Regioselective Annulation of 1,5-Diketones: Access to Functionalized Hagemann's Esters

Abdoulaye Gassama,[a] Jean d'Angelo,*[a] Christian Cavé,[b] Jacqueline Mahuteau,[a] and Claude Riche[c]

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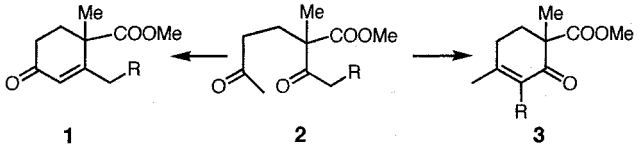
The synthesis of the "functionalized" Hagemann's ester (*S*)-**18** was investigated. The common starting material in these approaches was enamino ester (*S*,*Z*)-**5**, which was prepared through the condensation of keto diester **4** with (*S*)-1-phenylethylamine. The Michael addition reaction of **5** with methyl vinyl ketone gave the expected adduct (*S*)-**6** with an *ee* ≥ 95%. However, all attempts at annulation of **6** invariably afforded the unwanted cyclohexenone derivatives **7** or **8**. The addition of **5** to Nazarov reagent **9** furnished adduct (*S*)-**10** with an *ee* ≥ 95%. The Triton B-induced annulation of **10** unexpectedly gave aldol **11**. Depending on the reaction conditions, annulation of **11** afforded either the bicyclic lactone **12**, or cyclohexenones **13** or **15**. An efficient way of reversing the sense of the regiochemistry of the previous annulation was found, based on the use of diethyl 2-oxo-3-vinylphosphonate (**16**) as a Michael acceptor. Thus, the condensation of **5** with **16** gave (*S*)-**17** with an *ee* ≥ 95%, and cyclization of (*S*)-**17** under Horner–Wadsworth–Emmons conditions gave the desired Hagemann's ester (*S*)-**18**. The structural assignments for **18** were ascertained by chemical correlation with the known hydrindenedione (*S*)-**21**.

Introduction

The Hagemann's esters **1**, which are key intermediates in the synthesis of a variety of complex molecules,[1] are essentially elaborated through the annulation of 1,5-diketones **2**. A well known problem arises, however, from the fact that the desired aldol condensation regiochemistry of diketones **2** may be not that found under the usual conditions. It has long been established that the course of this cyclization is guided mainly by steric factors.[2] Thus, while the annulation of diketone **2**, R = H can be cleanly directed towards the Hagemann's ester **1**, R = H,[1] ring closure of the functionalized homologue **2**, R = CH_2COOMe furnished exclusively the unwanted regioisomer **3**, R = CH_2COOMe (Scheme 1).[2,3] In connection with our work on the synthesis of specifically labeled 17-ketosteroids, we were recently faced with the elaboration of the Hagemann's ester **1**, R = CH_2COOMe and analogs. We report here an efficient, highly selective approach to such compounds.

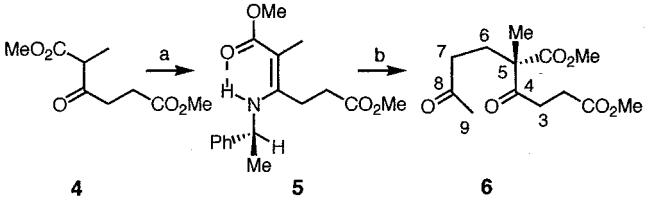


Scheme 1. Annulation of diketones **2**: the two competing pathways

[a] Unité de Chimie Organique Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris Sud,
5 rue J.-B. Clément, 92296, Châtenay-Malabry, France
Fax: (internat.) +33-1/46835752
E-mail: jean.dangelo@cep.u-psud.fr
[b] Laboratoire de Chimie Organique, Faculté de Pharmacie,
7 Bld Jeanne d'Arc, 21033 Dijon, France
[c] ICSN, CNRS,
Avenue de la Terrasse, 91198, Gif sur Yvette, France

Results and Discussion

We first decided to reexamine the annulation of diketone **2**, R = CH_2COOMe. This compound, in the proper "natural" (*S*) configuration (**6**), was synthesized by an original route involving the asymmetric Michael addition of chiral β-enamino esters to electrophilic alkenes (Scheme 2).[4] When the enamino ester (*S*,*Z*)-**5**, prepared from keto diester **4**[5] and (*S*)-1-phenylethylamine (80% yield), was exposed to methyl vinyl ketone in the presence of 1 equiv. of $ZnCl_2$, the expected Michael adduct (*S*)-**6** was obtained in 80% yield and *ee* ≥ 95% (determined by ^1H NMR spectroscopy, after adding $Eu(hfc)_3$ as a chiral shift reagent).



Scheme 2. Synthesis and Michael addition reaction of enamino ester **5** with methyl vinyl ketone: reagents and conditions: (a) (*S*)-1-phenylethylamine, 12 h, 80 °C; (b) i: methyl vinyl ketone, $ZnCl_2$, THF, 2 h, 0 °C, ii: AcOH, H_2O

As previously reported,[2] MeONa-induced annulation of **6** exclusively furnished the cyclohexenone (*S*)-**7** in 90% yield, instead of the desired regioisomer **1**, R = CH_2COOMe. Several other conditions for cyclization of **6** were also attempted, but they all exclusively furnished the compound **8**, arising from the removal of the methoxycarbonyl function of enone **7** (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU): 90% yield; Triton B: 95% yield; piperidine, AcOH: 70% yield, Scheme 3). Thus, the intramolecular aldol condensation of **6** invariably involved the methylene

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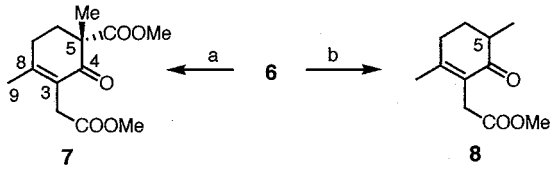
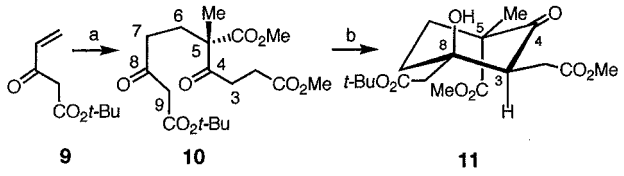
group at C-(3) and the carbonyl at C-(8), rather than the methyl at C-(9) and the hindered carbonyl at C-(4) (the atom numbering system here has been arbitrarily used throughout this paper, except in the Experimental Section).



Scheme 3. Annulation of Michael adduct **6**: reagents and conditions: (a) NaOMe in MeOH, 20 °C; (b) DBU in toluene at reflux, or Triton B in THF at reflux, or piperidine in AcOH at reflux

In view of the above results, we assumed that the introduction of an ester group at C-(9) in **6**, considerably increasing the kinetic acidity of this center, might redirect the regiochemistry of the six-center annulation in the sense desired. Addition of the enamino ester **5** to Nazarov reagent **9**,[6] in exact analogy with protocol [**5** → **6**], gave compound (*S*)-**10** in 78% yield and an *ee* ≥ 95%. However, quite unexpectedly, cyclization of **10** with Triton B again took place at the C-(3) and C-(8) centers, giving the aldol (3*S*,5*S*,8*R*)-**11** in 70% yield (Scheme 4). The structure of **11** in its energetically preferred conformation was established by NMR spectroscopy, including COSY, HMQC, HMBC, and NOESY experiments.

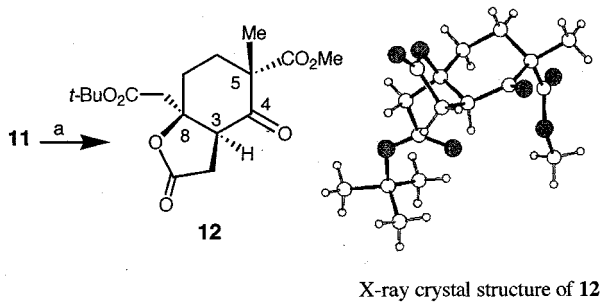


Scheme 4. Michael addition reaction of enamino ester **5** with Nazarov reagent **9**, and annulation of the resulting adduct **10**: reagents and conditions: (a) i: enamino ester **5**, $ZnCl_2$, THF, 2 h, 0 °C, ii: AcOH, H_2O; (b) Triton B, 20 min, 65 °C

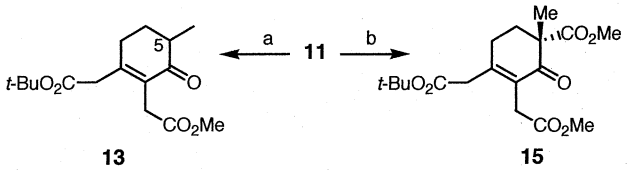
The dehydration of aldol **11**, an apparently straightforward task in view of the *trans*, *diaxial* relationship between the OH group at C-(8) and the H atom at C-(3), was examined next. Surprisingly, the sole product formed from **11** was the bicyclic lactone (3*S*,5*S*,8*R*)-**12**, whether by simple heating in benzene (55% yield), by treatment with strong acids (CF_3COOH: 67% yield, or dry HCl: 60% yield), or by treatment with MsCl in the presence of Et_3N (44% yield). The correctness of the structural assignments for lactone **12** was verified by X-ray diffraction analysis (Scheme 5).

Prolonged exposure of aldol **11** to Triton B furnished the cyclohexenone (±)-**13** in 70% yield, this product arising from the dehydration of **11** with concomitant removal of the methoxycarbonyl function at C-(5), while treatment with Burgess' inner salt **14**[7] gave the enone (*S*)-**15** in 72% yield (Scheme 6).

Finally, an efficient way of reversing the sense of the regiochemistry in these annulations was found. Based on the use of diethyl 2-oxo-3-vinylphosphonate (**16**)[8] as a Michael acceptor, the condensation of enamino ester **5** with **16**, in exact analogy with protocol [**5** → **6**], afforded the adduct

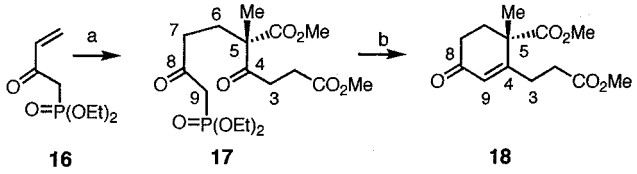


Scheme 5. Synthesis and X-ray crystal structure of bicyclic lactone **12**: reagents and conditions: (a) benzene at reflux (7 days), or CF_3COOH at 20 °C (7 days), or dry HCl in CH_2Cl_2 at 20 °C (12 h), or MsCl, Et_3N at 40 °C (2 days)



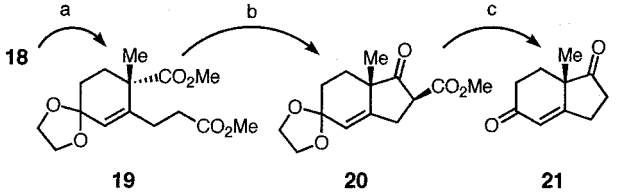
Scheme 6. Synthesis of cyclohexenones **13** and **15**: reagents and conditions: (a) Triton B, 12 h, 65 °C; (b) Burgess' inner salt **14** ($Et_3N^+SO_2N^-COOMe$), 50 °C

(*S*)-**17** in 70% yield and an *ee* ≥ 95%. The internal Horner–Wadsworth–Emmons condensation of **17** (DBU, LiCl)[9] now proceeded with the desired regiochemistry, furnishing our initial target Hagemann's ester (*S*)-**18**, in 70% yield (Scheme 7).



Scheme 7. Synthesis of Hagemann's ester **18** by Michael addition reaction of enamino ester **5** with acceptor **16**, and Horner–Wadsworth–Emmons annulation of the resulting adduct **17**: reagents and conditions: (a) i: enamino ester **5**, $ZnCl_2$, THF, 2 h, 0 °C, ii: AcOH, H_2O; (b) DBU, LiCl, THF, 1 h, −78 °C, then 12 h, 20 °C

The structural assignments for Hagemann's ester (*S*)-**18**, including the absolute configuration and the *ee*, were ascertained by converting the compound into the known hydrindenedione (*S*)-**21** (Scheme 8).[10] For that purpose, **18** was first transformed into the ketal **19** using $TMSOCH_2-CH_2OTMS$ in the presence of TMSOTf, in 85% yield.[11] NaOMe-induced Dieckmann cyclization of **19** then gave the bicyclic derivative **20** (65% yield), which was finally converted into the dione (*S*)-**21** by heating in DMSO in the presence of $MgCl_2$ hexahydrate (90% yield).[12,13]



Scheme 8. Chemical derivatization of Hagemann's ester **18** into bicyclic dione **21**: reagents and conditions: (a) $TMSOCH_2CH_2OTMS$, TMSOTf, 20 h, − 78 °C; (b) MeONa, benzene at reflux, 2 h; (c) $MgCl_2$ hexahydrate, DMSO, 130 °C

Conclusion

The aim of this project was to synthesize the "functionalized" Hagemann's ester (*S*)-**18**. To attain this goal, several strategies were evolved, all based on a Michael addition−Robinson annulation sequence, starting from the enamino ester (*S*,*Z*)-**5**. The use of methyl vinyl ketone and Nazarov reagent as Michael acceptors was unsuccessful, since all efforts to cyclize the diketones (*S*)-**6** and (*S*)-**10** invariably furnished cyclohexenones of the unwanted regiochemistry.

The key tactical element for orientating the regiochemistry of the annulation of the intermediary 1,5-diketones in the required sense was the utilization of 2-oxo-3-vinylphosphonate (**16**) as a Michael acceptor. The internal Horner−Wadworth−Emmons condensation of adduct (*S*)-**17** indeed proceeded with the desired regiochemistry, furnishing our target (*S*)-**18**. This Hagemann's ester was thus elaborated with a high degree of regio- and stereocontrol, in only three steps starting from the keto diester **4**, with an overall yield of 40%. In this respect, this strategy represents an efficient solution to the old and vexing problem of controlling the regioselectivity of the annulation of 1,5-diketones. Further synthetic developments of this promising methodology are currently under investigation in our laboratory.

Experimental Section

General: Infrared (IR) spectra were measured on a Perkin−Elmer 841 spectrometer as neat films between NaCl plates or KBr pellets. Only the most significant absorptions are listed. − The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 200 P (200 MHz and 50 MHz, for ^{1}H and ^{13}C, respectively), or Bruker ARX 400 (400 MHz and 100 MHz, for ^{1}H and ^{13}C, respectively) spectrometers. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C NMR spectra is based on the *J*-modulated spin-echo sequence. − Optical rotations were measured at 20 °C on a Perkin-Elmer 241 MC polarimeter in a 1 dm cell. − Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). − Column chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM). Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. − CH_2Cl_2 was distilled from calcium hydride. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware flame-dried under a positive pressure of nitrogen. Organic fractions were dried with anhydrous $MgSO_4$. Chemicals obtained from commercial suppliers were used without further purification. − All elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin−Elmer 2400 analyzer.

Dimethyl (*S*,*Z*)-2-Methyl-3-(1-phenylethylamino)hex-2-enedioate (5): A solution of ketodiester **4**[5] (1.97 g, 9.75 mmol), (*S*)-1-phenylethylamine (1.83 g, 14.60 mmol) and *p*-toluenesulfonic acid (20 mg) in anhydrous toluene (14 mL) was refluxed for 12 h with azeotropic removal of water. The solution was cooled to 20 °C, and the solvent was removed in vacuum to give an oil, which was chromatographed over silica gel (cyclohexane/AcOEt 4:1) to afford enamino ester **5** as a colorless oil (2.40 g, 80%). − $[\alpha]_D^{20}$ = +419 (*c* = 3.0, MeOH). − IR (neat) $\tilde{\nu}$ = 3266 cm^{-1} (NH), 1741 (C=O), 1645 (C=O), 1599 (C=C). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.4 (d, *J* = 6 Hz, 3 H, C*H*$_3$−CH), 1.7 (s, 3 H, C*H*$_3$−C=C), 1.9−2.6 (m, 4 H, C*H*$_2$−C*H*$_2$), 3.6 (s, 3 H, C*H*$_3$−O), 3.7 (s, 3 H, C*H*$_3$−O), 4.5 (quint, *J* = 6 Hz, 1 H, C*H*−CH$_3$), 7.1−7.3 (m, 5 H, aromatic H), 9.5 (d, *J* = 6 Hz, 1 H, N*H*). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 11.9 (CH$_3$, *C*H$_3$−CH), 24.1 (CH$_2$), 25.2 (CH$_3$, *C*H$_3$−C=), 31.4 (CH$_2$), 50.4 (CH, CH$_3$−CH), 51.6 (CH$_3$, *C*H$_3$−O), 52.9 (CH$_3$, *C*H$_3$−O), 88.2 (C, N−C=C), 125.4 (2 CH, aromatic C), 126.9 (CH, aromatic C), 128.6 (2 CH, aromatic C), 145.6 (C, aromatic C), 160.3 (C, *C*=C−N), 171.5 (C, C=O), 172.4 (C, C=O). − $C_{17}H_{23}NO_4$ (305.16): calcd. C 66.86, H 7.59, N 4.59; found C 66.46, H 7.82, N 4.37.

Dimethyl (*S*)-2-Methyl-3-oxo-2-(3-oxobutyl)hexanedioate (6): To a solution of freshly distilled methyl vinyl ketone (0.14 g, 2.0 mmol), $ZnCl_2$ (0.14 g, 1.0 mmol) and hydroquinone (5 mg) in THF (20 mL) at 0 °C was added enamino ester **5** (0.31 g, 1.0 mmol). The mixture was stirred for 2 h at this temperature and 5 mL of 20% aqueous acetic acid were added. The solvents were removed under reduced pressure and 1 N hydrochloric acid (10 mL) was added. The mixture was extracted with dichloromethane and the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (cyclohexane/AcOEt 2:1) gave diketo diester **6** (0.22 g, 80%) as a colorless oil. − $[\alpha]_D^{20}$ = +7.6 (*c* = 3.3, MeOH). − IR (neat) $\tilde{\nu}$ = 1749 cm^{-1} (C=O), 1717 (C=O). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.2 (s, 3 H, C*H*$_3$−C), 2.0 (s, 3 H, C*H*$_3$−C=O), 2.1 (m, 2 H, CH$_2$), 2.4 (m, 2 H, CH$_2$), 2.5 (m, 2 H, CH$_2$), 2.7 (m, 2 H, CH$_2$), 3.6 (s, 3 H, C*H*$_3$−O), 3.7 (s, 3 H, C*H*$_3$−O). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.2 (CH$_3$, *C*H$_3$−C), 27.4 (CH$_2$), 28.4 (CH$_2$), 29.6 (CH$_3$, *C*H$_3$−C=O), 32.8 (CH$_2$), 38.2 (CH$_2$), 51.4 (CH$_3$, *C*H$_3$−O), 52.2 (CH$_3$, *C*H$_3$−O), 58.0 (C, C-2), 172.5 (C, *C*=O), 172.7 (C, *C*=O), 205.7 (C, *C*=O), 207.0 (C, *C*=O). − $C_{13}H_{20}O_6$ (272.13): calcd. C 57.34, H 7.40; found C 57.47, H 7.63.

Methyl (*S*)-3-(Methoxycarbonyl)methyl-1,4-dimethyl-2-oxocyclohex-3-enecarboxylate (7): To a solution of sodium methoxide (0.17 g, 0.73 mmol) in methanol (5 mL) was added diketo diester **6** (0.20 g, 0.73 mmol). The mixture was stirred for 40 min at 20 °C, the solvent was removed and dichloromethane (30 mL) was added. The mixture was washed with 1 N hydrochloric acid (10 mL), dried and concentrated under reduced pressure. Chromatographic purification over silica gel (cyclohexane/AcOEt 4:1) gave keto diester **7** (0.17 g, 91%) as a colorless oil. − $[\alpha]_D^{20}$ = +16.4 (*c* = 2.75, MeOH). − IR (neat): $\tilde{\nu}$ = 1733 cm^{-1} (C=O), 1721 (C=O), 1669 (C=O), 1635 (C=C). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.4 (s, 3 H, C*H*$_3$−C), 1.80 (m, 1 H), 1.90 (s, 3 H, C*H*$_3$−C=C), 2.2−2.7 (m, 3 H), 3.4 (s, 2 H, C*H*$_2$−C=O), 3.6 (s, 3 H, C*H*$_3$−O), 3.7 (s, 3 H, C*H*$_3$−O). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.5 (CH$_3$), 21.5 (CH$_3$), 29.9 (CH$_2$), 31.0 (CH$_2$), 32.2 (CH$_2$), 43.6 (C, C-1), 52.1 (CH$_3$, *C*H$_3$−O), 52.4 (CH$_3$, *C*H$_3$−O), 128.2 (C, C=*C*−*C*=O), 157.5 (C, *C*=C−C=O), 171.5 (C, C=O), 173.2 (C, C=O), 195.4 (C, C=O). − $C_{13}H_{18}O_5$ (254.3): calcd. C 61.40, H 7.14; found C 61.07, H 7.48.

1-*tert*-Butyl 10-Methyl (*S*)-6-Methoxycarbonyl-6-methyl-3,7-dioxodecanedioate (10): To a solution of freshly distilled Nazarov reagent **9**[6] (0.14 g, 0.82 mmol), $ZnCl_2$ (0.14 g, 1.00 mmol) and hydroquinone (5 mg) in THF (20 mL) at 0 °C was added enamino ester **5** (0.20 g, 0.66 mmol). The mixture was stirred for 2 h at this temperature and 5 mL of 10% aqueous acetic acid were added. The solvents were removed under reduced pressure and 1 N hydrochloric acid (10 mL) was added. The mixture was extracted with dichloromethane (30 mL) and the combined organic phases were washed

with brine, dried and concentrated. Chromatographic purification over silica gel (cyclohexane/AcOEt 4:1) gave diketo triester **10** (0.19 g, 78%) as a colorless oil. − $[\alpha]_D^{20}$ = +8.6 (*c* = 4.0, MeOH). − IR (neat): $\tilde{\nu}$ = 1741 cm^{-1} (C=O), 1723 (C=O). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.3 (s, 3 H, C*H*$_3$−C), 1.4 (s, 9 H, (C*H*$_3$)$_3$−C), 2.1 (m, 2 H), 2.5 (m, 4 H), 2.7 (m, 2 H), 3.3 (s, 2 H, CO−C*H*$_2$−CO), 3.6 (s, 3 H, C*H*$_3$−O), 3.7 (s, 3 H, C*H*$_3$−O). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.1 (CH_3, *C*H$_3$−C-6), 28.1 (CH_2), 28.2 [3 CH_3, (*C*H$_3$)$_3$−C], 28.4 (CH_2), 31.5 (CH_2), 37.8 (CH_2), 48.8 (CH_2), 50.5 (CH_3, *C*H$_3$−O), 51.7 (CH_3, *C*H$_3$−O), 58.2 (C, C-6), 81.9 (C, O−C−*C*), 166.2 (C, C=O), 172.8 (C, C=O), 172.9 (C, C=O), 201.7 (C, C=O), 205.8 (C, C=O). − $C_{18}H_{28}O_8$ (372.5): calcd. C 58.05, H 7.58; found C 57.78, H 7.65.

Methyl (1*S*,3*S*,4*R*)-4-*tert*-(Butoxycarbonyl)methyl-4-hydroxy-3-(methoxycarbonyl)methyl-1-methyl-2-oxocyclohexanecarboxylate (11): To a solution of diketo triester **10** (0.37 g, 1.0 mmol) in THF (45 mL) was added a 40% solution of Triton B in methanol (0.1 mL, 0.2 mmol). The mixture was refluxed for 20 min, the solvent was removed and dichloromethane (30 mL) was added. The mixture was washed with 1 N hydrochloric acid (10 mL), dried and concentrated under reduced pressure. Chromatographic purification over silica gel (cyclohexane/AcOEt 4:1) gave aldol **11** (0.26 g, 70%) as a colorless oil. − $[\alpha]_D^{20}$ = +44.3 (*c* = 1.6, MeOH). − IR (neat) $\tilde{\nu}$ = 3508 cm^{-1} (OH), 1745 (C=O), 1729 (C=O). − ^1H NMR (C_6D_6, 400 MHz): δ = 1.27 (s, 3 H, C*H*$_3$−C-1), 1.34 [s, 9 H, (C*H*$_3$)$_3$−C], 1.77 (ddd, *J* = 14, 4, 3 Hz, 1 H, *H*-5eq), 1.89 (ddd, *J* = 14, 14, 4 Hz, 1 H, *H*-6ax), 2.07 (d, *J* = 15 Hz, 1 H, C*H*$_2$−C-4), 2.13 (ddd, *J* = 14, 14, 4 Hz, 1 H, *H*-5ax), 2.19 (d, *J* = 15 Hz, 1 H, C*H*$_2$−CH$_2$−C-4), 2.32 (ddd, *J* = 14, 4, 3 Hz, 1 H, CH$_2$, *H*-6eq), 2.40 (dd, *J* = 20, 5 Hz, 1 H, C*H*$_2$−CH$_2$−C-3), 3.33 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3O), 3.89 (br s, 1 H, OH). − ^{13}C NMR (C_6D_6, 50 MHz): δ = 21.4 (CH_3, *C*H$_3$−C-1), 27.9 (3 CH_3, (*C*H$_3$)$_3$−C), 28.8 (CH_2), 32.0 (CH_2), 34.4 (CH_2), 44.9 (CH_2), 51.3 (CH_3, *C*H$_3$−O), 52.1 (CH_3, *C*H$_3$−O), 53.7 (CH, *C*-3), 56.2 (C, *C*-1), 76.6 (C, *C*-4), 81.5 (C, O−C−*C*), 171.5 (C, C=O), 173.0 (C, C=O), 173.4 (C, C=O), 203.4 (C, C=O). − $C_{18}H_{28}O_8$ (372.5): calcd. C 58.05, H 7.58; found C 58.36, H 7.85.

Methyl (3a*S*,5*S*,7a*R*)-7a-*tert*-Butoxycarbonylmethyl-5-methyl-2,4-dioxooctahydrobenzofuran-5-carboxylate (12): A solution of trifluoroacetic acid (0.20 mL, 2.6 mmol) and aldol **11** (0.44 g, 1.2 mmol) in dichloromethane (15 mL) was kept at 20 °C for 7 days. The mixture was washed with a 2 N aqueous solution of sodium hydroxide, dried and concentrated under reduced pressure. The residue was crystallized from methanol to give bicyclic lactone **12** (0.27 g, 67%) as a colorless solid. − m.p. 95 °C (MeOH). − $[\alpha]_D^{20}$ = +8.4 (*c* = 1.55, MeOH). − IR (KBr): $\tilde{\nu}$ = 1796 cm^{-1} (C=O), 1738 (C=O), 1715 (C=O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (s, 3 H, C*H*$_3$−C-5), 1.41 (s, 9 H, (C*H*$_3$)$_3$−C), 1.67 (ddd, *J* = 18, 14, 4 Hz, 1 H, CH$_2$, *H*-7), 2.06 (ddd, *J* = 15, 4, 4 Hz, 1 H, CH$_2$, *H*-6), 2.19 (ddd, *J* = 15, 4, 4 Hz, 1 H, *H*-6), 2.29 (ddd, *J* = 18, 14, 4 Hz, 1 H, CH$_2$, *H*-7), 2.51 (d, *J* = 15 Hz, 1 H, OC−C*H*$_2$−C-7a), 2.61 (d, *J* = 15 Hz, 1 H, OC−C*H*$_2$−C-7a), 2.74 (dd, *J* = 18, 9 Hz, 1 H, CH$_2$, *H*-3), 3.30 (dd, *J* = 18, 1 Hz, 1 H, CH$_2$, *H*-3), 3.68 (dd, *J* = 9, 1 Hz, 1 H, C*H*), 3.72 (s, 3 H, OC*H*$_3$). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.9 (CH_3, *C*H$_3$−C-5), 27.9 (3 CH_3, (*C*H$_3$)$_3$−C), 28.8 (CH_2), 29.9 (CH_2), 30.5 (CH_2), 44.6 (CH_2), 49.1 (CH), 52.7 (CH_3, O−CH_3) 55.0 (C, *C*-5), 82.1 (C, (CH$_3$)$_3$−C), 87.4 (C, *C*-7a), 168.3 (C, C=O), 172.2 (C, C=O), 174.7 (C, C=O), 203.9 (C, C=O). − $C_{17}H_{24}O_7$ (340.4): calcd. C 59.99, H 7.11; found C 59.89, H 7.13. − Crystal data of **12**: $C_{17}H_{24}O_7$ M_W = 340.36, colorless crystal of 0.04 × 0.10 × 0.60 mm, monoclinic, space group $P2_1$, *Z* = 2, *a* = 10.592 (4), *b* = 6.053 (2), *c* = 13.926 (4) Å, β = 90.75(3)°, *V* = 892.8 (5) $Å^3$, d_{calc} = 1.27 g cm^{-3}, *F*(000) = 364, λ (Cu-K_α) = 1.5418 Å, μ = 0.82 mm^{-1}. Nonius CAD4 diffractometer, 3482 collected reflections, 3001 unique (R_{int} = 0.034), 2114 observed [$I \geq 2\sigma(I)$]. The structure was refined by full-matrix, least-squares with SHELX93, R = 0.052 for 2501 observed reflections and w R_2 = 0.150 for 3001 unique reflections. Residual electron density between −0.20 and 0.17 $eÅ^3$.[14]

Methyl (*S*)-9-Diethoxyphosphoryl-5-methoxycarbonyl-5-methyl-4,8-dioxononanoate (17): To a solution of reagent **16**[8] (1.5 g, 7.4 mmol), $ZnCl_2$ (0.9 g, 6.2 mmol) and hydroquinone (5 mg) in THF (20 mL) at 0 °C was added enamino ester **5** (1.9 g, 6.2 mmol). The mixture was stirred for 2 h at this temperature and 10% aqueous acetic acid (10 mL) was added. The solvents were removed under reduced pressure and 1 N hydrochloric acid (10 mL) was added. The mixture was extracted with dichloromethane (30 mL) and the combined organic phases were washed with brine, dried, and concentrated. Chromatographic purification over silica gel (cyclohexane/AcOEt 1:2) gave **17** (1.8 g, 70%) as a colorless oil. − $[\alpha]_D^{20}$ = −1.2 (*c* = 16.0, MeOH). − IR (neat) $\tilde{\nu}$ = 1735 cm^{-1}(C=O), 1716 (C=O). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.2 (t, *J* = 7 Hz, 6 H, 2 C*H*$_3$−CH$_2$), 1.3 (s, 3 H, C*H*$_3$−C-5), 1.9−2.2 (m, 2 H), 2.4−2.6 (m, 4 H), 2.65−2.8 (m, 2 H), 3.0 (d, *J* = 23 Hz, 2 H, C*H*$_2$−P), 3.6 (s, 3 H, OC*H*$_3$), 3.7 (s, 3 H, OC*H*$_3$), 4.1 (q, *J* = 7 Hz, 4 H, 2 C*H*$_2$−CH$_3$). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 16.2 (CH_3, *C*H$_3$−CH$_2$) 16.3 (CH_3, *C*H$_3$−CH$_2$), 19.4 (CH_3, *C*H$_3$−C-5), 27.7 (CH_2), 28.4 (CH_2), 33.1 (CH_2), 39.0 (CH_2), 41.1 (C, *C*-5), 43.6 (CH_2), 51.7 (CH_3, O*C*H$_3$), 52.5 (CH_3, O*C*H$_3$), 62.5 (CH_2, *C*H$_2$−CH$_3$), 62.6 (CH_2, *C*H$_2$−CH$_3$), 172.8 (C, C=O), 173.5 (C, C=O), 200.6 (C, C=O), 205.8 (C, C=O).

Methyl (*S*)-2-[2-(Methoxycarbonyl)ethyl]-1-methyl-4-oxocyclohex-2-enecarboxylate (18): To a solution of **17** (2.00 g, 4.9 mmol) and LiCl (0.23 g, 5.4 mmol) in THF (80 mL) at − 78 °C was added a solution of DBU (0.81 g, 5.4 mmol) in THF (20 mL). The mixture was stirred for 40 min at − 78 °C, allowed to warm to 20 °C and kept at this temperature for 4 h. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel (cyclohexane/AcOEt 1:2) to give enone **18** (0.96 g, 70%) as a colorless oil. − $[\alpha]_D^{20}$ = −56.3 (*c* = 3.0, MeOH). − IR (neat) $\tilde{\nu}$ = 1730 cm^{-1} (C=O), 1678 (C=O), 1623 (C=C). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.45 (s, 3 H, C*H*$_3$−C-1), 1.80−2.0 (m, 1 H), 2.3−2.45 (m, 3 H), 2.55 (br s, 4 H, 2 CH$_2$), 3.65 (s, 3 H, OC*H*$_3$), 3.7 (s, 3 H, OC*H*$_3$), 5.8 (s, 1H, *H*−C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.4 (CH_3, *C*H$_3$−C-1), 27.9 (CH_2), 31.3 (CH_2), 34.1 (CH_2), 34.6 (CH_2), 47.6 (C, *C*-1), 51.8 (CH_3, O*C*H$_3$), 52.6 (CH_3, O*C*H$_3$), 126.1 (CH, *C*-3), 162.8 (C, *C*-2), 174.5 (C, C=O), 177.3 (C, C=O), 197.9 (C, C=O).

Methyl (*S*)-7-[2-(Methoxycarbonyl)ethyl]-8-methyl-1,4-dioxaspiro-[4.5]dec-6-ene-8-carboxylate (19): To a solution of enone **18** (0.36 g, 1.4 mmol) and TMSOTf (0.02 mL, 0.77 mmol) in dichloromethane (1 mL) at −78 °C was added 1,2-bis(trimethylsilyloxy)ethane (0.7 mL, 2.9 mmol). The mixture was stirred for 20 h at this temperature. Pyridine (0.2 mL) was added and the solution was poured into an aqueous solution of sodium hydrogen carbonate. After extraction with dichloromethane (15 mL), the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (cyclohexane/AcOEt/triethylamine 20:80:1) gave **19** (0.36 g, 85%) as a white solid. − m.p. 58 °C. − $[\alpha]_D^{20}$ = −20.3 (*c* = 4.5, MeOH). − IR (neat): $\tilde{\nu}$ = 1731 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (s, 3 H, C*H*$_3$−C-8), 1.75 (m, 1 H), 1.80 (m, 2 H), 2.18 (ddd, *J* = 13.1, 8.3, 3.5 Hz, 1 H, C*H*$_2$−C-9), 2.32 (m, 2 H), 2.48 (m, 2 H), 3.66 (s, 6 H, 2 OC*H*$_3$), 4.01 (m, 4 H, 2 C*H*$_2$−O), 5.37 (t, *J* = 1.5 Hz, 1 H, *H*−C=

C); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.6 (CH_3, *C*H_3−C-8), 27.1 (CH_2), 30.2 (CH_2), 32.4 (CH_2), 33.6 (CH_2), 46.9 (C, *C*-8), 52.2 (CH_3, O*C*H_3), 53.0 (CH_3, O*C*H_3), 64.5 (2 CH_2, *C*H_2−O), 105.5 (C, *C*-5), 123.9 (CH, H−C=C), 143.9 (C, H−C=*C*), 173.3 (C, C=O), 176.0 (C, C=O). − $C_{15}H_{22}O_6$ (298.1): calcd. C 60.39, H 7.43; found C 60.42, H 7.49.

Methyl (2*R*,3a*S*)-6-Ethylenedioxy-3a-methyl-3-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indene-2-carboxylate (20): A solution of sodium methoxide (70 mg, 1.30 mmol) and **19** (120 mg, 0.40 mmol) in benzene (20 mL) was refluxed for 12 h. The mixture was cooled at 20 °C, and a solution of 10% aqueous acetic acid was added. The mixture was poured into an aqueous solution of sodium hydrogen carbonate. After extraction with dichloromethane (15 mL), the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (cyclohexane/AcOEt 1:2) gave **20** (69 mg, 65%) as a white solid. − m.p. 82 °C. − $[\alpha]_D^{20}$ = +130.4 (*c* = 3.4, MeOH). − IR (neat) $\tilde{\nu}$ = 1757 cm^{-1} (C=O), 1722 (C=O), 1688 (C=O). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (s, 3 H, C*H*$_3$−C-3a), 1.70 (ddd, *J* = 3.8, 13.2, 13.2 Hz, 1 H, C*H*$_2$−C-5), 1.85−2.00 (m, 3 H), 2.79 (dd, *J* = 15.0, 9.0 Hz, 1 H, C*H*$_2$−C-1), 3.17 (ddd, *J* = 15.0, 10.7, 1.4 Hz, 1 H, C*H*$_2$−C-1), 3.34 (dd, *J* = 10.7, 9.1 Hz, 1 H, C*H*−C-2), 3.77 (s, 3 H, OC*H*$_3$), 4.06 (m, 4 H, O−C*H*$_2$−C*H*$_2$−O), 5.53 (t, *J* = 1.4 Hz, 1 H, *H*−C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.7 (CH_3, *C*H_3−C-3a), 28.7 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 48.4 (C, *C*-3a), 52.7 (CH_3, O*C*H_3), 54.4 (CH), 64.5 (CH_2, *C*H_2−O), 64.7 (CH_2, *C*H_2−O), 106.0 (C, *C*-6), 121.8 (CH, H*C*=C), 145.5 (C, HC=*C*), 169.3 (C, C=O), 210.0 (C, C=O). − $C_{14}H_{18}O_5$ (266.1): calcd. C 63.15, H 6.81; found C 63.23, H 7.01.

(*S*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione (21): A solution of **20** (50 mg, 0.19 mmol), $MgCl_2$ hexahydrate (50 mg, 0.24 mmol) in DMSO (4 mL) was heated at 130 °C for 4 h. The mixture was allowed to cool to 20 °C, and 6 mL of water were added. After extraction with dichloromethane (15 mL), the combined organic phases were washed with brine, dried, and concentrated. Chromatographic purification over silica gel (cyclohexane/AcOEt 1:1.5) gave **21** (27 mg, 90%) as a white solid. − m.p. 68 °C (ref.[10] m.p. 66 °C). − $[\alpha]_D^{20}$ = + 352 (*c* = 1.1, benzene) (ref.[10] $[\alpha]_D^{20}$ = +367 (*c* = 1.0, benzene)). − IR (neat): $\tilde{\nu}$ = 1744 cm^{-1}(C=O), 1663 (C=O). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (s, 3 H, C*H*$_3$−C-7a), 1.85 (ddd, *J* = 13.5, 7.4, 5.0 Hz, 1 H, 3-*H*), 2.12 (dddd, *J* = 13.5, 7.4, 5.0, 2.5 Hz, 1 H, 3-*H*), 2.45−2.58 (m, 3 H), 2.70−2.83 (m, 2 H), 2.95 (dddd, *J* = 13.4, 11.1, 9.8, 2.5 Hz, 1 H, 6-*H*), 5.95 [t, *J* = 2.5 Hz,1 H, H−C=C]). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.6 (CH_3, *C*H_3−C-7a), 26.8 (CH_2), 29.2 (CH_2), 32.9 (CH_2), 35.8 (CH_2), 48.7 (C, C-7a), 123.9 (CH, H−C=C), 169.7 (C, H−C=C), 198.0 (C, C=O), 216.4 (C, C=O). − $C_{10}H_{12}O_2$ (164.2): calcd. C 73.15, H 7.37; found C 73.21, H 7.38.

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[14] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with deposition number CCDC-103105. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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