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Synthesis of 7a-Substituted Hajos−Wiechert Ketone Analogues

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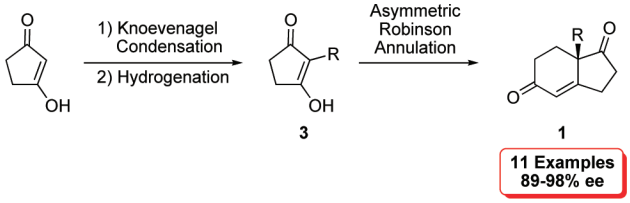
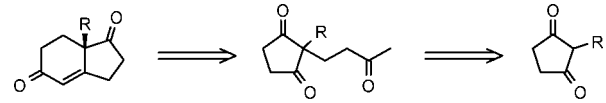


A general and efficient route to 2-substituted 1,3-cyclopentadiones **3** has been developed. This operationally simple, two-step procedure is amenable to multigram scale preparations of these useful synthetic intermediates. These compounds are then transformed to previously unknown, higher analogues of the Hajos−Parrish−Eder−Sauer−Wiechert ketone (enone **1**, R = Me) following an enantioselective Robinson annulation.

The Hajos−Parrish−Eder−Sauer−Wiechert ketone **1a** (Scheme 1, R = Me, henceforth referred to as the HW-ketone), first reported independently by researchers at Schering AG[1] and Hoffmann La Roche Inc.[2] over three decades ago, has found extensive use in organic synthesis. This ketone is of biological interest because it resembles the CD-ring system of steroids, and is of synthetic interest because it can be prepared in enantiomerically pure form from a remarkably simple organocatalyzed process.[3] Consequently, it has been used as a chiral building block in several syntheses.[4] Furthermore, its synthesis involves the first enantioselective aldol reaction developed by

SCHEME 1. Retrosynthesis of HW-ketones



chemists,[5] and is a rare example of the catalytic formation of a stereogenic quaternary carbon center.[6] In view of this long history and ongoing interest, it is surprising that very few analogues have been reported where the angular substituent is not a methyl group.[7]

These bicyclic diketones **1** are generally prepared via the proline-catalyzed aldol cyclization of triketone **2**, which in turn comes from the Michael addition of cyclic 2-substituted 1,3-dione **3** with methyl vinyl ketone **4** (Scheme 1). Key to this process is the availability of the 2-substituted dione **3**. Although these substituted diones are very useful synthetic building blocks for steroid and many other cyclopentanoid natural products,[8] their preparation presents some significant challenges[9] and their availability is limited.[10] Therefore, the first problem that needed to be solved in the development of a route to HW-ketone analogues was the establishment of a general route to 2-substituted 1,3-cyclopentadiones.

These diones are theoretically available by reaction of 1,3-cyclopentadione **3b** with electrophiles. However, yields for these additions are generally quite low because the anion from **3b** preferentially undergoes O- rather than C-alkylation.[8,11] While a solution to this problem for 2-substituted 1,3-cyclohexadiones was recently reported by Ramachary and Kishor in their preparation of analogues of the Wieland−Miescher ketone,[12] there remains no general synthetic approach to 2-substituted 1,3-cyclopentadiones.

Although simple alkylation of 1,3-cyclopentadione **3b** is not an effective reaction, an alternative approach starts with the Knoevenagel addition of the dione to aldehydes (Figure 1). However, this route is also not without its problems. The product from these additions is the excellent Michael acceptor ene-dione **5**, which, among other side reactions can then rapidly add a

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(1) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497.

(2) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

(3) For a recent review, see Section 2.21 in: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(4) Selected examples: (a) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 2665–2666. (b) Enev, V. S.; Petrov, O. S.; Neh, H.; Nickisch, K. *Tetrahedron* **1997**, *53*, 13709–13718. (c) Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4643–4646. (d) Renneberg, D.; Pfander, H.; Leumann, C. J. *J. Org. Chem.* **2000**, *65*, 9069–9079. (e) Molander, G. A.; Quirmbach, M. S.; Silva, L.F., Jr.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257–2260. (f) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091–1094. (g) Lugar, C. W., III; Magee, D.; Adrian, M. D.; Shetler, P.; Bryant, H. U.; Dodge, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4281–4284. (h) Chochrek, P.; Kurek-Tyrlik, A.; Michalak, K.; Wicha, J. *Tetrahedron Lett.* **2006**, *47*, 6017–6020.

(5) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839–5842.

(6) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146.

(7) For some notable exceptions, see refs 1 and 2, as well as the following: (a) Smith, H.; Hughes, G. A.; Douglas, G. H.; Hartley, D.; McLoughlin, J.; Siddal, J. B.; Wendt, G. R.; Buzby, G.C., Jr.; Herbst, D. R.; Ledig, K. W.; McMenamin, J. R.; Pattison, T. W.; Suida, J.; Tokolics, J.; Edgren, R. A.; Jansen, A. B. A.; Gadsby, B.; Watson, D. H. R.; Phillips, P. C. *Experientia* **1963**, *19*, 394–396. (b) Blazejewski, J. C. *J. Fluorine Chem.* **1990**, *46*, 515–519. (c) Lacoste, E.; Vaique, E.; Berlande, M.; Pianet, I.; Vincent, J.-M.; Landais, Y. *Eur. J. Org. Chem.* **2007**, 167–177.

(8) Schick, H.; Eichhorn, I. *Synthesis* **1989**, *47*, 7–492, and references cited therein.

(9) For example, Beilstein only lists three syntheses for benzyl-type analogues of **3**, which are either not general or unsuitable for large-scale preparations: (a) Hiraga, K. *Chem. Pharm. Bull.* **1965**, *13*, 1359–1361. (b) Tolstikov, G. A.; Ismailov, S. A.; Velder, Ya. L.; Miftakhov, M. S. *J. Org Chem. USSR (Engl. Transl.)* **1991**, *27*, 72–78. (c) Poss, A. J.; Belter, R. K. *J. Org. Chem.* **1988**, *53*, 891–891.

(10) The MDL Available Chemicals Directory reveals that only the methyl and ethyl analogues of **3** are commercially available.

(11) McIntosh, J. M.; Beaumier, P. M. *Can. J. Chem.* **1973**, *51*, 843–847.

(12) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056–5068.

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Published on Web 06/10/2008

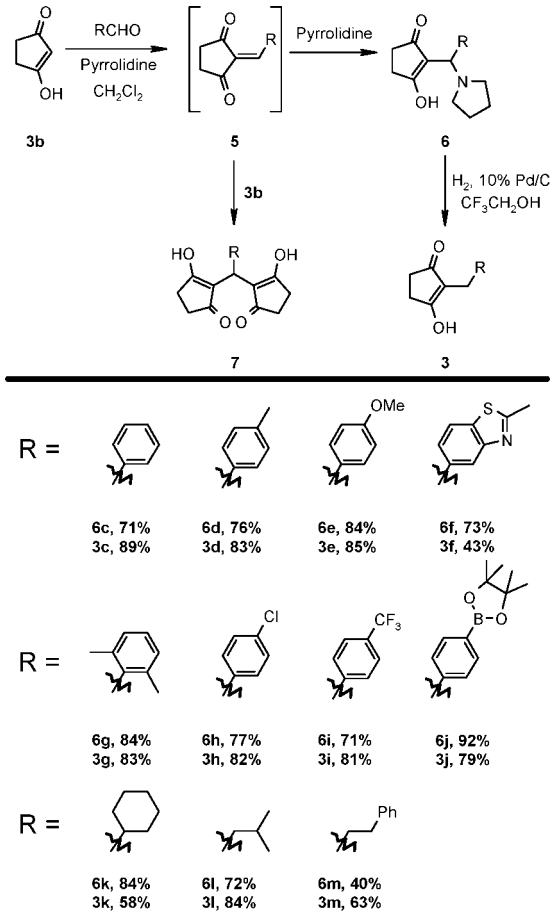

FIGURE 1. Yields for the Mannich bases **6** and diones **3**.

second molecule of cyclodione to give the bis-adduct **7**. However, Bolte and co-workers reported that **5** can be effectively trapped in the presence of pyrrolidine as the stable and easily isolated Mannich base **6**.[13,14] We reasoned that under reducing conditions in a weakly acidic solvent, Mannich base **6** would slowly regenerate ene-dione **5**, which would then rapidly undergo hydrogenation before unwanted side reactions could occur. In line with this theory, we were pleased to find that palladium-catalyzed hydrogenation of **6** in 2,2,2-trifluoroethanol afforded the desired substituted cyclopentadione **3** in good overall yields. ^{1}H NMR spectra of these compounds revealed that they exist exclusively in their enol forms. The use of trifluoroethanol is crucial for success in this hydrogenation, since hydrogenations in ethanol returned the Mannich base unchanged.

A variety of 1,3-cyclopentadiones bearing aromatic and aliphatic substituents were subsequently prepared with this methodology (Figure 1). Sterically demanding aldehydes, heterocyclic aldehydes, and aldehydes bearing boronic esters all undergo effective transformation to dione **3**. Similarly, the chlorinated compound **3h** can be prepared if the reduction is performed in the presence of Ph_2S.[15] Overall yields for this two-step process were generally good, although reactions with unbranched aliphatic aldehydes were noticeably lower yielding

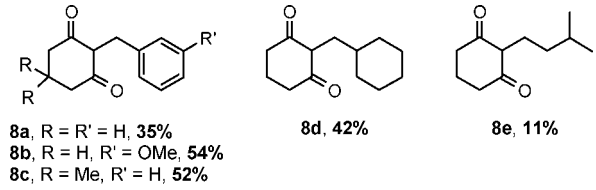

FIGURE 2. Preparation of 2-substituted 1,3-cyclohexadiones **8**. Combined yields for both the Knoevenagel and hydrogenation steps are shown.

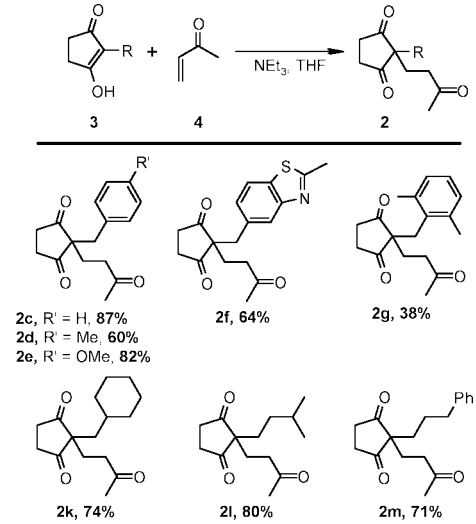

FIGURE 3. Preparation of the triketones **2**.

than reactions with branched aldehydes. This result is in line with the observation that the Knoevenagel addition with unbranched aldehydes is not efficient.[13] A significant advantage of this process is that the product from both the Knoevenagel and hydrogenation reactions is obtained simply by precipitation and filtration in sufficiently pure form to be used in subsequent reactions without any further treatment. Multigram amounts of these products are thus readily available from this methodology.

The overall efficiency of this preparation would be even further increased if the two steps could be performed as a one-pot, tandem process. In a preliminary experiment, stirring benzaldehyde with 1,3-cyclopentadione **3b**, pyrrolidine, and palladium catalyst in trifluoroethanol under hydrogen yielded the expected product **3c** in essentially the same yield as from the two-step process. Unfortunately, the reaction with benzaldehyde appears to be an exceptional case, and this tandem strategy could not be successfully applied to other aromatic or aliphatic aldehydes.

We were pleased to see that our methodology for preparing 2-substituted 1,3-diones is not limited to cyclopentadione. Both 1,3-cyclohexadione and dimedone afforded the expected 2-substituted products **8** in similar yields following our established protocol (Figure 2).[12] As with the 5-membered analogues, sequences with unbranched aliphatic aldehydes gave low yields in the Knoevenagel condensation.

Our attempts to prepare HW-ketone analogues started via the classical approach outlined in Scheme 1, where the triketone **2** is first isolated and then cyclized in a separate step. The requisite triketone was prepared via treatment of diketone **3** with MVK **4** in refluxing THF in the presence of NEt_3 (Figure 3).[16] Other procedures for this transformation were generally unsuccessful.[17]

(13) Bolte, M. L.; Crow, W. D.; Yoshida, S. *Aust. J. Chem.* **1982**, *35*, 1421–1429.

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(15) Mori, A.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Sajiki, H. *Org. Lett.* **2006**, *8*, 3279–3281.

(16) Zhuang, Z.-P.; Zhou, W.-S. *Tetrahedron* **1985**, *41*, 3633–3641.

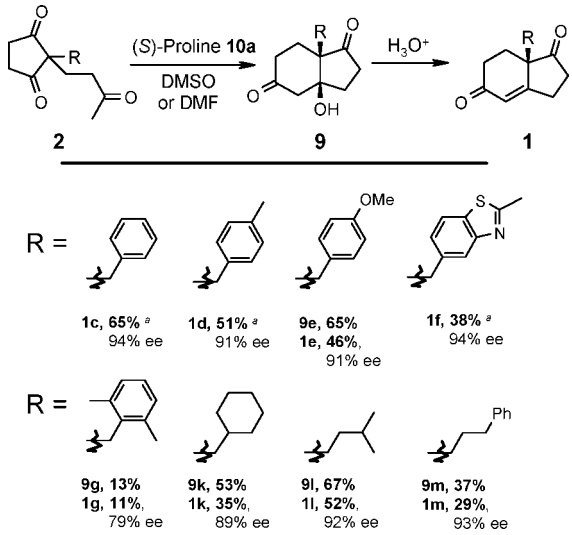

FIGURE 4. HW-ketone analogues **1** from triketone **2**. The superscript "a" indicates hydroxyketone **9** was not isolated. Yields reported for enone **1** are combined yields for the cyclization and dehydration of triketone **2**.

We next sought to optimize the conditions for the asymmetric aldol cyclization. With use of benzyl-substituted **2c** as a test substrate, several solvents and catalysts were screened for their suitability in this cyclization.[18] In organocatalyzed reactions with the triketones **2**, cyclization to the aldol product **9** takes place over a couple of days, but dehydration to the enone **1** does not readily occur under the reaction conditions (Figure 4). Subsequent treatment of the hydroxyketone **9** with acid then causes rapid elimination to the enone **1**. Although this dehydration can be performed without isolation of the hydroxyketone **9** by adding acid to the mixture after consumption of **2**, best results are obtained by isolating and purifying the intermediate alcohol first.[19]

While both DMSO and DMF gave good yields and high levels of enantioselectivity, other solvents led either to poor levels of enantioselectivity (MeCN, EtOH, THF, $CHCl_3$, DCE) or to no conversion (water, toluene). Proline **10a** turned out to be the best catalyst for the cyclization, generally affording reasonable yields and enantioselectivities greater than 95:5. Reactions with the sulfonamide and tetrazole proline analogues[20] were notably faster than those with proline, albeit with slightly lower yields and levels of enantioselectivity. Very low enantioselectivity was seen with phenylalanine as catalyst, and no reaction was observed with MacMillan's *tert*-butyl imidazolidinone catalyst.[21] During these cyclizations the formation of diketone **3** was often observed, which accounts for the modest yields in some reactions. This retro-Michael reaction has been previously reported in the study of intramolecular cyclizations of a triketone similar to **2**.[22]

These optimized conditions were then applied to the preparation of HW-ketone analogues (Figure 4). All of these compounds were prepared in good yield (except for the sterically demanding **1g**) and moderate to excellent enantiopurity as determined by chiral HPLC. X-ray crystallography of enone **1c** confirmed that the (*R*)-isomer was formed by reaction with (*S*)-proline **10a**, as would be expected from the generally accepted transition state model for these reactions.[5]

Despite this success, a limitation of the process soon became apparent. We were unable to procure triketone **2** from three of the diones listed in Figure 1: the *p*-Cl-, *p*-CF_3-, and the boronic ester-substituted **3h**, **3i**, and **3j**, respectively. The product obtained following standard treatment of these compounds with MVK and NEt_3 was a complex mixture that sometimes contained the desired triketone, but also the enone **1** along with other suspected aldol products. Although milder reaction conditions did lead to the isolation of triketone **2**, the formation of enone **1** suggested that the aldol cyclization with these substrates was a relatively facile process. Indeed, a tandem Michael addition−aldol cyclization approach to the HW-ketone **1a** with a stoichiometric amount of proline has already been reported,[23] and a catalytic version to the Wieland−Miescher ketone has been developed by Barbas.[24]

Building on our experience from the triketone cyclization optimization, we were delighted to see that this tandem reaction is indeed a viable process when applied to the substituted diones **3**. Treatment of a solution of MVK and dione **3** in DMSO with (*S*)-proline **10a** led to a slow formation of triketone **2** with concomitant conversion to hydroxyketone **9** and sometimes small amounts of enone **1**. Purification of this intermediate **9** followed by acid-catalyzed dehydration successfully generated enones **1** in good yields and excellent enantioselectivities (Figure 5). This new tandem method was applied not only to the substrates that were problematic under the first method but also to other representative diones.

To explore the scalable nature of this process, 1,3-cyclopentadione **3b** was converted without complications to the benzyl diketone **3c** in an 80% yield on a 100 mmol scale. Although the tandem Michael addition−enantioselective aldol cyclization at this scale still requires some optimization, dione **3c** was converted to enone **1c** in reasonable overall yield and purity and with an ee of >98%.

In conclusion, we have developed a general and readily scalable method to prepare 2-substituted 1,3-cyclopentadiones, allowing easy access to these synthetically useful compounds. These compounds were then readily transformed into previously unknown analogues of the HW-ketone. We expect that these steroid subunits will find wide use as valuable chiral building blocks.

Experimental Section

General Procedure for the Preparation of the Diones 3. A solution of aldehyde (15 mmol) and pyrrolidine (0.83 mL, 10 mmol) in CH_2Cl_2 (25 mL) was treated with a slurry of cyclopentadione **3b** (986 mg, 10.0 mmol) and pyrrolidine (0.41 mL, 5 mmol) in

(17) (a) Hajos, Z. G.; Parrish, D. R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 363−368. (b) Rajamannar, T.; Balasubramanian, K. K. *Synth. Commun.* **1994**, *24*, 279–292. (c) Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879–1882.

(18) Full details of the screening study can be found in the Supporting Information.

(19) Small amounts of triketone **2** are difficult to detect under the reaction conditions and are not readily separated from enone **1**.

(20) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96.

(21) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.

(22) Collins, D. J.; Fallon, G. D.; Skene, C. E. *Aust. J. Chem.* **1994**, *47*, 623–648.

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(24) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951–6954.

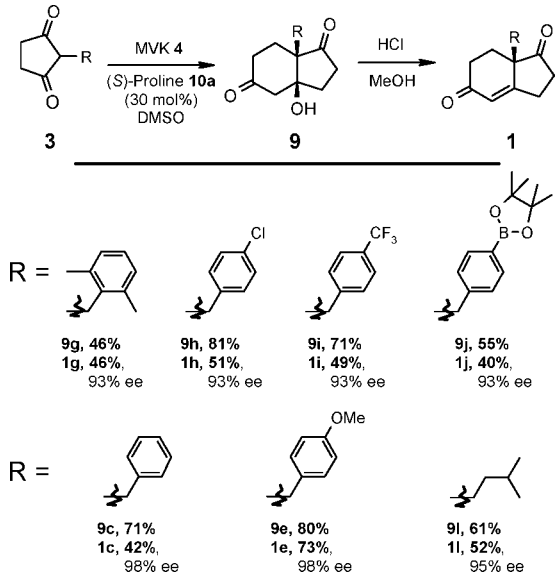

FIGURE 5. HW-ketone analogues **1** via tandem Michael addition−aldol cyclization. Yields reported for enone **1** are combined yields for the three steps from diketone **3**.

CH_2Cl_2 (25 mL). The resulting tan solution was stirred at rt for 3 h and then concentrated to give a brown residue. Addition of cold EtOAc caused precipitation of the desired Mannich base **6**, which was then isolated by filtration. A 0.1 M solution of this Mannich base in 2,2,2-trifluoroethanol was then treated with 10% palladium on charcoal (5 mol %) and hydrogenated under a balloon of H_2. After 23 h the catalyst was removed via filtration and the residue was concentrated. Treatment of the resulting oil with 1 M HCl caused precipitation of the product, which was filtered off and washed with water to give the desired dione **3**. Representative characterization data for the benzyl-substituted dione **3c**: TLC (10% MeOH/CH_2Cl_2, UV/$KMnO_4$) 0.54; ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (m, 5H), 3.40 (s, 2H), 2.48 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 199.5, 138.5, 128.7, 128.4, 128.0, 108.0, 68.2, 53.6, 32.4, 23.7; IR (KBr, cm^{-1}) 2920, 2580, 1580, 1370; MS (CI, *m*/*z* (%)) 189 (M + H$^+$, 100), 173 (18), 113 (10); HRMS (ES, *m*/*z*) calcd for $C_{12}H_{13}O_2$ 189.0916, found 189.0919.

General Procedure for the Preparation of the Triketones 2. A solution of dione **3** (1.0 mmol), MVK **4** (200 μL, 2.0 mmol), and NEt_3 (650 μL, 4.8 mmol) in THF (15 mL) was refluxed at 85 °C under Ar for 20 h. Removal of the solvent afforded an oil, which was then purified by flash chromatography to afford the desired triketone **2**. Representative characterization data for the benzyl-substituted triketone **2c**: TLC (30% EtOAc/hexane, $KMnO_4$) 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 3H), 7.01 (m, 2H), 2.93 (s, 2H), 2.49 (m, 4H), 2.10 (s, 3H), 2.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.2, 207.8, 135.1, 129.7, 128.6, 127.4, 61.1, 42.9, 37.8, 36.3, 29.9, 28.4; IR (KBr, cm^{-1}) 3017, 2939, 1722, 1708, 759, 708; MS (EI, *m*/*z* (%)) 258 (M$^+$, 21), 172 (25), 117 (28), 91 (100), 43 (22); HRMS (ES, *m*/*z*) calcd for $C_{16}H_{19}O_3$ 259.1334, found 259.1337.

General Procedure for the Preparation of the Enones 1 via Enantioselective Aldol Cyclization of the Triketones 2. A solution of triketone **2** (1.0 mmol) in either DMF (1 mL) or DMSO (10 mL) was degassed through 2 freeze−thaw cycles, treated with (*S*)-proline (30 mol %), and stirred under Ar in the dark. Aqueous workup and flash chromatography after 5−7 d afforded hydroxyketone **9**. Acid-catalyzed dehydration of **9** with either 1 M H_2SO_4/DMF or 1.25 M HCl/MeOH led to the desired enone **1**. Representative characterization data for the benzyl-substituted enone **1c**: TLC (50% EtOAc/hexanes, UV/$KMnO_4$) 0.50; $[\alpha]^{20}_D$ (+) 347.9 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 3H), 7.07 (m, 2H), 6.05 (d, J = 2.2 Hz, 1H), 3.07 (AB, J = 13.1 Hz, 1H), 3.04 (AB, J = 13.1 Hz, 1H), 2.51 (m, 3H), 2.25 (m, 3H), 2.04 (m, 1H), 1.83 (dt, J = 13.6 Hz, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.7, 198.2, 169.3, 135.6, 129.6, 128.7, 127.6, 125.2, 54.2, 42.4, 37.0, 32.9, 29.3, 28.2; IR (KBr, cm^{-1}) 3030, 2921, 1740, 1670, 1601, 1205, 763, 713; MS (EI, *m*/*z* (%)) 240 (M$^+$, 100), 181 (23), 169 (24), 119 (35); HRMS (EI, *m*/*z*) calcd for $C_{16}H_{16}O_2$ 240.115030, found 240.113514.

General Procedure for the Preparation of the Enones 1 via Tandem Michael Addition−Aldol Cyclization of Dione 3. A solution of dione **3** (1.0 mmol) and MVK **4** (188 μL, 2.0 mmol) in DMSO (10 mL) was degassed through 2 freeze−thaw cycles, treated with (*S*)-proline (30 mol %), and stirred under Ar in the dark. Aqueous workup and flash chromatography after 5−7 d afforded hydroxyketone **9**. Acid-catalyzed dehydration of **9** with either 1 M H_2SO_4/DMF or 1.25 M HCl/MeOH led to the desired enone **1**. Enones prepared via this tandem procedure were spectroscopically identical with those prepared via the enantioselective aldol cyclization of triketone **2**.

Acknowledgment. We gratefully acknowledge the technical staff of Bayer Schering Pharma, including Oliver Schenk and Ingrid Pissarczyk for HPLC analyses, and Siegfried Bäsler for the X-ray structure of **1c**.

Supporting Information Available: Complete experimental and characterization data for all compounds reported in this paper, details of the optimization studies for the aldol cyclization and the large scale preparation of enone **1c**, and X-ray crystal structure data for enone **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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