded **7f**. However, this latter process may be quite unfavourable due to a facile retro-Michael reaction. Hence, base deconjugation of the unsaturated ester appendage of intermediate **16** might produce the extended enolate **17**, which can cyclize to form alcohol **15** by attack of the methyl ketone moiety (Scheme 4).

These reaction conditions were not successful with cyclic 1,3-diketones, due to the propensity of the initial adduct to ring-open through a retro-Michael process. This was circumvented by the use of a 1:1 mixture of DBU and LiCl[8] instead of Cs_2CO_3 as base. Using these conditions,

Table 1. Reaction of stabilised nucleophiles with allylic acetate **4**



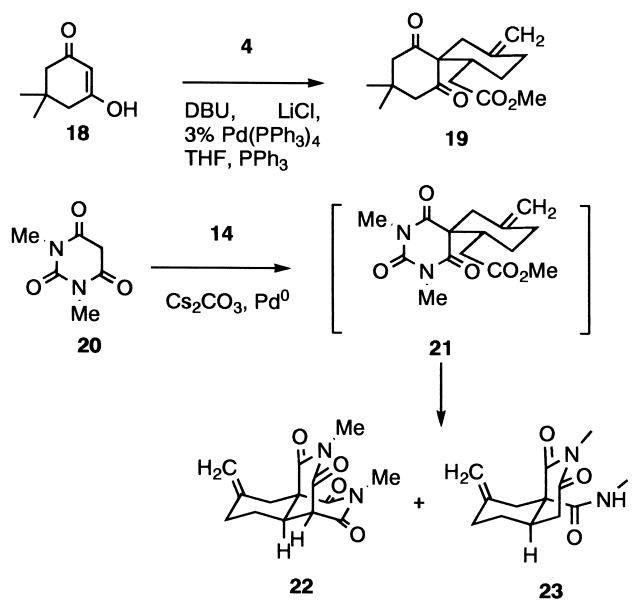
Nucleophile	EWG_1	EWG_2	Product	% Yield of **7**	Diastereomeric ratio of **7**
2a	CO_2Et	CO_2Et	**7a**	72	–
2b	CN	CN	**7b**	67	–
2c	CO_2Me	COMe	**7c**	70	2/1
2d	CO_2Et	CN	**7d**	77	1/0.8
2e	NO_2	CH_3	**7e**	62	3/1
2f	$PO(OEt)_2$	$COCH_3$	**7f**+**15**	40	1/0



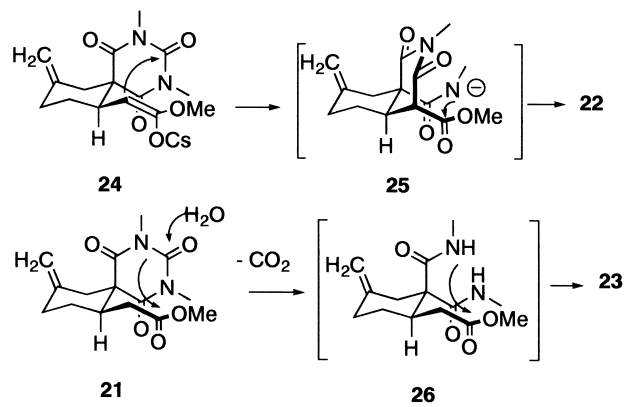
Scheme 4.

dimedone **18** afforded the spiroannulated derivatives **19** in 48% yield.[4]

Attempts at using barbituric acid as a substrate were unsuccessful whatever was the base (Cs_2CO_3, DBU-LiCl, NaH). Assuming that the poor solubility of the corresponding anion might be at the origin of this failure, we turned our attention to the use of *N*-protected derivatives. In the event, reaction of the more soluble 1,3-dimethylbarbituric acid **20** with allylic carbonate **14** occurred readily under the standard conditions (Cs_2CO_3, DMF, 50°C) to give cyclic imides **22** and **23** in 18 and 36% yield, respectively, the expected spirocyclic adduct **21** not being isolated. The *cis*-stereochemistry of the imide **23** was deduced from its ^{1}H NMR spectrum, upon observation of the junction proton at δ 2.85 ppm with distinguishable coupling constants characteristic of an equatorial proton coupled to one axial proton and three adjacent equatorial protons (Scheme 5).



Scheme 5.

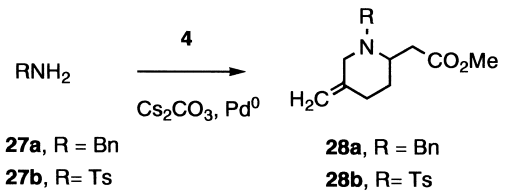


Scheme 6.

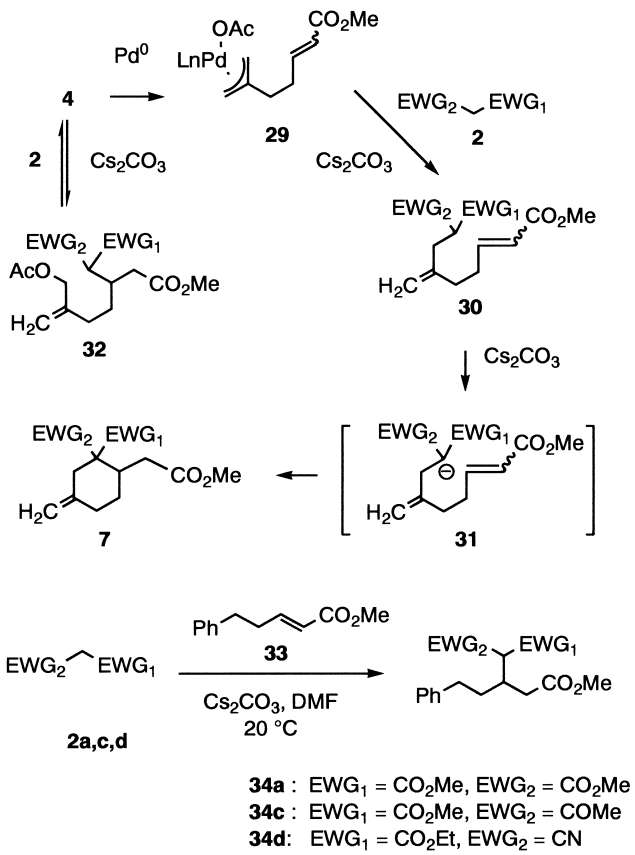
Formation of the tricyclic compound **22** is consistent with the rearrangement of the primary adduct **21**, through attack of the ester enolate on the ureido carbonyl group, followed by nucleophilic addition of the intermediate amide anion to the proximal ester function of **25**. Similarly, attack of water, present in small amount in the reaction mixture,[9] on the ureido carbonyl group of **21**, decarboxylation of the carbamic acid and cyclization by attack on the ester moiety may account for the formation of imide **23** (Scheme 6).

In an attempt to extend the methodology to the synthesis of nitrogen heterocycles,[10] a mixture of allylic acetate **4** and benzylamine was subjected to the standard conditions (Cs_2CO_3, 3% $Pd(PPh_3)_4$, DMF, 50°C). In the event, piperidine **28a** was obtained with a modest 39% yield. In search for a more efficient method, the less basic *p*-toluenesulfonamide was checked as a nucleophilic partner.[10b] Unfortunately the corresponding adduct **28b** was isolated in only 32% yield. The process was finally improved by using sodium *p*-toluenesulfonamide, which delivered adduct **28b** in 45% yield (Scheme 7).

Regarding the mechanism of this sequential reaction, the overall process could be rationalised according to our previously reported mechanism involving alkylation of the initially formed η^3-allylpalladium complex **29**, that delivers the unsaturated ester **30**, which then undergoes ring closure through intramolecular Michael addition to provide cyclized esters **7a**,**f**. An alternative mechanism for the production of **7**, involves initial Michael addition of the stabilized nucleophiles **2** to give adducts **32**, followed by an intramolecular Tsuji–Trost alkylation reaction. To date, we ruled out such a sequence because the first nucleophiles studied, namely 2-tetralone, and arylnitromethane **6** do not undergo Michael addition with β-substituted unsaturated esters in the reaction conditions (Cs_2CO_3, DMF, 20°C) In



Scheme 7.



Scheme 8.

the present case, the Michael addition–alkylation pathway cannot be definitively rejected because simple methylene active compound such as methyl malonate **2a** methyl acetoacetate **2c**, or ethyl cyanoacetate **2d** were found to be good Michael donors with β-substituted unsaturated esters in the reaction conditions. For instance, the treatment of methyl 5-phenyl-2-pentenoate **33** with **2a**, **2c**, or **2d** with Cs_2CO_3, in DMF provided adducts **34a**, **34c**, and **34d** in 90, 52 and 73% yield, respectively. Additional support for the alkylation–Michael addition pathway arose from the fact that when the reaction mixture was quenched before completion, a substantial amount of *C*-alkylated derivatives **30** was observed, but we didn't find Michael adducts of type **32**, with most nucleophiles tested (Scheme 8).[3]

In summary, we have established that the annulation reaction involving condensation of stabilised nucleophiles with allylic acetate **4** is a quite general process, allowing access to an array of six-membered functionalized synthons. Although the sequential η^3 palladium complex alkylation–Michael addition sequence may operate in some cases, the exact mechanism of the process remains to be clarified with the other nucleophiles. Further studies to extend this process, including an enantioselective version and some synthetic applications, are currently in progress.

3. Experimental

3.1. General

Melting points were recorded using a Büchi capillary tube melting point apparatus and were uncorrected. IR spectra were recorded using a Perkin–Elmer 841 spectrometer (neat films between NaCl plates or KBr pellets). The ^1H and ^{13}C NMR spectra were recorded using a Bruker AC 200 P (200 MHz and 50 MHz, for ^1H and ^{13}C, respectively) or a Bruker ARX 400 (400 and 100 MHz, for ^1H and ^{13}C, respectively) spectrometers. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Mass spectra were recorded on a Hewlett Packard G 1019 A (70 eV). Accurate mass spectra measurements were obtained on a Micromass LCT using electrospray (+ESI) at the Institut de Chimie des Substances Naturelles (Gif sur Yvette). Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). Column chromatography was performed on Merck silica gel 60 (230–400 mesh ASTM). Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methanol and ethanol were dried over magnesium and distilled. Benzene, toluene, DMF, and CH_2Cl_2 were distilled from calcium hydride, under a nitrogen atmosphere. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. The boiling points refer to oil-bath temperatures. Elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

3.1.1. 2-[2-(1,3-Dioxolan-2-yl)-ethyl]-propanedioic acid (9b). Diester **9a**[6] (24.0 g, 92.2 mmol) in 95% ethanol (50 mL) was added to a solution of KOH (15.0 g, 0.268 mol) in 95% ethanol (200 mL). The reaction mixture was stirred at 20°C for 12 h and concentrated under reduced pressure. The viscous residue was cooled to 0°C and acidified to pH 3 with 6N hydrochloric acid. The mixture was then concentrated to dryness under vacuum while keeping the temperature below 30°C. The residue was taken into methanol and filtered. The solid was thoroughly washed with methanol, and the filtrate was concentrated to give 17.5 g of diacid **9b** (93%); colorless crystals, mp 94–96°C (MeOH); IR (neat) 3200–2500, 1697, 1452, 1400 cm^{-1}; ^1H NMR (CD_3COCD_3, 200 MHz) δ 6.10–5.20 (broad s, 2H), 4.83 (t, J=4.5 Hz, 1H), 3.95–3.75 (m, 4H), 3.44 (t, J= 7.4 Hz, 1H), 2.10–1.90 10 (m, 2H), 1.85–1.63 (m, 2H); ^{13}C NMR (CD_3COCD_3, 50 MHz) δ 171.2 (2C), 104.5 (CH), 65.5 ($2CH_2$), 51.7 (CH), 32.1 (CH_2), 24.0 (CH_2); Anal. calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.11; H, 5.87.

3.1.2. Methyl 2-[2-(1,3-dioxolan-2-yl)-ethyl]-propenoate (10b). To a solution of diacid **9b** (14.0 g, 68.6 mmol) in DMSO (150 mL), was added 37% aqueous formaldehyde (21 mL, 280 mmol), 40% aqueous dimethylamine (8.5 mL, 68 mmol) and a drop of piperidine. The reaction mixture was heated at 100°C for 2 h. After cooling at 0°C, the solution was acidified to pH 3 with 1N hydrochloric acid. The mixture was extracted with ether, dried and concentrated under reduced pressure. The residue was taken up into toluene (100 mL) and *N*,*N*-dimethylformamide dimethylacetal (8.3 g, 69.6 mmol) was added. After stirring for 1 h at reflux, the mixture was concentrated under reduced pressure. Chromatographic purification on silica gel (hexane/

ethyl acetate/Et_3N, 4:1:0.002) gave 7.65 g of ester **10b** (60% overall); colorless oil; IR (neat) 1725, 1633 1440, 1411, 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.08 (s, 1H), 5.45 (s, 1H), 4.81 (t, J=4.8 Hz, 1H), 3.93–3.70 (m, 4H), 3.68 (s, 3H), 2.38 (t, J=8.5 Hz, 2H), 1.82–1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.2 (C), 139.8 (C), 124.7 (CH_2), 103.6 (CH), 64.7 ($2CH_2$), 51.6 (CH_3), 32.3 (CH_2), 26.2 (CH_2); Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.90; H, 7.55.

3.1.3. 2-[2-(1,3-Dioxolan-2-yl)-ethyl]-prop-2-en-1-ol (11). To a cold solution (−78°C) of ester **10b** (7.5 g, 40.2 mmol) in THF (70 mL) was added dropwise a toluene solution of DIBAL-H (1 M, 8.4 mL, 84 mmol). The mixture was stirred for 1 h at −78°C, and 5 mL of ethyl acetate was then carefully added. The clear solution was poured into an aqueous solution of potassium sodium tartrate (100 mL) and the resulting mixture was stirred for 12 h at 20°C. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate/Et_3N, 4:1:0.002) provided alcohol **11** (4.6 g, 72%) as a colorless oil, bp 79–80°C/0.5 Torr; IR (neat) 3680–3150, 1657, 1446, 1412, 1139 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.94 (s, 1H), 4.78 (m, 2H), 3.95 (s, 2H), 4.00–3.71 (m, 4H), 2.80 (m, 1H), 2.09 (t, J=7.3 Hz, 2H), 1.78–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.8 (C), 108.6 (CH_2), 103.6 (CH), 64.8 (CH_2), 64.3 ($2CH_2$), 31.5 (CH_2), 26.5 (CH_2).

3.1.4. (*Z*) and (*E*)-Methyl 6-hydroxymethyl-hepta-2,6-dienoate (13). To a solution of alcohol **11** (4.3 g, 27.2 mmol) in THF (60 mL) was added 2N HCl (30 mL, 60 mmol). After stirring the mixture for 5 h at 20°C, the pH was brought to 10 with solid $NaHCO_3$. Evaporation of the THF afforded a residue which was extracted thoroughly with CH_2Cl_2. The organic layers were dried and concentrated under reduced pressure to leave hemiketal **12** as a pale yellow oil. The crude hemiketal was taken into CH_2Cl_2 (50 mL) and methyl (triphenylphosphoranylidene)acetate (17.0 g, 50.9 mmol) was added portionwise. The reaction mixture was stirred at 20°C for 16 h. The solvent was removed under reduced pressure and the residue was taken into 100 mL a mixture of ether/pentane (1:1) and filtrated. The filtrate was concentrated in vacuo to leave a colorless oil. Chromatographic separation on silica gel (cyclohexane/ethyl acetate, 4:1) afforded first 0.70 g of unsaturated ester (*Z*)-**13** (15%), R_f=0.57; colorless oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.15 (td, J=12.1, 6.7 Hz, 1H), 5.80 (dt, J=12.1, 0.4 Hz, 1H), 5.07 (s, 1H), 4.89 (s, 1H), 4.10 (s, 2H), 3.71 (s, 3H), 2.90–2.75 (m, 2H), 2.24 (t, J=7.6 Hz, 2H), 1.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.9 (C), 149.7 (CH), 147.7 (C), 119.8 (CH), 110.4 (CH_2), 65.8 (CH_2), 51.1 (CH_3), 32.1 (CH_2), 27.1 (CH_2). Further elution gave 2.86 g of (*E*)-**13** (62%), R_f=0.48; colorless oil; IR (neat) 3590–3160, 1720, 1655, 1436, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.84 (td, J=16.8, 5.7 Hz, 1H), 5.71 (dt, J=16.8, 0.4 Hz, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 4.04 (s, 2H), 3.69 (s, 3H), 3.33 (m, 1H), 240–2.30 (m, 2H), 2.24 (t, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.9 (C), 148.5 (CH), 147.1 (C), 120.9 (CH), 109.8 (CH_2), 65.1 (CH_2), 51.1 (CH_3), 30.7 (CH_2), 29.9 (CH_2).

3.1.5. (*E*)-Methyl 6-acetoxymethyl-hepta-2,6-dienoate (4). A solution of alcohol (*E*)-**13** (1.50 g, 8.8 mmol) in CH_2Cl_2 (20 mL) was cooled at 0°C. Triethylamine (1.8 g, 17.8 mmol), DMAP (20 mg), and acetic anhydride (1.35 g, 13.2 mmol) were sequentially added. After stirring for 1 h at 20°C, 1N HCl was added. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2. After drying, the combined organic layers were concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give 1.81 g of acetate (*E*)-**4** (97%); colorless oil, bp 60–65°C/0.5 mm; IR (neat) 1745 1731 1657 1440, 1376 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.88 (td, J=15.4, 6.5 Hz, 1H), 5.77 (dt, J=15.4, 2.8 Hz, 1H), 5.00 (s, 1H), 4.88 (s, 1H), 4.43 (s, 2H), 3.63 (s, 3H), 2.30–2.35 (m, 2H), 2.20–2.14 (m, 2H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4 (C), 166.7 (C), 147.9 (CH), 142.3 (C), 121.4 (CH), 113.3 (CH_2), 65.2 (CH_2), 51.2 (CH_3), 31.3 (CH_2), 30.0 (CH_2), 20.8 (CH_3); Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.19; H, 7.64.

3.2. General procedure for the synthesis of the annulated compounds (7)

To a solution of the given methylene active compound **2** (3 mmol), allylic acetate **4** (4:1 *E*/*Z* mixture, 210 mg, 1 mmol), triphenylphosphine (16 mg, 0.06 mmol), and tetrakis(triphenylphosphine)palladium (35 mg, 0.03 mmol) in DMF (10 mL) was added cesium carbonate (975 mg, 3 mmol). The mixture was carefully degassed through two freeze-pump-thaw cycles and stirred at 50°C for 8 h. 1N HCl was then added, and the mixture was extracted with ether (3×10 mL). The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate, 4:1) afforded the corresponding adducts **7a**–**f**.

3.2.1. 2-Methoxycarbonylmethyl-5-methylene-cyclohexane-1,1-dicarboxylic acid diethyl ester (7a). The general procedure with diethyl malonate afforded triester **7a** as a colorless oil in 72% yield; bp 110–115°C (0.1 Torr); IR (neat) 1739, 1656, 1439, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.70 (s, 1H), 4.63 (s, 1H), 4.23–4.05 (m, 4H), 3.64 (s, 3H), 2.77 (d, J=13.5 Hz, 1H), 2.64–2.49 (m, 4H), 2.27–2.00 (m, 2H), 1.92–1.77 (m, 1H), 1.67–1.47 (m, 1H), 1.21 (t, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.1 (C), 170.7 (C), 169.7 (C), 143.5 (C), 110.6 (CH_2), 61.4 (CH_2), 60.9 (CH_2), 59.8 (C), 51.5 (CH_3), 39.9 (CH_2), 37.5 (CH), 35.9 (CH_2), 32.4 (CH_2), 29.3 (CH_2), 13.9 ($2CH_3$); Anal. calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.34; H, 7.81.

3.2.2. (2,2-Dicyano-4-methylene-cyclohexyl)-acetic acid methyl ester (7b). The general procedure starting with malonitrile afforded **7b** as a white solid in 67% yield; mp 86–87°C; IR (neat) 2249 (weak), 1731, 1657, 1446, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.04 (s, 1H), 5.02 (s, 1H), 3.74 (s, 3H), 2.96 (dd, J=13.6, 1.6 Hz, 1H), 2.87 (d, J=15.2 Hz, 1H), 2.70 (dd, J=13.6, 1.2 Hz, 1H), 2.62–2.35 (m, 3H), 2.20–2.00 (m, 2H), 1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6 (C), 137.8 (C), 115.6 (CH_2), 115.2 (C), 112.9 (C), 52.1 (CH_3), 42.9 (CH_2), 40.6 (CH), 39.4 (C), 37.1 (CH_2), 32.2 (CH_2), 28.8 (CH_2); Anal.

calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.86; H, 6.60; N, 12.67.

3.2.3. 1-Acetyl-2-methoxycarbonylmethyl-5-methylene-cyclohexanecarboxylic acid methyl ester (7c). The general procedure with methyl acetoacetate afforded triester **7c** as a colorless oil in 70% yield; bp 90–100°C (0.05 Torr); IR (neat) 1734, 1709, 1653, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) the presence of two diastereomers induces the splitting of some signals δ 4.70–4.60 (m, 2H), 3.69 and 3.68 (2s, 3H), 3.63 (s, 3H), 2.80–2.00 (m, 7H), 2.15 and 2.12 (2s, 3H), 1.95–1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) only the major diastereomer is described δ 203.9 (C), 172.8 (C), 171.5 (C), 143.7 (C), 110.3 (CH_2), 65.3 (C), 52.4 (CH_3), 51.4 (CH_3), 37.6 (CH_2), 36.3 (CH), 34.8 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 27.1 (CH_3); HRMS (ESI) calcd for $C_{14}H_{20}O_5Na$ 291.1203 [$(M+Na)^+$], found 291.1194.

3.2.4. 1-Cyano-2-methoxycarbonylmethyl-5-methylene-cyclohexanecarboxylic acid ethyl ester (7d). The general procedure with ethyl cyanoacetate afforded compound **7d** as a colorless oil in 77% yield; IR (neat) 2243 (weak), 1735, 1656, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) the presence of two diastereomers induced the splitting of most signals δ 4.91, 4.89 4.82 and 4.78 (4s, 2H), 4.23 (q, J=7.2 Hz, 2H), 3.64 and 3.65 (2s, 3H), 2.90–2.49 (m, 7H), 1.45 (m, 1H), 1.40 and 1.38 (2t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) the presence of two diastereomers induced the splitting of some signals δ 171.6 and 171.2 (C), 168.0 and 166.3 (C), 140.6 and 140.2 (C), 118.8 and 116.4 (C), 113.2 and 112.6 (CH_2), 62.8 and 62.5 (CH_2), 52.4 and 48.6 (C), 51.7 (CH_3), 42.1 and 40.0 (CH_2), 38.5 and 38.2 (CH), 37.0 and 34.8 (CH_2), 32.8 and 31.0 (CH_2), 29.6 and 27.7 (CH_2), 13.8 (CH_3); Anal. calcd for $C_{14}H_{19}NO_4$: C, 63.37; H, 7.21; N, 5.28. Found: C, 63.33; H, 7.05; N, 5.14.

3.2.5. (2-Nitro-2-methyl-4-methylene-cyclohexyl)-acetic acid methyl ester (2e). The general procedure with nitroethane afforded nitro ester **2e** as a colorless oil in 62% yield; IR (neat) 1736, 1670, 1535 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) the presence of two diastereomers induced the splitting of some signals δ 4.85–4.70 (m, 2H), 3.64 and 3.65 (2s, 3H), 3.00–2.80 (m, 2H), 2.50–1.60 (m, 6H), 1.58 and 1.40 (2s, 3H), 1.16 (qd, J=13.0, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) major diastereomer δ 171.6 (C), 142.4 (C), 112.1 (CH_2), 92.0 (C), 51.6 (CH_3), 47.0 (CH_2), 40.1 (CH), 35.3 (CH_2), 33.1 (CH_2), 29.3 (CH_2), 16.5 (CH_3), minor diastereomer δ 172.6 (C), 142.4 (C), 111.9 (CH_2), 90.7 (C), 51.6 (CH_3), 43.2 (CH_2), 40.3 (CH), 34.1 (CH_2), 31.1 (CH_2), 27.9 (CH_2), 25.6 (CH_3); Anal. calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.22; H, 7.58; N, 6.04.

3.2.6. [2-Acetyl-2-(diethoxy-phosphoryl)-4-methylene-cyclohexyl]-acetic acid methyl ester (7f) and 3-[3-(diethoxy-phosphoryl)-2-hydroxy-2-methyl-5-methylene-cyclo-hexyl]-acrylic acid methyl ester (15). The general procedure with (2-oxopropyl)-phosphonic acid diethyl ester **2f** afforded a mixture of the keto-phosphonate **7f** and the hydroxy phosphonate **15**. Chromatographic purification on silica gel (ethyl acetate) afforded first hydroxy phosphonate **15** (R_f=0.57) as a colorless oil in 15% yield; IR (neat) 3424, 1721, 1653, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.08 (dd, J=15.8, 9.5 Hz, 1H), 5.82 (d, J=15.8 Hz, 1H), 4.73 (s, 1H), 4.70 (s, 1H), 4.15–4.07 (m, 4H), 3.84 (s, 1H), 3.73 (s, 3H), 2.61 (ddd, J_{HH}=14.0, 13.8 Hz, J_{PH}=7.5 Hz, 1H), 2.54 (t, J=12.2 Hz, 1H), 2.38 (ddd, J_{HH}=13.7, 4.0 Hz, J_{PH}= 4.0 Hz, 1H), 2.08 (ddd, J=12.2, 9.5, 3.0 Hz, 1H), 2.01 (dd, J=12.2, 3.0 Hz, 1H), 1.94 (ddd, J_{HH}=14.0, 4.0 Hz, J_{PH}= 19.9 Hz, 1H), 1.36–1.30 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.6 (C), 149.1 (CH), 144.6 (d, J_{CP}=16 Hz, C), 122.5 (CH), 109.2 (CH_2), 69.9 (C), 62.6 (d, J_{CP}=7 Hz), 61.4 (d, J_{CP}=7 Hz), 52.8 (d, J_{CP}=16 Hz, CH), 51.4 (CH_3), 45.8 (d, J_{CP}=134 Hz, CH), 35.9 (CH_2), 30.9 (CH_2), 27.9 (CH_3), 16.3 ($2CH_2$); HRMS (ESI) calcd for $C_{16}H_{27}O_6PNa$ 369.1396 [$(M+Na)^+$], found 369.1407. Further elution provided **7f** (R_f=0.49) as colorless oil in 40% yield; IR (neat), 1732, 1711, 1653, 1437 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 4.59 (s, 1H), 4.57 (s, 1H), 3.95–3.80 (m, 4H), 3.38 (dd, J=16.7, 2.0 Hz, 1H), 3.33 (s, 3H), 3.20 (dd, J= 16.7, 10.7. Hz, 1H), 3.11 (ddd, J_{HH}=13.8, 2.0 Hz, J_{CP}= 6.2 Hz, 1H), 2.76 (m, 1H), 2.53 (dd, J_{HH}=13.8 Hz, J_{CP}= 10.0 Hz, 1H), 2.27 (s, 3H), 2.05 (m, 1H), 2.00–1.82 (m, 2H), 1.76 (dddd, J=13.4, 12.2, 12.2, 5.3 Hz, 1H), 0.99 (q, J=7.2 Hz, 6H); ^{13}C NMR (C_6D_6, 100 MHz) δ 203.8 (C), 173.7 (C), 144.2 (d, J_{CP}=12.8 Hz, C), 110.6 (CH_2), 62.9 (d, J_{CP}=7.2 Hz, CH_2), 62.3 (d, J_{C-P}=7.2 Hz, CH_2), 61.7 (d, J_{CP}=123 Hz, C), 50.9 (CH_3), 40.2 (d, J_{CP}=5.8 Hz, CH_2), 38.4 (d, J_{CP}=4.4 Hz, CH), 37.3 (CH_2), 34.1 (CH_2), 30.4 (d, J_{CP}=11.2 Hz, CH_2), 28.9 (CH_3), 16.3 ($2CH_3$); HRMS (ESI) calcd for $C_{16}H_{27}O_6PNa$ 369.1396 [$(M+Na)^+$], found 369.1420.

3.2.7. (1-Benzyl-5-methylene-piperidin-2-yl)-acetic acid methyl ester (28a). The general procedure with benzylamine afforded piperidine **28a** as pale yellow oil in 39% yield; IR (neat) 1735, 1654, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.30 (m, 5H), 4.81 (s, 1H), 4.63 (s, 1H), 3.71 (d, J=13.3 Hz, 1H), 3.68 (s, 3H), 3.55 (d, J=13.3 Hz, 1H), 3.28 (m, 1H), 3.21 (d, J=13.4 Hz, 1H), 2.90 (d, J=13.4 Hz, 1H), 2.78 (dd, J=14.3, 6.2 Hz, 1H), 2.49 (dd, J=14.3, 8.1 Hz, 1H), 2.42–2.19 (m, 2H), 1.94–1.78 (m, 1H), 1.68–1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.7 (C), 143.0 (C), 139.2 (C), 128.7 (2CH), 128.1 (2CH), 126.7 (CH), 109.5 (CH_2), 56.6 (CH), 55.5 (CH_2), 54.9 (CH_2), 51.5 (CH_3), 36.7 (CH_2), 30.7 (CH_2), 29.0 (CH_2).

3.2.8. 9,12-Dimethyl-3-methylene-9,12-diazatricyclo-[5.3.3.$0^{1,6}$]tridecane-8,10,11,13-tetraone (22) and 2-methyl-7-methylene-1,3-dioxo-octahydro-isoquinoline-8a-carboxylic acid methylamide (23). The general procedure with 1,3-dimethylbarbituric acid **20** and carbonate **14** gave a 1:2 mixture of tricyclic imide **22** and amide **23**. Chromatographic purification on silica gel (hexane/ethyl acetate, 1:1) afforded tricyclic imide **22** (R_f=0.6) as colorless crystals (18%); mp 197–198°C; IR (neat): 1716, 1688, 1651, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.99 (d, J=1.6 Hz, 1H), 4.88 (d, J=1.6 Hz, 1H), 3.95 (d, J= 2.7 Hz, 1H), 3.65 (dd, J=14.1, 1.3 Hz, 1H), 3.17 (s, 3H), 3.16 (s, 3H), 2.66 (ddd, J=13.4, 4.2, 2.7 Hz, 1H), 2.37 (dddd J=13.6, 4.2, 2.1, 2.1 Hz, 1H), 2.21 (dd, J=14.1, 1.4 Hz, 1H), 2.07 (broad t, J=13.6 Hz, 1H), 1.96 (m, 1H), 1.31 (qd, J=13.6, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9 (C), 166.9 (C), 166.1 (C), 165.6 (C), 141.0 (C), 114.2 (CH_2), 54.6 (CH), 54.5 (C), 37.7 (CH_2), 36.5 (CH), 32.7 (CH_2), 28.5 (CH_2), 27.7 (CH_3), 27.3 (CH_3); MS (70 eV) m/z: 276

($M^{+\cdot}$, 35), 217 (100), 218 (15), 189 (52), 163 (44), 162 (45), 161 (30), 134 (20);); HRMS (ESI) calcd for $C_{14}H_{17}N_2O_4$ 277.1184 [$(M+H)^+$], found 277.1199. Further elution provided lactam **23** (R_f=0.28), as a white solid (36%), mp 114–116°C; IR (neat): 3385, 1722, 1669, 1527 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.22 (broad s, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 3.15 (s, 3H), 3.13 (d, J=13.4 Hz, 1H), 2.99 (dd, J=17.6, 5.0 Hz, 1H), 2.85 (dddd, J=13.4, 5.0, 4.5, 2.6 Hz, 1H), 2.87 and 2.84 (2s, 3H), 2.53 (dd, J=17.6, 2.6 Hz, 1H), 2.29 (d, J=13.4 Hz, 1H), 2.25 (m, 1H), 2.07 (ddd, J=14.0, 13.4, 3.8 Hz, 1H), 1.88 (m, 1H), 1.23 (qd, J=13.4, 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (C), 171.6 (C), 168.7 (C), 142.5 (C), 111.9 (CH_2), 57.1 (C), 42.1 (CH_2), 36.8 (CH_2), 33.0 (CH_2), 31.8 (CH), 30.2 (CH_2), 26.8 ($2CH_3$); MS (70 eV) *m/z*: 250 ($M^{+\cdot}$, 5), 193 (20), 192 (100), 164 (16), 150 (12), 91 (14); Anal. calcd for $C_{13}H_{18}N_2O_3 \cdot 1/4H_2O$: C, 61.28; H, 7.32; N, 10.99; Found: C, 61.29; H, 7.41; N, 10.93.

3.2.9. Methyl 9,9′-dimehyl-4-methylene-7,11-dioxo-spiro-[5.5]undec-1-yl)acetate (19). To solution of dimedone **18** (280 mg, 2 mmol) and acetate **4** (215 mg, 1 mmol) in dry DMF (10 mL) were added triphenylphosphine (52 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (60 mg, 0.05 mmol), LiBr (174 mg, 2 mmol) and finally DBU (304 mg, 2 mmol). The mixture was heated at 50°C for 24 h. After cooling, HCl 1N was added until pH 4, and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried, filtrated and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate, 4:1) afforded 143 mg of spirodiketone **18** (48%), as colorless crystals; mp 84–86°C (ether); IR (neat) 1730, 1694, 1657 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) The spectra were recorded at 50°C due to the presence of two slowly interconverting conformers at 20°C, δ 4.73 (s, 1H), 4.64 (s, 1H), 3.65 (s, 3H), 2.77–2.70 (m, 4H), 2.45 (dd, J=15.1, 2.4 Hz, 1H), 2.43–2.31 (m, 2H), 2.27–2.23 (m, 2H), 2.12 (dd, J=15.6, 2.9 Hz, 1H), 2.10–1.90 (m, 2H), 1.80 (m, 1H), 1.08 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.2 (C), 207.5 (C), 172.9 (C), 142.7 (C), 110.4 (CH_2), 70.1 (C), 51.7 (CH_2), 51.5 (CH_3), 50.7 (CH_2), 44.0 (CH_2), 36.0 (CH_2), 34.8 (CH), 32.8 (CH_2), 30.9 (C), 30.1 (CH_3), 28.2 (CH_2), 26.9 (CH_3); Anal. calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; Found: C, 69.68; H, 8.30.

3.2.10. [5-Methylene-1-(toluene-4-sulfonyl)-piperidin-2-yl]-acetic acid methyl ester (28b). To a solution of sodium *p*-toluenesulfonamide (608 mg, 3.15 mmol) and acetate **4** (223 mg, 1.05 mmol) in dry DMF (6 mL) were added triphenylphosphine (16 mg, 0.06 mmol) and tetrakis(triphenylphosphine)palladium (36 mg, 0.03 mmol). The resulting mixture was heated at 50°C for 24 h. After cooling, HCl 1N was added until pH 4, and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried, filtrated and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate, 4:1) afforded 154 mg of sulfonamide **28b** (45%), as a colorless oil; IR (neat) 1734, 1680, 1656, 1598, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.70 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.4 Hz, 2H), 4.81 (s, 1H), 4.72 (s, 1H), 4.50–4.30 (m, 1H), 4.26 (d, J=15.4 Hz, 1H), 3.69 (d, J=15.4 Hz, 1H), 3.68 (s, 3H), 2.69 (d, J=7.4 Hz, 2H), 2.41 (s, 3H), 2.30–2.15 (m, 1H), 1.99 (dt, J=15.0, 4.8 Hz, 1H), 1.65–1.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.1 (C), 143.2 (C), 140.5 (C), 137.4 (C), 129.5 (2CH), 127.3 (2CH), 110.8 (CH_2), 51.8 (CH_3), 49.8 (CH), 46.8 (CH_2), 36.1 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 21.5 (CH_3); Anal. calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.29; H, 6.70; N, 4.21.

References

1. (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–312. (b) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103–13159.
2. For some representative examples, see: (a) Posner, G. H.; Hamill, T. G. *J. Org. Chem.* **1988**, *53*, 6031–6035. (b) Vergne, F.; Aitken, D. J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 6071–6075. (c) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931–5936. (d) d'Angelo, J.; Le Dréau, M.-A.; Desmaële, D.; Dumas, F. *J. Org. Chem.* **1993**, *58*, 2933–2935. (e) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811–11812. (f) Srikrishna, A.; Reddy, T. J.; Kumar, P. P. *Synlett* **1997**, 663–664. (g) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *J. Org. Chem.* **1998**, *63*, 900–902.
3. Desmaële, D.; Louvet, J.-M. *Tetrahedron Lett.* **1994**, *35*, 2549–2552. Le Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933–2935.
4. Jousse, C.; Mainguy, D.; Desmaële, D. *Tetrahedron Lett.* **1997**, *39*, 1349–1352.
5. (a) Jousse, C.; Desmaële, D. *Eur. J. Org. Chem.* **1999**, 907–915. (b) Jousse, C.; Desmaële, D.; Chiaroni, A.; Riche, C. *Eur. J. Org. Chem.* **2001**, 3631–3640.
6. Yamanaka, E.; Narushima, M.; Inukai, K.; Sakai, S.-i. *Chem. Pharm. Bull.* **1986**, *34*, 77–81.
7. Vig, O. P.; Vig, B.; Khertarpal, R. K.; Anand, R. C. *Indian J. Chem.* **1969**, 450–452.
8. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, P. A.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
9. Commercially available 1,3-dimethylbarbituric acid which contains ca. 6% of water was used.
10. (a) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727–1733. (b) Bunce, R. A.; Allison, J. C. *Synth. Commun.* **1999**, *29*, 2175–2186.